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Systematic Review: Management options for primary sclerosing cholangitis and variant forms; IgG4-associated cholangitis and overlap with autoimmune hepatitis

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3 **Title Page**
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8 **Systematic Review: Management options for primary sclerosing cholangitis and**
9 **its variant forms; IgG4-associated cholangitis and overlap with autoimmune**
10 **hepatitis**
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50 Primary sclerosing cholangitis, **IgG4-associated cholangitis, overlap with autoimmune**
51 **hepatitis**, ursodeoxycholic acid, cholangiocarcinoma, inflammatory bowel disease,
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55 liver transplantation
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ABSTRACT

Background: Primary sclerosing cholangitis (PSC) remains a challenging disease to manage. The main goals are prevention of disease progression and reduction of the increased cancer risk

Aims: To review the management strategies for PSC and its variant forms based on published studies.

Methods: Publications were identified using Pubmed, Medline and Ovid search engines.

Results: Distinguishing PSC from variants such as IgG4-associated cholangitis and overlap with autoimmune hepatitis is essential to guide treatment decisions. There is no proven efficacious medical treatment for PSC. Ursodeoxycholic acid has been disappointing in low and moderate doses, and potentially dangerous in higher doses, although its role and optimal dose in chemoprevention requires investigation. The novel bile acid 24-norursodeoxycholic acid has shown promise in mouse models; human trials are in progress.

Dominant strictures are optimally managed by dilatation and stenting to relieve obstructive complications, although exclusion of biliary malignancy is essential. Liver transplantation is the only proven therapy for those with advanced disease.

Cholangiocarcinoma remains the most unpredictable and feared complication. In highly selected groups, neo-adjuvant chemoradiation with liver transplantation seems

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3 promising but requires further validation. Screening for inflammatory bowel disease
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5 and surveillance for colorectal carcinoma should not be overlooked.
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10 **Conclusion:** The effective management ofPSC and its variantsis hindered by
11
12 uncertainties regarding pathogenesis of disease and factors responsible for its
13
14 progression. Genome studies may help to identify further targets for drug therapy and
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16 factors leading to malignant transformation.
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For Peer Review

INTRODUCTION

Primary sclerosing cholangitis (PSC) is a chronic progressive disorder characterised by inflammation, fibrosis and stricturing of intrahepatic and extrahepatic bile ducts, ultimately leading to liver cirrhosis. The aetiology is poorly understood; an immune-mediated basis is suggested by lymphocytic portal tract infiltration and association with autoantibodies, human leukocyte antigen (HLA) haplotypes (HLA B8 DR3 and DQ2), other autoimmune diseases and inflammatory bowel disease¹. It is not a classical autoimmune disease however, with a male predominance, ratio of 2 to 1, and a poor response to immunosuppressive agents. There is strong evidence for genetic susceptibility from genome wide association analysis². The current management of PSC is limited by uncertainties regarding its pathogenesis and factors responsible for its progression. In particular, the use of ursodeoxycholic acid in PSC has received much attention in light of recent studies, which will be discussed in this review, and the recognition of variant forms requiring careful diagnosis and individualised management.

METHODS

Publications were identified using pubmed, medline and ovid search engines to include controlled and randomized clinical trials, meta-analysis, practice guidelines, reviews and case reports in English language from January 1980 to January 2011 inclusive. Search words were primary sclerosing cholangitis (PSC), small duct PSC, IgG4-associated sclerosing cholangitis, autoimmune hepatitis overlap, ursodeoxycholic acid, cirrhosis and liver transplantation, inflammatory bowel disease, cholangiocarcinoma, and colorectal carcinoma. 2710 publications were identified, of which 974 met the search inclusion criteria. Abstracts with no full article available and any duplicate studies were further excluded from analysis.

DIAGNOSIS

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3 The clinical presentation of PSC is variable; about 50% are symptomatic at first
4 presentation with abdominal pain, pruritis, fatigue, weight loss and fevers³. Portal
5 hypertension and liver cirrhosis may manifest later in the disease. Asymptomatic
6 patients are often identified after investigation of persistent cholestatic liver function
7 or after a cholangiogram shows characteristic bile duct stricturing and segmental
8 dilatation, once secondary sclerosing cholangitis and other causes of cholestasis are
9 excluded⁴. Laboratory investigation often reveals cholestatic liver biochemistry; an
10 elevated alkaline phosphatase is the most common finding. Liver tests may be normal
11 in 8.5% of cases and may fluctuate during the disease course³. Elevations in
12 immunoglobulin G have been described in up to 60% of patients⁵. A wide range of
13 non-specific autoantibodies can be detected in the serum; atypical perinuclear
14 neutrophil cytoplasmic antibody has the strongest association with PSC, present in 33-
15 88% of cases⁶⁻⁷.

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36 The diagnosis of PSC is usually established on the basis of a cholangiogram,
37 demonstrating abnormal beading, irregularity and narrowing of the bile ducts.
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Magnetic resonance cholangiogram (MRC) is considered the gold standard as it is
non-invasive, uses non-ionizing radiation and can delineate distal bile duct anatomy in
the presence of proximal obstruction⁸. In a meta-analysis of 456 subjects, MRC had a
high sensitivity and specificity for detection of PSC, 0.86 and 0.94, respectively with
positive and negative predictive ratios of 15.3 and 0.15, respectively⁹. If MRC images
are suboptimal, endoscopic retrograde cholangiopancreatography (ERCP) can be
used, although it is usually reserved for sampling in the presence of a dominant
stricture and for intervention to relieve biliary obstruction. Liver biopsy may show
histological features diagnostic of PSC but only in one third of patients, and findings

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3 are often non-specific in early disease due to the patchy, focal nature of the disease¹⁰.
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6 In the presence of an abnormal cholangiogram, liver biopsy is considered to yield
7
8 little extra information, except in diagnosing suspected variants of PSC¹¹..
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11 12 13 **VARIANTS OF PSC**

14 15 **Small-duct PSC**

16
17 This refers to a subgroup of patients who have clinical, biochemical and histological
18
19 features compatible with PSC, but a normal cholangiogram. In the largest natural
20
21 history study of 83 patients with small-duct PSC, only 22.9% of patients progressed
22
23 to large-duct PSC over a median of 7.4 years (range 5.1-14 years)¹². The course of
24
25 small-duct PSC was less aggressive, with significantly longer transplantation-free
26
27 survival, 13 years versus 10 years (95% CI 1.82-5.06; P < .0001), confirming earlier
28
29 smaller studies¹³⁻¹⁵. Liver-related mortality, liver transplantation and post
30
31 transplantation recurrence have been reported in small-duct PSC; however
32
33 cholangiocarcinoma has only been described in those patients that progress to large-
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35 duct PSC¹².
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44 Diagnostic criteria for small-duct PSC remains to be defined, although a high-quality
45
46 cholangiogram is mandatory to exclude PSC with isolated intra-hepatic distribution,
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48 and mutation analysis may be necessary to exclude other cholangiopathies such as
49
50 ABCB4 deficiency causing compatible histological features¹⁶. Inflammatory bowel
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52 disease has been described in 50–88% of patients with small-duct PSC¹⁴⁻¹⁵. In patients
53
54 with IBD and cholestatic liver enzymes, a normal high quality MRC scan should
55
56 prompt liver biopsy and histological analysis for evidence of small-duct PSC.
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3 Management of patients with small-duct PSC is not well defined. In a longitudinal
4 cohort study of 42 patients with small-duct PSC followed up for up to 24.9 years, the
5 presence of IBD resulted in earlier diagnosis, but had no impact on long-term
6 prognosis. UDCA therapy in both groups improved liver biochemistry over an
7 average of 40 months ($p < 0.001$), but had no effect on delaying disease progression
8 (RR 0.95, CI 0.38-2.36)¹⁷. Liver transplantation is indicated for advanced liver
9 disease, with a risk of recurrence in the transplanted liver. There are currently no
10 agreed guidelines for surveillance of patients with small-duct PSC for the
11 development of large-duct PSC.
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27 **PSC with overlap features of autoimmune hepatitis**

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29 This is an ill-defined immune-mediated disorder with histological features of
30 autoimmune hepatitis (AIH) and cholangiographic findings typical of PSC. It has
31 been described predominantly in children, adolescents and young adults¹⁸⁻¹⁹. The
32 diagnostic criteria are not well defined. A retrospective diagnosis of 'PSC-AIH
33 overlap syndrome' was established in 8% of 113 PSC patients from The Netherlands
34 and 1.4% of 211 PSC patients from the United States, using the modified AIH score²⁰⁻
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21. Prospective analysis revealed an overlap syndrome in 17% of a cohort of 41 PSC
patients from Italy, defined by a revised AIH score of over 15, anti-nuclear antibody
or anti-smooth muscle antibody titre of at least 1:40, and characteristic histological
abnormalities²². Prevalence of AIH in adults with sclerosing cholangitis has been
reported to vary from 1.7%, when identified prospectively by MRC and liver biopsy
and not including intrahepatic duct abnormalities associated with fibrosis score on
biopsy, to 10% when identified prospectively on MRC and associated with a younger

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3 age, high ALP at baseline and bilirubin at the time of scan and lobular activity on
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5 initial biopsy²³⁻²⁴.
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10 The development of PSC and AIH may be sequential in occurrence, thus in patients
11 with PSC an elevation in serum transaminases should prompt a search for AIH, and
12 patients with AIH, cholestasis or resistance to immunosuppressive therapy should
13 raise suspicion of PSC²⁵. UDCA and immunosuppressive therapy are often prescribed
14 in combination in patients with PSC–AIH overlap syndrome, although there are no
15 controlled studies evaluating this approach. Retrospective studies have suggested a
16 benefit of corticosteroids in adult patients with PSC and AIH overlap features²⁶. In a
17 prospective Italian study, overlap patients treated with UDCA (15–20 mg/kg/day),
18 prednisolone (0.5 mg/kg/day, tapered to 10–15 mg/d) and azathioprine (50–75 mg),
19 showed a good biochemical response²². PSC–AIH overlap syndrome has a better
20 prognosis than PSC, as predicted by the Mayo score, but poorer outcome than
21 AIH^{19,22}. Liver transplantation is indicated for advanced disease.
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41 **IgG4-associated cholangitis**

42 Immunoglobulin G subclass 4-associated cholangitis (IAC) is a biliary disease of
43 unknown immunopathogenesis, with cholangiographic features indistinguishable
44 from PSC, but distinct histological findings and a dramatic response to
45 corticosteroids²⁷. In the largest cohort of 53 IAC patients from the Mayo clinic,
46 median age at diagnosis was 60 years in a predominantly male patient group (85%),
47 frequently presenting with obstructive jaundice²⁸. IBD is less frequently associated
48 with IAC than PSC, described predominantly in case reports and small series,
49 although IgG4 positive plasma cells have been detected in colonic specimens in
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3 patients with autoimmune pancreatitis and IgG4-related colitis may mimic IBD²⁹⁻³⁰.
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6 Diagnostic criteria have been proposed for IAC based on characteristic histological
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8 and cholangiographic findings, elevations in serum IgG4, systemic organ involvement
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10 and response to corticosteroids²⁸. These are still to be cross-validated in an
11
12 independent cohort of patients.
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18 It is important to differentiate IAC from PSC; elevated levels of serum IgG4 were
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20 found in 9% of 127 patients previously diagnosed with PSC in one series from the
21
22 Mayo Clinic. Patients with elevated IgG4 had more severe biochemical parameters,
23
24 higher Mayo risk score and a shorter time to transplantation suggesting a more severe
25
26 disease course³¹. Patients with elevated IgG4 had more aggressive course pre and post
27
28 transplantation³². The relevance of these observations remains to be determined,
29
30 although in the meantime cohorts of PSC patients should be scrutinised to detect
31
32 patients with IAC, given the different management strategies and possible outcome.
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35 Dominant strictures of IAC may also mimic hilar cholangiocarcinoma (CCA), which
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37 must be rigorously excluded prior to initiation of treatment³³. The importance of
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39 intrahepatic cholestasis and elevated serum IgG4, in the context of a normal
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41 cholangiogram, is still to be elucidated.
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49 Corticosteroids result in resolution of jaundice, improved liver biochemistry, a
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51 reduction of serum IgG4 levels and reversal of strictures on cholangiogram in patients
52
53 with IAC²⁸. Relapse has been documented in 40% of patients after completing an 11
54
55 week course of steroids in a retrospective study from the Mayo group; post-hoc
56
57 analysis revealing strictures of the proximal extrahepatic and intrahepatic bile ducts
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59 were associated with a higher risk of relapse compared with those with strictures of
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3 the distal ducts, the extent of disease perhaps affecting long-term
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5 response²⁸. Similarly, corticosteroids can be used in the management of IgG4-
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7 associated autoimmune hepatitis variant, which responds dramatically to steroids in
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9 the initial and maintenance phase of treatment with less relapse reported in a small
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11 retrospective study, although further studies are needed to confirm this³⁴. Azathioprine
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13 at doses up to 2 mg/kg/day should be considered in those with proximal and
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15 intrahepatic stenoses and those that relapse during and/or after corticosteroid therapy.
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17 Rituximab, a monoclonal antibody directed against CD20 antigen on B lymphocytes,
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19 has been used successfully in a patient unresponsive to other immunosuppressive
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21 agents³⁵. Natural history and prognosis has not been adequately defined.
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29 **MANAGEMENT OF PSC**

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31 The main goals of therapy are retardation and reversal of the disease process and
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33 management of progressive disease and its complications. Prognostic models have
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35 limited value in the individual patient because of disease variability and the presence
36
37 of confounding factors, such as biliary sludge and stones, main duct strictures, and
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39 CCA. The Mayo risk score provides the most valid survival information in early PSC
40
41 in patient cohorts³⁶⁻³⁷. Although the course is variable, PSC is generally progressive
42
43 and leads to biliary cirrhosis. The 10-year survival was approximately 65% in a
44
45 population study from the United States³⁸. A median transplantation-free survival of
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47 18 years was reported in a Dutch population³⁹. Liver failure and CCA are the two
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49 major complications that affect survival, malignancy becoming the most important
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51 cause of death over the last decade⁴⁰.
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SPECIFIC MEDICAL THERAPY

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3 The search for an effective medical treatment for PSC has been hindered by
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5 uncertainties regarding the pathogenesis of disease and factors responsible for its
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7 progression. There is no medical therapy to date that conclusively alters the natural
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9 history of disease. Ursodeoxycholic acid (UDCA), a hydrophilic dihydroxy bile acid,
10
11 is the most extensively studied medical therapy for PSC. It is believed to exert a
12
13 number of beneficial effects in chronic cholestatic conditions, including direct and
14
15 indirect cytoprotection, stimulation of hepatobiliary secretion, immunomodulation
16
17 and protection of hepatocytes from bile-induced apoptosis⁴¹. The relative importance
18
19 of each in alleviating cholestasis remains unclear. UDCA may also have a
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21 chemoprotective effect; inhibiting proliferation of tumour cell lines in vitro⁴².
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29 **UDCA in cholestasis and disease progression**

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31 A number of trials have attempted to address the clinical efficacy of UDCA in
32
33 the context of PSC, summarised in **Table 1**. Early pilot studies of UDCA, in doses
34
35 ranging from 10 to 15 mg/kg/day, demonstrated biochemical and in some, histological
36
37 improvement⁴³⁻⁴⁶. A larger double-blind placebo-controlled study of UDCA 13-
38
39 15mg/kg/day in 105 patients with PSC showed an improvement in liver biochemistry,
40
41 but no improvement in symptoms, histological progression, development of portal
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43 hypertension or liver transplantation after 2 to 5 years of therapy⁴⁷. Further analysis,
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45 suggested a trend towards increased transplant-free survival in the treated group⁴⁸.
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53 Higher doses of UDCA, 20 mg/kg/day, were evaluated in a double-blind placebo-
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55 controlled trial of 26 patients, showing improvements in liver biochemistry,
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57 cholangiographic appearance and histological progression, but no effect on survival
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59 after 2 years of therapy⁴⁹. A larger multi-centre randomised study of UDCA at 17-23
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3 mg/kg/day in 219 patients demonstrated a non-significant trend towards increased
4
5 survival in the UDCA treated group compared to placebo over 5 years, although it
6
7 was insufficiently powered to achieve statistical significance and biochemical
8
9 response was poor suggesting an issue with drug compliance⁵⁰.
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15 A randomised dose-ranging trial in 30 PSC patients was conducted to look at
16
17 outcomes of higher doses of UDCA over 2 years; the low dose (10 mg/kg/day) and
18
19 the standard dose (20 mg/kg/day) showed a trend towards improved survival, and the
20
21 high dose (30 mg/kg/d) significantly improved projected survival compared with the
22
23 Mayo risk score⁵¹. However, a multi-centre placebo-controlled randomised study
24
25 using high dose UDCA, 28-30 mg/kg/day in 150 patients over 5 years was
26
27 discontinued early as the patients randomised to UDCA, despite having improvement
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29 in liver biochemistry, were significantly more likely to reach the primary outcome of
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31 death, liver transplantation or development of varices compared with the placebo
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33 group, especially in more advanced disease⁵². The reason for this remains unclear; the
34
35 authors postulating that high-dose UDCA may cause direct hepatocyte necrosis in
36
37 patients with advanced PSC with downstream biliary obstruction due to strictures, or
38
39 that high-dose UDCA may lead to increased levels of hepatotoxic lithocholic acid,
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41 produced in the right colon⁵³⁻⁵⁴. A subsequent analysis of the serum bile acid profile
42
43 of 56 patients in the high dose UDCA group has so far demonstrated significant
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45 expansion of the total serum bile acid pool, including lithocholic acid compared to the
46
47 placebo group (P = 0.001)⁵⁵. Further analysis of this data is awaited.
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3 To date, many studies have enrolled patients with advanced stage disease; the role of
4 UDCA much earlier in the disease process may have a different impact but has not
5
6 been fully assessed.
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10 11 12 **UDCA in chemoprevention**

13 *Colorectal carcinoma in patients with PSC and IBD*

14
15 Retrospective studies support a role for UDCA in reducing the risk of colorectal
16 carcinoma (CRC) in patients with PSC and UC. A cross-sectional study of 59 PSC
17 patients with UC undergoing colonoscopic surveillance found a significantly reduced
18 prevalence of colonic dysplasia in patients taking UDCA (OR 0.18, 95% CI 0.05-
19 0.61), although there was an exceptionally high rate of dysplasia in the control
20 group⁵⁶. In a follow-up of 52 patients with PSC and UC, who participated in a
21 randomised placebo-controlled trial of UDCA, over 355 patient-years, the UDCA-
22 treated patients had a significant reduction in the relative risk of developing CRC or
23 dysplasia (RR 0.26, 95% CI 0.06–0.92, $p = 0.003$)⁵⁷. A historical cohort study,
24 comparing 28 patients with PSC and UC treated with UDCA with 92 patients not
25 treated with UDCA, reported a trend towards a lower risk of colonic dysplasia and
26 neoplasia and a significantly lower mortality in those treated with UDCA⁵⁸. However,
27 there have been no prospective controlled trials investigating the role of UDCA in
28 chemoprevention, and the most effective dose is still to be elucidated.
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51 *Cholangiocarcinoma in patients with PSC*

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53 Observational studies provide limited evidence for a beneficial effect of UDCA on the
54 risk of developing CCA. In a single controlled study of 150 patients with PSC treated
55 with UDCA over a median of 6.4 years, a lower annual incidence rate of CCA
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3 (3.3%) was reported in PSC patients treated with UDCA, this rate decreasing with
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6 length of treatment (0.59 in year 0 to 2.5, 0.58 in years 2.5 to 8.5, none in years 8.5 to
7
8 18)⁵⁹. In a study of 255 PSC patients listed for liver transplantation over a period of
9
10 11 years, the absence of UDCA was an independent risk factor for the development of
11
12 hepatobiliary malignancy⁶⁰. However, two randomized placebo-controlled UDCA
13
14 trials with 219 and 150 PSC patients, did not observe a difference in CCA
15
16 development in the UDCA and placebo-treated groups^{50,52}. Thus, there is insufficient
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18 evidence to support the use of UDCA for chemoprevention of CCA at this time.
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24 **24-norursodeoxycholic acid**

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26 An alternative novel bile acid, 24-norursodeoxycholic acid, an inhibitor in the
27
28 formation of toxic bile, has been shown to have antifibrotic, anti-inflammatory and
29
30 antiproliferative effects in a knockout multi-drug resistance protein 2-null (Mdr2^{-/-})
31
32 mouse model of cholangitis and biliary fibrosis, reversing sclerosing cholangitis
33
34 within 4 weeks of treatment⁶¹⁻⁶². Human studies are currently in progress.
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41 **Other therapies (summarised in Tables 2-4)**

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43 Studies of glucocorticoids and immunosuppressive agents have been disappointing,
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45 none demonstrating convincing evidence of benefit and a few associated with
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47 significant side effects⁶³. Antifibrotic agents, anti-TNF monoclonal antibodies, and
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49 other agents with TNF-alpha antagonising effects have been evaluated with no overall
50
51 benefit. Pilot studies of combination therapy have been encouraging but inconclusive,
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53 conducted in small number of patients treated for short periods of time, with end
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55 points focussing on improvements in biochemistry and Mayo risk score. There is no
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57 data evaluating survival or time to liver transplantation. The presence of PSC variants
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3 in some of the patient groups may overestimate benefits. Trials evaluating antibiotics
4 such as metronidazole and minocycline have been promising but inconclusive.
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10 **BILIARY COMPLICATIONS**

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12 PSC can be complicated by the formation of dominant strictures, recurrent bacterial
13 cholangitis, development of gallstones and gallbladder polyps, and the increased risk
14 of carcinoma of the biliary system and gallbladder⁶⁴.
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20 **Dominant strictures**

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22 A dominant stricture has been defined as 'a stenosis with a diameter of less than or
23 equal to 1.5mm in the common bile duct or of less than or equal to 1mm in the right
24 and/or left hepatic duct'⁶⁴. The majority of patients with advanced PSC develop
25 dominant stenoses of major bile ducts; in one of the largest studies of 125 patients
26 with PSC, 45% had a dominant stricture of the common bile duct and/or right or left
27 hepatic ducts⁶⁵. Furthermore, patients who do not have a stricture at diagnosis may
28 develop one over time; a study of 106 PSC patients reported 40% developed a
29 dominant stricture over five year follow-up⁶⁶. Dominant strictures are associated with
30 a reduced transplant-free survival; in one prospective study transplantation-free
31 survival at 18 years was 25% compared with 73% in those with or without dominant
32 stenoses, respectively (p=0.011)⁶⁷.
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52 Given their relative frequency, stenotic lesions are more likely to be benign than
53 malignant. However, the presence of a dominant stricture should always raise the
54 suspicion of CCA, which may develop in 10-15% of patients with PSC⁶⁸. Endoscopic
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3 brushings and/or biopsy and further imaging of the biliary system are usually required
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6 to differentiate the two.
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10 Interventions to decompress the biliary tree aim to reduce obstructive complications
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12 and prolong transplant-free survival, via an endoscopic, radiological or surgical
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14 approach. UDCA treatment has not been shown to prevent the development of
15
16 dominant stenoses in uncontrolled trials, although it has not been evaluated as an
17
18 independent variable⁶⁶.
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22 23 24 *Sphincterotomy, dilatation and stenting* 25

26
27 Endoscopic dilatation of dominant biliary strictures and drainage by sphincterotomy
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29 and stenting, may lead to symptomatic, biochemical and radiological improvement in
30
31 selected cases. The sphincter of Oddi may itself become sclerosed, contributing to
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33 biliary obstruction. Sphincterotomy alone has been shown to improve biochemical
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35 parameters in small uncontrolled studies; however its predominant role in PSC is to
36
37 facilitate dilatation, stent placement or stone extraction⁶⁹⁻⁷⁰. Balloon dilatation has
38
39 been shown to be effective alone in the treatment of dominant strictures⁷¹⁻⁷². Repeated
40
41 balloon dilatation and stenting has been assessed in retrospective studies of PSC
42
43 patients taking UDCA, suggesting a trend towards a benefit when comparing
44
45 jaundice, cholangitis, biochemical cholestasis, transplantation and actuarial survival
46
47 rates compared with predicted Mayo risk score⁷³⁻⁷⁴. The optimum method and
48
49 frequency of dilatation remains to be defined.
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57 Retrospective studies evaluating short-term and long-term stenting for dominant
58
59 strictures have demonstrated improvements in symptoms, cholestasis and rates of
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3 cholangitis⁷⁵⁻⁷⁶. Prospective uncontrolled trials have suggested transplant-free survival
4
5 advantage of combined UDCA and endoscopic balloon dilatation and/or biliary stent
6
7 placement, although the relative contribution of each is difficult to ascertain⁶⁶. Long
8
9 term outcome has yet to be evaluated in randomised controlled trials. Complications
10
11 from endoscopic therapy have been reported in 7 to 20% of PSC patients^{73,77}. Studies
12
13 comparing the role of balloon dilatation with stenting have demonstrated similar
14
15 efficacy but lower complications rates with balloon dilatation alone, especially
16
17 cholangitis (18% vs. 50%, respectively)⁷¹. Stenting is therefore usually reserved for
18
19 strictures that are refractory to dilatation.
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27 The percutaneous approach is reserved for those patients with proximal dominant
28
29 strictures and complex biliary anatomy, often after repeated and/or failed attempts at
30
31 endoscopic intervention. There are no randomised studies comparing percutaneous
32
33 transhepatic cholangiography (PTC) with ERCP in stricture management in modern
34
35 day practice. It is generally accepted, however, that the percutaneous approach is
36
37 associated with higher morbidity⁷⁸⁻⁷⁹.
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43 *Biliary surgery for strictures*

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45 Surgery is considered in selected patients without cirrhosis, who have marked
46
47 cholestasis or recurrent cholangitis due to focal extra-hepatic or hilar strictures, which
48
49 are not amenable to endoscopic or percutaneous dilatation⁸⁰. In those requiring liver
50
51 transplant, prior biliary surgery may lead to a longer operation time, greater intra-
52
53 operative blood loss and high incidence of biliary complications post transplantation,
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55 when compared to those with no history of biliary surgery⁸¹⁻⁸³. In those with cirrhosis,
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3 biliary surgery should be avoided as it is associated with high morbidity and
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5 mortality.
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10 Resection of the extra-hepatic biliary stricture and Roux Y hepaticojejunostomy, with
11
12 or without operative stent insertion, may be considered for selected non-cirrhotic PSC
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14 patients⁸⁴. It is associated with a readmission-free rate from cholangitis of 57%, 83%
15
16 and 60% at 3, 5 and 10 years, respectively⁸⁵. However, there is a risk of post-
17
18 operative infection and scarring in the porta hepatis, which may complicate future
19
20 transplantation⁸⁶. Biliary bypass by cholangio-enterostomy is infrequently the
21
22 operation of choice, as most dominant strictures are hilar and intra-hepatic duct
23
24 involvement limits the access and quality of ducts for bypass⁸⁷. There is no conclusive
25
26 evidence that surgical intervention alters the natural history or progression of liver
27
28 disease in patients with PSC.
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34 35 36 **Bacterial cholangitis**

37
38 Cholangitis can occur in PSC patients with dominant or tight biliary strictures, co-
39
40 existing bile duct stones, and in those undergoing endoscopic or percutaneous
41
42 interventions or surgical exploration. It may be the first presentation of PSC in 6.1%
43
44 of patients⁸⁸. Recurrent and severe cholangitis may have a role in disease progression.
45
46 Short courses of antibiotics are often insufficient to eradicate bacteria in the context of
47
48 an obstructed system; therapeutic drainage in addition is considered more effective⁸⁹.
49
50 The presence of bacteria in the bile was not associated with reduced survival in one
51
52 prospective non-randomised study, if stenoses were opened endoscopically and
53
54 infection was adequately treated with antibiotics⁶⁷. Patients with recurrent bacterial
55
56 cholangitis may have small benefits from prophylactic long term antibiotics, which
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3 may be rotated to reduce bacterial resistance. Routine bile collection for
4
5 microbiological analysis during cholangiography may help to define sensitivity of
6
7 bacteria and guide antibiotic management⁹⁰. In PSC patients with refractory severe
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9 bacterial cholangitis, but otherwise preserved liver function, transplantation may be
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11 indicated⁹¹.
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17 **Malignancy**

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19 PSC is associated with an increased risk of hepatobiliary malignancy, particularly
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21 CCA. In a large Swedish cohort of 604 PSC patients, 44% of deaths were due to
22
23 malignancy; 13.3% due to hepatobiliary carcinoma⁹². Guidelines for screening and
24
25 surveillance of malignancy in PSC are poorly defined and depend on the individual
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27 tumour.
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34 ***Cholangiocarcinoma***

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36 This may present as an intra-hepatic focal carcinoma or more commonly as a ductal
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38 infiltrating desmoplastic lesion. CCA has a cumulative lifetime incidence of 10-30%
39
40 in patients with PSC⁹³. It is found synchronously in 20-30% and within one year of
41
42 diagnosis in 50%, the yearly developmental rate being 0.5 to 1.5% thereafter^{92,94-96}.
43
44 There is no clear association between the duration of PSC and the development of
45
46 CCA; however the presence of cirrhosis may be associated with an increased risk⁹⁷⁻⁹⁸.
47
48 Deterioration in performance status, biochemical parameters or evidence of a
49
50 dominant stricture on cholangiogram raises suspicion of CCA, although these may
51
52 also be manifestations of progressive liver disease. Anatomic location of CCA
53
54 influences the ease of diagnosis; hilar tumours causing earlier biliary obstruction than
55
56 small or peripheral intrahepatic lesions⁹⁹. Differentiating benign and malignant
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3 strictures is challenging, currently based on a combination of imaging modalities such
4
5 as MR imaging and multi-slice spiral computer tomography (CT), in addition to
6
7 endoscopic evaluation with brush cytology and/or biopsies of stenotic lesions prior to
8
9 any intervention¹⁰⁰⁻¹⁰¹. The specificity of positive brush cytology is close to 100% but
10
11 sensitivity is low in most centres (17 to 73%); a negative sample not excluding
12
13 malignancy¹⁰²⁻¹⁰³. Digital image analysis and fluorescence in situ hybridisation may
14
15 increase the diagnostic yield of cytology further¹⁰⁴⁻¹⁰⁵. Regular brushing of dominant
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17 strictures with cytological analysis to detect early neoplastic transformation is adopted
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There is no reliable screening test for CCA in asymptomatic patients with PSC. In those who are symptomatic, serum Ca19-9 levels of >130 U/mL have been reported to have a sensitivity of 79% and a specificity of 98% for presence of CCA, although this often identifies advanced unresectable CCA which limits its use¹⁰⁶. Some clinicians screen asymptomatic patients with annual serum Ca19-9 levels and cross-sectional imaging of the hepatobiliary system, although this requires validation^{100,107}. In a study of 230 PSC patients, ultrasound, CT and MRI yielded a positive predictive value of 48%, 38% and 40%, respectively in identification of CCA¹⁰⁰. Endoscopic ultrasound with fine needle aspiration of hilar structures and lymph nodes may aid in diagnosis and staging¹⁰⁸⁻¹⁰⁹. The role of FDG-PET is controversial, as inflammation can yield false positives in patients with PSC.

The overall prognosis of patients with PSC complicated by CCA is poor, median survival of 5 to 11 months¹¹⁰. Curative extensive surgical resection of early CCA gives 3-year survival rates of 20 to 40%, but local recurrence is common due to micro

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3 metastases in lymph nodes or surgical margins¹¹¹. Early studies of liver transplant for
4
5
6 PSC and CCA did not show a survival benefit; small or incidental CCA found at liver
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8
9 transplant had a 5-year survival of 35%¹¹². Recently, single centre experience in a
10
11 highly select group of patients with CCA given neo-adjuvant chemoradiation in
12
13 combination with liver transplant has shown impressive results, with 5-year survival
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15 rates of 76 to 82%, similar to that of other indications for transplant¹¹³. This will
16
17 require validation in other centres¹¹⁴⁻¹¹⁵. The use of brachytherapy and continuous 5-
18
19 fluoracil infusion before liver transplant in Nebraska resulted in 45% long-term
20
21 cancer-free survival after follow up of 7.5 years¹¹⁶. External beam radiation therapy
22
23 is a palliative option in patients with CCA, although it has not been evaluated in the
24
25 context of PSC¹¹⁷.

26 27 28 29 30 31 32 ***Gallbladder polyps and carcinoma***

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34 Gallbladder abnormalities have been described in 41% of PSC patients in one large
35
36 retrospective series¹¹⁸. Gallbladder dysplasia, adenoma and carcinoma have all been
37
38 described in PSC patients, with a cumulative lifetime incidence of 2%⁹². Gallbladder
39
40 mass lesions in PSC frequently (>50%) represent adenocarcinomas, independent of
41
42 their size¹¹⁹⁻¹²⁰. A recent study reported a statistically significant association between
43
44 hilar and/or intra-hepatic biliary neoplasia and gallbladder neoplasia, suggesting a
45
46 'field defect' in the biliary tree in PSC¹²¹. Given the high risk of malignancy of
47
48 gallbladder polyps in PSC, cholecystectomy is advocated for gallbladder lesions of
49
50 any size in both European and American practice guidelines^{64,122-123}. Annual
51
52 ultrasound surveillance of the gallbladder has been recommended to detect early
53
54 abnormalities¹²³.

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Pancreatic carcinoma

The risk of pancreatic carcinoma in patients with PSC has been described in a Swedish cohort as 14-fold increased, when compared to a matched-control population⁹². This risk is lower in comparison to other hepatobiliary malignancy in PSC. There is currently no recommended screening for pancreatic disease.

Hepatocellular carcinoma

Cirrhotic patients with PSC are at risk of developing hepatocellular carcinoma (HCC). The cumulative lifetime incidence of HCC in PSC patients is 2%¹²⁴. Screening for HCC in cirrhotic patients, by 6 monthly abdominal imaging and/or alpha-feta protein levels, should follow guidelines as for other cirrhotic chronic liver diseases¹²⁵.

EXTRAHEPATIC COMPLICATIONS

Extra-hepatic complications of PSC include symptomatic pruritis and fatigue, malabsorption and fat-soluble vitamin deficiency, and the development of metabolic bone disease. *The management of these complications has been described in detail in the recent European guidelines and is summarised in Table 5¹²³.*

INFLAMMATORY BOWEL DISEASE

IBD in patients with PSC

PSC is strongly associated with IBD, with a reported prevalence in Northern Europe and Northern America of 60–80%¹⁴¹⁻¹⁴². IBD often precedes the development of PSC, although it may be diagnosed at any time during its course, even de novo after liver transplantation¹⁴³⁻¹⁴⁴. Ulcerative colitis (UC) accounts for the majority (80%) of cases, while 10% have Crohn's disease (CD) and 10% have indeterminate colitis¹⁴⁵.

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3 Compared to UC patients withoutPSC, the colitis in PSC is more often a
4
5 pancolitis(87% vs. 54%), with backwash ileitis (51% vs. 7%),and rectal sparing (52%
6
7 vs. 6%) and follows a quiescent or prolonged subclinical course¹⁴⁵⁻¹⁴⁷. Patients
8
9 withPSC and CD characteristically havecolonic involvement, although this too is
10
11 extensive¹⁴⁵.
12
13

14
15 Given the strong association with IBD, colonoscopy with biopsies is recommended as
16
17 part of the routine work-up in a patient diagnosed with PSC, even if the patient has no
18
19 symptoms of inflammatory bowel disease.
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23
24 PSC patients who have an ileal pouch anal anastomosis(IPAA) after colectomy for
25
26 UC have an increased risk of pouchitiscompared to those with UC alone, which
27
28 should be considered when planning colectomy for aggressive disease¹⁴⁸. Patients
29
30 with an ileostomy after proctocolectomy can develop peristomal varicies, which can
31
32 bleed recurrently and be difficult to manage¹⁴⁹. Local treatments with injection of
33
34 sclerosants, venous ligation and surgical revision are usually unsuccessful, and
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36 portosystemic shunting or liver transplantation may be necessary to control this
37
38 complication.
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45 46 **PSC in patients with IBD**

47

48 PSC is diagnosed in between 2.4 to 7.5% of patients with UC,and 3.4% with
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50 CD^{143,150}. It can be detected at any time during its course, and may present several
51
52 years after proctocolectomy.The prevalence of PSC is higher in those with substantial
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54 (5.5%) than distal colitis (0.5%)¹⁵¹. Patients with advanced PSC and IBD are more
55
56 likely to be male, asymptomatic on presentation, and have both intra and extrahepatic
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2
3 bile duct strictures (82% versus 46%) compared to those with PSC alone¹⁵³. There is
4
5 no routine screening of IBD patients for the presence of PSC.
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10 **Colorectal dysplasia and carcinoma**

11
12 Patients with PSC and UC are at a greater risk of developing colonic dysplasia and
13
14 carcinoma than those with UC alone; a meta-analysis of 11 studies concluded the risk
15
16 was increased by approximately fourfold (OR 4.26; 95% CI 2.80 to 6.48)¹⁵³. The
17
18 absolute cumulative risk seems to increase with disease duration; CRC risk of 9%,
19
20 31%, 50% respectively, after 10, 20, 25 years in patients with PSC and UC, compared
21
22 to 2%, 5% and 10% in those with UC alone¹⁵⁴. The reason for this is unclear, although
23
24 it is speculated that secondary bile acids play a role in the carcinogenesis of the
25
26 colorectal mucosa in PSC¹⁵⁵. This is supported by the observation that right-sided
27
28 cancers are more common in patients with UC and PSC (76%), compared to UC
29
30 alone¹⁵⁶⁻¹⁵⁷. Patients with PSC and UC continue to have a high risk of CRC after
31
32 transplantation, with a four-fold increased risk compared to pre-transplantation
33
34 estimates in one study, perhaps as a result of immunosuppressive medications or the
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36 duration of colitis¹⁵⁸.
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46 Diagnosis of IBD has implications for follow-up and dysplasia/cancer surveillance.
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48 PSC patients with ulcerative or Crohn's colitis should be enrolled in a surveillance
49
50 program with annual colonoscopy with biopsies from the time of diagnosis of PSC¹⁵⁹⁻
51
52 ¹⁶¹. This should be continued after liver transplantation in those with an intact colon
53
54 given the increased CRC risk¹⁶². There is no role for prophylactic colectomy or
55
56 increased intervals of surveillance in the transplantation setting¹⁵⁸. There is currently
57
58 no surveillance recommended for PSC patients with pouches.
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CIRRHOTIC COMPLICATIONS

PSC may follow a progressive course resulting in portal hypertension and liver failure. A median duration of 12 to 18 years from PSC diagnosis to the development of end-stage liver disease has been observed. Management of cirrhosis and its complications are the same as in other causes of chronic liver disease and has been discussed in detail in the recent European guidelines¹²³.

LIVER TRANSPLANT

Liver transplantation is the treatment of choice in PSC patients with advanced end-stage liver disease, and should be considered when the predicted life expectancy within one year is 85 to 90%. Evaluation of patients with PSC for transplantation is inherently difficult due the unpredictability in disease course and the risk of biliary tract malignancy¹⁶³. Prognostic models may help with timing decisions. The Model for End-Stage Liver Disease (MELD) score has become the primary tool to predict prognosis in and is an aetiology independent method to allocate organs in the United States¹⁶⁴⁻¹⁶⁵. Modified versions, including the United Kingdom End stage Liver Disease (UKELD) score, has been validated to allocate prioritisation for liver transplantation in the UK¹⁶⁶. Indications are outlined in Table 6.

One year and 5 year survival rates for PSC have been reported to be as high as 97% and 88%, respectively, from deceased donor allografts, comparing favourably to transplantation for other indications¹⁶⁷⁻¹⁶⁹. PSC can recur with a rate of 20 to 25% after 5 to 10 years of allograft transplantation, and at a higher rate after living donor transplant, if the graft is obtained from a biologically related donor¹⁷⁰⁻¹⁷². The

1
2
3 diagnosis of recurrence can be challenging, and is based upon consistent findings at
4
5 liver biopsy and cholangiography, in the absence of other conditions that cause non-
6
7 anastomotic stricturing¹⁷³. The natural history of recurrent disease is variable; about
8
9 one third with recurrence developing progressive disease over a 10-year follow up
10
11 period leading to re-transplantation or death¹⁷⁴. Re-transplantation rates seem higher
12
13 for patients with PSC compared to other diseases¹⁷⁵. Management after liver
14
15 transplantation in patients with PSC is similar to other indications, except an
16
17 increased risk of hepatic osteodystrophy and the role of IBD with increased risk of
18
19 CRC requiring yearly colonoscopic surveillance.
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27 CONCLUSION

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29 PSC remains a challenging disease to manage. It is important firstly to differentiate
30
31 PSC from variant forms, each requiring individualised management and follow-up.
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34 Despite considerable advancements, there is still no effective medical therapy that
35
36 alters the natural history of disease. UDCA in high doses has recently yielded
37
38 disappointing results, however there is a need to re-evaluate low to moderate
39
40 doses and to assess new therapies such as the novel bile acid 24-norursodeoxycholic
41
42 acid to prevent disease progression and provide chemoprotection against biliary and
43
44 colonic malignancy. Multi-centre randomised controlled trials are essential to evaluate
45
46 survival, recruiting large number of patients for a long duration of time. Pilot studies
47
48 are also important in carefully selected patients, given the relative rarity of disease,
49
50 using more robust markers of efficacy such as serum markers of fibrosis and MRCP.
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57 Dominant strictures are optimally managed with endoscopic dilatation and stenting to
58
59 relieve biliary obstruction and its complications, after careful exclusion of a malignant
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1
2
3 stricture. Cholangiocarcinoma remains the most unpredictable and feared
4
5 complication of PSC, with no reliable screening test yet available, although the
6
7 outcome in highly selected groups undergoing chemoradiation and liver transplant is
8
9 promising. Transplantation remains the only option for patients with advanced
10
11 disease; timing remains problematic due to disease variation and recurrent disease.
12
13 Further work to understand the pathogenesis of disease, using genome studies, may
14
15 provide further targets for drug therapy and identify factors that lead to malignant
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17 transformation, with the aim of halting its development.
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Declaration of Interests

There are no competing interests.

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Table1: Trials of UDCA in PSC

Reference	Type of study	No. of patients	Dose of UDCA	Duration (months)	Outcomes
Chazouillères et al, 1990 [44]	Prospective	15	750-1250 mg	6	Improved liver function and symptoms.
O'Brien et al, 1991 [45]	Open-label	12	10 mg/kg	30	Improved liver function and symptoms.
Beuers et al, 1992 [43]	Double-blind, placebo-controlled	6	13-15 mg/kg	12	Improved liver function and histology. No effect on symptoms.
Lo et al, 1992 [176]	Double-blind placebo controlled	23	10 mg/kg	24	Improved liver function. No effect on symptoms or histology
Stiehl et al, 1994 [177]	Double-blind, placebo-controlled	20	750 mg	12-48	Improved liver function and histology. No effect on symptoms.
De Maria et al, 1996 [178]	Double-blind placebo controlled	59	600 mg	24	No improvement in liver function.
Lindor et al, 1997 [47]	Double-blind, placebo-controlled	105	13-15 mg/kg	34	Improved liver function. No effect on histology and symptoms.
Van Hoogstraten et al, 1998 [179]	Double-blind	48	10 mg/kg	24	Improved liver function. No effect on symptoms.
Mitchell et al, 2001 [49]	Double-blind, placebo-controlled	26	20-25 mg/kg	24	Improved liver function, histology and cholangiography. No effect on symptoms. No survival benefit.
Harnois et al, 2001 [180]	Open label	30	25-30 mg/kg	12	Improved liver function and survival compared with Mayo risk score.
Okolicsanyi et al, 2003 [181]	Open-label, placebo-controlled	86	8-13 mg/kg	120	Improved liver function and symptoms. No effect on histology.
Olsson et al, 2005 [50]	multi-centre randomised Double-blind, placebo-controlled	219	17-23 mg/kg	60	Improved liver function. Non-significant trend towards increased survival. No effect on symptoms.
Cullen et al, 2008 [51]	Pilot dose range study	30	10 mg/kg 20 mg/kg 30 mg/kg/	24	Improved projected survival with low and standard dose. Significantly improved projected survival with high dose.
Lindor et al, 2009 [48]	multi-centre Double-blind, placebo-controlled	150	28-30mg/kg	60	Improved liver function. No improvement in symptoms or histology. Discontinued early (6yrs): significantly risk of death, need for liver transplant or development of varicies.

Table 2: Trials of immunosuppressants, antifibrinolytics, biological therapy and other agents in monotherapy in PSC

Reference	Type of study	No. of patients	Therapy	Duration	Outcomes
Angulo et al, 2000 [182]	Pilot study	21	Budesonide 9mg od oral	1 year	Improvement liver biochemistry. No effect on Mayo risk score. Significant worsening of osteoporosis (femoral neck and lumbar spine).
Knox et al, 1991 [183]	Open study	10 (pre cirrhotic)	Methotrexate 15mg/week oral, pulsed	12 months	Improved liver function and histology
Knox et al, 1994 [184]	Double-blind placebo controlled trial	24	Methotrexate 15mg/week oral, pulsed	24 months	Improvement in serum ALP. No effect on other liver biochemistry, liver histology, cholangiograms or outcome.
Sandborn et al, 1993 [185]	Controlled trial	35	Cyclosporine 4mg/kg/day oral	2 year FU	No improvement in biochemistry or histology. Controls associated UC.
Van Theil et al, 1995 [186]	Open study	10	Tacrolimus bd oral	12 months	Improvement liver biochemistry
Olsson et al, 1995 [187]	Double blind placebo controlled randomised study	84	Colchicine 1mg/day oral	36 months	No effect on symptoms, liver biochemistry, histology or survival.
LaRusso et al, 1988 [188]	Randomized,, double-blind trial	70	Penicillamine 250mg tds oral	36 months	No effect on symptoms, liver function, histology, or survival. Side effects in 21% -discontinued drug
Bharucha et al, 2000 [189]	Open pilot study	20 patients	Pentoxifylline 400 mg qds oral	1 year	No effect on symptoms or liver function tests
Duchini et al, 2000 [190]	Open label pilot trial	4	Cladribine oral	6 months (24 month follow-up)	Improvement in histology. No effect on symptoms, liver biochemistry, cholangiograms.
Angulo et al, 2002 [191]	Pilot study	24	Pirfenidone 2400mg oral	12 months	No effect in liver biochemistry, histology, cholangiogram, Mayo risk score.
Angulo et al, 1999 [192]	Open study	8	Nicotine 6 mg qds oral	12 months	No effect on liver function. Frequent side effects.
Vleggaar et al, 2001 [193]	Double blind placebo-controlled randomised cross-over study	12	Nicotine 15mg/day transdermal patch	2 months	No effect on symptoms or liver biochemistry.
Epstein et al, 2004 [194]	Pilot study	10	Etanercept 25mg twice/week sc t	6-12 months	Minimal improvement in pruritis only. No effect on liver biochemistry or cholangiograms.
Talwalkar et al, 2005 [195]	Pilot study	30	Mycophenolate mofetil 1-3g oral	12 months	Improved ALP. No effect on other liver biochemistry or Mayo risk score
Talwalkar et al, 2007 [196]	Open labelled phase II study	16	Tacrolimus 0.05mg/kg bd oral	1 year	Improvement ALP. Adverse side effects.
Hommel et al, 2008 [197]	Double blind placebo controlled study	10	Infliximab 5mg/kg (weeks 0, 2, 6, 12, 18, 24) intravenous	26 weeks, prematurely halted	no significant differences in liver biochemistry at week 18 or histological parameters at week 26
Angulo et al, 2008 [198]	Pilot study	30	Silymarin 140mg tds oral	12 months	Improvement in liver biochemistry (except bilirubin).
Mizuno et al, 2010 [199]	Non-controlled study	7 patients	Bezafibrate 400mg/day oral	8-27 months	Improved liver biochemistry. No effect on symptoms. Not assess progression or survival.

Table 3: Combination therapy in PSC

Reference	Type of study	No. of patients	Therapy	Duration	Outcomes
Lindor et al, 1991 [200]	Historical controlled trial	12	Prednisolone 10mg/day and colchicine 0.6mg bd	24 months	No benefit in liver biochemistry or histology. Trend towards improved survival.
Kyokane et al, 1994 [201]	Case report	1 ?definite PSC	Methylprednisolone and cyclosporine	unknown	Improved cholangiogram and pancreatography
Lindor et al, 1996 [202]	Pilot study	19	Methotrexate 0.25mg/kg/week and UDCA 13-15mg/kg/day	24 months	No effect on symptoms or liver biochemistry. Increased risks of toxicity with MTX.
Schramm et al, 1999 [203]	Case series	15	Azathioprine 1.5mg/kg/day and prednisolone 1mg/kd/day (taper to 10mg/day) and UDCA 500-750mg/day	41 months (median)	Improved liver biochemistry and histology. Adverse events in 2 patients leading to withdrawal of the drugs.
Van Hoogstraten et al, 2000 [204]	Double blind randomised pilot trial	18	UDCA 12mg/kg/day with no response at 5 months, add prednisone 10mg or budesonide 3mg or 9mg/day	2 month	No benefit of combining budesonide with UDCA. Minimal short-term improvements in liver biochemistry and symptoms with prednisolone and UDCA.
Stirling et al, 2004 [205]	Randomised controlled pilot study	25	UDCA 13-15mg/kg/day and Mycophenolatemofetil 1000mg bd	24 months	No effect on liver biochemistry, histology, cholangiograms.

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Table 4: Antibiotics trials in PSC

Reference	Type of study	No. of patients	Therapy	Duration	Outcomes
Davies et al, 2008 [207]	Pilot study	14 children	Vancomycin oral	2 months	Improvement in liver biochemistry and symptoms. Best results in those without cirrhosis.
Silveria et al, 2009 [208]	Pilot study	16	Minocycline 100mg bd oral	12 months	Significant improvement in liver biochemistry and Mayo risk score.
Farkkila et al, 2004 [209]	Randomized controlled trial	80	Metronidazole with or without UDCA	36 months	Improved serum ALP and new Mayo risk score with combination therapy. No effect on cholangiogram or disease progression.

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Table 5: Extrahepatic complications of PSC

Pruritis	<ul style="list-style-type: none"> • Exclude bile duct obstruction from a dominant stricture • Exclude UDCA causing a paradoxical worsening of pruritis • <u>1st line</u>: Cholestyramine or other resins. Effective in 80 to 90% of patients, despite a limited evidence base¹²⁶⁻¹²⁸ • <u>2nd line</u>: Rifampicin. Although drug-induced hepatitis, liver dysfunction and discolouration of bodily fluids limit its use¹²⁹⁻¹³⁰ • <u>3rd line</u>: Naltrexone; Sertraline; Ondansetron¹³⁰⁻¹³⁴. Etanercept has also been shown to relieve pruritis in a study without this as its primary aim¹³⁵ • Intractable pruritis is an indication for liver transplantation.
Fatigue	<ul style="list-style-type: none"> • Exclude other causes including hypothyroidism, anaemia, diabetes, depression, and medication • Management is supportive: <ol style="list-style-type: none"> 1. Minimise factors exacerbating autonomic dysfunction and sleep disturbance¹²³ 2. Provide psychological support to develop coping strategies¹²³ <ul style="list-style-type: none"> • Modafinil: can be effective in patients with primary biliary cirrhosis (PBC) who have fatigue associated with prominent daytime somnolence, but has not been studied in PSC¹³⁶ • Liver transplantation is not indicated for fatigue alone
Malabsorption	<ul style="list-style-type: none"> • Prolonged cholestasis can lead to the malabsorption of fat and fat-soluble vitamins. • Supplement vitamins A, E and K enterally in the presence of steatorrhoea or laboratory evidence of malabsorption • Parenteral vitamin K in overt cholestasis and in the context of bleeding, prior to invasive procedures such as sphincterotomy and/or stent insertion at ERCP¹²³
Metabolic bone disease	<ul style="list-style-type: none"> • Increased risk of hepatic osteodystrophy in advanced liver disease and/or overt cholestasis. Incidence between 4 and 10%. • Assess risk for osteoporosis in all PSC patients <p><u>Higher risk</u>: longer duration of IBD, more advanced liver disease and post-transplantation, especially within the first 3 months¹³⁷⁻¹³⁸</p> <p><u>Established population risk factors</u> for osteoporosis provide additional risk that outweighs cholestasis-related risk</p> <ul style="list-style-type: none"> • Bone mineral density assessment (DEXA) at presentation • DEXA re-screening between 1 and 5 years depending on outcome, degree of cholestasis and individual risk factors^{123,137} • Measures to prevent and treat hepatic osteodystrophy (based on evidence from PBC) including calcium and vitamin D supplements; bisphosphonates; hormone replacement therapy in post-menopausal females¹³⁹⁻¹⁴⁰

Table 6: Indications for Liver Transplantation in PSC

Indications similar to other end stage liver disease	<ul style="list-style-type: none">• Chronic liver failure• Complications of portal hypertension• Impaired quality of life
Special indications in PSC despite a low priority MELD (less than or equal to 17) or UKELD (less than or equal to 49) score	<ul style="list-style-type: none">• Intractable pruritis• Recurrent or refractory bacterial cholangitis• Severe extra-hepatic biliary obstruction that precludes operative repair• Uncontrolled peristomal variceal bleeding• Limited stage peripheral or hilar cholangiocarcinoma (in the context of a clinical trial with careful selection of patients and neo-adjuvant therapy)^{116,166}. The merits of these cases are decided on an individual basis.

For Peer Review