Clinical Practice Guidelines

JOURNAL OF HEPATOLOGY

EASL Clinical Practice Guidelines on sclerosing cholangitis☆

European Association for the Study of the Liver*

Summary

Management of primary or secondary sclerosing cholangitis is challenging. These Clinical Practice Guidelines have been developed to provide practical guidance on debated topics including diagnostic methods, prognostic assessment, early detection of complications, optimal care pathways and therapeutic (pharmacological, endoscopic or surgical) options both in adults and children.

Introduction

Sclerosing cholangitis spans several different aetiologies converging on final common pathways leading to a clinicopathologic presentation of fibrosis and strictures of the intra- and extrahepatic bile ducts, often with concomitant cholestasis and other complications related to bile duct obstruction.[1–3] Table 1 summarises known causes of sclerosing cholangitis, jointly comprising secondary sclerosing cholangitis. When no specific cause of sclerosing cholangitis can be identified, the entity is termed primary.

Primary sclerosing cholangitis (PSC) is often associated with inflammatory bowel disease (IBD), which is clinically evident in 50-80% of people with PSC, with the highest frequencies observed in Northern Europe and the US.[1] Patients with IBD may also exhibit PSC-like changes on magnetic resonance cholangiography (MRC) without concomitant abnormities in liver blood tests.[4] The prevalence and incidence of PSC in Northern Europe has been estimated at approximately 1 per 10,000 and 1 per 100,000 per year, respectively; in Southern Europe rates are probably approximately 10-fold lower. An important feature of PSC is the inherent risk of neoplasia at the affected mucosal surfaces, most commonly in the form of cholangiocarcinoma (CCA) and colorectal cancer.[5–7]

The cause of PSC is unknown. The close relationship with IBD is likely relevant, as shown by variable disease behaviour depending on the clinical presentation of IBD.[6,8] Proof-of-concept trials show an impact from antibiotics on liver blood tests,[9,10] and detailed assessments of the gut microbiota have demonstrated distinct associations.[11,12] Similarly, several drugs known to affect bile homeostasis also improve liver blood tests,[13,14] suggesting an involvement of these systems in PSC development. Genetic studies have identified a number of susceptibility genes for PSC, none of which are primarily related to bile formation but rather represent a pool of genes known to be involved in autoimmune conditions.[15] Although the precise mechanisms by which gut, biliary and genetic factors interact to cause PSC are unknown, their downstream hepatic consequence is represented by chronic inflammation and peribiliary fibrosis, as for sclerosing cholangitis more broadly.[16]

Management of sclerosing cholangitis, PSC included, is challenging and the evidence base for practice guidance remains poor. Over the last decade, learned societies from Europe, the US and Asia have nevertheless provided guidelines to help clinical decision-making in PSC.[17–22] In 2009, the European Association for the Study of the Liver (EASL) published guidelines for the management of cholestatic liver diseases.[20] This manuscript focused on patients presenting with features of cholestasis, and covered PSC, primary biliary cholangitis (PBC) along with other entities (*e.g.* IgG4-related cholangitis [IRC], genetic cholestasis and cholestasis in pregnancy). Given significant developments and the large number of relevant publications, along with an updated methodology,[23] the EASL Governing Board mandated a panel of experts to provide updated clinical practice guidelines (CPGs) for sclerosing cholangitis. We elaborate herein on the current recommendations.

Methodology used for the development of the present CPGs

The EASL Governing Board has involved a panel of experts in this field to elaborate the present CPGs according to the new format recently adopted, based on PICO (**P** Patient, Population, or Problem; **I** Intervention, Prognostic Factor, or Exposure; **C** Comparison or Intervention (if appropriate), **O** Outcome) questions.[23] These CPGs are directed at consultant hepatologists, specialists in training, and general practitioners and refer to adult and paediatric patients. Their purpose is to provide guidance on the best available evidence on the management of sclerosing cholangitis.

The panel initially established the most relevant topics that needed to be addressed and updated considering the content of the previous EASL guidelines on this topic.[20] The Panel decided to develop PICO questions with a homogeneous format for each section. PICO questions were sent to the Delphi panel composed of 24 international experts in hepatology (including paediatricians and biliary endoscopists), pathology and radiology from Europe and America, and 3 patient representatives. The questions were evaluated using an online platform. Based on the PICO questions, a literature search was performed using PubMed, and expanded to Embase, Google Scholar, and Scopus when needed.

Received 16 May 2022; accepted 16 May 2022; available online 21 June 2022

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https://doi.org/10.1016/j.jhep.2022.05.011

Table 1. Causes of secondary sclerosing cholangitis.

Predominant aetiology of secondary sclerosing cholangitis	Disease
Chronic obstructive	Choledocholithiasis
	Cholangiocarcinoma, other benign and malignant neoplasms
	Portal hypertensive biliopathy
	Surgical trauma (*e.g.*, during cholecystectomy)
	Anastomotic stricture after surgery (*e.g.*, liver transplantation, hepaticojejunostomy)
	Chronic pancreatitis
Immune-mediated	IgG4-related cholangitis
	Hepatic sarcoidosis
	Eosinophilic cholangitis
	Mast cell cholangiopathy
	Hepatic allograft rejection
Infectious	Recurrent pyogenic cholangitis
	Chronic biliary infestation (liver fluke, ascaris)
	Histiocytosis X
	Cryptosporidiosis, microsporidiosis
	Cytomegalovirus
	AIDS-related cholangiopathy
Ischaemic	Non-anastomotic strictures after liver transplantation
	Hepatic artery thrombosis (*e.g.*, after liver transplantation)
	Transarterial chemotherapy / embolisation therapy
	Sclerosing cholangitis of the critically ill patient including COVID-19-related cholangiopathy
	Systemic vasculitis
Hereditary	Cystic fibrosis-associated cholangiopathy
	ABCB4 deficiency (histological)
Toxic	Ketamine

References from papers were searched and identified further. The selection of references was based on appropriateness of study design, number of patients, and publication in peer reviewed journals. Whenever available, meta-analyses were used; otherwise original data were privileged. The resulting literature database was made available to all members of the panel, but the panel noted that for some of the topics considered evidence of good quality was scarce.

The Level of Evidence (LoE) based on the Oxford Centre for Evidence-based Medicine and the QUADAS-2 tool for accuracy of diagnostic studies were used to judge the quality of the evidence[24] (Table 2).

Each expert took responsibility and made proposals for statements for a specific section of the guideline and shared tables of evidence and text with the full panel.

The Panel met in person on 2 occasions, during the 2019 EASL International Liver Congress and AASLD Liver Meeting. Because of the COVID-19 pandemic, subsequent meetings (5) were held by teleconference for discussion and voting.

Besides the evidence, consistency of studies, risk-benefit ratio, patient preferences, ethical obligations and feasibility were also considered when grading recommendations. The strength of the recommendation was therefore graded in 2 categories: strong or weak (Table 3).

All recommendations (LoE and grade) were discussed and approved by all participants.

Then the CPGs were sent to the Delphi Panel for their review and vote. The result of the vote was taken into account as follows: less than 50% approval: re-write recommendation and resubmit to the Delphi panel; 50%-75% approval: re-write/improve the recommendation, but no resubmission to the Delphi panel; 75-90% approval: consensus, no need to re-write the recommendation but the document will take into account the comments; ≥90% approval: assumed as strong consensus, no change needed but small corrections possible.

The suggested changes were integrated into a revised version, which was reviewed and approved by the EASL Governing Board.

Table 2. Levels of evidence based on the Oxford Centre for Evidence-based Medicine.

Level	Criteria	Simple model for high, intermediate and low evidence
1	Systematic Reviews (SR) (with homogeneity) of Randomised-controlled trials (RCT)	Further research is unlikely to change our confidence in the estimate of benefit and risk
2	Randomised-controlled trials (RCT) or observational studies with dramatic effects; Systematic Reviews (SR) of lower quality studies (*i.e.* non-randomised, retrospective)	
3	Systematic Reviews (SR) of lower quality studies (*i.e.* non-randomised, retrospective)	Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate
4	Case-series, case-control, or historically controlled studies (systematic review is generally better than an individual study)	
5	Expert opinion (Mechanism-based Reasoning)	Any estimate of effect is uncertain

Table 3. Grades of recommendation.

Grade	Wording	Criteria
Strong	Must, shall, should, is recommended Shall not, should not, is not recommended	Evidence, consistency of studies, risk-benefit ratio, patient preferences, ethical obligations, feasibility
Weak or open	Can, may, is suggested May not, is not suggested	

The Delphi Panel agreement on each of the initial recommendations is shown in the Appendix.

How is PSC diagnosed in adults?

Recommendations

- In adult patients presenting with elevated serum markers of cholestasis, a diagnosis of large duct PSC should be made in the presence of typical findings of sclerosing cholangitis on high-quality cholangiography and after exclusion of secondary causes. The preferred diagnostic test is magnetic resonance cholangiopancreaticography (MRCP) **(LoE 2, strong recommendation, 93% consensus).**
- A diagnosis of small duct PSC should be considered in patients with elevated serum markers of cholestasis of unknown cause, normal high-quality cholangiography, and compatible histology of PSC, particularly in those with concomitant inflammatory bowel disease (IBD) **(LoE 3, strong recommendation, 88% consensus).**
- Autoantibodies should not be used to diagnose or risk-stratify people with PSC **(LoE 4, strong recommendation, 100% consensus).**

PSC is suspected in the presence of persistently elevated serum liver tests in a cholestatic pattern. Most patients are asymptomatic, but right upper quadrant abdominal pain, jaundice and/or pruritus may be present. Occasionally the initial presentation will be an episode of acute cholangitis, with right upper quadrant abdominal pain, fever and jaundice. Secondary causes of sclerosing cholangitis should be excluded. Importantly, 50-80% of people with PSC also have IBD. Therefore, elevation in serum liver tests, especially serum alkaline phosphatase (ALP), should raise suspicion for PSC and trigger further evaluation (Fig. 1). However, some rare patients may present with typical findings of sclerosing cholangitis on cholangiography but without elevation of serum ALP and gamma-glutamyltransferase (GGT); such patients need careful follow-up.

Although MRCP can be used as a quick standalone non-contrast test to diagnose PSC, performing a more complete, high-quality MRI evaluation will also provide information on bile duct thickness and enhancement, the status of hepatic parenchyma and complications of liver disease including evidence of portal hypertension.[25,26] The classic features of PSC are multifocal strictures and dilatations or ectasias involving the intra- and/or extrahepatic biliary tree. Other findings include ductal thickening and pruning. In a meta-analysis, the pooled sensitivity and specificity of MRCP for the diagnosis of PSC were 86% and 94%, respectively.[27] Advantages of MRCP over endoscopic retrograde cholangiopancreaticography (ERCP) include its non-invasive nature, lack of radiation use and lower cost, in addition to the potential to add MR elastography (MRE) for further information on disease staging and prognosis.[28,29] Limitations of MRCP include poor visualisation of peripheral intrahepatic branches, which limits the ability to diagnose very early intrahepatic PSC, and false-positive findings in cirrhosis of any aetiology due to tapering and duct distortion.[30,31] In a high-quality MRCP, bile ducts up to third order are depicted without artifacts over the biliary tree and without motion blurring. For

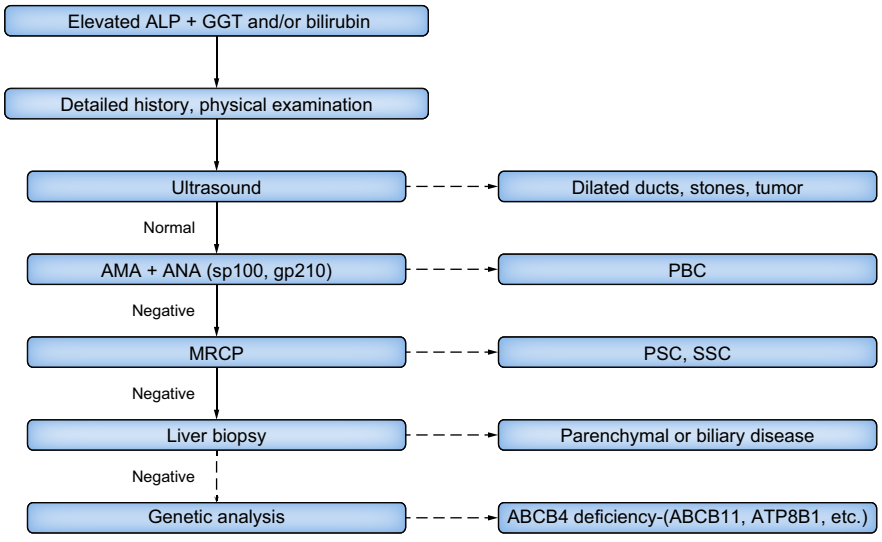

Fig. 1. Algorithm of diagnostic measures in chronic cholestasis (derived from[20,51]). Once a positive finding has been achieved (right part of the figure), additional diagnostic steps should be taken, if needed, according to relevant guidelines. ALP, alkaline phosphatase; AMA, anti-mitochondrial antibody; ANA, anti-nuclear antibody; GGT, gamma-glutamyltransferase; MRCP, magnetic resonance cholangiopancreaticography; PBC, primary biliary cholangitits; PSC, primary sclerosing cholangitis; SSC, secondary sclerosing cholangitis.

details on MRI in PSC and reporting standards please refer to the recently published position statements.[26,32]

A liver biopsy it not mandatory for diagnosis in patients with cholangiographic abnormalities compatible with PSC. However, in roughly 10% of cases, PSC involvement is limited to the peripheral ductules and not visible in MRCP or ERCP images, so-called small duct PSC.[7] In these cases, a liver biopsy is required for diagnosis and should demonstrate histologic findings typical or compatible with PSC as recommended by International PSC Study Group (IPSCSG) consensus.[33–35] According to IPSCSG, typical findings include periductal fibrosis/fibro-obliterative ductal lesions (see next section). A number of fibrosing small duct cholangiopathies may mimic the histopathological findings observed in 'small duct PSC',[36] including genetic ATP-binding cassette B4 (*ABCB4*) deficiency. Therefore, critical evaluation is required before a diagnosis of 'small duct PSC' can be made, particularly in the absence of IBD.

The diagnosis of PSC should be made only after potential causes of secondary sclerosing cholangitis have been ruled out (Table 1).

Among these, IRC, like PSC, is associated with biliary strictures, elevated serum markers of cholestasis, elevated serum IgG4 and similar clinical signs and symptoms; thus, IRC and PSC may be very difficult to distinguish.[3] Still, IRC is most commonly found in elderly men, often with a long-term exposure to potentially harmful chemicals ("blue collar workers").[37,38] The diagnosis of IRC can be made using HISORt criteria, based on histological, imaging and serological (IgG4) findings, other organ involvement (autoimmune pancreatitis, sialadenitis, among others) and response to corticoid treatment[39] as further outlined in the section 'How should people with PSC be monitored for disease progression?'. In comparison to PSC where the 'skip' strictures appear more circumscribed, the constrictions of the bile ducts, due to wall thickening, appear lengthier and band shaped in IRC. Bile duct wall thickening above 2.5 mm on MRI imaging has been proposed as a criterion to distinguish IRC from PSC.[40]

Next to IRC, sclerosing cholangitis of the critically ill patient (SC-CIP) has recently received increasing attention due to its dismal prognosis and rapid progression to cirrhosis and hepatic failure.[41] A prerequisite for the diagnosis of SC-CIP is no prior history of liver or bile duct disease explaining bile duct obstruction by biliary casts. Characteristic biliary cast formation is thought to result from necrosis of the biliary epithelium. SC-CIP has been particularly observed in severely ill patients after long-term treatment in intensive care units. The pathogenesis of SC-CIP may involve ischaemic injury of intra- and extrahepatic bile duct epithelia and/or toxic effects of biliary bile acids due to impaired biliary phospholipid and bicarbonate secretion – protective mechanisms against toxic biliary bile acids – which are associated with prolonged hypotension, administration of vasopressors, and/or mechanical ventilation during intensive care.[41]

Autoantibodies are frequently detected in people with PSC; anti-nuclear antibodies have been reported in 8-77% of patients, smooth muscle antibody in up to 83% and the anti-neutrophil cytoplasmic antibody (ANCA) in 26-96%.[42,43] ANCA has distinctive staining patterns on immunofluorescence according to the antigen being targeted: cytoplasmic (c-ANCA), targeting the cytoplasmic protein leukocyte proteinase 3 (PR3-ANCA), and perinuclear (p-ANCA), targeting another cytoplasmic protein, myeloperoxidase. A third immunofluorescence pattern is called atypical p-ANCA (perinuclear anti-neutrophil nuclear antibody), directed against components of the nuclear envelope However, these antibodies lack diagnostic specificity. Testing for anti-nuclear antibody, smooth muscle antibody and anti-soluble liver antigen is suggested when the diagnosis of overlapping features of PSC and autoimmune hepatitis (AIH) is suspected.[44] Both p-ANCA and atypical p-ANCA have been identified in people with PSC.

A relationship between ANCA positivity and clinical phenotype in PSC has not been clearly established and data are conflicting. It appears that this antibody is intermittently positive, further limiting its usefulness as a diagnostic test in PSC.[45] ANCA positivity may be associated with worse cholestasis and more severe biliary stricturing[46,47], and it has been suggested as a marker for PSC-IBD subphenotypes[48] as well as increased risk for CCA.[49]

IgA antibodies against glycoprotein 2 have been observed in approximately 50% of people with PSC independent of the presence of IBD; these antibodies may identify a subgroup of patients at increased risk of CCA[49,50] and decreased transplant-free survival.[49] Thus, anti-glycoprotein 2 and PR3-ANCA might have prognostic relevance but demonstration of additional value in comparison with known prognostic markers is required.

Once PSC is diagnosed, it is important to perform a colonoscopy with random biopsies for those patients who are not known to have IBD. Monitoring of people with PSC-IBD is discussed later in this document.

What is the role of liver biopsy in adults suspected of having PSC?

Recommendations

- A liver biopsy should be performed in adults suspected of having PSC whose high-quality MRCP is normal, to confirm or exclude small duct PSC **(LoE 4, strong recommendation, 88% consensus)**.
- A liver biopsy should be considered in people with PSC and co-existing features of AIH including markedly elevated transaminases, high IgG levels, and positive autoantibodies compatible with AIH **(LoE 4, strong recommendation, 92% consensus)**.

Even though the cholangiographic appearance of bile ducts is normal in patients with small duct PSC, other abnormal findings may be seen on MRI which can increase clinical suspicion for the disease. These include periductal enhancement, heterogeneous parenchymal signal on T2-weighted and post contrast-enhanced images, enlarged gallbladder and enlarged periportal lymph nodes.[52]

Histologic features compatible with PSC should be observed to confirm a diagnosis of small duct PSC. These include periductal fibrosis (observed in fewer than half of samples), fibro-obliterative cholangitis (observed in only 5-10% of samples),

ductular reaction, periductal inflammation, ductopenia and variable amounts of portal inflammation.[16,33] There is, however, great controversy regarding how typical the histology findings should be to ensure a diagnosis of small duct PSC, as not even periductal fibrosis can be considered pathognomonic of PSC. Based on specific genetic associations, small duct PSC may represent very early stages of PSC in patients who also have IBD, but not in those without.[53] Although ulcerative colitis (UC) is still the most common type of IBD associated with small duct PSC, we tend to see a larger proportion of patients with Crohn's disease among those with small duct disease, and the male preponderance is less striking compared to large duct PSC.[54]

Small duct PSC has a more protracted and benign course compared to large duct PSC, resulting in longer survival with fewer patients progressing to cirrhosis or requiring liver transplantation.[55–57] Notably, approximately 23% of patients with small duct PSC will progress to large duct PSC within a median of 7.4 years.[57] CCA is very rarely seen in patients with small duct PSC.[6]

A variable proportion of people with PSC may present with features of AIH or develop them during the course of the disease. In these cases, given that the diagnosis of AIH cannot be established without a liver biopsy, one has to be obtained to diagnose this variant syndrome of PSC with features of AIH.[58]

Substantial variation exists with respect to the diagnosis and management of PSC with co-existing features of AIH.[59] This variation arises from 2 main caveats: first, PSC and AIH share several core features and, second, there is no reliable serum biomarker to diagnose either condition. Hypergammaglobulinemia, presence of various autoantibodies and elevation of serum transaminases can be seen both in AIH and in PSC. Similarly, mild interface hepatitis can be seen in liver biopsies of people with PSC. However, presence of moderate to severe interface hepatitis in a patient with known PSC defines the co-existence of AIH.[60] We therefore propose considering liver biopsy in people with PSC with alanine aminotransferase (ALT) >5x the upper limit of normal (ULN) and/or IgG level >1.5x ULN.

When the revised International Autoimmune Hepatitis Group (IAIHG) scoring system was applied to patients with known PSC, 7-14% of patients were classified as having PSC-AIH overlap syndrome.[61–63] Conversely, approximately 10% of adult patients with AIH have abnormal cholangiographic features on MRCP which are consistent with PSC.[64] However, it is important to note that the IAIHG scoring system was not designed with the purpose of diagnosing variant syndromes, hence these numbers are only rough estimates.

People with small duct PSC may have a particularly increased rate of features that overlap with AIH,[65] and as many as 52% of paediatric patients with large duct PSC fulfil the revised IAIHG criteria for AIH,[66] which is also referred to as autoimmune sclerosing cholangitis (ASC). Paediatric presentation and management will be discussed in more detail later in this document.

A small study evaluating the natural history of patients with co-existing features of PSC and AIH suggests that these patients tend to be younger, with higher ALT and IgG levels, and that treatment with immunosuppressants may be beneficial, with long-term survival appearing favourable compared to "pure" PSC forms.[67] Several other case reports and very small case series indicate a beneficial biochemical response to immunosuppressants, although randomised-controlled trials (RCTs) have not been performed. In general, medically treated people with PSC-AIH have better long-term outcomes than people with classic PSC, but worse than those with classic AIH.[58,68]

Should serum IgG4 be determined in every patient with sclerosing cholangitis?

Recommendation

- Determination of serum IgG4 is suggested in every adult patient with large duct sclerosing cholangitis at the time of diagnosis **(LoE 3, weak recommendation, 91% consensus).**

IRC is known as one of the most frequent organ manifestations of systemic IgG4-related disease (IgG4-RD) next to type 1 autoimmune pancreatitis.[3] The clinical presentation of IRC may mimic difficult-to-treat diseases such as CCA, primary or secondary sclerosing cholangitis. Accurate diagnostic markers are lacking, and awareness of the disease among physicians is still low. Therefore, patients often suffer from delayed diagnosis or misdiagnosis, some of whom are subjected to erroneous extensive hepatobiliary or pancreatic surgery (or systemic chemotherapy), which has been reported in up to a third of patients with IRC prior to diagnosis of IgG4-RD.[39]

At present, the HISORt criteria still form the cornerstone in the diagnosis of IRC, combining histopathological (H), imaging (I), and serological (S) features including serum IgG4, other organ manifestations (O) of IgG4-RD and response to treatment (Rt).[39]

The accuracy of serum IgG4 to distinguish IRC from PSC or CCA is limited.[39,69,70] IgG4 serum levels >4x the ULN had a specificity of 100% for the diagnosis of IRC when compared to CCA and PSC, respectively, in large cohorts from the US and Europe. Still, the sensitivity was low: 26% in a test cohort and 17% in a validation cohort from the US[69] and 42% in a European cohort.[70] Elevation of serum IgG4 above the ULN of 1.4 mg/ml was associated with a diagnosis of IgG4-RD in only 22% of patients in a large mixed cohort of 1,510 patients examined for the suspicion of IgG4-RD and was also found in people with PSC and CCA, among others.[71] Still, elevated serum IgG4 represents one of the key markers for the diagnosis of IRC according to the multiparametric HISORt criteria,[39] although up to 25-30% of patients with IRC may present with normal levels of serum IgG4 at diagnosis. In patients with a mildly elevated serum IgG4 >1.4 and <2.8 g/L, incorporating the serum IgG4/IgG1 ratio with a cut-off at 0.24 in the diagnostic algorithm improved positive predictive value and specificity to distinguish IRC from PSC.[70] A blood IgG4/IgG RNA ratio determined by PCR did not accurately discriminate pancreatobiliary IgG4-related disease from pancreatobiliary cancer.[72] Notably, elevated serum IgG4, which is described in up to 15% of people with PSC,[70] has been associated with a more severe course of PSC in one cohort from the US,[73]

but not in a larger one from Europe.[74] New biomarkers for the diagnosis and management of IRC are urgently needed.

How should surrogate markers of PSC or prognostic scoring systems be applied in clinical practice?

Recommendation

- Risk assessment at the time of diagnosis and sequentially is recommended, based on phenotypic factors and non-invasive tests including: (1) standard biochemistry (including serum bilirubin, albumin, ALP, ALT, platelets, prothrombin time), (2) MRI of the liver with MRCP, and (3) liver elastography or serum fibrosis tests **(LoE 2, strong recommendation, 96% consensus).**

The natural history of PSC is highly variable and difficult to predict but in numerous affected patients the disease evolves to end-stage liver disease or CCA. The mean time to death or LT has been reported to be 10-22 years in different studies. Mortality in PSC is fourfold that of the general population.[7] As most data come from tertiary centres, the risk of complications or death is probably overestimated. For example, in a population-based study from the Netherlands, the median time from the diagnosis to liver-related death or LT was 21 years and markedly better than that of a PSC cohort followed in transplant centres in parallel (13 years).[7] Despite this overall grim prognosis, a proportion of patients may never need a liver transplant. In the large study from the Netherlands, CCA and colorectal cancer accounted for 32% and 8% of PSC-related mortality, respectively, compared to liver failure (15%) and liver transplant-related complications (9%).[7] In this regard, it is important to assess whether or not PSC is associated with IBD, by performing total colonoscopy with biopsies in each patient in whom the diagnosis of PSC has been established without known IBD.[20,22]

A number of simple prognostic factors have been identified (Box 1) [75] but determining the prognosis of people with PSC remains a challenge. Indeed, compared with other chronic liver diseases, competing risk events not associated with severe liver fibrosis occur more frequently, especially development of CCA and (in patients with IBD) colon cancer. Asymptomatic patients are likely to have a better prognosis than those with symptoms, but a lead time bias may play a role with diagnosis at an early stage.[76] Markedly elevated serum ALP activity is consistently associated with worse prognosis[77,78] but its naturally fluctuating course in PSC (unlike in PBC) complicates its usability as a prognostic surrogate marker in individual patients[79] and predictive cut-off values vary across studies (*e.g.* 1.5x ULN). Furthermore, in ursodeoxycholic acid (UDCA) trials, low ALP serum activities were often, but not always, associated with better outcomes.[80] Therefore, based on available evidence, ALP cannot be recommended as a standalone surrogate marker. As in other chronic cholestatic diseases, serum bilirubin has been shown to be a strong marker of prognosis, but it only rises permanently above the ULN in late-stage disease.

Histology, despite the robust association of fibrosis stage with outcome, was abandoned in recent scores due to its invasive nature and limited diagnostic value. Over recent years, there has been increasing interest in the non-invasive evaluation of liver fibrosis in PSC. The serum enhanced liver fibrosis (ELF) test, a direct marker panel of liver fibrosis based on 3 components of fibrogenesis and matrix remodelling, has shown ability to predict outcomes (death, liver transplantation) in retrospective and prospective studies, with an optimal cut-off of 9.8.[81–83] Patients with values <7.7 had an excellent prognosis with a very low clinical event rate.[81] Regarding liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE), it has been shown that LSM was independently linked to the stage of histological fibrosis, with cut-off values of 9.6 and 14.4 kPa for extensive fibrosis and cirrhosis, respectively, and a diagnostic accuracy higher than 0.80.[84] Moreover, an association between clinical outcomes and both baseline values (especially >9.9 kPa) and changes over time has been demonstrated in several retrospective studies.[84,85] The rate of events was very low in patients with VCTE values <6.5 kPa.[84] The interim analysis of an ongoing large prospective study found that 13.1 kPa was the optimal cut-off to differentiate low and high-risk groups in terms of transplant-free survival and liver complications after a median follow-up of 3 years.[86] In the 2021 EASL CPG on non-invasive tests, values above 9.5 kPA have been proposed to support the diagnosis of advanced fibrosis in compensated patients with normal bilirubin and without high-grade stenosis.[87]

A consensus process initiated by the IPSCSG resulted in a short list of 5 candidates for measuring disease progression: ALP, VCTE, histology, combination of ALP + histology, and bilirubin.[88] The 2015 EASL CPG on non-invasive tests stated that non-invasive assessment of fibrosis using VCTE should be considered in people with PSC (grade B2),[89] acknowledging that cholestasis related to untreated dominant biliary strictures influences liver stiffness assessment. The 2021 EASL CPG on non-invasive tests confirmed this recommendation and added that the ELF score could also be used for risk stratification both at baseline and during follow-up.[87]

LSM is also useful in the non-invasive prediction of high-risk varices in people with PSC. Indeed, in a series of 80 people with PSC and cirrhosis, it has been shown that Baveno-VI criteria (LSM-VCTE <20 kPa and platelet count >150x10^9/L), commonly used to avoid unnecessary screening oesophagogastroduodenoscopy in patients with compensated cirrhosis, had a 0% false negative rate, obviating the need for 30% of oesophagogastroduodenoscopy procedures, and demonstrating that expanded Baveno criteria (LSM-VCTE <25 kPa and platelet

Box 1. Main phenotypic prognostic factors in primary sclerosing cholangitis (adapted from[75]).

Good prognostic factors:
- Younger age at diagnosis
- Female sex
- Small duct disease
- Crohn's disease (as opposed to ulcerative colitis)
- Normal or mildly elevated ALP (with or without UDCA)

Poor prognostic factors:
- Extensive intra- and/or extra-hepatic biliary involvement
- Liver synthetic dysfunction or portal hypertension
- Severe parenchymal fibrosis or cirrhosis
- Jaundice

ALP, alkaline phosphatase; UDCA, ursodeoxycholic acid.

Table 4. Main PSC-specific prognostic scoring systems.

	Wiesner 1989 [76]	Farrant 1991 [98]	Broome 1996 [99]	Revised Mayo Score 2000 [100]	Boberg 2002 [101]	Ponsioen 2002 [92]	Tischendorf 2007 [93]	Amsterdam-Oxford 2017 [102]	UK-PSC 2019 [103]	PREsTo 2020 [104]
Age	Y	Y	Y*	Y	Y*	Y*	Y	Y*	Y	Y (+ PSC duration)
Bilirubin	Y		Y	Y	Y		Y	Y	Y	Y
Albumin				Y	Y		Y	Y	Y	Y
AST				Y				Y		Y
ALP		Y						Y	Y	Y
Hb	Y								Y	Y (+ Na)
Platelets								Y		Y
IBD	Y									
Histology	Y	Y	Y							
Splenomegaly /Hepatomegaly		Y					Y			
Variceal bleed				Y					Y	
Cholangiogram						Y	Y	Y (small *vs* large)	Y	
Outcome	Death	Liver-related death/LT	Liver-related death/LT	Death	PSC-related death/LT	Liver-related death/LT	Death/LT	PSC-related death/LT	Death/LT	Hepatic decompensation

ALP, alkaline phosphatase; AST, aspartate aminotransferase; IBD, inflammatory bowel disease; LT, liver transplantation; PSC, primary sclerosing cholangitis. *At diagnosis. Note that PSC-related death may include colorectal cancer mortality.

count >110x10^9/L) have an adequate performance and platelet count alone (200x10^9/L) has a high discriminative value.[90] Similarly, MRE has also been shown to have prognostic value, with prognostic cut-off values in keeping with the corresponding VCTE values,[91] but MRE is not broadly available and is less affordable. The use of non-invasive markers to monitor liver fibrosis specifically related to PSC is rapidly evolving.

Cholangiographic abnormalities assessed by scoring systems, either with ERCP[92,93] or MRI/MRCP[94] also have prognostic value, but ERCP is no longer routinely performed and the reproducibility of MRI/MRCP scores (based on intrahepatic bile duct dilatation, hepatic dysmorphia and portal hypertension) awaits prospective evaluation in large multicentric studies which should include non-expert centres. Dominant stenosis has been associated with decreased transplant-free survival (linked or not to CCA development) in several retrospective studies based on ERCP,[95] but an MRI/MRCP-based definition of such a lesion is still lacking and the prognostic long-term impact of endoscopic interventions needs assessing. As a result, the 2017 IPSCSG position paper providing recommendations on the use of MRI/MRCP in PSC, stated that, at this time and despite its potential, there was insufficient evidence to recommend the routine use of MRI/MRCP as a prognostic tool.[26] However, there is growing evidence supporting its prognostic value. As such, the complementary prognostic value of MR scores and LSM has recently been shown in a large retrospective study.[96] Lastly, artificial intelligence has enabled quantitative MRCP (MRCP+), which is a novel technique to automatically segment biliary anatomy and provide quantitative biliary tree metrics.[97]

Generic scores (Child-Pugh, model for end-stage liver disease [MELD]) are relevant in late-stage disease but not in early PSC as they have been developed for people with cirrhosis. Several attempts have been made to develop a PSC-specific risk stratification or prognostic model[76,92,93,98–104] (Table 4) but a head-to-head comparison between recent models is yet to be conducted. The PSC-specific revised Mayo risk score is the most widely used model despite its relatively short horizon (4 years) and the limited discriminant information it provides in early-stage disease.[100] Because of the progressive nature of PSC, it is important to update patients about their risk profile over sequential visits, given that a significant number classified as low risk become high risk over time (25% over 5 years with the Amsterdam-Oxford model[105]).

The naturally fluctuating course of symptoms and serum liver tests (transient elevations may be related to evolving strictures, biliary calculi or acute bacterial cholangitis) adds to the difficulty of assessing disease stage and prognosis. Nevertheless, there are currently no single established surrogate markers that reliably estimate prognosis and the use of prognostic models to predict clinical outcome in an individual patient cannot be recommended at present.

Lastly, the relevance of prognostic variables is likely to vary according to disease stage. For instance, measures of biliary involvement are probably more helpful for predicting long-term outcomes in early stages, whereas measures of the extent of parenchymal disease (fibrosis) may be more helpful for predicting immediate events in advanced stages.[106] It should also be kept in mind that early prognostic markers are likely to be overridden by those directly linked to the burden of liver fibrosis.

It is currently agreed that, in the design of phase III clinical trials, surrogate endpoints should measure more than one aspect of the disease (*i.e.*, bile duct pathology and liver fibrosis). For example, a potential combined "reasonably-likely-to-predict"

Table 5. Rational approaches to non-invasive risk stratification in PSC.

Level of applicability	Prognostic tools
High (High applicability, robust validation)	◦ Baseline (early *vs.* advanced) disease stage as defined by biochemical (bilirubin, albumin, platelets, prothrombin time) and imaging analyses ◦ Small duct PSC *vs.* classical PSC
Moderate (High applicability, further validation pending)	◦ ALP ◦ LSM by VCTE ◦ ELF test ◦ MRI/MRCP
Indeterminate (Insufficient applicability and/or validation)	◦ Age, gender and type of IBD ◦ AIH features ◦ IgG4 serum levels ◦ PSC-specific prognostic scores* (except for Mayo Risk Score in advanced PSC)

AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ELF test, serum enhanced liver fibrosis test; IBD, inflammatory bowel disease; LSM, liver stiffness measurement; MRCP, magnetic resonance cholangiopancreaticography; VCTE, vibration-controlled transient elastography.
*Likely to move to higher level of applicability in the near future.

Box 2. Potential approaches to simple risk stratification of PSC at initial work-up using non-invasive tools (adapted from[106,108]).

"Low risk" of events:
- Small duct PSC and no evidence of cirrhosis

OR

- Classical PSC and (all to be present): asymptomatic with normal bilirubin, albumin, platelets, and PT, ALP <1.5 ULN, LSM (VCTE) <6.5 kPa (or ELF test <7.7), limited biliary changes on MRI/MRCP.

"Significant risk" of events if any present:
- Symptomatic, ALP >1.5 ULN, abnormal bilirubin, albumin, platelets or PT, LSM (VCTE) >9.9 kPa (or ELF test >10.6), extensive biliary changes (especially intra-hepatic biliary dilatation) on MRI/MRCP.

Patients with in-between criteria (for example VCTE <9.9 kPa, but >6.5 kPa or minimal liver test abnormalities) can be classified as "intermediate risk". This group has to be further defined. ALP, alkaline phosphatase; ELF test, serum enhanced liver fibrosis test; LSM, liver stiffness measurement; MRCP, magnetic resonance cholangiopancreaticography; PSC, primary sclerosing cholangitis; PT, prothrombin time; VCTE, vibration-controlled transient elastography.

surrogate endpoint would be improvement in serum ALP levels and no progression of fibrosis based on either non-invasive methods (*e.g.*, VCTE) or histology.[107]

Table 5 summarises and grades the non-invasive prognostic tools for PSC according to their actual level (high, moderate, mild, indeterminate) of applicability and validity. Box 2 indicates potential approaches to simple risk stratification in PSC using non-invasive tools (adapted from[106,108]). Patients identified at marked risk of events are those with at least one clearly recognised poor prognostic factor.

How should people with PSC be monitored for disease progression?

Recommendations

- Non-invasive routine liver surveillance is suggested, based on:
  - Clinical review and standard serum liver tests including bilirubin, albumin, ALP, aspartate aminotransferase, platelets and prothrombin time, every 6 or 12 months depending on risk stratification, are recommended **(LoE 2, strong recommendation, 96% consensus).**
  - Liver elastography and/or serum fibrosis tests at least every 2 to 3 years are recommended **(LoE 3, strong recommendation, 96% consensus).**
  - Liver ultrasound and/or abdominal MRI/MRCP every year are suggested **(LoE 3, weak recommendation, 96% consensus).**

Current recommendations for PSC monitoring are based, at least in part, on empirical insights and clinical experience (Box 3, part A). The goal of monitoring is the regular reappraisal of clinical complaints, disease progression and cancer risk, keeping in mind that the cancer risk is not strongly associated with the development of liver fibrosis. Except for colon surveillance in patients with IBD and for liver surveillance in patients with cirrhosis, there is no evidence-based algorithm for the routine follow-up of people with PSC. The general goal is the early detection of complications that could benefit from adapted treatment (when available). Special attention should be paid to hepatobiliary and colorectal malignancies (see specific recommendations in later sections) and, in clinical practice, the 2 objectives (early detection of malignancies and liver disease progression) are intertwined. Quality of life including complaints of fatigue, pruritus and depression should be regularly checked and, if impaired, therapeutic interventions should be considered. This surveillance topic is in sore need of further research.

Monitoring of liver disease progression is based on the assessment of clinical signs and symptoms, degree of biliary involvement and of parenchymal fibrosis/cirrhosis (and its consequences, *i.e.* portal hypertension and signs of liver failure). People with PSC should have at least an annual evaluation. Those with more advanced disease require more frequent follow-up. When new symptoms develop, additional tests should be performed as clinically indicated (Box 3, part B).

Next to serum bilirubin and albumin in more advanced stages of PSC, serum ALP has also served as an independent surrogate prognostic marker of early-stage PSC in large patient cohorts, despite being less reliable than in PBC.[87,89] Serum ALP activity is affected by various factors including anticholestatic treatment with UDCA. Serum ALP activity <1.5x ULN has been associated with a favourable long-term prognosis in PSC.[109]

Liver fibrosis assessment

Liver stiffness measurement - LSM

The prognostic utility of annual LSM for PSC progression by both VCTE (>1.5 kPa/year) and MRE (0.34 kPa/year) has been shown in 2 large retrospective studies.[84,91] The 2015 and 2021 EASL CPG on non-invasive tests recommended follow-up assessment of fibrosis with VCTE in PSC (grade B2) but the timeframe of repeated examinations remained to be defined.[87,89] Other elastography methods probably have similar prognostic value but data are still scarce. Results of prospective studies that will hopefully provide further insight are expected soon. It is worth noting that LSM should not be used in

Box 3. Suggested algorithm for follow-up of primary sclerosing cholangitis.

A) Routine surveillance (reappraisal of disease progression and risk)

- Every 12 months (for all, every 6 months in patients with significant risk):
  - Clinical evaluation (including quality of life)
  - Serum liver-related tests including bilirubin, ALP, AST, platelets, and PT
- Every 12 months (even for patients at low risk):
  - MRI/MRCP and/or US (with a special attention for gallbladder wall abnormalities)* §
  - Colonoscopy**
  - Elastography and/or ELF test
- Every 2 to 4 years (for all): DEXA for bone mineral density assessment (and serum vitamin D measurement)

B) Additional work-up when clinically indicated (new symptoms or evolving abnormalities in routine investigations (ALP/bilirubin rising) or ΔLSM >1.5 kPa/year or ductal progression):

- Suspected cholangiocarcinoma: serum CA 19.9 and MRCP/MRI liver with contrast and ERCP with cytologic or histologic sampling
- Suspected features of auto-immune hepatitis or drug toxicity: serum IgG and autoantibodies of AIH, consider liver biopsy
- Suspected clinically relevant portal hypertension (Baveno VII criteria[114]): EGD, consider non-selective beta blockers

In UDCA treated patients, consider non-compliance

*Liver imaging by US every 6 months in patients with cirrhosis. §Ductal imaging every 3 years in small duct PSC with stable liver tests. **Every 5 years in those without IBD at initial staging. AFP, alpha fetoprotein; ALP, serum alkaline phosphatase; DEXA, dual energy X-ray absorptiometry; EGD, esophagogastroduodenoscopy; ELF test, serum enhanced liver fibrosis test; IBD, inflammatory bowel disease; LSM, liver stiffness measurement; MRCP, magnetic resonance cholangiopancreaticography; PT, prothrombin time; US, ultrasound.

isolation but rather interpreted in conjunction with clinical, biochemical and radiological features. In particular, a marked increase in LSM may be related to the development of bile duct obstruction.[110]

ELF test

The ELF test can predict transplant-free survival in PSC[81,82] and retains predictive value longitudinally despite dynamic fluctuations in the course of PSC with regard to progression to cirrhosis (but without association between reduced values and improved outcome).[79] The 2021 EASL CPG on non-invasive tests recommended the use of LSM and/or ELF score during follow-up.[87]

Biliary involvement

As universally agreed, MRI/MRC is the best non-invasive tool to assess large bile duct changes in PSC.[20–22] In addition, MRI allows for detection of liver parenchymal changes and features of portal hypertension. Lastly, MRE can be performed at the same time without adding, at least theoretically, a significant amount of time or cost to the examination.

Some centres perform annual MRI/MRC in order to assess ductal changes, liver parenchymal appearance and portal hypertension, independently from CCA screening. Changes develop in 60% of patients over 4 years[111] and MRI/MRC scores were prognosticators of clinical outcome in a large retrospective multicentric study.[94] However, the prognostic value of dynamic changes in these scores was not specifically assessed and inter-centre reproducibility remains an unsolved issue.[112] Lastly, some preliminary retrospective studies suggest the utility of 'MRCP+' as a prognostic tool for prediction of clinical outcomes in PSC.[113]

Despite the fact that sequential assessment of ductal changes makes sense in PSC and that MRI/MRC can occasionally replace ultrasound during surveillance of people with PSC (every year for detection of mass lesions in the gallbladder[20,22] and every 6 months for patients with cirrhosis to exclude hepatocellular carcinoma [HCC]), systematic regular use of MRI/MRC for liver disease progression monitoring cannot be generally recommended at present and should be an individualised decision that also considers local availability and expertise.

How should adult people with PSC be monitored for hepatobiliary malignancy?

Recommendations

- Surveillance with ultrasound and/or MRI/MRCP for CCA and gallbladder malignancy is suggested at least yearly in patients with large duct disease regardless of disease stage. Carbohydrate antigen 19-9 (CA 19-9) is not suggested for surveillance purposes due to its insufficient accuracy **(LoE 3, weak recommendation, 96% consensus).**
- Surveillance for hepatobiliary malignancy is suggested every 6 months in the presence of cirrhosis **(LoE 3, weak recommendation, 93% consensus).**

Diagnosis of hepatobiliary cancers at early disease stages is essential for curative treatment. Early tumour detection in PSC has been associated with a favourable outcome but tumour recurrence is common and long-term survival is reduced.[115,116] The nature of PSC with multiple biliary strictures entails an obvious challenge for early tumour diagnosis. A well-founded surveillance programme requires an appropriate screening method, which is simple, cheap, accepted by the patient, generally available, safe, and has a high sensitivity. Unfortunately, no such tool exists for the early detection of CCA or high-grade dysplasia in PSC. Also, precise tools to identify patients at high risk of malignancy are lacking and most people with PSC have benign strictures leading to end-stage disease and will not develop hepatobiliary malignancy.[6] The lack of evidence for which monitoring strategy is best has led to the implementation of many different strategies globally.[117] Regular surveillance with ultrasound or MRI has been proposed [118–120] and is already clinical practice in most centres.[117]

Evidence for the efficacy, including survival and cost benefits, of surveillance is limited and contradictory. The incidence rate of hepatobiliary malignancy in the population-based setting is reported to be around 0.5 % per year.[7,121,122] One large retrospective study from a tertiary care centre including 830 people with PSC showed that regular surveillance was associated with better survival after a cancer diagnosis. Patients who were exposed to surveillance were diagnosed earlier and were candidates for curative treatment with liver transplantation. Five-year survival in this study was 68% in the

surveillance and 20% in the non-surveillance group.[115] Data from a population-based registry study shows an association between exposure to annual imaging and a 2-fold reduction in the risk of hepatobiliary cancer-related death.[123] In a prospective multicentre study from Sweden, yearly MRI/MRCPs was evaluated. The incidence rate of CCA was 0.4% and yearly imaging with MRI/MRCP followed by investigations with ERCP and cytology/histology was not able to detect cancer early enough to improve long-term survival.[122] In another large retrospective study including 2,975 people with PSC from 28 centres in 11 countries, different surveillance strategies were compared. Overall survival was improved (risk of death was halved) in patients exposed to scheduled imaging.[117] Patients diagnosed with hepatobiliary malignancy were more often treated with potentially curative regimens (surgical resection or liver transplantation). The improved survival associated with scheduled imaging in this study could not only be explained by earlier tumour detection but also by many other factors, such as early detection and dilatation of significant asymptomatic benign strictures, as well as confounding factors. There is no study on the cost effectiveness of regular imaging in PSC. The contradictory results from the different studies are likely caused by selection and lead time bias. The cost effectiveness of surveillance in all patients can be questioned and individualised strategies need to be developed.

Based on current data, a rational approach for CCA/gallbladder carcinoma (GBC) surveillance is an interval imaging assessment of the biliary tree and the gallbladder, using MRI with MRCP or ultrasound.[118–120] The sensitivity for CCA detection is higher for MRI/MRCP (89%) than for ultrasound (57%).[118] MRI gives more detailed information and the opportunity to compare and evaluate progression of strictures or other changes in the liver over time, whereas ultrasound may be more suitable for evaluation of the gallbladder. One study supports the use of MRI over ultrasound for early detection of CCA,[116] while the gallbladder is easily evaluated at ultrasound.

To enable high-quality evaluations on MRI, the use of standardised reporting must be underscored. Criteria for standardised reporting have recently been published and their widespread use has the potential to improve quality of surveillance and care by reducing inter-reader variability, facilitating assessment of disease progression and evaluating management.[32]

The value of CA 19-9 as a surveillance tool is more debatable. Increased CA 19-9 levels support a diagnosis of CCA, especially in the absence of bacterial cholangitis, but a normal level does not rule out a tumour. Longitudinal series with repeated measures of CA 19-9 are contradictory[124,125] and increased levels are common in benign disease.[126] Normal levels are frequently seen in patients with CCA. CA 19-9 is therefore an inadequate marker for regular surveillance in PSC.[124,125,127–129]

ERCP is not recommended for cancer surveillance purposes in people with PSC due to its invasiveness and procedural risks.[130] However, data from Finland suggest that ERCP, especially in advanced extrahepatic PSC, may be beneficial for detection of premalignant or malignant lesions regardless of symptoms.[131] In order to be beneficial, surveillance strategies with ERCP require liver transplantation to be an option in case of dysplasia.

The risk of HCC in people with PSC has been reported to be quite low.[7,132,133] Longitudinal data from the US of 830 people with PSC detected 20 (2.4%) patients with HCC during a 9.5-year follow-up, which represented 22% of all hepatobiliary cancers in this study.[115] Current guidelines recommend surveillance in people with PSC-related cirrhosis with ultrasound every 6 months.[134]

The increased risk for gallbladder polyps and their potential to become malignant warrants regular surveillance of the gallbladder. In patients with cirrhosis this is preferably done by ultrasound at the same time as surveillance for HCC. GBC can occur at any stage of the disease; in patients without cirrhosis the gallbladder should be visualised by imaging at least every 12 months.[135,136] If MRI is chosen as a primary surveillance method, gallbladder evaluation deserves attention and additional ultrasound investigations with contrast may be needed to confirm or rule out GBC when suspicious gallbladder pathology is found.

How should adult people with PSC be monitored and treated for metabolic bone disease?

Recommendation

- Assessment of bone mineral density is recommended in all people with PSC at the time of diagnosis using dual energy X-ray absorptiometry (DEXA). Follow-up and treatment of osteopenia and osteoporosis should follow current practice guidelines **(LoE 4, strong recommendation, 92% consensus).**

According to the World Health Organization, osteopenia is defined as a T-score between -1 and -2.5 SD as measured by DEXA, and osteoporosis by a T-score less than -2.5, derived from measurement at the femoral neck or the lowest value from either the lumbar spine or femoral neck.[137,138]

People with PSC are at greatly increased risk of bone mass loss and osteoporosis. In 2 similarly sized PSC cohorts, the prevalence of osteoporosis was 11-15% and that of osteopenia around 40%.[139,140] The mechanisms of bone loss in PSC are poorly defined. A recent study confirmed earlier reports[141] that increased bone resorption contributes significantly to bone loss in PSC, which was most marked at the cortical site.[140] Various risk factors for osteoporosis have been reported, such as increasing age, low BMI, steroid use and presence and duration of associated IBD,[139] which could not be confirmed by others.[140] Stage of liver disease does not appear to be a major risk factor,[140,142] underlining the need to search for bone disease even in early-stage disease.

There is no specific treatment for PSC-associated bone loss. Although data is lacking, supplementation of vitamin D in case of deficiency seems advisable and sufficient dietary intake of calcium and exercise should be advised according to current guidelines.[137,138]

Fragility fractures significantly impair patients' quality of life. Fracture risk approximately doubles with every SD T-score reduction.[137,138] People with PSC that require liver transplantation are especially vulnerable to additional loss of bone mass post-transplant, mainly due to high-dose corticosteroid treatment and immobility.[143] An additional 25% of patients transplanted for cholestatic liver disease developed *de novo* fractures after transplantation.[143] Therefore, fracture risk should be assessed in every patient with PSC (*e.g.* using online calculators such as FRAX) after DEXA. Individual fracture risk should

guide preventive and therapeutic recommendations, such as the use of bisphosphonates.[137,138]

Should people with PSC be treated with ursodeoxycholic acid?

Recommendations

- UDCA at doses of 15-20 mg/kg/d can be given since it may improve serum liver tests and surrogate markers of prognosis. Available data does not allow for a firmer recommendation **(LoE 1, weak recommendation, 76% consensus).**
- UDCA at doses of 28-30 mg/kg/d should not be given **(LoE 1, strong recommendation, 100% consensus).**

UDCA and progression of PSC

UDCA is licensed for treatment of PSC in some European countries such as France or Switzerland although currently no established drug exists for the treatment of PSC. UDCA is a hydrophilic bile acid with broad anti-cholestatic, cytoprotective, anti-inflammatory and antifibrotic actions which is used to treat a wide range of cholestatic liver diseases (including PSC), although a clear survival benefit has only been demonstrated for PBC.[144] Two meta-analyses of published data in people with PSC revealed no survival benefit from UDCA therapy.[145,146] A number of smaller pilot studies and larger RCTs[13,80,147–156] demonstrated improvement of serum liver tests (except for 2 of them[150,155]), but these studies were all underpowered for the identification of "hard" clinical outcome parameters such as death or liver transplantation. Among the larger RCTs, the study by Lindor showed that 13–15 mg/kg of UDCA over 2 years improved serum liver tests but not symptoms, liver histology or survival in 105 people with PSC.[151] A 5-year Scandinavian multicentre trial investigating higher doses of UDCA (17–23 mg/kg/d) *vs.* placebo could not show a significant difference in outcomes, including symptoms, liver biochemistry, CCA, death or liver transplantation, although a trend towards a reduction in mortality/transplantation was observed for the UDCA group.[155] However, liver biopsy was not included in this study, and biochemical tests such as ALP, in contrast to numerous pilot studies, did not improve, raising concerns about long-term compliance. Notably, even this large PSC drug trial, which recruited 219 patients and analysed 198 patients, was still underpowered and did not reach the calculated required sample size of 346 to adequately judge the long-term efficacy of UDCA treatment in PSC.

Smaller pilot trials with even higher UDCA doses (20–30 mg/kg/d) demonstrated improvement of liver tests,[153,154,156] histological (Ishak staging) and cholangiographic features,[153] Mayo risk score and projected survival.[154,156] A subsequent study of UDCA (28–30 mg/kg/d) in 150 people with PSC by Lindor *et al.*[80] had to be prematurely terminated after analysis showed higher rates of serious adverse events and the primary endpoint defined as time to first failure (death, transplant, meeting minimal listing criteria, development of varices, CCA or progression to cirrhosis) in the UDCA-treated group despite improvement of biochemical parameters.[80] The underlying mechanisms of this negative effect of high-dose UDCA in PSC (also seen in mouse models of PSC[157]) are still poorly understood but could include changes in bile acid metabolism with formation of toxic bile acid species such as lithocholic acid.[158]

Several studies have reported improved prognosis in people with PSC in whom liver biochemistries (in particular ALP) normalise or improve, whether this occurs spontaneously or with UDCA therapy.[77,159,160] However, the considerable inter- and intra-individual variation of serum ALP may limit its prognostic utility in daily clinical practice.[79] One uncontrolled study investigating the short-term effects of stopping UDCA in patients already established on treatment demonstrated worsening of liver biochemistry and pruritus after stopping treatment.[161] A prospective trial in paediatric PSC made similar observations, with a deterioration of serum liver tests after UDCA withdrawal that responded to reinstitution of UDCA.[162] Based on these results, UDCA has been reconsidered for PSC at doses up to 20 mg/kg/d, although data regarding hard clinical endpoints and a survival benefit are lacking for this dose range.[109] In a recent Japanese nationwide registry study comprising 435 people with PSC, UDCA treatment was significantly associated with reduced mortality or need for liver transplantation and possibly CCA, but publication of the full paper is still awaited.[163] In summary, based on current fully published evidence, whether UDCA at moderate/medium doses has a role in slowing the progression of PSC-related liver disease is still unclear, while high doses of UDCA are clearly harmful and need to be avoided. Since the use of UDCA in PSC is widely accepted by patients and treating physicians across many countries, ongoing phase III study designs allow for and stratify for its continued use (NCT03872921, NCT03890120).

UDCA and colorectal neoplasia in PSC

Data on the chemopreventive effects of UDCA in PSC are conflicting. Smaller retrospective or cross-sectional studies (with 52 or 59 patients) indicated that people with PSC treated with UDCA had a lower incidence of colonic dysplasia or colorectal cancer than untreated patients,[164,165] although another larger retrospective study with 120 patients reported no difference.[166] Moreover, an RCT (n = 98) of UDCA (17–23 mg/kg) also showed no difference in the rate of colorectal neoplasia at either 5 or 15 years,[167] while one study reported a higher rate of low-grade dysplasia associated with the use of high-dose (28-30 mg/kg/d) UDCA in a highly selected group of patients.[168] Finally, 2 meta-analyses report no significant overall effect of UDCA on rates of colorectal neoplasia in people with PSC.[169,170] However, in one meta-analysis, a significant chemopreventive effect was found when only the more clinically relevant advanced lesions (colorectal cancer and/or high-grade dysplasia) were considered. Further subgroup analysis revealed that low and standard-dose UDCA treatment (8-15 mg/kg/d) was associated with a significant reduction in the risk of colorectal neoplasia.[170] Subgroup analysis in the other meta-analysis[169] also suggested a possible trend towards decreased colorectal cancer risk in low-to-medium-dose groups.

UDCA and CCA in PSC

The evidence for a potential beneficial effect of UDCA on the risk of CCA is very limited. The larger Scandinavian and US UDCA trials did not observe any difference between UDCA- and placebo-treated patients regarding CCA development.[151,155] A German cohort study following 150 people with PSC under UDCA treatment over a median of 6.4 years reported CCA in 3.3% of cases, which is about half of the expected rate.[171] Moreover, a Scandinavian study of 255 people with PSC followed over 11

years identified a lack of UDCA treatment as a risk factor for the development of hepatobiliary malignancy.[172]

Future bile acid-targeted therapies

Novel bile acid-based therapeutic options including 24-norursodeoxycholic acid (norUDCA, recently renamed as norucholic acid or NCA),[173] steroidal and non-steroidal bile acid receptor/farnesoid X receptor (FXR) agonists (*e.g.*, obeticholic acid,[174] cilofexor[175]) as well as the FXR-downstream target fibroblast growth factor-19 (FGF19: non-tumorigenic recombinant FGF19/NGM-282 [aldafermin][176]) have been tested in PSC with promising initial results in phase II studies. Other nuclear receptors such as peroxisome proliferator-activated receptors (PPARs) are also of considerable interest and can be targeted with available drugs (*e.g.* fibrates).[177] Other options such as immunomodulatory and anti-inflammatory drugs are discussed in the section 'How should portal hypertension be managed in PSC?'.

Should people with PSC be treated with corticosteroids/immunosuppressives/biologics?

Recommendations

- Use of corticosteroids/immunosuppressives/biologics is not suggested for the routine treatment of PSC **(LoE 4, weak recommendation, 96% consensus).**
- In people with PSC with biochemically (ALT, IgG, autoantibodies) and histologically suggestive features of AIH, it is suggested to consider corticosteroids or other immunosuppressive therapies under close monitoring **(LoE 3, weak recommendation, 88% consensus).**
- It is not suggested to use corticosteroids or immunosuppressive therapies in people with PSC with mildly elevated serum IgG4 (<2x ULN) **(LoE 5, weak recommendation, 91% consensus).**

Although immune-mediated mechanisms in the liver and the gut play a key role in the pathogenesis of PSC, immunosuppressive strategies have led to disappointing results. A long list of agents with immunosuppressive potency have been tested for treatment of classic PSC without demonstrating an improvement in disease activity or outcome. These include predniso(lo)ne, budesonide, azathioprine, cyclosporine, methotrexate, mycophenolate, and tacrolimus, agents with TNFα-antagonizing effects like pentoxifyllin, etanercept and anti-TNF monoclonal antibodies as well as anti-fibrotic agents like colchicine, penicillamine, or pirfenidone.[20,21]

Several retrospective multicentre studies analysing the impact of the α4β7 integrin blocker vedolizumab in people with PSC did not reveal a beneficial effect on cholestatic serum liver tests.[178–181] A retrospective cohort study of 88 cases of IBD with concomitant PSC who received biological therapy (42 infliximab, 19 adalimumab, 27 vedolizumab) did not show efficacy for PSC.[181] In a retrospective analysis of 141 people with PSC and IBD, anti-TNF agents (infliximab and adalimumab) were moderately effective in reducing ALP with a possible positive signal for adalimumab warranting further investigations.[182] Other IBD drugs targeting the immunology of the gut-liver axis (*e.g.* other integrin blockers such as etrolizumab, MAdCAM and VAP-1 inhibitors, ustekinumab, and tofacitinib) are also attractive candidates for clinical testing in PSC and for some of these agents clinical studies have already been initiated.[1]

However, a response to immunosuppressive therapy has been documented in children with autoimmune hepatitis/sclerosing cholangitis variant syndrome (also called autoimmune sclerosing cholangitis).[66] UDCA in combination with an immunosuppressive regimen (usually prednisolone and azathioprine) is an adequate medical treatment for adults with PSC and features of AIH (PSC-AIH variant syndrome),[67] although no data from controlled clinical trials exist. Dose adjustments and monitoring of immunosuppressive therapy should follow current recommendations for AIH.[183] People with PSC-AIH variant syndrome were reported to have a better prognosis/transplant-free survival than patients with classical PSC.[67] However, a large multicentre study revealed no significant difference in transplant-free survival between the PSC/AIH variant and the classic PSC group, although patients with the former were at a low risk of developing hepatobiliary malignancy.[6]

In clinical practice, biochemical, serological and/or histological features of inflammatory activity may trigger immunosuppressive therapy even in the absence of all/full criteria of PSC-AIH variant syndrome. A retrospective study in adults also suggested a beneficial role of steroids in a PSC subgroup with biochemical features of AIH (such as higher serum levels of ALT and bilirubin).[184] A simplified AIH score >5 and a modified histological activity index greater than 3/18 points were associated with the initiation of immunosuppressive therapy in people with PSC,[185] although clinical efficacy was not evaluated in this study. Transplant-free survival of 13 patients with classic PSC on long-term treatment with azathioprine exceeded the reported survival of patients in the literature.[186] Importantly, azathioprine does not increase the risk of CCA in people with PSC.[187]

Corticosteroids have also been used in a subset of people with PSC and elevated serum IgG4 (after exclusion of typical IgG4-RC), a feature which has previously been identified as a negative prognostic factor for PSC in one American cohort,[73] but not confirmed in an independent European cohort.[188] In a small study of 18 people with PSC and elevated serum IgG4 (>140 mg/dl), corticosteroids reduced ALP and bilirubin, but corticosteroid-related side effects and relapse after corticosteroid weaning were common.[189]

Since PSC is a fibro-obliterative bile duct disease, directly targeting fibrosis may also be of interest. A recent phase II trial with the anti-lysyl oxidase like-2 antibody simtuzumab was negative.[83] In contrast, the FGF19 analogue aldafermin exerted antifibrotic effects (without improving cholestatic serum liver tests) as determined by validated biomarkers in people with PSC during a 3-month randomised, placebo-controlled phase II trial.[176] Cenicriviroc blocks CCR2/5 on macrophages and hepatic stellate cells and there is an increasing interest in the role of macrophages in causing bile duct injury and driving biliary fibrosis in PSC.[190] Cenicriviroc potentiates all-trans retinoic acid to reduce cholestatic liver injury in rodents.[191] Recently a phase II study with cenicriviroc in PSC (PERSEUS trial) was completed and showed negative results.[192]

Should people with PSC be treated with long-term antibiotics to prevent disease progression or decrease PSC-related complications?

Recommendation

- Long-term use of antibiotics is not recommended for treatment of PSC in the absence of recurrent bacterial cholangitis **(LoE 3, strong recommendation, 100% consensus).**

Since dysregulation of the gut microbiome (dysbiosis) may be a critical factor in the development and/or progression of PSC, manipulation of the gut microbiome could confer a therapeutic benefit in PSC.[193] High levels of circulating markers of bacterial translocation are associated with poor prognosis, indicating that ongoing gut leakage of bacterial products could have a clinical impact in PSC.[194] More recently, alterations of the bile microbiome have been reported in the absence of bacterial cholangitis in PSC.[195] Beneficial effects of several absorbable and non-absorbable antibiotics have been reported, but only a few systematic clinical trials are available (reviewed in[196–198]). In a recent systematic review and meta-analysis[198] that included 124 patents with PSC from 3 RCTs and 2 open-label studies, antibiotics were associated with improvements in ALP (by 33%), Mayo PSC risk score (by 36%) and total bilirubin (by 29%); the ALP reduction was greatest with vancomycin (65%) and smaller with metronidazole (23%). This suggests that antibiotics, in particular vancomycin, may have a positive effect on PSC, either via direct effects on gut microbiota or via indirect host-mediated mechanisms. However, further systematic studies are needed, before antibiotic treatment of PSC (in the absence of bacterial cholangitis) can be generally recommended.

Metronidazole has been examined as a potential add-on therapy to UDCA in the largest (n = 80 patients) and longest (36 months) clinical trial on the use of antibiotics in PSC to date.[9] After 36 months of treatment, the metronidazole (800 mg/d)/UDCA group showed a more pronounced improvement in serum ALP as well as histological grade and stage than the placebo/UDCA group. No significant differences in cholangiographic features (assessed by ERCP) were seen. However, more than half of patients in the metronidazole/UDCA group (53%) experienced side effects which was significantly more than in the placebo/UDCA group (19%); 5 patients required dose reductions but there were no study drug discontinuations. In a second RCT comparing vancomycin to metronidazole,[10] vancomycin (see below) but not metronidazole (250 mg or 500 mg 3 times a day) reached the primary endpoint (decrease in ALP) after 12 weeks, and with less adverse effects requiring drug discontinuation. A network meta-analysis of UDCA-based combination therapies suggests that metronidazole plus UDCA was the more effective therapy compared to UDCA alone.[199]

Vancomycin is the most extensively studied antibiotic in PSC with several uncontrolled/open-label studies/case series in paediatric populations but only 2 RCTs in adults [reviewed in[197]].

In an RCT from the Mayo Clinic comparing the effects of oral vancomycin *vs.* metronidazole in 35 adults with PSC,[10] both the low-dose (125 mg 4 times a day) and high-dose (250 mg 4 times a day) vancomycin group experienced a significant reduction in serum ALP after 12 weeks of treatment.[10] Interestingly, only low-dose vancomycin led to normalisation of ALP and a decrease in the Mayo PSC score. Moreover, vancomycin was more tolerable than metronidazole (also tested in 2 different doses), and the incidence of serious adverse events requiring discontinuation of study medication was lower in the vancomycin group compared with the metronidazole group, although the absolute numbers were very small (2 *vs.* 4 patients).[10]

A second RCT in 29 people with PSC investigated the effects of vancomycin (125 mg 4 times a day) *vs.* placebo.[200] A decrease in Mayo PSC score, ALP, gamma-glutamyltransferase, fatigue, pruritus, diarrhoea and anorexia was observed in the oral vancomycin (but not placebo) group after 12 weeks of treatment. However, comparison of outcomes in 264 carefully matched children with PSC (88 each with vancomycin, UDCA or observation) did not show an improvement in outcomes with vancomycin or UDCA compared to a strategy of observation.[201] Patients progressed to end-stage liver disease at similar rates and spontaneous normalisation of biochemistry was common in children receiving no therapy, particularly in children with a mild phenotype and an early stage of disease.

The potential mechanisms of action of vancomycin in PSC are still unclear.[193,197] Since oral vancomycin is not significantly absorbed at the intestinal level and the systemic concentrations are negligible, vancomycin could exert its effects by reducing the concentration of bacteria and/or their potentially toxic metabolites in the portal circulation in PSC. Another mechanism could include immunomodulatory properties including a stimulation of regulatory T cells.[202] In line with reports in the paediatric literature, improvement of PSC-associated colitis and related symptoms has been reported in one study which addressed this in adults.[200]

Notably, an open-label study with another non-absorbable antibiotic, rifaximin, did not show significant changes in liver biochemistries, including serum ALP.[203] Tetracyclines were the first group of antibiotics studied for the treatment of PSC, with reports of the beneficial effects of open-label tetracycline on serum liver tests dating back to the late 50s and 60 s.[204,205] A modest reduction in ALP was observed in an open-label study with 16 patients receiving minocycline (100 mg/d) over 1 year.[206] Azithromycin (added to UDCA treatment) improved serum liver tests in a single reported case.[207] In contrast to these beneficial effects, doxycycline has even been linked to the onset of PSC in a few cases.[208]

Sulfasalazine (combining a sulfonamide antibiotic with mesalazine) may not only alter intestinal inflammation and microbial composition, but it may also exert anti-apoptotic effects in the liver and modulate bile acid toxicity.[209] Open-label sulfasalazine (alone or in combination with UDCA) has been reported to improve serum liver tests.[210,211] Sulfasalazine is again receiving considerable attention and is currently being studied for the treatment of PSC/PSC-IBD (NCT03561584).

Regarding probiotics and faecal microbiota transplant, a small study (n = 14) with a probiotic containing *Bifidobacillus* and *Lactobacillus* showed no beneficial effects on liver biochemistries, including serum ALP, compared to placebo at the end of treatment over 3 months.[212] Recently a pilot study of faecal microbiota transplant in 10 people with PSC showed good safety and some preliminary efficacy signals with improved bacterial diversity and ALP in a subset of patients.[213] In addition, bacteriophage therapy of intestinal pathobionts is receiving increasing attention, with encouraging

early results for an approach targeting *Klebsiella pneumoniae* in PSC.[214]

How should pruritus be managed in people with PSC?

Recommendations

- It is recommended to exclude relevant bile duct strictures in large duct sclerosing cholangitis as the cause of progressive pruritus. If present and reachable, relevant strictures should be treated by endoscopic balloon dilatation (or stenting, if balloon dilatation alone is insufficient) after brushing **(LoE 4, strong recommendation, 95% consensus).**
- Pharmacological treatment of moderate to severe pruritus in sclerosing cholangitis with bezafibrate or rifampicin is recommended **(LoE 4, strong recommendation, 83% consensus).**

For endoscopic details, we refer to the EASL/EASL CPG 'Role of endoscopy in primary sclerosing cholangitis'.[215]

Pruritus affects the majority of people with PSC during the course of the disease and may become their major clinical burden dramatically impairing quality of life and even leading to suicidal ideations in the most severe cases. Pruritus may also affect patients with secondary sclerosing cholangitis and various other cholestatic syndromes. The intensity of pruritus may vary, but daily peak hours are usually reported in the late evening and night. Typical sites of itch include upper and lower extremities as well as the face, although generalised pruritus is also reported.[216] The molecular pathogenesis of cholestatic pruritus has not been fully unravelled, but major pathophysiological insights have been achieved during the last decade.

General recommendations for patients suffering from cholestasis-associated pruritus include using emollients to prevent dryness of skin, avoiding hot baths or showers, using cooling gels (*e.g.*, menthol gels) for affected skin areas, or keeping nails shortened.[20,51]

The formerly recommended first-line treatment of cholestasis-associated pruritus used to be cholestyramine (4-16 g/day, administered separately from other drugs), and in case of its ineffectiveness or intolerance, rifampicin (150-300 mg daily), naltrexone (12.5-50 mg daily) and sertraline (25-75 mg daily).[20,51] The evidence for the antipruritic effectiveness of the non-absorbable anion exchange resin cholestyramine in sclerosing cholangitis is limited when compared to PBC,[20,51] and that of the more potent anion exchange resin colesevelam is non-existent.[217] Therefore, we excluded anion exchange resins as evidence-based medical treatments for cholestasis-associated pruritus in sclerosing cholangitis, also considering that cholestyramine can impair the absorption of various medications such as UDCA.[218] The largest RCT on pruritus in the field investigated the efficacy of the broad PPAR agonist bezafibrate in the treatment of moderate to severe cholestasis-associated pruritus in PSC and PBC (FITCH trial, 'fibrates for cholestasis-associated itch') and showed a clear-cut benefit of bezafibrate *vs.* placebo in alleviating moderate to severe itch[219] in people with PSC and PBC treated with UDCA. *A post hoc* analysis of only people with PSC again showed significant improvement of moderate to severe itch complaints.[219] As bezafibrate in combination with UDCA also exerts strong additive anticholestatic effects in PSC and PBC,[219,220] and the antipruritic effect of bezafibrate has been described as sustained under cholestatic conditions,[220,221] we propose bezafibrate as the first-line pharmacological treatment for moderate to severe pruritus in PSC and other forms of fibrosing cholangiopathy (Table 6). No major side effects of bezafibrate were observed during short-term treatment (3 weeks) in the FITCH trial,[219] nor during the 2-year treatment of PBC in the BEZURSO trial.[220] Still, serum creatinine may mildly increase (no difference compared to placebo in the FITCH trial) and myalgia and myopathies have been described in the past (not observed in the FITCH trial), as well as a few cases of increased serum transaminases. Rifampicin was so far regarded as the most effective evidence-based treatment of cholestasis-associated pruritus, but it may induce drug-induced hepatitis after 4-12 weeks in up to 12% of cholestatic patients while the first 2 weeks are regarded as safe.[20,51] As third-line treatment, the oral opioid antagonist naltrexone may still have a role, but starting at very low doses (12.5 mg) is recommended to avoid early side effects resembling an opioid withdrawal syndrome.[20,51] For sertraline as fourth-line treatment, no sufficient data for sclerosing cholangitis-associated itch exist.[20,51] Novel medical antipruritic strategies include the application of non-absorbable inhibitors of the ileal apical sodium bile salt transporter (ASBT encoded by SLC10A2) and selective PPARα or PPARδ agonists. It remains to be shown whether they can compete with bezafibrate and rifampicin in terms of effectiveness and tolerability.

How should acute bacterial cholangitis be diagnosed and managed in PSC?

Recommendation

- Acute bacterial cholangitis should be treated with antibiotics and subsequent biliary decompression if an underlying relevant stricture is present **(LoE 3, strong recommendation, 96% consensus).**

Background

Bacterial cholangitis is an important and common complication of PSC and usually occurs in patients with a high-grade biliary stricture. Therefore, an episode of an acute bacterial cholangitis should elicit imaging/MRCP studies for assessment of potentially flow limiting biliary strictures and when necessary biliary intervention/ERCP.[1] However, the definition and diagnosis of acute cholangitis in PSC is challenging, since symptoms may include a wide spectrum of severity and can be atypical. Standard definitions for acute cholangitis (Tokyo guidelines)[222] may not be universally applicable.[1] Signs of bacterial cholangitis can be mild and nonspecific, and patients may present even without significant change in baseline liver biochemistry, as infections can be limited to smaller

(parts of) liver segments. In milder cases, it is often only the response to antibiotics that confirms the clinically suspected diagnosis. Recently, new criteria for acute cholangitis in people with PSC have been proposed[129] which have not yet been validated in larger PSC populations. According to this definition the diagnosis of acute bacterial cholangitis requires either a single criterion (suppurative cholangitis on ERCP), or at least 1 major criterion (body temperature >38°C, leukocyte count >12/nl or C-reactive protein >75 mg/L), and at least 2 minor criteria (positive bile culture, increase in ALP or total bilirubin above 2x ULN, no other focus of infection).[129] A recent panel of the IPSCSG was unable to reach consensus through the Delphi process on the definition of acute bacterial cholangitis in the context of PSC.[35] The highly variable criteria may also be problematic when using "bacterial cholangitis" as a clinical endpoint for studies. In a recent "negative" phase II trial of simtuzumab (providing insights into the natural history of the disease) in 234 people with PSC,[83] cholangitis was the most common PSC-related clinical event observed in 13% of patients over a median follow-up of 23 months. Superimposed bacterial cholangitis can also be the first presentation of the disease – as reported in 6% of people with PSC in a study by Kaplan *et al.*[223] In addition to the risk of biliary sepsis, recurrent cholangitis may play a role in the progression of the disease.[1]

Most people with PSC with a naïve biliary tree (without prior ERC/instrumentation) have negative microbial bile cultures, although data are scarce and numbers of included patients in this type of (invasive) study are small. In one study,[224] positive cultures were obtained from 3 of 12 ERCP-naive people with PSC (25%) and from 6 of 10 people with PSC with previous ERCP (60%; not significant. 75% of the positive bacterial cultures consisted of Gram-positive isolates and 25% were enteric bacteria, which differed statistically from the 74% enteric bacteria and 26% Gram-positive bacteria found in disease controls with common duct stones studied for comparison.[224]

High-grade strictures with stagnation of bile may facilitate bacterial colonisation. Portal bacteraemia, reported in patients with active colitis, may be another important contributing factor.[225,226] Bacterial infection of bile was reported in 23 out of 37 (62%) people with PSC with a high-grade stricture but only in 4 out of 13 (31%) when stenosis was absent; in this study, enteric bacteria were detected in the bile of 19 out of 37 people with PSC and high-grade stenosis (51%) but never in the absence of high-grade stenosis, emphasising the relevance of a bile duct stricture in the pathogenesis of bacterial cholangitis.[227]

ERCP (especially with stenting) is a major risk factor for bacterial cholangitis in PSC and antibiotics should be routinely used as recommended by current EASL-EAGE guidelines, but use in terms of type, timing and duration of antibiotic varies markedly.[215] In a multicentre, randomised trial of people with PSC and a high-grade stricture, short-term stents were not superior to balloon dilatation in regard to recurrence-free patency but were associated with a markedly higher occurrence of treatment-related adverse events including bacterial cholangitis (12% *vs.* 3%).[228]

Many endoscopists prefer a small sphincterotomy in PSC in order to avoid ascending cholangitis.[215] Generally, biliary sphincterotomy is not recommended as a routine procedure (prior to biliary stenting) because of the associated risk of short-term complications, but it should be considered if cannulation is difficult.[215,229,230]

Biliary decompression for treatment of cholangitis

EASL-EAGE guidelines[215] suggest dilation of a high-grade stricture if it is regarded as the cause of complications such as bacterial cholangitis. Patients with severe acute cholangitis and high-grade bile duct strictures are at high risk of mortality and require urgent biliary decompression.[231,232] It may be possible to wait longer for a response to antibiotic treatment in patients with milder bacterial cholangitis, prior to ERCP and dilatation of strictures if indicated.[232] Without endoscopic intervention, short-course antibiotic treatment alone is not sufficient to eradicate bacteria from the bile ducts of patients with high-grade strictures,[227] but most patients will respond to endoscopic drainage of the obstruction in combination with antibiotics.[231,233] Bacteria in bile do not worsen the outcome if high-grade stenoses are treated endoscopically and infection is adequately treated with antibiotics.[95] In contrast, *Candida* in bile is associated with a poor prognosis, is often observed in late-stage disease and affected patients may require a liver transplantation relatively quickly (see below).[95]

Choice of antibiotics

Biliary infections are often polymicrobial and the choice of the antibiotic should be directed by local practice considering bacterial sensitivities and the degree of liver and/or renal impairment.[233] The most frequently encountered organisms are Gram-negative bacteria such as *Escherichia coli, Klebsiella, Pseudomonas* and *Bacteroides* species, as well as Gram-positive *Enterococci*, or *Streptococci*.[233–235] The initially selected antibiotic should cover gram-negative and -positive bacteria and a common first-line agent for mild episodes is an aminopenicillin/beta-lactamase inhibitor since these agents can be administered orally. Fluoroquinolones, that were used first line in the past, due to their effective penetration into the obstructed biliary tree and their oral administration, should be saved only for use in specific cases for antimicrobial stewardship reasons (high resistance to fluoroquinolones and unfavourable side effect profile). More severe cases are treated with intravenous antibiotics with piperacillin/tazobactam (sufficient anaerobic coverage in itself) or third generation cephalosporins with inclusion of anaerobic coverage.[236] Antibiotic treatment should be tailored to local epidemiology, risk factors for multidrug-resistant bacteria and severity of infection. Pending biliary decompression, in patients with sepsis and those who do not quickly respond to antibiotic treatment, the addition of antibiotic coverage against gram-positive organisms, targeted against *Enterococci*, such as glycopeptide antibiotics (*e.g.* vancomycin) or oxazolide antibiotics (*e.g.* linezolid) may be an option.[233,237,238]

Rotating antibiotics

Occasionally patients with recurrent bacterial cholangitis due to complex intrahepatic cholangiopathy may require prophylactic long-term antibiotics (*e.g.* co-trimoxazole) and rotation of antibiotics.[1] This option should only be considered under exceptional circumstances because of the associated risk of antibiotic resistance. Biliary cultures and multidisciplinary expert assessment with formal microbiology advice is recommended.

Fungal infection, *Candida*

In an initial study from Heidelberg, *Candida* species have been isolated from bile in 8/67 (12%) people with PSC undergoing ERCP, whereas *Aspergillus* was not detected.[239] Most (7/8)

Table 6. Medical treatment of pruritus in sclerosing cholangitis.

Evidence	Drug	Potential side effect	References
1st line	Bezafibrate (400 mg daily)	Renal insufficiency, myalgia, myopathy, hepatitis	219
2nd line	Rifampicin (150-300 mg/d)	Hepatitis	20,51
3rd line	Naltrexone (12.5-50 mg/d)	Opioid withdrawal syndrome	20,51
No evidence for PSC	Anion exchange resins (cholestyramine [4 g once to four times daily], colesevelam [1,250-1,875 mg twice daily]; 4 hours separate from other medication)	Abdominal discomfort	20,51
No evidence for PSC	Sertraline (50-75 mg/d)		20,51
Experimental	ASBT inhibitors	Diarrhoea	
Experimental	Selective PPARα and PPARδ agonists		

patients had advanced disease with a high-grade stenosis and all had received antibiotics. Patients with biliary *Candida* had more severe cholangitis with higher C-reactive protein and serum bilirubin compared to those without *Candida* infection. Persistence of biliary candidiasis was associated with markedly reduced transplantation-free survival in people with PSC. In a follow-up retrospective single centre analysis form Heidelberg, 30 out of 150 (20%) patients had biliary candidiasis.[240] Although all patients demonstrated comparable baseline characteristics, those with persistent biliary candidiasis showed reduced transplantation-free survival along with a markedly elevated frequency of CCA. However, since the advantage of antifungal treatment of biliary *Candida* is unclear, patients are often not treated for their fungal infection in the absence of an immunosuppressive condition or overt cholangitis.[95,239,240] Risk factors associated with the acquisition of biliary candidiasis were age at PSC diagnosis and number of ERCPs.[240] Moreover, a fucosyltransferase 2 (*Fut2*) genotype has been identified as a risk factor for high-grade stenosis and biliary *Candida* infections in PSC.[241]

Bacterial cholangitis as a primary indication for liver transplantation

Although the simple presence of bacteria in bile does not worsen the outcome if high-grade stenoses are opened endoscopically and infection is adequately treated with antibiotics,[95] the persistence of bacteriobilia may be clinically relevant and greater numbers of bacterial isolates have been associated with a shorter interval to liver transplantation.[235] Recurrent cholangitis can be so severe as to become the primary indication for liver transplant when repeated episodes of cholangitis are not controlled by antibiotics.[242] In many countries/under specific circumstances, people with PSC and documented non-iatrogenic recurrent bacterial cholangitis receive additional MELD points and, thereby higher waiting list priority. As such, MELD exception points can be granted for recurrent cholangitis with ≥2 episodes of bacteraemia or ≥1 episode of septic complications within a certain timeframe (*e.g.* 6 months).[243] However, transplant candidates with PSC and bacterial cholangitis had no increased risk of waitlist mortality in a study from 2 US transplant centres.[244] This has called into question whether recurrent cholangitis should be an accepted indication for liver transplantation given the limited organ supply. Part of this discrepancy may be due to the lack of a coherent definition of bacterial cholangitis in PSC (see above). There is a wide variation in practice internationally with 17% of people with PSC transplanted for this indication in Norway[245] while less than 5% of people with PSC are listed for this indication in the UK.[1]

How should portal hypertension be managed in PSC?

Recommendation

- It is recommended to manage complications of portal hypertension in PSC according to Baveno/EASL guidelines (for advanced chronic liver diseases in general) **(LoE 4, strong recommendation, 92% consensus).**

Progressive hepatic fibrosis and cirrhosis may result in portal hypertension in PSC. Clinically significant portal hypertension (CSPH) is defined by either endoscopic finding of gastro-oesophageal varices (GEVs), invasive measurement of hepatic venous pressure gradient (HVPG) ≥10 mmHg, or pathognomonic imaging findings including portosystemic collaterals and ascites (given that non-portal hypertensive conditions including malignancy have been excluded).[246,247] Extrapolating data from clinical findings, such as the presence of splenomegaly and oesophageal varices, suggests that CSPH may be present in 30% of people with PSC.[93,98] Among 283 people with PSC treated for the first time at the Mayo Clinic over 8 consecutive years, 36% (102 of 283) of patients had oesophageal varices, of which 56% (57 of 102) were moderate/large varices.[248] In a "negative" phase II trial of simtuzumab[83] that recruited 234 patients (of whom 40% already had bridging fibrosis and 11% had cirrhosis at baseline), 47 (20%) experienced PSC-related clinical events over a median follow-up of 23 months, the most common events were cholangitis (13% [n = 31]) and evidence of hepatic decompensation, including (but not exclusively representing) portal hypertension-related events such as ascites and variceal haemorrhage, in 9% (n = 21) of patients. In the high-dose UDCA (28–30 mg/kg) trial by Lindor *et al.*,[80] GEVs developed in 15 out of 76 (20%) patients in the UDCA group *vs.* 5 out of 74 patients (7%) in the placebo group over 6 years, which led to termination of the trial due to futility. The baseline data from the 150 patients of this study were also reviewed for predictors of varices at baseline and newly developing varices (after exclusion of the 26 patients who already had oesophageal varices at baseline).[249] In a multivariable logistic regression, a higher Mayo risk score (>0.87) or a higher aspartate/alanine aminotransferase ratio (>1.12) were associated with the presence of varices at initial endoscopy. Moreover, a lower platelet count and higher total bilirubin at 2 years were associated with an increased risk of developing new varices in the 25 patients (20%) who developed new varices (8).

In a small percentage of patients, CSPH in PSC (in analogy to PBC) may occur early in the disease course, *i.e.* even in people with PSC with F2 or F3 fibrosis in the absence of full-blown histologic cirrhosis.[250] The reasons for "non-cirrhotic" CSPH in PSC are not fully understood, but include potential "pre-sinusoidal" block at the level of the portal tract, where ductular proliferation and pronounced portal fibrosis may have a profound impact on hepatic vascular resistance. A potential pre-sinusoidal component of portal hypertension in PSC could also explain why HVPG often underestimates the full degree of portal hypertension, as GEVs may be present in people with PSC with HVPG values <10 mmHg, which is not the case in patients with alcohol-related liver disease or viral hepatitis. Some people with PSC may also develop nodular regenerative hyperplasia and obliterative portal venopathy as other features of pre-sinusoidal portal hypertension occurring in the absence of histological cirrhosis.[251] Among 306 patients transplanted for PSC at 2 institutions, 11/306 (3.3%) patients had portal hypertension without cirrhosis due to nodular regenerative hyperplasia or obliterative venopathy.[251]

In general, the management of portal hypertension-related complications, such as variceal bleeding, ascites and hepatic encephalopathy should follow AASLD[252] and Baveno[253]/EASL[114,254] guidelines that are largely based on evidence derived from studies including mostly patients with alcohol-related and viral aetiologies. Patients with portal hypertension should be treated with non-selective beta blockers (NSBBs) to prevent portal hypertension-related decompensation. In compensated patients with high-risk varices, who have contraindications or intolerance to NSBBs, endoscopic band ligation (EBL) is recommended to prevent first variceal bleeding . The combination of vasoactive drugs and EBL is recommended as the first therapeutic option for acute variceal bleeding. Transjugular intrahepatic portosystemic shunt (TIPS) can be performed as rescue TIPS in patients with refractory/uncontrollable variceal bleeding, or pre-emptive TIPS (<72 h) for acute variceal bleeding in high-risk patients (Child-Pugh class C patients, patients with Child-Pugh class B and active bleeding at endoscopy or HVPG ≥20 mmHg). For prevention of rebleeding (secondary prophylaxis), combined therapy with NSBBs plus EBL is recommended. Elective TIPS is an effective option for treatment failures/intolerance to secondary prophylaxis of variceal bleeding or in patients with refractory ascites. However, there is an enhanced risk of TIPS infection during passage through infected bile ducts and TIPS may be regarded as contraindicated in case of dilated intrahepatic ducts in the tract of TIPS.

As "aetiologic" therapies, such as antiviral therapy in patients with hepatitis C[255] and abstinence from alcohol[256] have been shown to improve CSPH and reduce the risk of CSPH-related complications,[257] it seems reasonable to assume that any effective treatment of PSC (when/as soon as available) should also result in an improvement of PSC-related portal hypertension. However, except for demonstrating the negative impact of high-dose UDCA (28–30 mg/kg),[80] no systematic studies have evaluated the impact of treatment with medium/moderate dose UDCA on HVPG or the risk of portal hypertension-related complications in PSC.

VCTE is increasingly used for non-invasive screening for CSPH. A recent study[90] has demonstrated that patients with compensated cirrhosis in whom NSBBs are not indicated (contraindication/intolerance) for the prevention of decompensation should undergo an endoscopy for variceal screening if LSM by VCTE is ≥20 kPa or platelet count is ≤150x10^9L. Applying these criteria in 80 people with PSC-related compensated advanced chronic liver disease, 30% of endoscopies could be saved with an associated risk of missing varices needing treatment of <5%.[90]

A Scandinavian study[258] showed that statin use is associated with reduced risk of all-cause mortality but also of liver-related mortality (also including death related to variceal bleeding). As statins have been shown to decrease portal hypertension in studies including patients of other aetiologies,[259] it seems reasonable to assume that statins would also have beneficial effects on CSPH-related complications in the setting of PSC.

Peristomal variceal bleeding is a significant complication in people with PSC who undergo panproctocolectomy and ileostomy for associated UC[260] and has been reported in up to 26% of patients.[261] To avoid development of peristomal varices, patients who require colectomy should preferably have a distal anastomosis/ileal pouch-anal anastomosis rather than a terminal ileal stoma.[262,263] Such decisions should be made in multidisciplinary teams since people with PSC are at an increased risk of pouchitis, may have advanced cirrhosis with increased surgical risk and may be potential transplant candidates. Bleeding of peristomal varices can be managed with local therapy and/or decompression of the underlying portal hypertension. Treatment options include sclerotherapy,[264] injection of cyanoacrylate or microcoil embolisation under sonographic/endoscopic ultrasound and/or fluoroscopic guidance,[265–268] TIPS,[269,270] or percutaneous transhepatic[271] or trans-splenic embolisation of peristomal varices[272] as reported in single anecdotal cases. In a retrospective review of 10 cases, TIPS appeared to be more effective than sclerotherapy in treating peristomal variceal bleeding, but sclerotherapy/local therapy may serve as an effective bridging mechanism for more definite vascular decompression in critically ill patients.[273] Some patients may even require liver transplantation for control of peristomal varices.[260]

In summary, CSPH is common in people with PSC and may occur early, thus, screening for varices and treatment of CSPH-related complications represent clinical management priorities. While controlled studies on the efficacy of treatments to reduce portal hypertension for the specific aetiology of PSC are scarce, it seems reasonable to follow current EASL/Baveno/AASLD guidelines for the management of CSPH in people with PSC.

When and how should endoscopic intervention be considered in PSC?

Recommendations

- The indication for endoscopic intervention should ideally be discussed in multidisciplinary meetings of hepatologists, biliary endoscopists and abdominal radiologists. The procedure should be performed by experienced endoscopists **(LoE 5, strong recommendation, 96% consensus).**
- Therapeutic endoscopic intervention is recommended in patients with relevant strictures, defined as high-grade strictures on imaging in the common bile duct or hepatic ducts and signs or symptoms of obstructive cholestasis and/or bacterial cholangitis **(LoE 4, strong recommendation, 87% consensus).**

Table 7. Definition and nomenclature of strictures in primary sclerosing cholangitis.

Type	Definition
Relevant stricture	A high-grade biliary stricture on imaging in the common bile duct or hepatic ducts with signs or symptoms of obstructive cholestasis and/or bacterial cholangitis.
High-grade stricture	A biliary stricture on MRI/MRCP with >75% reduction of duct diameter in the common bile duct or hepatic ducts.

MRCP, magnetic resonance cholangiopancreaticography.

Endoscopic interventions in PSC are performed with both diagnostic and therapeutic intention. In patients with a new or worsening bile duct stricture or other signs and symptoms suspicious of malignancy, endoscopic sampling of tissue/cells should be performed for diagnostic purposes (see section diagnosis of CCA).[215] The indication for endoscopic intervention should be made by physicians experienced in the treatment of people with PSC and after review of non-invasive imaging as part of a multidisciplinary approach.[26] Of note, there is some discussion regarding the term "dominant" among experts of various professional societies. Some favour limiting the use of the word "dominant" to morphologic findings only at ERCP and add the term "(clinically) relevant" to indicate functional impairment. In addition, when describing strictures on MRCP, only morphologic descriptors, *e.g.* "high grade" or" severe" should be used rather than "dominant". In an effort to align definitions and nomenclature on strictures between AASLD and EASL practice guidelines, a new term has been introduced, "relevant strictures", denoting high-grade strictures that lead to functional impairment and thus should prompt an assessment of appropriate therapeutic interventions (Table 7). More detailed guidance on the definitions in PSC can be found in the IPSCSG consensus paper and details on the reporting of MRI findings including strictures in PSC were published by the MRI working group of the IPSCSG.[32,35]

Endoscopic stricture dilatation using bougies or balloon catheters is applied to improve bile flow from obstructed parts of the liver. As a basic principle, relief of biliary obstruction may improve hepatic fibrosis.[274] The prevalence of high-grade strictures reaches 50% in PSC.[275] Detailed recommendations on endoscopy in PSC have recently been published by EASL/European Society of Gastrointestinal Endoscopy (ESGE) and should be reviewed together with this guideline.[215] In short, stricture dilation is most useful for single or a few well defined high-grade strictures (>75% narrowing) in the common bile duct or the left or right hepatic duct within 2 cm from the bifurcation. However, treatment needs to be individualised and, sometimes, a patient may benefit from the successful dilation of multiple strictures or more peripheral strictures. As a general rule, the common bile duct should not be dilated to more than 8 mm and the hepatic ducts to more than 6 mm diameter, but this should be adapted to the diameter of the duct before and after the stricture to reduce procedural risk. ERCP in PSC is associated with risks, reported in up to 18%, such as perforation, cholangitis and pancreatitis, which are highest after first ERCP and sphincterotomy.[215] Risk does not seem to be increased in patients with cirrhosis.[276] The risk of post-ERCP cholangitis seems to be increased in PSC compared to other indications.[277] To reduce the risk of post-ERCP cholangitis, peri-interventional antibiotics should be applied, but choice of drug and duration of treatment remain unclear.[215] Usually, after first dilation, it is advisable to perform a repeat dilation within 3 months and thereafter depending on the individual course of the patient. If no follow-up ERCP is performed, it seems advisable to perform MRCP within a year after the last dilatation treatment. In patients with complex strictures or a lack of apparent dilation effect during ERCP, a stent may be placed after successful stricture dilation. However, a recent randomised trial demonstrated that stent placement was associated with increased risk of serious adverse events such as pancreatitis and bacterial cholangitis.[228] Therefore, the stent should be removed within 2-4 weeks of placement. If a hilar stricture cannot be overcome via endoscopic intervention, a percutaneous rendez-vous approach or temporary external-internal drainage can be applied. There is a paucity of data on percutaneous drainage in PSC[278] and the technical complexity of this procedure necessitates performance by an experienced team.

There are no controlled trials comparing stricture dilatation *vs.* observation in PSC. In a patient with worsening symptoms such as pruritus, jaundice or fever as a sign of cholangitis, or in a patient with worsening serum liver tests and/or bilirubin not otherwise explained, or an increase in CA19-9, imaging should be performed, preferentially with contrast-enhanced MRI/MRCP.[26] If a stricture that seems clinically relevant or stones are seen, an endoscopic intervention should be performed by an experienced endoscopist. Stricture dilatation improves serum liver tests and symptoms associated with obstruction[215] and is fundamental in the setting of bacterial cholangitis.[95] In people with PSC and cirrhosis, stricture dilation may not lead to a lasting improvement of serum liver tests[276] and the decision to perform endoscopic intervention needs to be individualised and weighed against other treatment options such as liver transplantation.

A therapeutic endoscopic intervention is indicated in symptomatic patients with relevant strictures. It is unclear whether regular ERCP, including stricture dilation as indicated during ERCP, improves transplant-free survival in asymptomatic people with PSC. In a recent retrospective study, the outcome of asymptomatic patients undergoing regular ERCP was better than in patients who received endoscopy on demand. This effect was restricted to patients with dominant strictures.[279] Currently, however, regular ERCP in asymptomatic people with PSC cannot be recommended.

What are the medical treatment options for IgG4-related cholangitis (IRC)?

Recommendations

- Predniso(lo)ne (0.5 to 0.6 mg/kg/d) is recommended as the first-line therapy for untreated active IRC. Treatment response should be evaluated after (2 to) 4 weeks, prior to predniso(lo)ne tapering, by clinical, biochemical and/or radiological criteria **(LoE 4, strong recommendation, 100% consensus).**
- Maintenance treatment of IRC is suggested with steroid-sparing immunosuppressants for up to 3 years (*e.g.* azathioprine, 6-mercaptopurine, mycophenolate mofetil) and potentially beyond, starting during predniso(lo)ne tapering, to reduce the risk of IRC relapse. Rituximab can alternatively be considered when relapse has occurred **(LoE 5, weak recommendation, 100% consensus).**

Treatment response to corticosteroids is regarded as a major diagnostic criterion for IRC.[3,39] The vast majority of patients with IRC are clinical, biochemical and cholangiographic responders. But no RCTs specifically focused on the short-term treatment of IRC, or with corticosteroid response as a criterion for the diagnosis of IRC, have been performed. In 2 prospective studies, 6 retrospective observational studies (>20 patients) and a systematic review, all heterogeneous with regard to inclusion criteria, bile duct involvement, definition of response (clinical, biochemical, radiologic), type and dose of corticosteroids and length of treatment, mode of tapering and additional surgical or endoscopic treatment modalities, the rate of corticosteroid response ranged from 62 to 100% and the relapse rate as defined by biochemical and/or imaging findings during tapering or after withdrawal was 30%.[3] Involvement of perihilar and intrahepatic bile ducts has been associated with higher relapse rates and may warrant sustained immunosuppressive therapy.[39] Response failure was also associated with a more fibrotic phenotype, multiple bile duct strictures, and multi-organ involvement.[3]

Recommendations for the starting dose of predniso(lo)ne vary for systemic IgG4-related disease and randomised trials in IRC are lacking. Starting doses of 40 mg daily or 0.6-0.8 mg/kg daily for the first 4 weeks have been widely recommended in Japanese, American and European Guidelines. Still, retrospective analyses from the Netherlands indicated that initial doses of 10-20 mg predniso(lo)ne daily may be as effective in controlling at least type 1 autoimmune pancreatitis and preventing disease relapse.[280] This information may be particularly relevant for elderly patients with IRC and relative contraindications for corticosteroid treatment, such as insulin-dependent diabetes (as a consequence of often otherwise silent autoimmune pancreatitis) or severe osteoporosis.

As long-term corticosteroid therapy is complicated by long-term side effects, conventional corticosteroid-sparing agents, including azathioprine, 6-mercaptopurine, mycophenolate mofetil, cyclosporine A, tacrolimus, or periodic treatment with rituximab, must be considered for long-term care. After disease relapse during or after tapering of predniso(lo)ne, 3 regimens have been described in IgG4-related disease: i) high-dose corticosteroids tapered to maintenance treatment with low-dose corticosteroids (equivalent to 2.5-10 mg daily predniso(lo)ne) and a corticosteroid-sparing agent such as azathioprine or mycophenolate mofetil; ii) high-dose corticosteroids without maintenance treatment; or iii) rituximab induction with or without maintenance rituximab (*e.g.*, 2 infusions of 1,000 mg rituximab 15 days apart every 6 months including premedication with methylprednisolone and an antihistaminic agent[3]).

UDCA is widely used in fibrosing cholangiopathies due to its anticholestatic and anti-inflammatory effects,[144] leading to improved transplant-free survival (at least in PBC[281]) without relevant side effects. Anticholestatic and anti-inflammatory effects have also been observed with UDCA in patients with IRC. It remains to be studied whether UDCA has corticosteroid-sparing effects in IRC.

Distal or hilar bile duct strictures in IRC may become unresponsive to medical treatment when advanced fibrosis has developed, particularly in individuals with a more fibrotic phenotype of IRC. Endoscopic intervention with balloon dilatation of fibrotic strictures and – if unresponsive to balloon dilatation alone – short-term stenting may be the treatment of choice, as recommended for endoscopic treatment of PSC.[215] Antibiotic prophylaxis before ERCP appears mandatory, as recommended for PSC.[215]

What are the medical treatment options for sclerosing cholangitis of the critically ill patient (SC-CIP) and patients with ABCB4 deficiency?

Recommendations

- Endoscopic removal of biliary casts can be considered and low-to-medium-dose UDCA (10-15 mg/kg/d) can be given in patients with SC-CIP. Available data does not allow a firmer recommendation **(LoE 5, weak recommendation, 100% consensus).**
- Low-to-medium-dose UDCA (10-15 mg/kg/d) can be given in patients with ABCB4 deficiency. Available data does not allow a firmer recommendation **(LoE 5, weak recommendation, 89% consensus).**

SC-CIP often rapidly progresses to biliary cirrhosis and hepatic failure and strongly affects life expectancy (mean survival 17-40 months).[41] No evidence-based medical treatment is known and therapeutic options include antibiotic treatment of bacterial cholangitis, which is often observed in SC-CIP, and endoscopic removal of biliary casts. Liver transplantation is the only effective treatment option in advanced stages. UDCA exerts anticholestatic and anti-inflammatory effects in multiple fibrosing cholangiopathies and exerts protective effects on biliary epithelia including stimulation of biliary bicarbonate secretion[144] at moderate therapeutic doses of 10-15 mg/kg/d. Still, controlled trials studying the efficacy of UDCA in SC-CIP are lacking.

Progressive familial intrahepatic cholestasis type 3 is an autosomal recessive disease that usually presents in childhood and is caused by biallelic mutations in the *ABCB4* gene. ABCB4 deficiency describes the milder clinical course of carriers of heterozygous *ABCB4* mutations, leading to impaired ABCB4 function, but not complete loss of function. ABCB4 deficiency has been associated with low phospholipid-associated cholelithiasis syndrome, intrahepatic cholestasis of pregnancy, oral contraceptive-induced cholestasis, small duct sclerosing cholangitis, and persistent hepatocellular secretory failure.[282,283] Although the long-term clinical course of most people with ABCB4 deficiency is mild under UDCA treatment, decompensated biliary cirrhosis is observed in a minority, and a limited risk of CCA has been described.[284] In order to medically treat small duct sclerosing cholangitis (potentially leading to biliary fibrosis and cirrhosis) and the hepatolithiasis/cholecystolithiasis typical of low phospholipid-associated cholelithiasis syndrome, UDCA has been propagated for more than a decade for people with ABCB4 deficiency[20] due to its litholytic and cholangioprotective properties.[144] Still, no RCTs have so far proven the long-term efficacy of UDCA for ABCB4 deficiency.

How is CCA best diagnosed in PSC?

Recommendations

- CCA must be suspected in i) newly diagnosed PSC with high-grade stricture(s) and in ii) known PSC with worsening of signs or symptoms, progressive stricture(s) or a new mass lesion identified on imaging **(LoE 4, strong recommendation, 93% consensus).**
- Diagnostic work-up by an experienced multidisciplinary team is recommended in people with PSC and suspected CCA **(LoE 5, strong recommendation, 100% consensus).**
- Contrast-enhanced, cross-sectional imaging is recommended as the initial diagnostic test when CCA is suspected, potentially followed by ERCP with ductal sampling (brush cytology, endobiliary biopsies) for diagnosis and staging of the suspected CCA **(LoE 1, strong recommendation, 96% consensus).**
- Serum CA 19-9 can be assessed in all patients where CCA is suspected and fluorescence *in situ* hybridisation (FISH) or equivalent chromosomal assessments can be considered when brush cytology and/or histology are equivocal **(LoE 3, weak recommendation, 91% consensus).**

People with PSC are at increased risk of developing hepatobiliary cancer, particularly CCA, for which the risk is increased 161-398-fold compared to that in the general population.[5,7,285,286] CCA is the most common cause of death in PSC.[5,7,287] The annual incidence of CCA is estimated to be 0.6-1.5% with a lifetime risk of developing CCA of up to 20%.[5–7,288] CCA can present at any stage of the disease and is not related to underlying cirrhosis. There is no convincing evidence that the risk of CCA is associated with the duration of PSC. The risk is highest the first year after PSC diagnosis, which accounts for 30-50% of all CCAs in PSC.[5–7,287–289] Many of those patients most likely have had a longstanding asymptomatic disease and development of CCA triggered symptoms leading to the diagnosis of PSC and CCA. Identified risk factors for CCA in PSC are older age, male sex, presence and/or long duration of UC, history of colorectal malignancy, advanced liver disease (Mayo risk score >4, high bilirubin, history of variceal bleeding), smoking and alcohol and they may all contribute to a small increase in disease risk.[6,288–292] Patients with small duct disease rarely develop CCA.[55,57]

Clinically, CCA can be suspected in patients with complaints of rapidly increasing jaundice, pruritus, weight loss, upper abdominal pain and persistently increased levels of CA 19-9. However, patients with end-stage liver disease also present in a similar way[118,289,292] and detection of CCA in PSC is challenging, especially in patients with cirrhosis.

Diagnosis of CCA

Imaging

The diagnosis of CCA in PSC is very difficult in the presence of multiple pre-existing strictures. The tumours often occur in the hilum and are characterised by local invasion and longitudinal growth along the common bile duct. Intrahepatic mass-forming CCAs occur only in a minority of patients.[287,293] Cross-sectional imaging by ultrasound, CT and MRI/MRCP may fail to safely detect or rule out a tumour due to limited diagnostic sensitivity and specificity,[118] especially if a mass is absent. MRI has been shown to be superior to ultrasound for early detection of CCA.[116,294] Once a strong suspicion of a liver tumour has risen a dedicated multiphasic contrast-enhanced CT scan and/or MRI/MRCP with contrast is warranted.[116,295]

Criteria and standard reporting of MRI findings for definite and possible early-stage perihilar CCA have recently been suggested.[32] The presence of a perihilar mass or periductal soft tissue thickening with progressive enhancement on delayed phase imaging and vascular encasement are considered diagnostic.[32,116] Possible criteria for CCA in PSC require further validation.

Development of a new or rapidly progressive high-grade stricture on imaging raises the suspicion of CCA and should be further evaluated with ERCP and tissue sampling if technically possible. Both PSC and CCA are rare conditions, and the patient should be referred to a specialised centre for a multidisciplinary evaluation and management when CCA is suspected or diagnosed. An algorithm for CCA diagnosis in PSC is shown in Fig. 2.

Imaging positron emission tomography (PET) has been suggested as a diagnostic tool to complement cross-sectional imaging.[296] This technique lacks specificity and sensitivity for detection of CCA, especially in PSC.[297–299] False-positive results are seen in cases with active inflammation and bacterial cholangitis. In sporadic CCA, the specificity for detection of mass-forming tumours by PET has been shown to be 85%, but this drops to 18% in cases with infiltrative morphology.[297] PET is most useful for late-stage disease and for the evaluation of recurrence after surgery.[297,300] The routine use of PET for the diagnosis of CCA in PSC is, therefore, not recommended.

Tumour markers

In clinical practice, CA 19-9 and carcinoembryonic antigen are used as tumour markers for CCA diagnosis. They are of limited diagnostic sensitivity and specificity, either alone or in combination.[124,126,128,301,302] CA 19-9 is the most investigated, though repeated case series have failed to prove its efficacy as a screening marker for early tumour detection.[124,128] No cut-off level is tumour specific. Low stable levels of CA 19-9 speak against a CCA.[125] Persistently high levels in the absence of bacterial cholangitis should strengthen tumour suspicion and lead to further investigations to detect or rule out malignancy.

CA 19-9 rises in the presence of bacterial cholangitis, which is common in PSC.[129] Recent studies have shown that CA 19-9 shows a low intra-individual variability over time[125] and the individual levels are affected by genetic differences in the *FUT2/3* genes.[127] This data suggests that, in the absence of bacterial cholangitis, the change or relative increase of the CA 19-9 level indicates tumour development and that absolute cut-off levels are less relevant.[125] In the largest retrospective series published so far, CA 19-9 was an independent predictor of mortality and CCA-related adverse events, as was participation in surveillance programmes.[115] However, all tumours in this study had signs on imaging leading to the suspicion of cancer and further investigations and 70% of the perihilar CCAs had CA 19-9 levels that were normal or below 100 U/ml. Thus, measurement of CA 19-9 is recommended as an additional diagnostic tool when cancer is suspected, but it is not recommended for surveillance purposes.

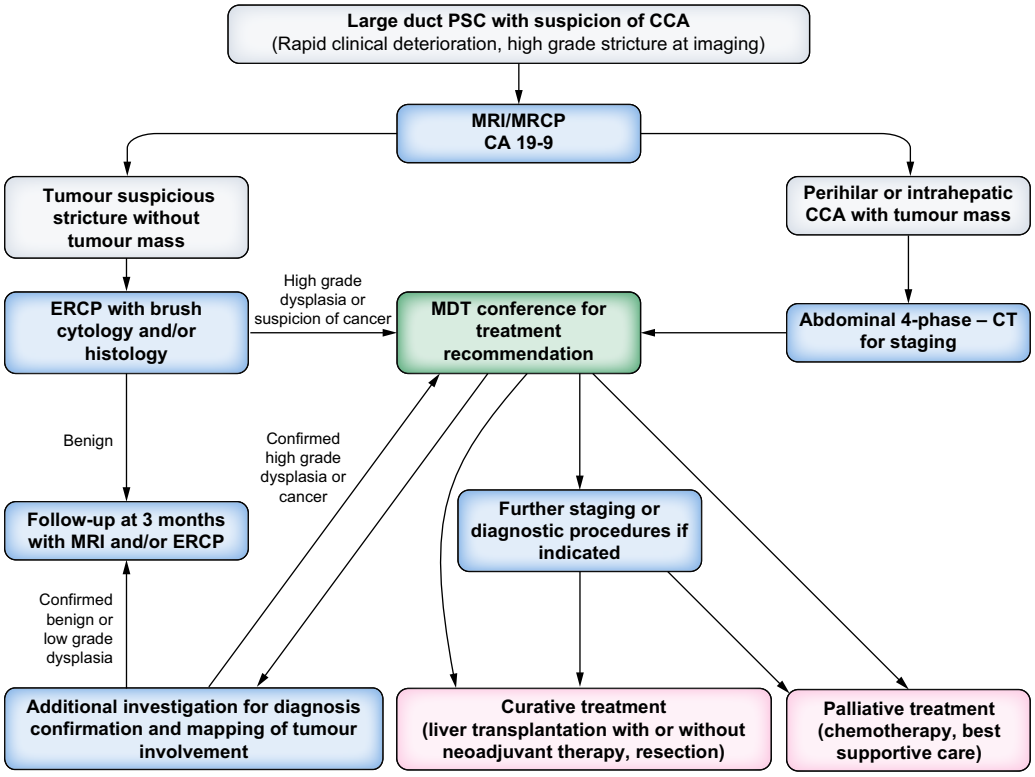

Fig. 2. Algorithm for diagnosis of CCA in people with PSC with a suspicion of CCA. A high-quality MRI with contrast should be performed. When strong suspicion of cancer or high-grade dysplasia is found at a brush sample the patient should be evaluated at a high-volume centre/specialised unit. Severe inflammation and biliary stenting may confound the diagnosis of true high-grade dysplasia and a repeated ERCP with biopsies (if not already performed in the first ERCP) is recommended for confirmation of high-grade dysplasia and/or malignancy, and tumour mapping of tumour involvement and spread before making a treatment decision. In cases with low-grade dysplasia or benign brush sample, a follow-up within 3 months is recommended with a new ERCP or MRI. CCA, cholangiocarcinoma; ERCP, endoscopic retrograde cholangiopancreaticography; MDT, multidisciplinary team; MRCP, magnetic resonance cholangiopancreaticography; PSC, primary sclerosing cholangitis.

ERCP and diagnosis of CCA in PSC

ERCP with tissue sampling plays an important role in the diagnosis of CCA in PSC. The additional role of cholangioscopy is under evaluation. Guidelines from EASL and ESGE, published in 2017, describe the role of endoscopy in PSC in detail.[294]

Brush cytology at ERCP is a cornerstone in the diagnosis of CCA in PSC and is the most common and the best evaluated method for tissue sampling in the bile ducts. However, the technique is limited due to its poor sensitivity.[303,304] A systematic review, including 11 studies and 747 people with PSC, shows a pooled sensitivity of 43% (95% CI 35%-52%) and specificity of 97% (95% CI, 95%-98%) for CCA diagnosis in people with PSC.[303] Repeated brushings can improve sensitivity.[305] Systematic brushings regardless of symptomatology at PSC diagnosis were described in a case series of 261 patients.[131] Most of these patients were asymptomatic and brush cytology suspicious or diagnostic for malignancy was found in 7%. The lack of sensitivity and specificity for brush cytology in PSC limits its utility for the early detection of CCA.

DNA aberrations measured by FISH analysis, digital image analysis, flow cytometry and next-generation sequencing markers may add value and increase diagnostic accuracy in addition to cytology alone in brush samples in PSC.[306–312] Of these methods, FISH is the most used and evaluated in clinical practice. In a systematic meta-analysis, including 8 studies, the pooled sensitivity and specificity of FISH for the diagnosis of CCA in people with PSC were 68% (95% CI 61%-74%) and 70% (95% CI 66%-73%), respectively.[309] The poor specificity makes it reasonable to always evaluate the result of FISH together with cytology and FISH adds value, especially in cases where cytology is equivocal.[294,313] To perform FISH in all cases may be misleading, as it is associated with a high number of false positives.[314] In a study of 201 people with PSC undergoing clinically indicated ERCP, only cases with equivocal cytology were tested with FISH. The specificity and sensitivity were shown to be 98% and 80%, respectively. The negative predictive value of 98% for detection of CCA[313] speaks in favour of this strategy for ruling out an underlying CCA in a brushed stricture. New diagnostic tests for cells from brush samples are under development but have not yet reached clinical practice.[312]

Other ERCP-based modalities including single-operator cholangioscopy with targeted biopsies, probe-based confocal laser endomicroscopy (pCLE) and endoscopic ultrasound for diagnosis of CCA in PSC are less studied.[304,315–317] Cholangioscopy with targeted ductal biopsies can increase diagnostic accuracy.[304,317] One meta-analysis of different diagnostic modalities, including 21 studies altogether, compared bile duct brush cytology, FISH polysomy and trisomy and cholangioscopy with targeted biopsies.[304] Cholangioscopy with targeted biopsies was the best performing modality, with a diagnostic accuracy of 96%, based on data from 4 studies including 169 patients. The pooled sensitivity was 65% (95% CI 35–87%) and the specificity was 97% (95% CI

87–99%).[304] It is difficult to differentiate between benign and malignant strictures of the inflamed bile duct mucosa based on macroscopic appearance. The benign inflamed biliary mucosa in PSC strictures range from mildly inflamed and scarred to a more severely inflamed appearance with an irregular surface and erythema. Findings of papillary projections, ulcerations, and vessel pathology with dilated, enlarged and tortuous vessels are important hallmarks for malignancy in the bile ducts.[318,319] Diagnostic accuracy is affected by stents used prior to the cholangioscopy which reduce the value of this investigation.[320] Targeted ductal biopsies should be combined with brush cytology due to the small sampling area.[294] It remains unknown to what extent the use of a combination of different modalities increases sensitivity and diagnostic accuracy.

Techniques of potential, but still unknown utility, are pCLE and endoscopic ultrasound with fine needle aspiration. pCLE has, in small series, shown promising results with high sensitivity, but the evidence for its diagnostic accuracy and availability in clinical practice are still limited.[304,321,322] Evidence for the efficacy of endoscopic ultrasound with fine needle aspiration for detection of CCA in PSC is also scarce[316] and sampling from detectable masses and locoregional lymph nodes is regarded as a contraindication for liver transplantation due to the risk of seeding spread in some centres. Such sampling should therefore be discussed locally in the multidisciplinary team.[294] Percutaneous biopsies are usually contraindicated because of the risk of tumour spread[323] and should be avoided in patients where curative treatment with liver resection or liver transplantation is possible.

How should gallbladder polyps be managed in PSC?

Recommendation

- Cholecystectomy is recommended in people with PSC with gallbladder polyps greater or equal to 8 mm in size and smaller polyps growing in size, due to the high risk of malignancy or dysplasia **(LoE 4, strong recommendation, 89% consensus).**

Gallbladder pathology,including cholecystitis, gallstones, and polyps, is very common in PSC.[136,324] People with PSC are at an increased risk of gallbladder carcinoma, with an incidence reported to be 1.1 per 1,000 person-years.[324] The prevalence of gallbladder polyps in PSC is 6-17%.[136,324] The risk of malignant development in a polyp increases with size and polyps over 10 mm are associated with a higher risk of GBC.[324] In series on patients undergoing cholecystectomy for a gallbladder mass in PSC, around half had a premalignant or malignant lesion[135,136] and the reported rate of GBC was 8.8 per 1,000 person-years in patients with a radiographically detected gallbladder polyp.[324] Many small polyps, less than 8 mm, are not found on follow-up exams or are reported to spontaneously decrease in size.[324] One study supports the cut-off value at a polyp size of 0.8 cm with a sensitivity of 97% and a specificity of 53%.[325] Smaller polyps should be characterised with contrast-enhanced ultrasound and, if a contrast-enhancing polyp is found, cholecystectomy should be considered regardless of polyp size. Small non-contrast-enhancing polyps should be followed-up for growth with a repeat ultrasound after 3-6 months.

People with PSC at severe disease stages with liver decompensation are at an increased risk of complications after cholecystectomy. A careful risk-benefit assessment is required; thus, prophylactic cholecystectomy cannot be recommended in all patients.

How should CCA be treated in PSC?

Recommendation

- Referral to a specialised centre is recommended when CCA or high-grade dysplasia is confirmed. In a multidisciplinary approach, therapeutic options including liver transplantation, liver resection, irradiation, brachy- or systemic therapy or combinations should be considered **(LoE 3, strong recommendation, 96% consensus).**

Potentially curative treatments for CCA are surgical resection or liver transplantation. Liver transplantation should be considered in the context of clinical trials (see section 'When should liver transplantation be considered in people with PSC?'). Surgical resection may not be possible in most cases with PSC due to underlying chronic liver disease, owing to the risk of post-operative liver failure or late-stage CCA with infiltrative growth. Intrahepatic mass-forming CCAs are more often subject to resection in PSC whereas perihilar CCAs with their local bile duct invasion and tumour spread preclude surgery with tumour free margins. In patients without underlying chronic liver disease, overall survival rates after resection for hilar CCA are reported to be around 27-45% at 5 years with negative tumour margins (R0) and 0-23% in patients with positive margins.[326] For mass-forming intrahepatic CCA the prognosis is in a similar range, with 5-year overall survival rates of 20-40% after surgical resection.[327]

Surgical resection in PSC demands careful selection due to the risk of post-operative liver failure and larger series on post-operative outcomes after CCA resection in PSC are lacking. A retrospective multicentre study compared outcome after resection of perihilar CCA in PSC *vs*. non-PSC and included 1,128 patients resected for perihilar CCA, of whom 34 (3.0%) had underlying PSC. Median 3-year overall survival after surgical resection was similar, 39% and 43%, for patients with and without PSC. The complication rate was higher in PSC but it did not affect post-operative mortality.[328] Surgical resection should be considered in cases where liver transplantation is not possible. Careful evaluation, risk assessment and selection of patients before surgery is crucial and should be carried out by the multidisciplinary team.

Early transplant series show that people with PSC with advanced CCA have a poor prognosis[329,330] and CCA was long considered a contraindication for liver transplantation. Also, more recent studies report poor survival and high recurrence rates, both with and without PSC.[331–333] However, liver transplantation is a potentially curative treatment option and has been reported to be associated with better long-term outcomes than resection for hilar CCA.[334,335] A careful selection of patients is essential and tumour stage before liver transplantation has a major impact on prognosis.[329] Liver transplantation following

neoadjuvant chemoradiation in carefully selected patients, with early cancers without tumour spread, was trialled in the US (Mayo protocol) and was associated with a 5-year overall survival rate of 65%.[323,336] The Mayo Clinic criteria for liver transplantation for CCA is an unresectable tumour above the cystic duct, ≤3 cm in size, absence of intra-or extrahepatic metastasis in an otherwise suitable transplant candidate.[323] Data from the European Transplant registry (ELTR) report 59% 5-year survival in patients with adherence to the Mayo protocol criteria.[337] In a meta-analysis comprising 20 studies and 428 patients, the pooled 1-, 3-, and 5-year overall survival rates following liver transplantation without neoadjuvant therapy were 71%, 48% and 32% which improved to 83%, 66% and 65% if neoadjuvant chemoradiation was completed.[338] Recurrence after 3 years was also lower in patients receiving neoadjuvant chemoradiation (24% *vs.* 52%).[338] However, strict patient selection alone (no previous attempt to remove CCA, no neoadjuvant or adjuvant therapy, no percutaneous biopsy of the tumour or no lymph node metastasis) has been shown to confer similar outcomes as liver transplantation with neoadjuvant chemoradiation.[337]

Biliary dysplasia is closely associated with CCA risk and there is evidence that CCA develops through a metaplasia–low-grade dysplasia–high-grade dysplasia–carcinoma sequence in PSC. The term biliary dysplasia is commonly used to describe non-papillary lesions or *in situ* neoplastic lesions in the bile ducts. The terminology used for premalignant non-papillary lesions in the bile duct has been suggested to align with the World Health Organization classification of tumours[339] and the term biliary intraepithelial neoplasia (BilIN) has therefore been suggested instead of biliary dysplasia and is increasingly used. BilIN-1, 2 and 3 in flat lesions in PSC corresponds to low-grade dysplasia, high-grade dysplasia and carcinoma *in situ*, respectively.[340] With increased use of cholangioscopy, papillary lesions in the large bile ducts can also be detected. Such macroscopic papillary lesions (intraductal papillary neoplasm of the bile duct) are regarded as the biliary counterpart of pancreatic intraductal mucinous neoplasms.[341] The frequency and malignant potential of biliary intraductal papillary neoplasms in PSC is not known. Diagnosis and grading of biliary dysplasia/BilIN require experienced and dedicated pathologists. Confirmation of the grade of dysplasia from an external pathologist is recommended.

Biliary dysplasia of any grade has been reported in 83% of explant livers with PSC-CCA, compared with 36% of those without CCA and the dysplastic changes are often multifocal.[342] 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.[342] The indication for, and timing of, liver transplantation in patients with dysplasia and no signs of CCA is controversial.[20,22,343] Outcome after liver transplantation in patients with preoperative dysplasia without signs of CCA is reported to be in line with benign PSC.[305,308,343]

Pre-emptive liver transplantation is not recommended because of the short- and long-term risks associated with liver transplantation such as rejection, recurrence of disease, cancer, and side effects from immunosuppression. However, due to the strong association between CCA and dysplasia it is reasonable to consider liver transplantation in the presence of high-grade dysplasia. Confirmation of the diagnosis of high-grade dysplasia, especially in patients with severe inflammation and/or biliary stenting, is important. Presence of dysplasia without cancer strengthens the indication for liver transplantation, whereas a confirmed diagnosis of CCA may preclude transplantation (Fig. 2). Early transplantation in asymptomatic patients on the indication of any grade of dysplasia may lead to a high frequency of benign findings in the explant.[308] Low-grade dysplasia found in brush samples before liver transplantation has a specificity of only 84% for the diagnosis of high-grade dysplasia or CCA in the explanted liver.[343] Transplantation for the indication of low-grade dysplasia may expose patients to unnecessary risk of transplantation too early in their disease course. Confirmation of low-grade dysplasia on ≥2 occasions may increase the diagnostic accuracy for malignancy.[305]

How should PSC-IBD be diagnosed and followed?

Recommendations

- Ileocolonoscopy with biopsies from all colonic segments including the terminal ileum, regardless of the presence of lesions, is recommended at the time of PSC diagnosis **(LoE 3, strong recommendation, 100% consensus).**
- A diagnostic colonoscopy can be considered every 5 years in people with PSC where no IBD is present or whenever complaints suspicious for IBD occur **(LoE 5, weak recommendation, 92% consensus).**
- Annual surveillance (or every 1 to 2 years in individualised patients without inflammatory activity) colonoscopy with biopsies is recommended in all adult PSC-IBD patients regardless of the duration of IBD or liver transplant status **(LoE 3, strong recommendation, 92% consensus).**

Abnormal liver function tests are common in IBD and reported in nearly 30% of patients, but underlying liver disease is much rarer.[344,345] The reason for elevated liver function tests in IBD should be investigated and viral, metabolic or toxic hepatitis should be ruled out. PSC is one of the most common chronic progressive liver diseases in IBD followed by AIH.[346] Non-alcoholic fatty liver disease is also frequent, but is less frequent in people with PSC-IBD than in those with IBD alone.[347] The prevalence of PSC in extensive colitis IBD is around 5%.[345,348] A concomitant diagnosis of PSC in IBD is often overseen and the prevalence underestimated. In one large population-based study of patients with longstanding IBD, screening with MRCP revealed an increase in prevalence from 2.2% to 7.5%.[4] A liberal use of MRI in IBD is recommended when symptoms or signs (abnormal liver tests) or chronic liver disease occur. However, general screening for PSC with MRI in patients with IBD is not yet justified due to the lack of a specific treatment that can slow down PSC progression in early disease.

The strong association between PSC and IBD is well established but varies geographically. The prevalence of IBD in PSC has been estimated to be 50-85% with the highest prevalence in Northern Europe (around 80%).[349,350] It has been reported that UC accounts for approximately 80%, Crohn's disease for 15% and indeterminate colitis for 5% of IBD in PSC.[349,351] IBD in PSC represents its specific phenotype which is different from UC and Crohn's without PSC[349,351,352] and is characterised by a high prevalence of pancolitis, a mild disease course, predominant inflammation on the right side and rectal sparing, pouchitits, and a high risk of developing

colorectal cancer.[349,351–357] Endoscopically the mucosa can even appear normal while the biopsies reveal an underlying mild IBD.[349,352] The increased risk for colorectal neoplasms and asymptomatic disease makes colonoscopy with biopsies essential in all patients at PSC diagnosis.[294]

PSC can present both before and after the diagnosis of IBD, but is often picked up at screening of liver function tests in the IBD clinic. IBD may also present many years after PSC diagnosis, or even after liver transplantation.[349] Clinical presentation varies and there may be a long subclinical asymptomatic period in people with PSC-IBD,[358] which could lead to the underestimation of the presence of IBD. Studies on the prevalence of IBD in PSC that review both endoscopic and histological data report a higher prevalence of IBD than studies only reporting endoscopic data.[349] Thus, a colonoscopy with biopsies from all segments from the colon is required before an IBD can be ruled out in PSC even in the absence of endoscopic changes. A colonoscopy during follow-up is indicated whenever complaints suspicious for IBD occur and may also be considered every 5 years to rule out IBD.[294]

Risk for colorectal cancer in PSC-IBD

There is a well-established increased risk for colorectal cancer in IBD colitis.[123] Risk factors for development of colorectal dysplasia or cancer in IBD are early onset, long duration, extensive mucosal involvement, chronic continuous inflammation, family history of colorectal cancer, and presence of PSC.[353,355,359] The presence of PSC further increases the risk 3-5-fold compared with that of IBD alone. In one meta-analysis of 11 studies including 564 people with PSC-IBD, Soetniko *et al.* reported an odds ratio of 4.79; (95% CI 3.58–6.41), while in a meta-analysis of 16 studies including 1,022 people with PSC-IBD, Zheng *et al.* reported an odds ratio of 3.24 (95% CI 2.14–4.90) in people with PSC-IBD compared to patients with IBD alone.[353,355] In a population-based study, the prevalence of colorectal cancer in PSC-IBD was 7% after 20 years disease duration.[7] The high risk of colorectal cancer remains after liver transplantation.[360] The high risk of colorectal dysplasia warrants regular colonoscopy surveillance, which has been shown to lower the risk for colorectal cancer-related mortality in PSC.[7] This recommendation is in line with guidelines from the ESGE, European Crohn's and Colitis Organisation (ECCO) and American College of Gastroenterology.[21,294,361,362] Targeted biopsies using dye-based chromoendoscopy with indigo carmine or methylene blue increase the detection rate compared to standard white light endoscopy with random biopsies and should be used in PSC-IBD as a standard surveillance investigation, as stated by the most recent guidance recommendations from ESGE.[361] The importance of good preparation of the colon needs to be underscored since it significantly affects the detection rate.

How to treat PSC-related IBD?

Recommendation

- Treatment of PSC-related IBD in line with current practice guidelines with the goal of achieving mucosal healing is recommended **(LoE 3, strong recommendation, 92% consensus).**

PSC-IBD generally runs a mild disease course.[351,352,357] The need for treatment with steroids is reported to be lower than in UC without PSC.[363,364] More recently the natural history from onset of UC in patients with and without PSC have been compared and similar needs regarding courses of steroids and treatment with immunomodulators were shown.[365] Due to prominent right-sided inflammation in PSC-IBD, symptoms are milder than in patients with UC and inflammatory involvement of the rectum. The inflammatory activity can be underestimated and awareness of possible underestimation on IBD activity is important.[349,352] There is a high risk of endoscopic and histological inflammatory activity despite clinical remission in both adults and children with PSC-IBD.[366,367] Objective measures of mucosal healing, such as endoscopy and/or measurements of faecal calprotectin, are therefore recommended.[366]

The impact of active treatment of gut inflammation on progression of PSC is unknown. The migration of activated inflammatory immune cells from the gut to the liver via the portal vein is an attractive hypothesis for the association between IBD activity and PSC progression. Data supporting that IBD (and its inflammatory activity) is important for PSC progression is that UC, as opposed to no IBD[368] or Crohn's disease, is associated with faster PSC progression.[6] Other potential evidence that gut inflammation may affect PSC progression is the association between a more favourable outcome in people with PSC-IBD undergoing colectomy.[8] Higher inflammatory activity of IBD after liver transplantation has also been shown to increase the risk for recurrent PSC and colorectal cancer.[369] However, IBD is not included in the different prognostic scores of importance in PSC and altogether the evidence that gut inflammation affects progression of PSC is scarce.

Despite the limited evidence for the association between active IBD inflammation and PSC progression, it is important to actively treat IBD in PSC to reduce the symptom burden in this affected patient group and to improve quality of life. Also, chronic inflammation in IBD is associated with increased risk for colorectal malignancy.[359,369–371] Strategies for treatment of PSC-IBD do not differ from IBD alone.[362,372,373] 5-aminosalicylic acid is recommended in colitis because it reduces the risk of development of colorectal cancer/dysplasia.[374]

Treatment with biologics is often not indicated in patients with mild inflammation but they should be used if needed. The effect of anti-TNF in IBD with concomitant PSC has been studied in small or retrospective studies where biologics have been used for the IBD indication.[181,182] Treatment was shown to be moderately effective for gut inflammation and no concerning safety signals were found. The side effects of anti-TNF treatment in PSC-IBD are reported to be similar to those in IBD alone, and no exacerbation of PSC symptoms or specific liver-related side effects have been noted.[182] Similar results have been reported for vedolizumab, the monoclonal antibody against integrin $\alpha4\beta7$, with a favourable safety profile and a moderate effect on the IBD.[178–180] Neither anti-TNF, nor vedolizumab have shown convincing effects on serum liver tests. There is currently no evidence to recommend one biologic treatment over another in PSC-IBD. In the post-transplant setting, anti-TNF has proven effective for IBD and is safe.[375,376]

When should colectomy be performed in PSC-IBD?

Recommendation

- Colectomy is recommended in patients with high-grade colonic dysplasia or neoplasia or if symptomatic colonic inflammatory activity persists despite optimum medical therapy. Colectomy may also be considered in confirmed low-grade dysplasia at repeated occasions and/or at multiple locations **(LoE 3, strong recommendation, 79% consensus).**

Total proctocolectomy is recommended in the case of high-grade dysplasia or adenocarcinoma or non-adenoma-like dysplastic lesions of any grade due to the high risk for concomitant and future colorectal carcinoma,[377] and also if symptomatic colonic inflammatory activity persists despite optimum medical therapy. Confirmation of low or high-grade dysplasia from an external pathologist is recommended.[377]

Evidence for colectomy in PSC-IBD with low-grade dysplasia is scarce. ECCO guidelines recommend individual assessment to balance risk and benefit of colectomy in this situation.[377] Studies on the risk for progression from low-grade to high-grade dysplasia are contradictory. Some studies show very low risk for progression to high-grade dysplasia[378–380] while others show progression in a significant number of cases.[381–384] The timing of colectomy can therefore be individualised according to patient preference or more frequent colonoscopic surveillance. PSC has been identified as a risk factor for dysplasia progression together with invisible dysplasia, distal location, and multifocal low-grade dysplasia.[382]

The optimal restorative surgical management for PSC-IBD requiring colectomy is controversial. A higher risk for pouchitis and pouch failure after ileal pouch-anal anastomosis (IPAA) has been reported for PSC-IBD than for IBD alone. A recent systemic review including 11 studies and 4,108 patients, of whom 309 (8%) had PSC, shows that the presence of PSC led to a 6-fold and 2-fold increase in the risk of chronic pouchitis and pouch failure, respectively.[385] The increased risk of pouchitis and adverse pouch-related outcomes for people with PSC-UC should not prevent restorative surgery. However, the risk-benefit of IPAA, ileorectal anastomosis or a non-restorative approach (ileostomy) should be considered. The risk for rectal neoplasia remains after ileorectal anastomosis, and PSC is risk factor, thus endoscopic surveillance is recommended.[386] Obtaining relevant risk information for the patient is desirable before making a treatment decision. A nationwide study shows that restorative surgery was not withheld from people with PSC-IBD and PSC-IBD was associated with a higher frequency of restorative surgery than UC alone.[387]

When should liver transplantation be considered in people with PSC?

Recommendations

- Liver transplantation should be considered for people with PSC and decompensated cirrhosis or hepatocellular carcinoma according to standard guidelines **(LoE 3, strong recommendation, 100% consensus).**
- Liver transplantation should be considered for people with PSC with recurrent bacterial cholangitis and/or severe pruritus or jaundice despite endoscopic and pharmacological therapy **(LoE 3, strong recommendation, 100% consensus).**
- Liver transplantation can be considered in people with PSC and high-grade biliary dysplasia confirmed by cytology or ductal histology **(LoE 4, weak recommendation, 92% consensus).**
- Liver transplantation for early-stage CCA in PSC can be performed within the context of clinical trials **(LoE 4, weak recommendation, 92% consensus).**

Liver transplantation is typically considered in people with PSC in 3 different settings – advanced cirrhosis, symptoms from widespread or pronounced biliary strictures and suspected early-stage biliary neoplasia. There are no strict demarcations between these groups of indications, and often a combination of features is present in the same individual. The relative size of each of these 3 categories ultimately admitted to the transplant waiting list varies between programmes depending on local policies and organ availability.[1,245,388–390] Altogether, PSC represents 4-5% of the total liver transplants performed in Europe and North America,[390,391] with higher rates reported in the Nordic countries.[392] Upon disease progression, people with PSC develop cirrhosis with typical complications and MELD score deterioration. However, due to the increasing attention paid to the risk of CCA and clinical symptoms, the fraction of people with PSC and decompensated cirrhosis is declining in many transplant programmes.[245]

Prognosis after liver transplantation in people with PSC is excellent, with 1- and 5- year overall survival rates of 91% and 82%, based on ELTR data from the last 15 years, respectively.[393] Notions that people with PSC may develop pre-cirrhotic portal hypertension are disputed and hold little practical relevance,[251] and in fact variceal bleeding is a rare cause of waitlist mortality in people with PSC.[394] Concurrent cholestasis adversely affects risk of sarcopenia,[395] and people with PSC and cirrhosis often represent frail candidates for transplant surgery.[396] In a significant proportion of people with PSC, the driving indication for liver transplantation is symptomatic burden in the form of recurring bacterial cholangitis or progressive cholestasis with pruritus despite repeated endoscopic interventions and appropriate medical intervention. For optimal therapy of severe cholestasis-associated pruritus, advice should be sought from an expert in this field beyond guideline recommendations. Fatigue is less prevalent than in people with PBC and should not in isolation lead to transplant considerations in people with PSC; however, it can be considered during work-up. Some analyses suggest that people with PSC have a better outcome following liver transplantation than patients with similar MELD scores transplanted for other indications,[397] and that bacterial cholangitis does not increase waitlist mortality, adding to the difficulty in applying standardised listing procedures to the PSC population both in MELD-based and consensus-based transplant programmes.[389]

In some transplant programmes, liver transplantation is also an accepted treatment modality for people with PSC and

cytologically confirmed biliary dysplasia.[245,388,398] Due to the challenges of differentiating early-stage biliary neoplasia from benign bile duct strictures and inflammatory epithelial changes, histology in up to 20% of the liver explants in these individuals may show no signs of neoplasia in real-world settings.[245] It is thus important to have educated conversations with people with PSC and biliary dysplasia on the pros and cons of liver transplantation in this controversial setting. In some programmes (*e.g.* in the UK[22]), the practice of offering liver transplantation on the basis of isolated biliary dysplasia has not been adopted. Organ shortage and the scarcity of data on the natural history of biliary dysplasia are common arguments against this practice, and more research is needed to determine the ultimate criteria for liver transplantation related to the risk of neoplasia in PSC.

HCC in people with PSC should be carefully evaluated to discount the possibility of intrahepatic localisation of CCA, and, if HCC is confirmed, patients should be offered therapeutic interventions according to standard guidelines.[134] Liver transplantation in people with PSC and manifest CCA is mostly performed in the context of clinical studies according to strict inclusion criteria.[336] Only highly selected cases with early-stage CCA are eligible, most often after neoadjuvant therapy, including external beam radiotherapy and endoluminal brachytherapy.[399,400] Strict selection is likely a critical success factor,[401,402] and results have been generally better in people with PSC (74% 5-year overall survival) than in people with spontaneous CCA (58% 5-year overall survival).[399] One reason for this difference may be the intra- and periductal pattern of growth and lower frequency of a detectable tumour among people with PSC in these series,[399] leaving the question open as to what radial tumour size (traditionally below 3 cm) should be allowed.

What are the medical and surgical specificities of liver transplantation in PSC?

Recommendation

- Liver transplantation in PSC should be performed using a duct-to-duct anastomosis unless anatomical disease location or technical surgical factors warrant a Roux-en-Y hepaticojejunostomy **(LoE 4, strong recommendation, 79% consensus).**

Work-up for liver transplantation in PSC is done according to standard principles, requiring biochemical, serological, virological, endoscopic and radiological data.[242] However, the possibility of biliary and colorectal malignancy requires particular attention. A recent abdominal CT scan or MRI/MRC (less than 3 months old) and colonoscopy within the last 6-12 months is mandatory. Upon clinical or radiological suspicion of malignancy, diagnostic procedures to clarify the situation should be performed as described elsewhere in these guidelines. CA 19-9 holds little specificity for malignancy at this disease stage, as it is often elevated due to recurrent bacterial cholangitis and advanced strictures with cholestasis. Status of bone disease (densitometry) and vitamin D levels provide important information prior to corticosteroid treatment after transplantation, particularly after prolonged cholestasis in advanced disease. Sarcopenia is common, particularly in people with cirrhosis, and nutritional status needs to be assessed and monitored during a patient's time on the waiting list.[403] People with PSC and intense and frequent bacterial cholangitis may in severe cases be considered for permanent rotating antibiotics up to time of transplantation.

As for other autoimmune liver diseases, people with PSC are at higher risk for early and late cellular rejection than in other indications for liver transplantation.[404] The possible triad of interactions between the intensity and type of immunosuppression, the risk of acute cellular rejection and recurrent disease make firm recommendations regarding immunosuppressive regimens in PSC particularly challenging. Furthermore, variable induction protocols and immunosuppressive regimens, over time and between centres, make retrospective studies of acute cellular rejection in PSC exceedingly difficult to translate into recommendations regarding clinical practice. The cornerstone of immunosuppression after liver transplantation in PSC is a calcineurin inhibitor, typically tacrolimus,[405] and whilst most experienced centres also prescribe long-term double immunosuppression by adding mycophenolate mofetil, there is no consensus and practice is variable regarding long-term, maintenance low-dose prednisolone (5 mg daily). For induction, basiliximab is now considered in most individuals with autoimmune liver disease, PSC included. Individualised considerations must be made based on history of cellular rejections, liver biochemistry, and the potential for side effects from triple immunosuppression, including osteopenia and infections.

Surgical specificities related to liver transplantation in PSC mostly pertain to the choice of biliary anastomosis. Historically, Roux-en-Y choledochojejunostomy has been used in people with PSC undergoing liver transplantation owing to the perceived risk of biliary complications. However, the literature is not conclusive on this point, and several studies suggest that in selected instances, duct-to-duct anastomosis should be considered, as it is associated with similar outcomes as choledochojejunostomy, but easier endoscopic access and possibly a lower risk of ascending cholangitis.[406] Recent practice is thus to perform duct-to-duct anastomosis in people with PSC without significant extrahepatic disease and no suspected biliary dysplasia in relevant compartments of the biliary tree. Choledochoduodenostomy has not gained widespread use and is currently mostly avoided due to the serious clinical implications of early bile and duodenal leakage.[407] In the end, anatomical features or previous surgery (*e.g.* colectomy, IPAA or in the context of re-transplantation) may influence choice of procedure.

What are the diagnostic criteria and management of recurrent PSC after liver transplantation?

Recommendation

- A diagnosis of recurrent PSC can be made based on progressive biliary strictures on cholangiography and/or histological findings compatible with PSC more than 90 days after liver transplantation upon exclusion of other identifiable causes **(LoE 4, weak recommendation, 92% consensus).**

The first reports on recurrent PSC (rPSC) started appearing in 1988, an expected 4-5 years after the implementation of liver transplantation programmes for PSC.[408] Diagnosis of rPSC in early stages is not straightforward, and relies on an alignment of biochemical abnormalities, radiological signs of biliary strictures and biopsy findings. Due to the relatively lower threshold for liver biopsy for the diagnosis of graft disturbances, protocol biopsies included, biopsy plays a more pronounced role in the diagnosis of rPSC than in PSC. In 1999, Graziadei proposed standardised criteria for diagnosing rPSC which have since been quite consistently applied in research (Box 4).[409] Central to the definition is the exclusion of other causes of bile duct irregularities after liver transplantation, particularly anastomotic and ischaemic strictures. However, in everyday clinical practice, these exclusion criteria appear less absolute, since overlapping aetiologies may operate in the same individual. Time is a helpful co-factor in concluding a diagnosis of rPSC in these instances, as often indicated by progressive radiological and histological features, despite resolution of other causes (*e.g.* dilation of anastomotic biliary strictures or arterial stenting).

The frequency of rPSC varies from less than 10% to more than 50% in various series,[404] with a commonly accepted prevalence probably residing somewhere in the 20-30% range. Median time from transplant to rPSC has been suggested to be approximately 5 years,[410] but natural history varies considerably, from mild cases not requiring re-transplantation to progressive forms requiring re-transplantation within a few years. For early rPSC (within 5 years), the 15-year probability of graft survival drops from 81% to 25% compared with late presentation (after 5 years) where the 15-year graft survival is 38%, indicating time of presentation as an indicator of severity.[410,411] Furthermore, local procedures, for instance related to research projects such as protocol MRC or protocol biopsies, may lead to an earlier diagnosis. With the exception of acute cellular rejection and colectomy, there is little consistency in risk factors between different reports.[404] For acute cellular rejections, differentiation is quite straightforward for the experienced pathologist. In steroid refractory cases of cellular rejections with only moderate elevation of serum liver tests, and where biopsy findings are less characteristic, a heightened suspicion of early rPSC is sometimes warranted.

There has been considerable debate associated with findings that colectomy appears to protect against rPSC.[412,413] Albeit less pronounced, findings are also seen in independent studies.[414] Regarding IBD activity, observations are inconsistent, but an association between graft survival and severity of colitis is seen in some series.[415] From a pathophysiological perspective, the association supports a role of the gut-liver axis in PSC and rPSC development.[416,417] From a practical perspective, implications are less clear, as pre-emptive colectomy prior to liver transplantation is advised against. Striving for optimal management of post-transplant IBD in people with PSC, as discussed in the following section, is also a message to take from these data.

Management of rPSC is subject to the same limitations as in the pre-transplant setting and there is no consistent evidence base for any recommendation. In principle people with PSC should be followed like other transplant recipients, and receive endoscopic therapy and evaluation for re-transplantation as described elsewhere in this guideline. *De novo* CCA is a rare event in rPSC but has been reported. Based upon the potential impact of UDCA on PBC recurrence after liver transplantation,[418] it may be speculated that UDCA prescription may be considered after re-transplantation for rPSC. Similarly, given the association of tacrolimus-based immunosuppression regimens and rPSC and rPBC in some series,[414,418] switching to cyclosporine may be of benefit in cases of repeated rPSC following a second liver transplantation. Any such management consideration should be handled by experienced transplant hepatologists in large volume centres.

Box 4. Graziadei-criteria for the diagnosis of recurrent primary sclerosing cholangitis.[409]

- **Diagnosis**
  Confirmed diagnosis of primary sclerosing cholangitis prior to liver transplantation

AND

- **Cholangiography**
  Intrahepatic and/or extrahepatic biliary stricturing, beading, and irregularity >90 days after LT

OR

- **Histology**
  Fibrous cholangitis and/or fibro-obliterative lesions with or without ductopenia, biliary fibrosis, or biliary cirrhosis

- **Exclusion criteria**
  Hepatic artery thrombosis/stenosis
  Established ductopenic rejection
  Anastomotic strictures alone
  Non-anastomotic strictures before post-transplantation day 90
  ABO incompatibility between donor and recipient

How to manage PSC-IBD in the post-transplant setting?

Recommendation

- Management of IBD after liver transplantation can follow pre-transplant recommendations of annual (or biennial under conditions of complete remission) endoscopic surveillance, with particular attention to risk of infectious colitis, mycophenolate-related colitis and timely consideration for colectomy in refractory cases **(LoE 5, weak recommendation, 92% consensus).**

Approximately one-third of people with PSC experience exacerbation of IBD after transplantation, with the remainder experiencing no change or improvement. Medical treatment of IBD follows a “bottom-up” treatment algorithm similar to those described for the pre-transplant setting.[19,362,419] However, several points warrant particular attention. Prior to intensified IBD treatment, repeat colonoscopy with biopsies is necessary to exclude colitis due to mycophenolate mofetil or cytomegalovirus, which in some instances may be difficult to differentiate. Other infectious aetiologies, *e.g. Clostridioides difficile* or *Cryptosporidium colitis*, should also be considered.

Despite concerns of infectious complications, anti-TNF treatment warrants consideration in severe cases and has a

reasonable safety profile.[376] Vedolizumab also appears safe,[420] with occasional reports of worsening serum liver tests that are not clearly related to the drug. Any preference for either of these compounds for post-transplant IBD exacerbations in people with PSC cannot be determined by present data and individualised considerations, including overall immunosuppression and pre-transplant experience, must be made. In patients with rPSC who suffer from severe colitis, switching from tacrolimus to cyclosporine may be considered in selected cases.[421] However, given the overall risks associated with long-term suboptimal IBD control and complex immunological interventions in a post-transplant setting, colectomy in refractory cases should be considered at a slightly lower threshold than in pre-transplant people with PSC.

Notably, the risk of colonic neoplasia persists and may even be heightened after liver transplantation for PSC.[360,422] Annual screening colonoscopy as described previously is thus mandatory in people with PSC-IBD following transplantation.

Do diagnostic criteria in paediatrics differ from adult criteria?

Recommendations

- The diagnostic practice in paediatric patients should be similar to adult practice, based on MRCP as the diagnostic modality of choice **(LoE 4, strong recommendation, 96% consensus).**
- It is suggested to explore features of AIH in children with PSC and to check for PSC using MRCP in children with a diagnosis of AIH **(LoE 4, weak recommendation, 89% consensus).**

In children, sclerosing cholangitis is associated with a variety of diseases including biliary atresia and ciliopathies as well as rarer conditions including inherited and immunological diseases, hence further exploration is required, particularly in those presenting at a younger age.[423] Data regarding the prevalence of PSC in paediatrics is scarce. A population-based multicentre study in the USA estimated the prevalence of PSC as 0.2/10,000 children compared to up to 16/100,000 in adults.[424]

As in adults, MRCP has replaced ERCP as the modality of choice to diagnose the presence of a cholangiopathy in patients with suspected PSC.[425] In a prospective study including 45 children with PSC who underwent a diagnostic MRCP the modified Majoie ERCP classification was found to be reliable and to predict outcomes in paediatric PSC.[426] Whereas MRCP performs similarly to ERCP in diagnosing PSC and the presence of intrahepatic strictures, ERCP is better for the assessment of extrahepatic strictures,[31] but should be restricted to high-grade strictures which may require diagnostic and therapeutic endoscopic interventions.

Overlap of PSC with AIH, often defined as ASC has been well described in paediatrics. In the only published protocol-based study, 27 out of 55 consecutive children presenting with clinical, biochemical and immunological features in keeping with AIH, were found to have evidence of a cholangiopathy on cholangiography.[66] Applying the standard IAIHG diagnostic criteria did not distinguish between the 2 types. In a large, multicentre international retrospective study including 781 children and young people diagnosed with PSC, 67% fulfilled the diagnostic criteria for AIH, in contrast to 6.6% in a similar study including 7,121 adults, suggesting higher prevalence in the paediatric population.[6,427]

A diagnostic scoring tool including cholangiography to distinguish between AIH and ASC has been suggested but requires further validation in larger patient populations.[428]

When should endoscopic intervention be considered in paediatric PSC?

Recommendation

- Therapeutic endoscopic intervention is recommended in children with high-grade strictures on imaging and signs or symptoms of obstructive cholestasis and/or bacterial cholangitis. Referral to a centre with expertise in paediatric interventional ERCP is highly recommended **(LoE 4, strong recommendation, 96% consensus).**

As in adults, over time MRCP has replaced ERCP as a diagnostic modality for cholangiopathy in patients with suspected PSC.[31,425] Current practice is for ERCP to be considered as in adults for further interventional management purposes.

With regard to peri- and post-procedural care and interventions, such a balloon dilation or stenting, there is no specific guidance for the paediatric population and adult guidance is followed.[429]

What are the criteria and methods for screening paediatric people with PSC for IBD?

Recommendation

- Non-invasive screening for IBD in children with PSC can be performed by faecal calprotectin at presentation and further endoscopic assessment in those with raised faecal calprotectin or symptoms **(LoE 5, weak recommendation, 81% consensus).**

The current literature on paediatric PSC-IBD is limited. The IBD phenotype in children is suggested to be similar to adults with features of pancolitis and rectal sparing with less evidence to support right colon predilection.[430]

Of note and demonstrated in a concurrent prospective study of 87 children with colitis, including 37 with and 50 without PSC, symptoms under-represent mucosal inflammation in those with associated PSC-IBD who despite being in clinical remission had significantly greater odds of active endoscopic and histologic inflammation compared to those with isolated IBD. Furthermore, faecal calprotectin was found to perform better than the

symptom-based clinical activity index with values below 100 μg/g reliably indicating mucosal healing in children with PSC-IBD.[366] In another study of 58 children with IBD, faecal calprotectin correlated well both with histologic and endoscopic grade of inflammation, with a sensitivity of 94% and specificity of 64%.[431]

Is surveillance for hepatobiliary and colonic malignancy required in paediatric PSC?

Recommendation

- Routine surveillance for biliary and colonic malignancy is not suggested in children with PSC **(LoE 5, weak recommendation, 81% consensus).**

Population-level data on the prevalence of gastrointestinal malignancy including hepatobiliary and colonic malignancy in paediatric PSC is scarce. A US study consulting the Surveillance, Epidemiology, and End Results Program (SEER 18) database between 1973-2013 identified 15 cases of CCA in patients <20 years, with an incidence rate of 0.0036/100,000 compared to the estimated incidence rate of 1.67/100,00 in adults.[432] No information was available regarding the presence of an underlying aetiology such as PSC. In addition, when reviewing the literature (1946-2016), 22 cases were found of which 7 had PSC. The authors commented on the lack of guidance on surveillance for CCA in children.[432] In a large, multicentre international retrospective study including 781 children and young people diagnosed with PSC, CCA was diagnosed in 1% – all patients with large duct involvement were >15 years.[427] In the retrospective outcome analysis of patients diagnosed with PSC from 1980 through 2010 at 37 centres in Europe, North America, and Australia including 7,121 patients, the incidence of CCA in 940 patients ≤20 years-old was 1.2/100 patient-years increasing with age to 21/100 patient-years for those over the age of 60.[6] Patients with associated UC were at higher risk of developing CCA.

In a prospective, observational multinational study exploring malignancy in IBD, children with PSC and IBD were at a higher risk of fatal malignancy than children with IBD only (relative risk 7.08; 95% CI 2.34–21.44; $p = 0.0005$).[433]

A large Swedish cohort study found that the risk of developing malignancy in 9,405 patients with IBD aged <18 years was 3.3/1,000 patient-years compared to 1.5/1,000 in the matched general population; patients with IBD were at a higher risk of developing gastrointestinal malignancy, including colorectal carcinoma, CCA and small bowel cancer (hazard ratio of 18; 95% CI 14.4–22.7) and in particular liver-related malignancy (hazard ratio 134; 95% CI 59.6–382). Risk factors associated with the development of malignancy were PSC, present in 7% of patients, longstanding colitis and malignancy in a first degree relative aged <50.[434] In other terms, relative risks for abdominal cancer were high but absolute risks were low: only 0.2% of patients with childhood-onset IBD will develop cancer in childhood.

Clear guidance with regard to surveillance in children and young people is not available, including what age to start screening (particularly for CCA). Some suggest applying adult screening practices to those aged >15 years.[429]

What are the features of a good transition between childhood and adulthood liver disease services in patients living with PSC?

Recommendation

- A coordinated multidisciplinary transition process from paediatric services to adult care is recommended, based on shared information and special attention on psychosocial issues and adherence to treatment **(LoE 3, strong recommendation, 96% consensus).**

PSC in children is typically diagnosed during puberty, a period of significant biological and neurodevelopmental changes that are known to continue into the mid 20s.[435] Concerns of poorer health outcomes for young people compared to older and younger age populations, in particular following transition of care from paediatric to adult services, has led to the development of transition services, mainly driven by paediatric professionals. The adolescent Health society in 1993 defined transition as 'a purposeful, planned process that addresses the medical, psychosocial and educational/vocational needs of adolescents and young adults with chronic physical and medical conditions from child-centred to adult-orientated healthcare systems.' In addition, in 2002, the following consensus was published by the American Academy of Pediatrics, 'The goal of transition in health care for young adults with special health care needs is to maximise lifelong functioning and potential through the provision of high-quality developmentally appropriate health care services that continue uninterrupted as the individual moves from adolescence to adulthood'.[436] Examples of good practice, particularly in the transplant setting, have led to improved outcomes for young people supported by specialised teams during this period.[437,438]

Aside from providing care related to the medical condition, more attention needs to be given to psychosocial issues. Mental health problems such as depression and anxiety and non-adherence to treatment are more prevalent in this age group: 17.7% of a group of 187 young people with liver disease looked after by a multidisciplinary transition team screened positive for anxiety or depression.[439] A systemic review into the psychological wellbeing of adults with PSC found that the condition is associated with a significant reduction in psychological health and quality of life. The need to consider integrating psychological perspectives and therapeutic approaches into the treatment of PSC was highlighted.[440]

An audit in the UK involving secondary/tertiary adult liver centres demonstrated that only half of the centres provided transition care for young people, while nearly two-thirds of these centres used a documented formal transition programme. Notably, the constituents of the multidisciplinary team varied hugely among centres. The main barriers to a successful

transition were poor adherence to treatment and ongoing dependence on the paediatric providers and both were less prevalent in the centres with a dedicated transition service.[441]

How to manage women with PSC during pregnancy?

Recommendation

- Preconception counselling in women with PSC willing to become pregnant is suggested. Close monitoring and interdisciplinary specialist care is suggested for pregnant women with PSC and cirrhosis, and especially in those with suspected portal hypertension **(LoE 4, weak recommendation, 92% consensus).**

Maternal outcome

There is a paucity of data on pregnancy in PSC. Pregnancy in patients with advanced cirrhosis, as in other patients with advanced cirrhosis, is associated with maternal complications related to portal hypertension, increased maternal mortality and with adverse foetal outcome.[442] Risk of bleeding from oesophageal varices is highest in the second trimester and during birth. In patients with cirrhosis, screening for oesophageal varices using gastroscopy should therefore be performed prior to conception and independently of the risk criteria for variceal bleeding based on liver stiffness and platelet count. Varices should be prophylactically treated with non-selective beta blockers or ligation. If gastroscopy was not performed prior to conception, it should be done in the second trimester (for more detailed guidance see recent AASLD practice guidance[443]). In patients without advanced cirrhosis published studies did not report a negative effect of pregnancy on maternal outcome.[444–447] In general, vaginal delivery should be attempted. Serum liver tests may rise during pregnancy or after delivery in up to 30% of women,[444] similar to other autoimmune liver diseases, but emergency therapeutic ERCP is rarely required. Pruritus may occur or worsen during the second and third trimester and may occasionally lead to preterm delivery.[444,446]

Pregnancy outcome

Fertility in women with PSC was not reduced in a survey-based study from Germany.[444] Active IBD, and ileoanal pouch reconstruction reduces fertility in IBD and may also do so in people with PSC.[448] Laparoscopic pouch reconstruction was associated with less impact on fertility.[449] In PSC, active IBD in addition may negatively impact on pregnancy outcome, underlining the need for sufficient control of disease activity prior to conception.[450] Foetal outcome was reported to be unaffected by the presence of PSC and the risk of foetal malformations was not increased.[444–447] However, a population-based study[445] and the largest case series to date[447] reported an increased rate of prematurity compared to controls, which may be related to the severity of liver disease, as measured by ALT levels, or increasing levels of serum bile acids during pregnancy.[447]

Drug treatment during pregnancy

Use of UDCA during the second and third trimester of pregnancy is safe.[451] Limited data on UDCA intake during the first trimester do not indicate negative effects on pregnancy outcomes.[444,447] Patients interrupting ongoing UDCA treatment during pregnancy may experience a rise in serum liver tests.[444] UDCA being a hydrophilic bile acid, concentrations of UDCA in breast milk were shown to be very low.[451] Recommendations on UDCA during pregnancy should be individualised, but in general, UDCA in standard doses seems safe throughout pregnancy and during breastfeeding.

In case of increasing pruritus severity, biliary obstruction caused by progressive strictures or stones should be ruled out, preferably using ultrasound. For the treatment of pruritus, cholestyramine and rifampicin are considered safe during pregnancy,[443] as is UDCA. Cholestyramine may exacerbate cholestasis induced vitamin K deficiency and thereby increase bleeding risk.[443] Due to a lack of data, bezafibrate is not recommended during pregnancy.

Is contraceptive use possible in women with PSC?

Recommendation

- Oral contraceptives can be used in patients with non-advanced PSC as they appear safe. Regular monitoring of serum liver tests is advisable **(LoE 5, weak recommendation, 91% consensus).**

Combined hormonal contraception contains oestrogen and progestin. Since oestrogens are metabolised in the liver, this raises theoretical concerns about oral contraceptive use in chronic liver disease, especially in advanced stages of cirrhosis (Child B and C).[452] Current formulations do not carry an increased risk of elevated serum liver tests, although cholestatic liver injury has been reported with higher dose oestrogens.[443] The US Centers for Disease Control accept hormonal contraception in patients with chronic liver disease in its updated guidance for the safe and effective use to prevent conception.[453] Combined hormonal contraception, progestin only pills and intrauterine devices are considered safe in chronic liver disease, patients under immunosuppression and compensated cirrhosis.[443]

There are no published data on contraceptive use in people with PSC. Extrapolated from the experience with other liver diseases and the negligible effect of increased sex hormone levels on maternal disease course during pregnancy, oral contraceptives and intrauterine devices can be safely used by people with PSC, unless advanced cirrhosis is present, as long as serum liver tests are monitored regularly (*e.g.* every 6 months).

When should people with PSC be referred to an experienced centre in PSC care?

Recommendation

- Initial expert consultation for people with PSC at diagnosis and referral for those with symptomatic and/or progressive PSC to an experienced centre with ready access to PSC clinical trials and a dedicated multidisciplinary team are recommended **(LoE 5, strong recommendation, 100% consensus).**

As a general rule, referral should be at the point where a patient's management is beyond local expertise and knowledge of the responsible physician and team. Physicians' experience in caring for people with PSC is highly heterogeneous and the timing of referral to a regional/national expert liver centre will vary accordingly. The complexity and rarity of PSC might suggest that patients benefit from monitoring by centres with experience of large cohorts. Access for people with PSC to national dedicated PSC websites which contain information on open clinical trials should be made possible

The definition of an experienced centre may vary across countries considering their specific healthcare systems and local configuration, but a number of criteria can be proposed: minimal annual volume of people with PSC (>20-30), multidisciplinary team including hepatologists, gastroenterologists, abdominal radiologists, biliary endoscopists and liver surgeons.

Referral to centres experienced in PSC care is particularly important in 2 instances: i) at diagnosis for all patients in order to provide adequate information on the disease, risk stratification and plan for follow-up and ii) when the disease is complicated (see below). As a general rule, all symptomatic patients (those with jaundice especially) and/or evolving disease and/or suspicion of malignancy (including gallbladder polyps) should be under the care of an experienced centre. If those patients are unable to travel to the experienced hepatopancreatobiliary (HPB) centre, they should have their medical file reviewed in a HPB multidisciplinary meeting. In particular, people with PSC should ordinarily not undergo ERCP without expert multidisciplinary assessment to justify endoscopic intervention in order to minimise unnecessary risk.

Lastly, clinical trials for PSC are usually concentrated in experienced centres and patients should be offered the chance to enter into such trials. However, patients with early, asymptomatic, stable disease (low risk of events) can usually be managed by non-expert clinicians with adherence to management guidelines.

A key point is the regular discussion and consultation between the local physician and the team of the experienced centre throughout the follow-up, resulting eventually in combined liver centre and local monitoring within the context of a true partnership between patients, local care and liver-specialised centres. Furthermore, the delivery of high-level care in Europe for people with PSC will be aided by the development of the European Reference Network for Rare Liver Diseases (ERN RARE-LIVER) (https://rare-liver.eu/) which is a Europe-wide network for centres of excellence in the clinical management of rare liver diseases in adults and in children. One of the tools used by RARE-LIVER to improve communication is the clinical patient management system that provides access to expert consultation for European physicians confronted with a patient with rare liver disease, including PSC.

How can wellbeing of people with PSC be optimised?

Recommendation

- Clinicians should explore and assess quality of life issues in people with PSC as part of routine standard of care **(LoE 5, strong recommendation, 96% consensus).**

Health-related quality of life is substantially decreased in people with PSC when compared to the general population.[188,454–456] Symptoms are among the top concerns of people with PSC; according to a recent systematic review, the 5 most common symptoms in PSC are pruritus, fatigue, abdominal pain, diarrhoea and nausea/vomiting.[457] In particular, pruritus is associated with reduced social and physical functioning as well as general and mental health, and depression is significantly worse in patients with severe pruritus.[458] The mental component scores appear to be influenced by lifestyle modifications secondary to liver disease, social interactions and loneliness, and were worse in patients with more severe itching, shorter IBD duration and depression.[456] People with PSC fear the unknown and the shortened life expectancy, requiring emotional and mental support. Unfortunately, there is often a disconnect between patients' perspectives on wellbeing and physicians' documentation of patients' symptoms and wellbeing.

The use of patient-reported outcome measures (PROMS) in routine clinical practice may help to guide the implementation of a more patient-centred approach to care in PSC.[457,459] By using PROMS in the clinical setting, we expect to i) improve communication between patients and clinicians, ii) enhance patient engagement in his/her care and improve adherence to treatment, iii) improve monitoring and reporting of symptoms and iv) aid patient recall of issues to be discussed during the clinic appointment.[459]

Although it is expected that the use of PROMS in clinical settings will be very beneficial, well-validated, disease-specific instruments are scarce in PSC. The PSC-PRO appears to have good psychometric properties but requires further validation.[460] The PBC-40 was validated in people with PSC and could be used specially to assess the impact of pruritus and fatigue in this population.[461] A new instrument to evaluate health-related quality of life in PSC is currently under development, though large-scale international validation is awaited.[462]

Outside of using instruments to assess patients' perceptions, clinicians managing people with PSC should understand that their quality of life is broadly affected both by physical symptoms, especially pruritus, fatigue and IBD-related issues, as well as mental and emotional struggles including depression, anxiety and social isolation.[463] Therefore, carefully addressing these issues in a timely fashion and seeking external support when needed will have a positive impact on patients' wellbeing.

What should be the role of patient support groups?

Recommendation

- Information on existing patient support groups should be provided **(LoE 5, strong recommendation, 100% consensus).**

People with PSC have a decreased quality of life and dealing with uncertainties about course of disease and risk of cancer can generate anxiety, depression and social isolation.[456,464] In this regard, patient support groups should play a key role. Patients with IBD should also be encouraged to contact the related support groups.

The list of the main European support groups for People with PSC is available on the ERN RARE-LIVER site (https://rare-liver.eu). The overall aims of these patient support groups are to provide patients and families with high-quality, accessible information and the support they need. Additionally, most of them collaborate closely together with healthcare providers to shape and fund research. In this regard, their respective websites provide support forums, friendly information, lists of liver units and meetings, new developments and other items. Patient support groups play an important role in providing much needed emotional support for patients, especially when doctors have only minutes with patients in appointments. Patient organisations are also key partners of the ERN RARE-LIVER and are part of its governance structure. One of the major aims of the ERN RARE-LIVER programme is to develop patient information leaflets building on best practices across Europe with content, style and language targeted to the specific needs of patients within the countries covered by the clinical centres.

In line with the actions presently carried out, it can be suggested to stress the following:

- ➢ Advocate for the needs of people affected by PSC in policy development and clinical services, both at the national and European levels.
- ➢ Better define and demonstrate patients' unmet needs such as effective symptom management options including pain, fatigue, anxiety, sleep difficulties and answer questions about nutrition, supplements or vaccinations.
- ➢ Explore the scope for psychological approaches such as cognitive behavioural therapy because of the often-unrecognised emotional needs.
- ➢ Shape, fund and co-produce PSC research.

Future directions

Each form of sclerosing cholangitis poses its own challenges and priorities. The greatest unmet needs reside with PSC, which poses a significant disease burden both for the affected individuals and the healthcare sector.[465] For people with PSC, the liver and bowel manifestations each pose particular problems, ranging from cholestatic symptoms (*e.g.* pruritus) and complications of cholangitis, through secondary bone disease and complications related to progressive cirrhosis, to diarrhoea and issues related to colectomy. Liver transplantation is associated with its own set of challenges, long-term immunosuppression and disease recurrence included, and the psychological burden of living with a high lifetime risk of CCA should not be underestimated.

The aetiology of PSC is unknown, and the search for causal factors in PSC development must continue. Much hope is currently associated with the exploration of the gut microbiome and its widespread interactions with liver and biliary physiology. Whilst genetic studies brought insights on inherited disturbances of relevance to immunology, there is still limited granularity on immune function *in vivo* in livers and bile ducts of people with PSC. Cholangiocyte biology is an under-researched area and needs to be explored in the context of the fibrotic lesions characteristic of PSC. Novel technologies, allowing large-scale and single-cell resolution assessments *in vivo* and in organoid-based model , need to be applied to PSC to overcome these gaps in understanding.

Even without significant advances in our basic understanding of PSC pathophysiology, much can be done to improve the management of patients. Among the greatest needs are probably the lack of accurate markers of PSC severity, the lack of medical therapy which prevents progression to liver transplantation and the lack of sensitive tools for early detection of CCA. Drug development pipelines are significantly hampered by the shortage of consensus endpoints with proven relevance to risk of liver transplantation and death, leading to a low level of interest from the pharmaceutical industry. Given the scarcity of resources available for research in a rare disease like PSC, academic efforts should be maximised in these areas.

Having scrutinised the current state-of-the-art throughout the production of this report, this panel proposes 5 future research priority areas in PSC;

1) Diagnosis of PSC, tools for detection of early manifestations of PSC with minimal fibrosis;
2) Diagnosis of CCA in PSC, tools for early identification of neoplasia in PSC at curative stages,
3) Endpoint clarification; tools for measuring PSC severity with characteristics appropriate for assessing drug efficacy in phase II and phase III clinical trials,
4) Pathophysiology; searching for causal factors in PSC development,
5) Proof-of-concept clinical trials; building from existing knowledge and repurposing opportunities, with an implementation of patient-reported outcome measures.

With such an emphasis, we feel confident that upon the next iteration of these guidelines, recommendations can be provided with increased confidence for the benefit of patients.

Abbreviations

AASLD, American Association for the Study of Liver Diseases; ABCB4, ATP-binding cassette 4; AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANCA, anti-neutrophil cytoplasmic antibody; ASC, autoimmune sclerosing cholangitis; BilIN, biliary intraepithelial neoplasia; CA 19-9, carbohydrate antigen 19-9; c-ANCA, cytoplasmic ANCA; CCA, cholangiocellular carcinoma; CPGs, Clinical Practice Guidelines; CSPH, clinically significant portal hypertension; DEXA, dual energy X-ray absorptiometry; EASL, European Association for the Study of the Liver; EBL, endoscopic band ligation; ECCO, European Crohn's and Colitis Organisation; ELF, enhanced liver fibrosis; ELTR, European Liver Transplant Registry; ERCP, endoscopic retrograde cholangiopancreaticography; ERN RARE-LIVER, European Reference Network for Rare Liver Diseases; ESGE, European Society of Gastrointestinal Endoscopy; FGF19, fibroblast growth factor 19; FISH, fluorescence *in situ* hybridisation; FUT, fucosyltransferase; FXR, farnesoid X receptor; GBC, gallbladder carcinoma, GEVs, gastro-oesophageal varices; HCC, hepatocellular carcinoma; HPB, hepatopancreatobiliary; HVPG, hepatic venous pressure gradient; IAIHG, International Autoimmune Hepatitis Group; IBD, inflammatory bowel disease; IPAA, ileal pouch-anal anastomosis; IPSCSG, International PSC study group; IRC, IgG4-related cholangitis; LoE, Level of evidence; LSM, liver stiffness measurement; MAdCAM, mucosal addressin cell adhesion molecule; MELD, model for end-stage liver disease; MRC, magnetic resonance cholangiography; MRCP, magnetic resonance cholangiopancreaticography; MRE, magnetic resonance elastography; NSBBs, non-selective beta blockers; OCEBM, Oxford Centre for Evidence-Based Medicine; p-ANCA, perinuclear ANCA; PBC, primary biliary cholangitis; pCLE, probe-based confocal laser endomicroscopy; PET, positron emission

tomography; PICO, Patient, Population, or Problem / Intervention, Prognostic Factor, or Exposure /Comparison or Intervention (if appropriate) / Outcome; PPAR, peroxisome proliferator-activated receptor; PR3, proteinase 3-ANCA; PROMS, patient-reported outcomes measures; PSC, primary sclerosing cholangitis; RCT, randomised-controlled trial; rPSC, recurrent primary sclerosing cholangitis; Rt, response to treatment; SC-CIP, sclerosing cholangitis of the critically ill patient; TIPS, transjugular intrahepatic portosystemic shunt; TNF, tumour necrosing factor; UC, ulcerative colitis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal; VAP-1, vascular adhesion protein; VCTE, vibration-controlled transient elastography.

Conflict of interest

Please refer to the accompanying EASL disclosure forms for details.

Acknowledgements

We would like to thank

- the members of the Delphi Panel of this Clinical Practice Guideline for their valuable contribution: Lionel Arrive, Kirsten Boberg, Chris Bowlus, Nora Cazzagon, Dominique Debray, Larissa de Lannoy, Jessica Dyson, Martti Farkkila, Peter Fickert, Gideon Hirschfield, Stefan Hubscher, Helena Isoniemi, Deirdre Kelly, Angela Leburgue, Ansgar Lohse, Hanns-Ulrich Marschall, Piotr Milkiewicz, Albert Pares, Stephen Pereira, Cyriel Ponsioen, Kristina Ringe, Simon Rushbrook, Doug Thorburn, Palak Trivedi, Joanne Verheij, Martine Walmsley, Tobias Weismuller.

- Yves Chretien for his expert technical help.

Members of the European Reference Network for Rare Liver Diseases (ERN RARE-LIVER):

OC, UB, AB, THK, CS, MT

Appendix. Delphi round agreement on the recommendations of the present CPGs

Recommendation	Consensus
In adult patients presenting with elevated serum markers of cholestasis, a diagnosis of large duct PSC should be made in the presence of typical findings of sclerosing cholangitis on high-quality cholangiography and after exclusion of secondary causes. The preferred diagnostic test is magnetic resonance cholangiopancreatography (MRCP) **(LoE 2, strong recommendation).**	93%
A diagnosis of small duct PSC should be considered in patients with elevated serum markers of cholestasis of unknown cause, normal high-quality cholangiography, and compatible histology of PSC, particularly in those with concomitant inflammatory bowel disease (IBD) **(LoE 3, strong recommendation).**	88%
Autoantibodies should not be used to diagnose or risk-stratify people with PSC **(LoE 4, strong recommendation).**	100%
A liver biopsy should be performed in adults suspected of having PSC whose high-quality MRCP is normal, to confirm or exclude small duct PSC **(LoE 4, strong recommendation)**.	88%
A liver biopsy should be considered in people with PSC and co-existing features of AIH including markedly elevated transaminases, high IgG levels, and positive autoantibodies compatible with AIH **(LoE 4, strong recommendation)**.	92%
Determination of serum IgG4 is suggested in every adult patient with large duct sclerosing cholangitis at the time of diagnosis **(LoE 3, weak recommendation).**	91%
Risk assessment at the time of diagnosis and sequentially is recommended, based on phenotypic factors and non-invasive tests including: (1) standard biochemistry (including serum bilirubin, albumin, ALP, ALT, platelets, prothrombin time), (2) MRI of the liver with MRCP, and (3) liver elastography or serum fibrosis tests **(LoE 2, strong recommendation).**	96%
Non-invasive routine liver surveillance is suggested, based on: • Clinical review and standard serum liver tests including bilirubin, albumin, ALP, aspartate aminotransferase, platelets and prothrombin time, every 6 or 12 months depending on risk stratification, are recommended **(LoE 2, strong recommendation).** • Liver elastography and/or serum fibrosis tests at least every 2 to 3 years are recommended **(LoE 3, strong recommendation).** • Liver ultrasound and/or abdominal MRI/MRCP every year are suggested **(LoE 3, weak recommendation).**	96%
Surveillance with ultrasound and/or MRI/MRCP for CCA and gallbladder malignancy is suggested at least yearly in patients with large duct disease regardless of disease stage. Carbohydrate antigen 19-9 (CA 19-9) is not suggested for surveillance purposes due to its insufficient accuracy **(LoE 3, weak recommendation).**	96%
Surveillance for hepatobiliary malignancy is suggested every 6 months in the presence of cirrhosis **(LoE 3, weak recommendation).**	93%
Assessment of bone mineral density is recommended in all people with PSC at the time of diagnosis using dual energy X-ray absorptiometry (DEXA). Follow-up and treatment of osteopenia and osteoporosis should follow current practice guidelines **(LoE 4, strong recommendation).**	92%
UDCA at doses of 15-20 mg/kg/d can be given since it may improve serum liver tests and surrogate markers of prognosis. Available data does not allow for a firmer recommendation **(LoE 1, weak recommendation).**	76%
UDCA at doses of 28-30 mg/kg/d should not be given **(LoE 1, strong recommendation).**	100%
Use of corticosteroids/immunosuppressives/biologics is not suggested for the routine treatment of PSC **(LoE 4, weak recommendation).**	96%
In people with PSC with biochemically (ALT, IgG, autoantibodies) and histologically suggestive features of AIH, it is suggested to consider corticosteroids or other immunosuppressive therapies under close monitoring **(LoE 3, weak recommendation).**	88%

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Recommendation	Consensus
It is not suggested to use corticosteroids or immunosuppressive therapies in people with PSC with mildly elevated serum IgG4 (<2x ULN) **(LoE 5, weak recommendation).**	91%
Long-term use of antibiotics is not recommended for treatment of PSC in the absence of recurrent bacterial cholangitis **(LoE 3, strong recommendation).**	100%
It is recommended to exclude relevant bile duct strictures in large duct sclerosing cholangitis as the cause of progressive pruritus. If present and reachable, relevant strictures should be treated by endoscopic balloon dilatation (or stenting, if balloon dilatation alone is insufficient) after brushing **(LoE 4, strong recommendation).**	95%
Pharmacological treatment of moderate to severe pruritus in sclerosing cholangitis with bezafibrate or rifampicin is recommended **(LoE 4, strong recommendation).**	83%
Acute bacterial cholangitis should be treated with antibiotics and subsequent biliary decompression if an underlying relevant stricture is present **(LoE 3, strong recommendation).**	96%
It is recommended to manage complications of portal hypertension in PSC according to Baveno/EASL guidelines (for advanced chronic liver diseases in general) **(LoE 4, strong recommendation).**	92%
The indication for endoscopic intervention should ideally be discussed in multidisciplinary meetings of hepatologists, biliary endoscopists and abdominal radiologists. The procedure should be performed by experienced endoscopists **(LoE 5, strong recommendation).**	96%
Therapeutic endoscopic intervention is recommended in patients with relevant strictures, defined as high-grade strictures on imaging in the common bile duct or hepatic ducts and signs or symptoms of obstructive cholestasis and/or bacterial cholangitis **(LoE 4, strong recommendation).**	87%
Predniso(lo)ne (0.5 to 0.6 mg/kg/d) is recommended as the first-line therapy for untreated active IRC. Treatment response should be evaluated after (2 to) 4 weeks, prior to predniso(lo)ne tapering, by clinical, biochemical and/or radiological criteria **(LoE 4, strong recommendation).**	100%
Maintenance treatment of IRC is suggested with steroid-sparing immunosuppressants for up to 3 years (*e.g.* azathioprine, 6-mercaptopurine, mycophenolate mofetil) and potentially beyond, starting during predniso(lo)ne tapering, to reduce the risk of IRC relapse. Rituximab can alternatively be considered when relapse has occurred **(LoE 5, weak recommendation).**	100%
Endoscopic removal of biliary casts can be considered and low-to-medium-dose UDCA (10-15 mg/kg/d) can be given in patients with SC-CIP. Available data does not allow a firmer recommendation **(LoE 5, weak recommendation).**	100%
Low-to-medium-dose UDCA (10-15 mg/kg/d) can be given in patients with ABCB4 deficiency. Available data does not allow a firmer recommendation **(LoE 5, weak recommendation).**	89%
CCA must be suspected in i) newly diagnosed PSC with high-grade stricture(s) and in ii) known PSC with worsening of signs or symptoms, progressive stricture(s) or a new mass lesion identified on imaging **(LoE 4, strong recommendation).**	93%
Diagnostic work-up by an experienced multidisciplinary team is recommended in people with PSC and suspected CCA **(LoE 5, strong recommendation).**	100%
Contrast-enhanced, cross-sectional imaging is recommended as the initial diagnostic test when CCA is suspected, potentially followed by ERCP with ductal sampling (brush cytology, endobiliary biopsies) for diagnosis and staging of the suspected CCA **(LoE 1, strong recommendation).**	96%
Serum CA 19-9 can be assessed in all patients where CCA is suspected and fluorescence *in situ* hybridisation (FISH) or equivalent chromosomal assessments can be considered when brush cytology and/or histology are equivocal **(LoE 3, weak recommendation).**	91%
Cholecystectomy is recommended in people with PSC with gallbladder polyps greater or equal to 8 mm in size and smaller polyps growing in size, due to the high risk of malignancy or dysplasia **(LoE 4, strong recommendation).**	89%
Referral to a specialised centre is recommended when CCA or high-grade dysplasia is confirmed. In a multidisciplinary approach, therapeutic options including liver transplantation, liver resection, irradiation, brachy- or systemic therapy or combinations should be considered **(LoE 3, strong recommendation).**	96%
Ileocolonoscopy with biopsies from all colonic segments including the terminal ileum, regardless of the presence of lesions, is recommended at the time of PSC diagnosis **(LoE 3, strong recommendation).**	100%
A diagnostic colonoscopy can be considered every 5 years in people with PSC where no IBD is present or whenever complaints suspicious for IBD occur **(LoE 5, weak recommendation).**	92%
Annual surveillance (or every 1 to 2 years in individualised patients without inflammatory activity) colonoscopy with biopsies is recommended in all adult PSC-IBD patients regardless of the duration of IBD or liver transplant status **(LoE 3, strong recommendation).**	92%
Treatment of PSC-related IBD in line with current practice guidelines with the goal of achieving mucosal healing is recommended **(LoE 3, strong recommendation).**	92%
Colectomy is recommended in patients with high-grade colonic dysplasia or neoplasia or if symptomatic colonic inflammatory activity persists despite optimum medical therapy. Colectomy may also be considered in confirmed low-grade dysplasia at repeated occasions and/or at multiple locations **(LoE 3, strong recommendation).**	79%
Liver transplantation should be considered for people with PSC and decompensated cirrhosis or hepatocellular carcinoma according to standard guidelines **(LoE 3, strong recommendation).**	100%
Liver transplantation should be considered for people with PSC with recurrent bacterial cholangitis and/or severe pruritus or jaundice despite endoscopic and pharmacological therapy **(LoE 3, strong recommendation).**	100%
Liver transplantation can be considered in people with PSC and high-grade biliary dysplasia confirmed by cytology or ductal histology **(LoE 4, weak recommendation).**	92%
Liver transplantation for early-stage CCA in PSC can be performed within the context of clinical trials **(LoE 4, weak recommendation).**	92%

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Recommendation	Consensus
Liver transplantation in PSC should be performed using a duct-to-duct anastomosis unless anatomical disease location or technical surgical factors warrant a Roux-en-Y hepaticojejunostomy **(LoE 4, strong recommendation).**	79%
A diagnosis of recurrent PSC can be made based on progressive biliary strictures on cholangiography and/or histological findings compatible with PSC more than 90 days after liver transplantation upon exclusion of other identifiable causes **(LoE 4, weak recommendation).**	92%
Management of IBD after liver transplantation can follow pre-transplant recommendations of annual (or biennial under conditions of complete remission) endoscopic surveillance, with particular attention to risk of infectious colitis, mycophenolate-related colitis and timely consideration for colectomy in refractory cases **(LoE 5, weak recommendation).**	92%
The diagnostic practice in paediatric patients should be similar to adult practice, based on MRCP as the diagnostic modality of choice **(LoE 4, strong recommendation).**	96%
It is suggested to explore features of AIH in children with PSC and to check for PSC using MRCP in children with a diagnosis of AIH **(LoE 4, weak recommendation).**	89%
Therapeutic endoscopic intervention is recommended in children with high-grade strictures on imaging and signs or symptoms of obstructive cholestasis and/or bacterial cholangitis. Referral to a centre with expertise in paediatric interventional ERCP is highly recommended **(LoE 4, strong recommendation).**	96%
Non-invasive screening for IBD in children with PSC can be performed by faecal calprotectin at presentation and further endoscopic assessment in those with raised faecal calprotectin or symptoms **(LoE 5, weak recommendation).**	81%
Routine surveillance for biliary and colonic malignancy is not suggested in children with PSC **(LoE 5, weak recommendation).**	81%
A coordinated multidisciplinary transition process from paediatric services to adult care is recommended, based on shared information and special attention on psychosocial issues and adherence to treatment **(LoE 3, strong recommendation).**	96%
Preconception counselling in women with PSC willing to become pregnant is suggested. Close monitoring and interdisciplinary specialist care is suggested for pregnant women with PSC and cirrhosis, and especially in those with suspected portal hypertension **(LoE 4, weak recommendation).**	92%
Oral contraceptives can be used in patients with non-advanced PSC as they appear safe. Regular monitoring of serum liver tests is advisable **(LoE 5, weak recommendation).**	91%
Initial expert consultation for people with PSC at diagnosis and referral for those with symptomatic and/or progressive PSC to an experienced centre with ready access to PSC clinical trials and a dedicated multidisciplinary team are recommended **(LoE 5, strong recommendation).**	100%
Clinicians should explore and assess quality of life issues in people with PSC as part of routine standard of care **(LoE 5, strong recommendation).**	96%
Information on existing patient support groups should be provided **(LoE 5, strong recommendation).**	100%

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.05.011.

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Author names in bold designate shared co-first authorship

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Update

Journal of Hepatology
Volume 79, Issue 5, November 2023, Page 1339

DOI: https://doi.org/10.1016/j.jhep.2023.09.005

JOURNAL
OF HEPATOLOGY

Corrigendum to "EASL clinical practice guidelines on sclerosing cholangitis" [J Hepatol (77) 761–806]

European Association for the Study of the Liver*

Journal of Hepatology **2023**. vol. 79 | 1339

It has come to our attention that a copy and paste error has been introduced into the published version of these clinical practice guidelines. Thus, there is an error in Table 2 of the published version of these clinical practice guidelines. The Table has been presented as below:

Level	Criteria	Simple model for high, intermediate and low evidence
1	Systematic reviews (SR) (with homogeneity) of randomised controlled trials (RCT)	Further research is unlikely to change our confidence in the estimate of benefit and risk
2	Randomised controlled trials (RCT) or observational studies with dramatic effects; systematic reviews (SR) of lower quality studies (*i.e.* non-randomised, retrospective)	
3	Systematic reviews (SR) of lower quality studies (*i.e.* non-randomised, retrospective)	Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate
4	Case-series, case-control, or historically controlled studies (systematic review is generally better than an individual study)	
5	Expert opinion (mechanism-based reasoning)	Any estimate of effect is uncertain

However, the Criteria for Level 3 are incorrect. The correct version of the Table is included below:

Level	Criteria	Simple model for high, intermediate and low evidence
1	Systematic reviews (SR) (with homogeneity) of randomised controlled trials (RCT)	Further research is unlikely to change our confidence in the estimate of benefit and risk
2	Randomised controlled trials (RCT) or observational studies with dramatic effects; systematic reviews (SR) of lower quality studies (*i.e.* non-randomised, retrospective)	
3	Non-randomised controlled cohort/follow-up study/control arm of randomised trial (systematic review is generally better than individual study)	Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate
4	Case-series, case-control, or historically controlled studies (systematic review is generally better than an individual study)	
5	Expert opinion (mechanism-based reasoning)	Any estimate of effect is uncertain

We apologise for any inconvenience caused.

DOI of original article: https://doi.org/10.1016/j.jhep.2022.05.011.
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https://doi.org/10.1016/j.jhep.2023.09.005