Received: 25 May 2022 | First decision: 6 July 2022 | Accepted: 1 October 2022

DOI: 10.1111/apt.17251

AP&T Alimentary Pharmacology & Therapeutics WILEY

Systematic review: microbial manipulation as therapy for primary sclerosing cholangitis

Damjana Bogatic[1,2] | Robert V. Bryant[1,2] | Kate D. Lynch[2,3] | Samuel P. Costello[1,2]

[1]Department of Gastroenterology, The Queen Elizabeth Hospital, Woodville, South Australia, Australia

[2]Faculty of Health Sciences, School of Medicine, University of Adelaide, Adelaide, South Australia, Australia

[3]IBD Service, Department of Gastroenterology and Hepatology, Royal Adelaide Hospital, Adelaide, South Australia, Australia

Correspondence
Samuel P. Costello, IBD Service, Department of Gastroenterology and Hepatology, The Queen Elizabeth Hospital, Woodville, South Australia, 5000, Australia.
Email: sam.costello@sa.gov.au

Summary

Background: Primary sclerosing cholangitis (PSC) is a progressive liver disease with poor prognosis and no effective therapies to prevent progression. An aetiopathological link between PSC and gastrointestinal microbial dysbiosis has been suggested.

Aim: To evaluate all potential medical therapies which may exert their effect in PSC by modulation of the gut-liver axis.

Methods: We conducted a comprehensive scoping review of PubMed and Cochrane Library, including all articles evaluating an intervention aimed at manipulating the gastrointestinal microbiome in PSC.

Results: A wide range of therapies proposed altering the gastrointestinal microbiome for the treatment of PSC. In particular, these considered antibiotics including vancomycin, metronidazole, rifaximin, minocycline and azithromycin. However, few therapies have been investigated in randomised, placebo-controlled trials. Vancomycin has been the most widely studied antibiotic, with improvement in alkaline phosphatase reported in two randomised controlled trials, but with no data on disease progression. Unlike antibiotics, strategies such as faecal microbiota transplantation and dietary therapy can improve microbial diversity. However, since these have only been tested in small numbers of patients, robust efficacy data are currently lacking.

Conclusions: The gut-liver axis is increasingly considered a potential target for the treatment of PSC. However, no therapies have been demonstrated to improve transplant-free survival. Innovative and well-designed clinical trials of microbiome-targeted therapies with long-term follow-up are required for this orphan disease.

The Handling Editor for this article was Professor Gideon Hirschfield, and this uncommissioned review was accepted for publication after full peer-review.

1 | INTRODUCTION

Primary sclerosing cholangitis (PSC) is a rare chronic liver disease, characterised by progressive inflammation and stricturing of the intrahepatic and extrahepatic bile ducts. Progressive fibrosis of the small and large ducts can lead to liver cirrhosis and related sequelae, with a median transplant-free survival of 21 years.[1] PSC is associated with a significantly increased risk of hepatobiliary and colonic malignancies, including cholangic, hepatocellular, gallbladder and colorectal carcinomas.[2] The majority of patients with PSC have concurrent inflammatory bowel disease (IBD), most commonly ulcerative colitis (UC), suggesting an unknown aetiological factor common to both conditions.[3]

Currently, no medical therapy has been demonstrated to alter the disease course in PSC. Existing medical management strategies target amelioration of symptoms, screening for and treating IBD, and surveillance for PSC-associated malignancy. Ursodeoxycholic acid (UDCA), a secondary bile acid normally synthesised by intestinal bacteria, has been the most extensively studied drug in PSC, partly due to its established benefit in primary biliary cholangitis (PBC).[4] In PSC, UDCA has been shown to significantly improve serum liver enzymes, but has no demonstrated mortality benefit and does not reduce the need for liver transplantation.[5] Other pharmacological interventions that have been investigated in clinical trials include tauro-ursodeoxycholic acid, glucocorticoids, methotrexate, mycophenolate, etanercept, copper-chelating agents and colchicine.[6] Currently, there is insufficient evidence to support the effectiveness of any pharmacological intervention in improving mortality, health-related quality of life, cirrhosis or time to liver transplant, compared with no intervention in patients with PSC.

Beyond pharmacological therapies, endoscopic interventions to preserve bile flow, including balloon dilation and stenting of dominant strictures, are part of PSC management.[7] Significant improvement in transplantation-free survival compared to that expected from the Mayo Risk Score has been reported with balloon dilatation but not stenting of dominant strictures, and additionally, balloon dilation is associated with less risk of complications than stenting.[8] However, orthotopic liver transplantation (OLT) remains the only definitive treatment for PSC, indicated for patients with end-stage liver disease, recurrent acute cholangitis or refractory symptoms. Long-term graft and patient survival are significantly impacted by recurrence of biliary strictures or recurrent PSC, which occurs in up to 37% of transplanted patients.[9]

The concept that the gut microbiota may contribute to the pathogenesis of PSC has arisen from a number of observations. Dysbiosis can lead to inflammation, impairment of the intestinal epithelial barrier and immune dysregulation (Figure 1).[10] The portal vein transports many products of the gut microbiota directly to the liver, and it is possible that some of these products contribute to the duct pathology seen in PSC. Human studies have consistently demonstrated an altered gut microbial composition in PSC, characterised by reduced colonic alpha diversity and beta diversity as well as shifts in multiple bacterial taxa (Table 1). Of note, organisms of the *Veillonella* and

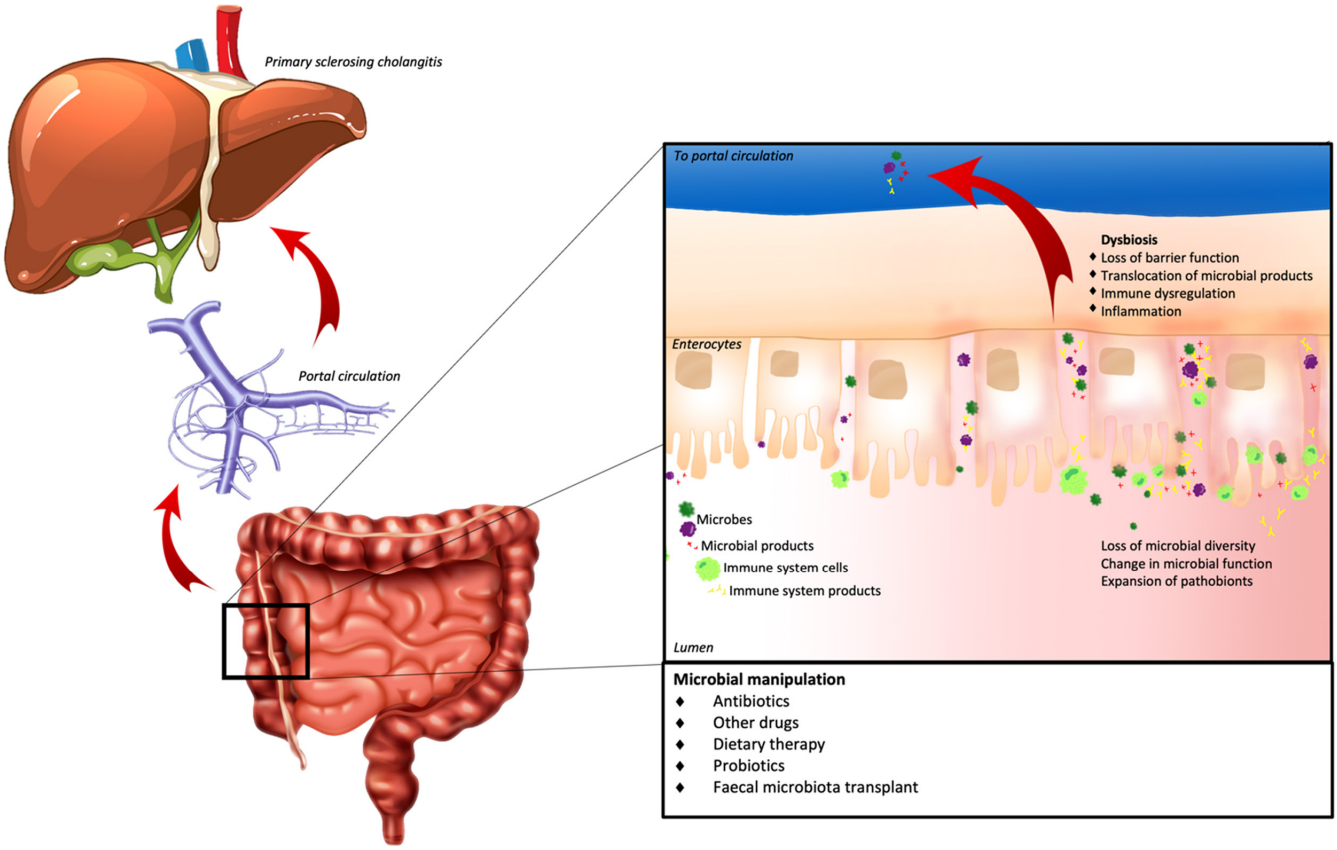

FIGURE 1 The link between dysbiosis and primary sclerosing cholangitis: The gut–liver axis

TABLE 1 Studies comparing the microbial composition of primary sclerosing cholangitis to healthy controls and inflammatory bowel disease

References	Study groups	Sequencing methods	Alpha-diversity	Beta-diversity	Changes in taxa
Rossen et al.[70]	12 PSC-IBD (8 PSC-UC and 4 PSC-CD); 11 UC; 9 HC 32 total	16 s rRNA sequencing of ascending colon and terminal ileum mucosal biopsies (HITChip)	PSC-IBD vs HC: reduced	No significant difference in PSC-IBD vs UC vs HC	Decreased in PSC-IBD vs UC and HC: uncultured Clostridiales II by twofold
Torres et al.[71]	19 PSC-combined (13 PSC-UC, 6 PSC-CD and 1 PSC); 15 IBD (13 UC and 2 CD); 9 HC 44 total	16s rRNA sequencing of terminal ileum, right colon and left colon mucosal biopsies (Illumina MiSeq)	PSC-combined vs IBD vs HC: no significant difference	No significant difference	Increased in PSC-combined vs HC: Barnesiellaceae, Clostridiales, *Bacteroides* and *Blautia*
Kevans et al.[72]	31 PSC-UC; 56 UC 87 total (2 cohorts based on two centres: Oslo and Calgary)	16S rRNA sequencing of left-sided colonic biopsies (Illumina MiSeq)	Not significantly different in either cohort	PSC-UC decreased in 1 cohort (Oslo) but not in the other (Calgary)	Several genera showed a nominal association with PSC-UC vs UC. However, there were no significant changes across both cohorts following false-discovery rate (FDR) correction
Sabino et al.[73]	27 PSC-UC; 21 PSC-CD; 12 PSC; 13 UC; 30 CD; 66 HC 175 total[a]	16S rDNA sequencing of faecal specimens (Illumina MiSeq)	HC vs PSC-combined (PSC, PSC-UC and PSC-CD): increased HC vs PSC-UC: increased HC vs CD: increased	HC vs PSC vs IBD all significantly different; no difference between PSC, PSC-UC and PSC-CD	Increased in PSC, PSC-UC and PSC-CD vs HC (after adjusting for confounders): *Enterococcus*, *Fusobacterium* and *Lactobacillus*
Kummen et al.[11]	44 PSC-UC; 11 PSC-CD; 30 PSC; 36 UC; 263 HC 384 total[a]	16S rRNA sequencing of faecal specimens (Illumina MiSeq)	PSC vs HC: reduced PSC vs UC: no difference	Clear shift in PSC vs HC	Increased in PSC vs HC: *Veillonella* (4.8 fold increase). Decreased in PSC vs HC: *Coprococcus*, *Phascolarctobacterium*, *Desulfovibrio*, *Succinivibrio* and 7 other unknown genera
Bajer et al.[12]	32 PSC-IBD; 11 PSC; 32 UC; 31 HC 106 total	16S rRNA sequencing of faecal specimens (Illumina MiSeq)	HC vs PSC: no difference HC vs PSC-IBD: no difference PSC vs PSC-IBD: no difference	HC vs PSC: clear shift in microbiota composition PSC-IBD vs UC: clear shift PSC-IBD vs PSC: no significant shift	Increased in PSC vs HC: *Rothia*, *Enterococcus*, *Streptococcus*, *Clostridium*, *Veillonella*, *Haemophilus*
Torres et al.[74]	15 PSC-IBD (11 PSC-UC and 4 PSC-CD); 15 IBD (12 UC and 3 CD) 30 total	16S rRNA sequencing of faecal specimens (Illumina MiSeq)	PSC-IBD vs IBD: not significantly different	PSC-IBD vs IBD: significantly dissimilar	Increased in PSC-IBD vs IBD: Fusobactereriaceae, *Fusobacterium* and *Ruminococcus*. Decreased in PSC-IBD vs IBD: *Dorea*, *Veillonella*, *Lachnospira*, *Roseburia* and *Blautia*
Lemoinne et al[13]	22 PSC; 27 PSC-IBD; 33 IBD; 30 HC 112 total	16s DNA sequencing of faecal specimens (Illumina MiSeq) for bacterial composition; ITS2 sequencing of faecal specimens for fungal composition	PSC-IBD vs IBD: reduced PSC-IBD vs HC: reduced PSC was not significantly different to any other group. Fungal diversity: PSC vs PSC-IBD vs IBD vs HC: not significantly different. PSC-combined (PSC and PSC-IBD) vs IBD: significantly higher PSC-combined vs HC: trend towards higher diversity, but not significant	PSC-IBD vs IBD vs HC: all significantly dissimilar PSC vs HC: trend towards but not significantly dissimilar Fungal diversity: PSC vs HC: significantly dissimilar PSC vs PSC-IBD: significantly dissimilar PSC-IBD vs IBD: significantly dissimilar	Increased in PSC vs HC: Sphingomonadaceae, *Veillonella*, Alphaproteobacteria and *Rhizobiales*. Decreased in PSC vs HC: *Ruminococcus*, *Ruminiclostridium*, *Faecalibacterium*, *Lachnoclostridium* and *Blautia*. Increased fungal taxa in PSC vs HC: Exophiala (more than 100 fold increase), Sordariomycetes. Decreased fungal taxa in PSC vs HC: Saccharomycetes

(Continues)

TABLE 1 (Continued)

References	Study groups	Sequencing methods	Alpha-diversity	Beta-diversity	Changes in taxa
Ruhlemann et al.[14]	62 PSC; 75 PSC-IBD; 118 UC; 133 HC 388 total (2 cohorts based on 2 centres: German and Norwegian)	16S rRNA sequencing of faecal specimens (Illumina MiSeq)	Norwegian cohort: PSC vs HC: reduced PSC vs UC: not significantly different German cohort: PSC vs HC: not significantly different PSC vs UC: increased	PSC vs UC and HC: significantly dissimilar	Increased in PSC vs HC (in individual cohorts and when combined): *Veillonella*, *Streptococcus*, *Bacteroides*, *Parabacteroides*, Proteobacteria, Lactobacillales, Bacilli and Gammaproteobacteria. Decreased in PSC vs HC (in individual cohorts and when combined): *Coprococcus*
Ladipot et al.[75]	35 PSC-combined (17 PSC, 18 PSC-IBD (12 PSC-UC and 6 PSC-CD); 30 HC 65 total	16S rRNA sequencing of faecal swabs (Illumina MiSeq)	PSC-combined vs HC: decreased	PSC vs HC: significantly dissimilar PSC-IBD vs HC: significantly dissimilar PSC vs PSC-IBD: no significant difference	261 species were diminished in PSC-combined vs HC. 32 species were significantly overrepresented. There was a strong inverse correlation between the relative abundance of *Enterococcus* and bacterial diversity in the PSC-combined group
Denoth et al.[76]	7 PSC-UC; 42 UC; 28 HC 77 total	16S rRNA sequencing of terminal ileum, right colon, left colon and rectum biopsies (Thermo Fisher Ion PGMTM System)	PSC-UC vs HC: increased PSC-UC vs UC: increased	PSC-UC vs HC: significantly dissimilar PSC-UC vs UC: significantly dissimilar	The *Firmicutes/Bacteroides* ratio was significantly higher in the PSC-UC and UC groups than HC. *Roseburia*, *Fusobacterium*, *Bifidobacterium* and *Actinobacillus* were increased in PSC-UC vs HC. *Bacteroides* was lower in PSC-UC. This difference was non-sustained when analysed for individual sampling site
Ostadmohammadi et al.[77]	14 PSC-IBD (12 PSC-UC and 2 PSC-CD); 12 UC; 8 HC 34 total	16S rRNA sequencing of faecal specimens (Rotor-Gene® Q)	Not assessed	PSC-IBD vs UC: significantly dissimilar PSC-IBD vs HC: no significant difference	The *Firmicutes/Bacteroides* ratio was significantly higher in the UC group vs both PSC-IBD and HC. Enterobacteriaceae were increased in PSC-IBD vs HC, but similar vs UC. Decreased in PSC-IBD vs UC: *Enterococcus*, *Lactobacillus* and *Bifidobacterium*
Hole et al.[16]	84 PSC-combined (66 PSC-IBD and 18 PSC only); 51 PSC-LT-combined (42 PSC-IBD-LT and 9 PSC-LT); 40 HC 175 total	16s rRNA sequencing of mucosal biopsies from terminal ileum, ascending colon, descending colon or sigmoid colon (Illumina MiSeq and v3 kit)	PSC-combined and PSC-LT-combined vs HC: decreased PSC-combined vs PSC-LT-combined: similar PSC-IBD vs PSC: not significantly different	PSC-combined vs HC: significantly dissimilar PSC-LT-combined vs HC: significantly dissimilar PSC-IBD vs PC: significantly dissimilar, regardless of LT status	Eight genera were increased in both PSC-combined and PSC-LT-combined vs HC, including *Haemophilus*, *Veillonella*, *Roseburia Akkermansia* was reduced in PSC-IBD vs PSC regardless of LT status.

Abbreviations: CD, Crohn's disease; HC, healthy controls; IBD; inflammatory bowel disease; LT, liver transplant; PSC, primary sclerosing cholangitis; UC, ulcerative colitis.

[a]Included exploration and validation groups.

Fusobacterium genus are commonly elevated in PSC compared to healthy controls whereas other changes in bacterial taxa have often varied between studies.[11–14] Dysbiosis in PSC is independent of the presence of IBD. Approximately 70% of patients with PSC have concomitant inflammatory bowel disease, the majority of whom suffer from UC.[3] The PSC-UC phenotype is distinct, generally characterised by mild inflammatory burden of an extensive or right-sided distribution.[3] The etiopathogenic link between PSC and dysbiosis is further supported by a number of observations arising from experimental models of PSC.[15] Liver transplantation does not normalise the gastrointestinal microbiome, and some genera associated with PSC correlate with recurrent PSC after liver transplantation.[16]

Emerging data demonstrate that manipulation of the gut microbiota holds promise as an effective therapeutic strategy in PSC. Oral

antibiotic therapy may improve serum liver enzymes and Mayo Risk Score in PSC patients.[17] Some antibiotics have been found to exert immunomodulatory and anti-inflammatory effects independent of their antimicrobial properties, which may also contribute to their efficacy in the treatment of PSC. Other modulators of the enteric microbiome including probiotics, dietary strategies and faecal microbiota transplantation (FMT) have also come under investigation due to their potential benefit in PSC via manipulation of the gut-liver axis.

Given the plausible efficacy of microbial manipulation in PSC and a dearth of effective therapies available for this orphan disease, this scoping review aims to outline the role of the microbiome in the pathogenesis of PSC, and to evaluate the potential for microbial manipulation as a therapeutic strategy in PSC.

2 | METHODS

A comprehensive literature search of PubMed and the Cochrane Library was performed from inception to December 2021, identifying all studies and reports that evaluated the use of an agent which manipulates the gastrointestinal microbiome for the treatment of PSC. A detailed description of the queries used in the databases is included in Appendix A. Additionally, the references of all articles were screened to identify any additional studies or reports. As this is a scoping review, we incorporated all eligible papers including randomised controlled trials, observational studies, case series, case reports and letters to the editor. Paediatric studies were included. As many therapeutics have been evaluated in PSC, consensus among the authors was required for which of these had potential for microbial manipulation.

2.1 | Interpreting therapeutic efficacy in PSC

Diagnosis of PSC is based on a combination of clinical, laboratory, cholangiographic and histologic findings, after exclusion of other causes of liver disease.[18] Diagnosis and evaluation, however, is made difficult by its frequent subclinical presentation, and some patients may have normal liver enzymes. Evaluating the response to treatment in investigational studies of PSC is complicated by the lack of a validated surrogate biomarker of disease.[19] Liver function test changes, in particular, a reduction or normalisation of ALP are often used as a primary endpoint in therapeutic studies in PSC, and have been associated with improved survival and decreased risk of requiring liver transplantation in PSC.[20] The revised Mayo Risk Score is a survival model based on predictors of outcome in PSC, including age, serum bilirubin, AST and albumin, and history of variceal bleeding.[21] It is often used in clinical practice for prognostication, and in studies for assessing response to therapy. Two other PSC-specific prognostic models include the Amsterdam-Oxford PSC Score and the UK PSC Risk Score.[22,23] The Model for End-Stage Liver Disease (MELD) is also widely used for prognostication of patients with liver disease of any cause, including PSC.

2.2 | Microbial manipulation in PSC

2.2.1 | Antibiotic therapy

Vancomycin

Oral vancomycin has shown promising results in two randomised controlled trials, in addition to a number of cohort studies and case reports where it was used as therapy for PSC (Tables 2 and 3). Vancomycin is a glycopeptide antibiotic that, when given orally, is minimally absorbed from the gastrointestinal tract. Consequently, the on-label uses for oral vancomycin are restricted to enteric diseases such as *Clostridioides difficile* and *Staphylococcal enterocolitis*. Oral vancomycin has been reported to induce and maintain remission of ulcerative colitis in patients with concurrent PSC, including some who had failed standard treatments.[24–26] Additionally, vancomycin has been shown to significantly alter the microbial composition in patients with PSC and IBD, predominantly associated with an increase in *Blautia* abundance and decrease in *Bacteroides*.[27]

The possible therapeutic effect of oral vancomycin in PSC was first recognised in 1998, when Cox and Cox[28] described three children with PSC and IBD whose symptoms and liver enzymes improved following treatment with oral vancomycin. Since then, a number of case reports involving both children and adults have been published, with positive results.[29–32] Whilst there is likely a degree of publication bias, with negative cases less likely to be published, these observations are certainly promising, particularly those cases where radiological and/or histological improvement is seen, as this is not usually expected as part of the natural history of the disease.

There are two randomised controlled trials investigating vancomycin as therapy for PSC. Rahimpour et al[33] randomised 29 adult patients with PSC in a blinded fashion with confirmed PSC into two groups: vancomycin 125 mg four times a day (n = 18) or placebo (n = 11), for a period of 12 weeks. Twenty-one of these patients (75%) had concomitant IBD. All patients were simultaneously commenced on ursodeoxycholic acid 300 mg t.d.s. before the study. The primary end points were a reduction in Mayo Risk Score and ALP at 12 weeks. A reduction in Mayo Risk Score was achieved in the vancomycin group but not in the placebo group at 12 weeks (−322.03%, $p = 0.026$ vs −45.45%, $p = 0.337$). There was no significant change in ALP at 12 weeks, in either vancomycin or placebo groups (Table 4). Patients in the vancomycin group experienced a significant reduction in subjective symptoms including fatigue (p = 0.002), pruritis (p = 0.022), diarrhoea (p = 0.011), and anorexia (p = 0.041), but no significant reduction in abdominal pain (p = 0.36), blood in stool (p = 0.36) or nausea and vomiting (p = 0.36). The only significant improvement in the placebo group was in pruritis ($p = 0.011$). Pruritis was measured on a visual analogue scale and fatigue using a validated Persian version[34] of the fatigue impact scale; however, it is not specified how the remaining symptoms were measured. Vancomycin was well tolerated in this study. The significant reduction in Mayo Risk Score and symptoms achieved in this study make vancomycin a promising therapeutic option in PSC. This sample size was limited, however, and treatment and control groups were unevenly

TABLE 2 Summary of case reports of the use of oral vancomycin in PSC

Author (year)	Patient details	Oral vancomycin protocol	Change in biochemistry	Change in histology	Change in cholangiographic findings
Cox and Cox[28]	15yo M with unspecified colitis	250 mg vancomycin q.d.s. for 7 months intermittently	Normalisation of ALT, GGT and ESR	Less portal inflammation and portal fibrosis when compared to pre-vancomycin biopsies	Resolution of intra- and extra-hepatic strictures seen on ERCP
	14yo F with CD	125 mg vancomycin t.d.s. for 3 months	Normalisation of ALT and ESR; reduction of GGT to near normal	Not assessed	Normalisation of dilated common bile duct seen on ultrasound
	14yo M with CD	250 mg vancomycin t.d.s. for 2 weeks, then b.d. for 4 weeks	Normalisation of ALT, GGT and ESR	Not assessed	Not assessed
Davies et al[29]	12yo F with UC, recurrence of PSC following liver transplant	500 mg vancomycin t.d.s.	Normalisation of ALT, AST, GGT, ESR and CRP	Resolution of inflammation and cirrhosis, with return to normal liver structure and anatomy; no evidence of previously observed "onion skin" fibrosis	Not assessed
Buness et al.[30]	13yo F with UC	500 mg vancomycin t.d.s., increased to 750 mg t.d.s.	Minor elevation in GGT; normalisation of other liver enzymes	Not assessed	MRCP showed normal liver with resolution of localised hepatic duct prominence and normal bile ducts
Hey et al[31]	33yo M with UC and liver transplantation	250 mg vancomycin b.d.	Normalisation of ALT, ALP and GGP	Not assessed	Stable but persistent intrahepatic duct stricturing and beading on MRCP
de Chambrun et al (2018)[32]	20yo F with UC	500 mg vancomycin b.d.	Normalisation of ALT, ALP and AST	Not assessed	Not assessed
	69yo M with UC	500 mg vancomycin b.d. maintenance following induction of remission with ciprofloxacin and metronidazole	Maintenance of normal liver enzymes	Not assessed	Not assessed
	24yo M with UC	500 mg vancomycin b.d.	Worsening of liver enzymes	Not assessed	Not assessed
Dubrovsky and Kitts[78]	16yo F with UC	500 mg vancomycin t.d.s.	Normalisation of liver enzymes	Not assessed	Not assessed
Buness et al (2020)[79]	15yo F with UC (same child) reported in Buness et al.[30]	1000 mg vancomycin b.d. (opening capsules)	Normalisation of liver biochemistry with Vancomycin generic branded vancomycin	Not assessed	MRCP continued to show normal bile ducts and elastography values remained within normal limits

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; b.d., twice a day; CD, Crohn's disease; CRP, C-reactive protein; ERCP, endoscopic retrograde cholangiopancreatography; ESR, erythrocyte sedimentation rate; GGT, gamma-glutamyltransferase; MRCP, magnetic resonance cholangiopancreatography; q.d.s., four times a day; t.d.s., three times a day; UC, ulcerative colitis.

TABLE 3 Summary of results of investigational studies involving oral vancomycin for PSC

	Davies et al.[37a]	Abarbanel et al.[38a]	Rahimpour et al.[33b]		Tabibian et al.[35b]			
Change from baseline % (p)								
	Vancomycin *n* = 14	**Vancomycin *n* = 14**	**Vancomycin *n* = 18**	**Placebo *n* = 11**	**Vancomycin Low Dose *n* = 8**	**Vancomycin High Dose *n* = 9**	**Metronidazole Low Dose *n* = 9**	**Metronidazole High Dose *n* = 9**
ALP	—	—	−44.49% ($p = 0.112$)	−7.93% ($p = 0.490$)	−46% (**$p = 0.03$**)[c]	−40% ($p =$ **0.02**)	13% ($p = 0.47$)	−33% ($p = 0.22$)
AST	-	-	−33.36% ($p = 0.053$)	−4.96% ($p = 0.135$)	—	—	—	—
GGT	↓ (**$p = 0.005$**)[d]	↓ (**$p = 0.0022$**)[d]	−63.81% ($p = 0.087$)	−30.7% ($p = 0.966$)	—	—	—	—
ALT	↓ (**$p = 0.007$**)[d]	↓ (**$p = 0.018$**)[d]	−46.31% ($p = 0.074$)	7.22% ($p = 0.739$)	—	—	—	—
ESR	↓ (**$p = 0.008$**)[d]	—	−41.25% (**$p = 0.005$**)	−4.83% ($p = 0.845$)	—	—	—	—
CRP	—	—	—	—	−69% ($p = 0.06$)	26% ($p = 0.78$)	−49% (**$p = 0.03$**)	250% ($p = 1.0$)
Bilirubin (total)	—	—	−38.68% ($p = 0.410$)	−37.91% ($p = 0.280$)	−33% (p = 0.06)	0% ($p = 0.48$)	−20% (**$p = 0.03$**)	+6% ($p = 0.78$)
Mayo Risk Score	—	—	−322.03% (**$p = 0.026$**)	−45.45% ($p = 0.337$)	−0.55% (**$p = 0.02$**)	−0.03% ($p = 0.98$)	−0.16% (**$p = 0.03$**)	−0.28% ($p = 0.16$)

Note: Statistically significant *p* values are shown in bold.

Abbreviations: ALP, alkaline phosphatase; AST, aspartate aminotransferase; ALT: alanine aminotransferase; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; GGT, gamma-glutamyltransferase.

[a]Studies with child participants only.

[b]Studies with adult participants only.

[c]Outlier omitted from results.

[d]Numerical value not given.

distributed. There was also no follow-up period after the cessation of treatment to assess whether biochemical and symptomatic benefits were sustained.

Tabibian *et al*[35] randomised 35 adult patients with PSC into four groups in a blinded fashion: vancomycin 125 mg ($n = 8$) or 250 mg ($n = 9$) four times a day, or metronidazole 250 mg ($n = 9$) or 500 mg ($n = 9$) three times a day, for a period of 12 weeks. Serum biochemistry was performed at baseline, week 3 and week 12. The primary end point was a decrease in the serum ALP at 12 weeks. This was reached in both the low and high-dose vancomycin groups (−46%, $p = 0.03$ and −40%, $p = 0.02$, respectively), but not in the metronidazole groups (low dose +13%, $p = 0.47$ and high dose −33%, $p = 0.22$) (Table 4). Mayo Risk Score was significantly reduced in the low-dose vancomycin group (−0.55, $p = 0.02$), but no other secondary biochemical endpoints were reached in the vancomycin groups, including reduction in total bilirubin or CRP, and improvement in symptoms of pruritis and fatigue. Two patients withdrew due to side effects of vancomycin, namely migraines, diarrhoea and fatigue. However, side effects were rare, and vancomycin was overall better tolerated than metronidazole in this study. Again, despite some promising outcomes, group sizes in this study were small, and it was not powered to detect small changes.

A recent retrospective propensity-matched observational study investigated the effect of oral vancomycin therapy in children with PSC, compared to carefully matched patients receiving ursodeoxycholic acid or observation.[36] Eighty-eight patients received oral vancomycin with a median dose of 21 mg/kg/day. The primary outcome measured was GGT less than 50 U/L after 12 months or at least 75% less than pre-treatment GGT, with no adverse hepatobiliary complications (encompassing portal hypertensive complications, complications of strictures, hospitalisation for acute bacterial cholangitis, cholangiocarcinoma, listing for liver transplantation or death). Median GGT was similar between groups at initiation. Patients in all three groups achieved a significant reduction in GGT, with similar GGT levels between groups after 1 year of treatment (44 U/L in vancomycin group, 46 U/L in ursodeoxycholic acid group, and 58 U/L in observation group, $p = 0.657$). The use of GGT as a primary endpoint is somewhat unusual given the lack of data surrounding it as surrogate biomarker in PSC. There was no significant difference between any of the treatment groups in secondary outcomes, including serum bilirubin, AST to platelet ratio index, fibrosis stage and 5-year probability of liver transplantation.

There are further two cohort studies investigating vancomycin as therapy for PSC. Davies *et al*[37] evaluated oral vancomycin in 14

TABLE 4 Comparison of studies which reported change in alkaline phosphatase

	References	Study group	1 time of assessment from baseline	Mean change in ALP from baseline IU/L (%) *p* value	2 time of assessment from baseline	Mean change in ALP from baseline IU/L (%) *p* value	Number of patients achieving >50% reduction in ALP (%)
Vancomycin	Rahimpour et al.[33]	Vancomycin	4 weeks	−376.76 (−32.5%) p NR	12 weeks	−519.68 (−44.8%) p = 0.112	NR
		Placebo		−13.18 (−1.5%) *p* NR		−71.24 (−7.9%) *p* = 0.490	NR
	Tabibian et al.[35]	Vancomycin low dose	12 weeks	−188 (−46.3%) *p* = 0.03%[a]			NR – however, 2/8 (25%) experienced normalisation of ALP
		Vancomycin high dose		−136 (−39.4%) *p* = 0.02			NR
Metronidazole		Metronidazole low dose		+46 (+13.0%) *p* = 0.47			NR
		Metronidazole high dose		−138 (−32.5%) *p* = 0.22			NR
	Farkkila et al.[43]	Metronidazole and UDCA	36 months	−390 (−60.7%) *p* < 0.01			NR
		Placebo and UDCA		−254 (−44.8%) *p* < 0.01			NR
Rifaximin	Tabibian et al.[48]	Rifaximin	12 weeks	+3 (+0.9%) *p* = 0.47			NR
Minocycline	Silveira et al.[49]	Minocycline	1 year	−65 (−19.6%) *p* = 0.04			2/12 (17%)
Probiotics	Vleggaar et al.[57]	Probiotic	3 months	NR (−9%) p NR			NR
		Placebo		NR (−9%) p NR			NR
Faecal Microbiota Transplant	Allegretti et al.[68]	Faecal microbiota transplant	24 weeks	NR			3/10 (30%)

Abbreviations: ALP, alkaline phosphatase; NR, not reported; UDCA, ursodeoxycholic acid.

[a]Outlier omitted corresponding to a patient who did not take medication for 1 month.

children with PSC. Vancomycin was commenced at a dose of 50 mg/kg/day and continued until there was normalisation or no further improvement in liver enzymes and ESR. Ten of 14 children (71.4%) had complete normalisation of alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT) and erythrocyte sedimentation rate (ESR), whilst the other four (28.6%) showed improvement in these biomarkers without normalisation. Each of those in the latter group had cirrhosis prior to the initiation of vancomycin. Other biochemical analyses, including total bilirubin and complete blood count, did not change significantly. Only one patient had pre- and post-treatment liver biopsies. These showed improvement in inflammation and fibrosis of the biliary tree.

Abarbanel *et al*[38] reported a significant decrease of serum GGT (effect size not reported, $p = 0.026$) and ALT ($p = 0.037$) in 14 children treated with 50 mg/kg/day oral vancomycin for 3 months. This improvement was sustained after 12 months of treatment ($p = 0.0022$ for GGT; $p = 0.018$ for ALT). Nine patients had pre- and post-treatment biliary imaging or biopsies, all of which had evidence of improvement in inflammation, fibrosis or remodelling following vancomycin therapy. Both of these small open-label cohort studies again demonstrate some promise, but the lack of numerical data with regards to the size of biochemical changes make any meaningful conclusions difficult. Furthermore, these studies did not report on ALP or Mayo Risk Score, the primary markers of disease response which are used today.

The current evidence described here suggests that vancomycin therapy may be effective for improving biomarkers of PSC, but the trials are relatively small, mainly observational and a mix between adults and children with PSC. Furthermore, the impact on the clinical outcomes such as liver transplantation progression-free survival is unclear. The results of currently planned or ongoing larger randomised placebo-controlled trials are awaited before we can recommend vancomycin as a beneficial agent in PSC.

Metronidazole

Metronidazole is a bactericidal antibiotic which is highly active against Gram-negative and Gram-positive anaerobes. It is successfully used in the treatment of bacterial and protozoal infections of the gastrointestinal tract, including giardiasis, amoebiasis, *C. difficile* and *Helicobacter pylori*. It is also one of the first-line medications in the treatment of suppurative complications of inflammatory bowel disease, including abscesses and fistulae associated with Crohn's disease,[39] as well as pouchitis following surgical resection in UC.[40] Metronidazole has demonstrated restorative effects on the gastrointestinal epithelium.[41,42] These observations prompted the evaluation of metronidazole in two randomised clinical trials in patients with PSC. However, prolonged use is often poorly tolerated and is associated with risk of development of peripheral neuropathy, limiting capacity for long-term therapy.

The potential therapeutic effect of metronidazole in PSC was first appreciated in Lewis and Wistar rats with surgically created jejunal self-filling blind loops which resulted in histological and cholangiographic biliary abnormalities resembling PSC.[15] In this model, rats treated with metronidazole had significantly less thickened bile ducts ($p < 0.005$) and reduced abnormal cholangiographic ($p < 0.01$) and histological (p not stated) scores than untreated rats with self-filling blind loops.

In a multi-centre double-blind randomised controlled trial undertaken by Farkkila *et al*[43] 80 patients with PSC were randomised to receive 600–800 mg (based on weight) metronidazole per day ($n = 39$), or placebo ($n = 41$). Both groups were also treated with ursodeoxycholic acid. After 36 months, both metronidazole and placebo groups recorded a significant decrease from baseline in all serum liver enzymes. The mean difference in ALP from baseline was significantly larger ($p < 0.05$) in the metronidazole group (−337 IU/L, 95% CI: [−283, − 391]) than that of the placebo group (−214 IU/L, 95% CI: [−164, −264]) (Table 4). Metronidazole resulted in a significant improvement in the Mayo Risk Score (−0.32, $p < 0.05$), whereas placebo did not (−0.32, $p > 0.05$). Liver biopsies were collected before and after the treatment period, and classified according to stage, representing disease progression and morphological changes, and grade, reflecting necroinflammatory activity. Improvement of histological stage and grade were seen in 34.4% and 43.8% of the metronidazole patients, respectively, significantly more often than in the placebo group (14%, $p = 0.047$ and 16.6%, $p = 0.014$, respectively). However, metronidazole failed to halt disease progression, with a similar rate of worsening histological stage and grade between the intervention and control groups. There was no significant change in ERCP findings between the two groups. This was a well-designed study with multiple important endpoints, including the evaluation of disease progression via histological assessment and cholangiography. However, the treatment period was high at 36 months, which aimed to allow sufficient time for improvement in liver histological staging and grading to be seen. Because of its side effect profile, however, metronidazole was poorly tolerated for this amount of time, with an increased incidence of side effects in the treatment group (18 vs 7, $p < 0.05$).

The second double-blind placebo-controlled trial of metronidazole by Tabibian *et al*[35] is mentioned above, and compared low- (125 mg q.d.s) and high-dose (250 mg q.d.s) vancomycin to low- (250 mg t.d.s) and high-dose (500 mg t.d.s) metronidazole ($n = 35$ altogether). In this study, metronidazole did not reach the primary end point of reduction in ALP after 12 weeks of treatment, compared to baseline. In the low-dose metronidazole group, there was a 13% increase in ALP compared to baseline ($p = 0.47$), and in the high-dose metronidazole group a 33% reduction in ALP ($p = 0.22$). The low-dose metronidazole group did however, achieve a significant reduction in Mayo Risk Score (−0.16, $p = 0.03$), CRP (−49%, $p = 0.03$) and total bilirubin (−20%, $p = 0.03$). There was a trend towards a reduction in fatigue and pruritis scores in the metronidazole groups, however, this did not reach statistical significance. Four patients withdrew from the study due to intolerable side effects of metronidazole, including persistent dyspepsia, nausea, ophthalmalgia, diarrhoea and anorexia.

Taken together, the data for metronidazole in PSC are less compelling than vancomycin, and its use would be significantly limited by its likelihood of side effects if taken long term.

Rifaximin

Rifaximin is a semi-synthetic broad-spectrum gut-specific antibiotic, predominantly used in gastrointestinal disorders due to its limited systemic absorption. Its localised activity gives it a favourable side-effect profile and low potential for drug interactions relative to some other antibiotics.

It has been demonstrated to have significant clinical benefits in the setting of hepatic encephalopathy by reducing future hospital admissions.[44] It is proposed that Rifaximin exerts this benefit via this mechanism, as well as by decreasing overall bacterial density. Above its bactericidal and bacteriostatic properties, rifaximin exerts a number of additional effects on microbiome functionality, including reduced endotoxemia and decreased formation of potentially toxic secondary bile acids.[45,46] Moreover, it may reduce inflammatory cell infiltration of the lamina propria, an effect likely mediated by *Lactobacillus*-induced downregulation of the pro-inflammatory cytokines IL-6 and TNF-α.[47]

Tabibian et al[48] investigated the safety and efficacy of rifaximin in 16 patients with PSC, using open-label 550 mg oral rifaximin twice a day for 12 weeks. End points included change in serum ALP, AST, GGT, total bilirubin, albumin, CRP, Mayo PSC risk score, fatigue and pruritis symptom scores, a liver-specific health questionnaire, a general health and wellbeing questionnaire and adverse effects. At the conclusion of the study, there was no meaningful change in ALP (+0.9%, $p = 0.47$) (Table 4) or in any of the secondary end points. Three patients withdrew due to adverse effects, including severe headaches, rapid rise in liver enzymes, and need for ERCP. Four other patients reported mild adverse effects not requiring treatment withdrawal. This is the only study that has examined the potential benefit of rifaximin in patients with PSC. The study was a small pilot study without a control arm and larger studies are therefore required before rifaximin could be considered a potential therapeutic agent in PSC.

Minocycline

Minocycline is a second-generation tetracycline antibiotic, active against a wide spectrum of Gram-positive and Gram-negative bacteria. In addition to antibacterial activity, minocycline has demonstrated anti-inflammatory and anti-apoptotic properties. The use of minocycline in PSC has been investigated by Silveira et al who evaluated the safety and efficacy of 100 mg minocycline twice daily in 16 patients with PSC, for 1 year.[49] Minocycline resulted in a significant decrease in ALP (−330 U/L, $p = 0.04$), with a trend towards benefit in Mayo Risk Score (−0.55, $p = 0.05$), compared to baseline. However, only two patients (12.5%) achieved a reduction in ALP of 50% or more (Table 4), a more meaningful measure of treatment success. Additionally, nine patients (56%) experienced potential drug-related adverse effects, three of whom withdrew from the study. Overall, current albeit limited data do not support the use of minocycline for the management of PSC.

Azithromycin

Azithromycin is a broad-spectrum macrolide antibiotic with a long half-life and excellent tissue penetration. Evidence for azithromycin in PSC is limited to a single case report describing the improvement of cholestasis-related symptoms and serum markers in a patient with PSC.[50] Boner *et al* reported on a 45-year-old woman with Crohn's disease and PSC who described alleviation of cholestasis-related symptoms after inadvertently continuing azithromycin therapy for 5 months, having been prescribed it for suspected bronchiectasis. Her symptoms had previously remained unchanged for 10 years despite regular ursodeoxycholic acid therapy. The patient was additionally found to have a reduction in serum liver enzymes, and furthermore, resolution of nodular irregularities on liver ultrasound. Three weeks after ceasing azithromycin, the patient had a recurrence of dark urine and pruritis. Liver enzymes were found to be elevated after 6 weeks. Azithromycin was subsequently reinitiated and the patient's symptoms and biochemical abnormalities were again reversed. There have been no other reports or studies, to the best of our knowledge, of the use of azithromycin in PSC. As such, the therapeutic possibility of azithromycin in PSC remains unknown.

Additionally, azithromycin has been shown to have a number of potentially deleterious effects on the microbiome, including reduced gastrointestinal alpha-diversity in children,[51,52] and decreased concentrations of important microbial products such as short-chain fatty acids and secondary bile acids in the colon.[53] Clearly, further safety and efficacy data are required before azithromycin could be considered a therapeutic option for PSC.

Summary.. Multiple antibiotics have been investigated as therapy for PSC, with some showing promising early results. The most widely investigated antibiotic has been vancomycin, however, further studies are required before antimicrobial therapy could be recommended as routine treatment for PSC.

2.2.2 | Dietary therapy

Dietary therapy has been proposed as a potential therapeutic strategy in PSC, arising from the known efficacy of exclusive enteral nutrition in inducing clinical remission and mucosal healing in Crohn's disease.[54] In a single case report, exclusive enteral nutrition for a period of 10 weeks induced complete normalisation of GGT, ALP, ESR, CRP, haemoglobin and albumin, as well as resolution of symptoms including abdominal pain and diarrhoea in a 13-year-old girl with PSC and ulcerative colitis.[55] The patient was then transitioned to a 'specific carbohydrate diet'. After 1 year, repeat magnetic resonance enterography revealed focal regions of minimal intrahepatic biliary duct prominence, which had improved in appearance compared to pre-treatment imaging. Currently, an explorative study is investigating the potential benefit of a gluten-free diet in patients with PSC.[56] Further investigational studies are required before dietary therapy could be considered a potential therapy for PSC.

2.2.3 | Probiotic, prebiotic and postbiotic therapies

Probiotics are live microorganisms that are thought to provide beneficial health effects to the host when administered in adequate amounts. In a single randomised placebo-controlled crossover trial investigating a probiotic containing four *Lactobacillus* and two *Bifidobacillus* species in 14 patients with PSC-IBD, there was no improvement in ALP (Table 4), liver function tests or clinical symptoms.[57] It must be noted, however, that each microorganism or combination of microorganisms has a unique therapeutic potential and therefore different species or strains may have different therapeutic effects. There is modest evidence for the efficacy of certain probiotic preparations for the treatment of ulcerative colitis,[58] pouchitis[59] and non-alcoholic fatty liver disease[60] and given the paucity of research into live bacterial therapeutics for PSC, further studies in this area are warranted. Prebiotics, which are non-digestible compounds thought to promote growth or activity of beneficial microbiota, may have benefits in other liver diseases such as non-alcoholic steatohepatitis.[61] However, no studies to date have investigated the role of prebiotics in PSC. Postbiotics are bioactive compounds produced by the microbiota. At present, there are no trial data testing postbiotics in PSC.

2.2.4 | Faecal microbiota transplantation

Faecal microbiota transplantation (FMT) involves the transfer of stool from a healthy individual to a person with disease with the aim of treating that disease. FMT is currently the standard of care for recurrent or refractory *C. difficile* infection with evidence of efficacy from multiple randomised controlled trials.[62–64] There is also evidence that FMT can induce remission in ulcerative

colitis.[65,66] In a meta-analysis of four randomised controlled trials, FMT was significantly more likely to induce clinical remission than placebo with an odds ratio of 3.67 (95% CI: [1.82, 7.39], $p < 0.01$) and a number need to treat of five.[66] These data have encouraged research interest in FMT as a therapy for PSC given the majority of patients with PSC have concurrent ulcerative colitis and there may be overlapping pathophysiological mechanisms between these diseases.

The first use of FMT in PSC was described in a single case report of a 38-year-old man who suffered from recurrent bacterial cholangitis whilst awaiting liver transplant for PSC.[67] He underwent FMT from a healthy donor once weekly via colonoscopy for 4 weeks. Concurrent microbiome analysis demonstrated that after completion of treatment, the patient's microbial community was modified from baseline to more closely resemble that of the donor. This was associated with substantial reductions in liver enzymes, bilirubin and toxic bile acids including cholic acid, deoxycholic acid and chenodeoxycholic acid. ALP decreased from 456 IU/L at baseline to 344 IU/L 3 months after treatment, which was sustained after 12 months (352 IU/L). He was afebrile and anicteric after the completion of treatment and remained so at 1 year.

A single open-label pilot trial involving FMT in PSC was published by Allegretti et al in 2019.[68] In this study, each of 10 patients with PSC received a single 90 ml FMT from a single donor, administered in the right colon via colonoscopy. Participants underwent a standard bowel preparation on the day before colonoscopy. The primary outcome was safety and the secondary outcome was a decrease in ALP levels by ≥50% from baseline by week 24 post-FMT. The study demonstrated the short-term safety of FMT as a therapy for PSC, with no reported adverse events. Three out of 10 (30%) patients experienced a decrease in ALP of more than 50% from baseline (Table 4). Assessment of microbial composition pre- and post-FMT showed that alpha-diversity increased in all patients, as early as 1 week post-FMT and all patients developed greater microbial similarity to the donor. This microbiological trend was largely sustained at 24 months after treatment. A total of 2024 organisms which were absent in the patients pre-FMT but present in the donor, were found to have engrafted 1 week post FMT. The richness of frequently engrafted species was correlated with decreased ALP levels, including those belonging to the Erysipelotrichaceae, *Paraprevotella*, *Bacteroides* and *Alistipes* taxa. There was no change in bile acid profiles after FMT. This was a small pilot study that was not powered to assess clinical end points and as such, further research is required to assess FMT as a potential therapy for PSC.

3 | DISCUSSION

PSC remains an orphan disease with a poor prognosis and no effective medical therapies to prevent disease progression. The development of therapies for PSC has been hindered by the rarity of the condition, heterogeneity in its phenotype, the lack of ideal surrogate markers, as well as a limited understanding of the pathogenesis of the disease. To surmount these difficulties, new therapeutics with novel mechanisms are needed and innovative adaptive clinical trial designs may make testing these therapies more feasible.

The gut–liver axis and the gut microbiome in particular have become increasingly recognised as a therapeutic target for the treatment of gastrointestinal and liver diseases, including PSC. Inflammation and injury to the gastrointestinal tract are thought to lead to the trafficking of microbes and their metabolites via the portal system, triggering cross-reactivity with a common biliary epithelial antigen. The recent quantum leaps in gut microbial genomic sequencing as well as culturing methods may yield mechanistic insights into PSC that translate into therapeutic discovery.

To date, vancomycin has been the most widely studied microbiome-targeted agent as therapy for PSC. Oral vancomycin exhibits a low side effect profile and has shown promising results in two randomised controlled trials, demonstrating reductions in both ALP and Mayo Risk Scores.[33,35] The ideal dose and treatment duration of oral vancomycin remain unknown, and larger trials with longer follow-up periods are required to determine the long-term benefit and risks of this therapy.

Other antibiotics such as metronidazole, rifaximin, minocycline and azithromycin have demonstrated variable and less impressive clinical results, however, trials of these agents have been small and further data is required to determine any long-term clinical benefit. Combinations of antibiotics, or modulation with non-antibiotic therapy have not been tested in PSC although have been shown to enhance anti-microbial efficacy in some settings by widening antibiotic spectrum and creating synergistic effects.[69] Intolerance and allergy to antibiotics are common and the emergence of antibiotic-resistant organisms is an important risk that needs to be considered by both the patient taking the therapy and the community more widely. In addition, patients with PSC have been noted to have reduced gut microbial diversity compared to healthy controls and hence antibiotic therapies may perpetuate this dysbiosis which may have potential negative long-term health effects.

Increased microbial diversity has been correlated with health and therefore treatments that enhance microbial diversity may have potential advantages over therapies that diminish the microbiota. Whole stool donor FMT involves the transfer of an entire microbial ecosystem into the gut of the patient. FMT has been demonstrated to induce remission in UC and given that the majority of patients with PSC also have UC it is worth exploring this as a therapy. The only clinical trial evaluating FMT for PSC is small but holds promise for possible benefit, and larger studies with longer follow-up are required to demonstrate long-term benefits of FMT in PSC. In addition, FMT trials have the potential to yield data that may be used to formulate defined microbial therapies to treat PSC.

4 | CONCLUSION

PSC is a rare but morbid disease with no effective medical therapies. It is therefore incumbent upon the medical community to investigate

new treatment paradigms for this orphan disease. The advancements in genomic sequencing and microbiological techniques make the exploration of microbial therapeutics now possible. This scoping review demonstrates the early promise of microbial manipulation as therapy for PSC, and new approaches to microbial therapeutic development and clinical trial design may finally bring an effective therapy to the clinic.

AUTHOR CONTRIBUTIONS

Damjana Bogatic: Conceptualization (equal); data curation (lead); writing – original draft (lead). **Robert V Bryant:** Conceptualization (equal); writing – review and editing (supporting). **Kate D Lynch:** Conceptualization (equal); writing – review and editing (supporting). **Samuel P Costello:** Conceptualization (equal); writing – review and editing (lead).

ACKNOWLEDGEMENT

Declaration of personal interests: Dr Kate Lynch received consultancy and advisory board fees and/or research support from Abbvie, Intercept Pharmaceuticals, Janssen-Cilag, Emerge Health and Guidepoint, Bristol Myers Squibb and speaker honoraria or travel expenses from Bristol Myers Squibb, Dr Falk, Takeda, Abbvie, Chiesi, Gilead, Pfizer, Intercept Pharmaceuticals, Norgine, MSD and Ferring. Assoc Prof Robert V Bryant received consultancy and advisory board fees and/or research support from Janssen, Shire, Takeda, Abbvie, Gilead, Pharmaco, Emerge, Takeda, Ferring, Faulk and is a shareholder in BiomeBank. Dr Samuel Costello received consultancy and advisory board fees and/or research support from Janssen, Ferring, Shire, Takeda, Microbiotica and is a shareholder in BiomeBank. Dr Damjana Bogatic has no interests to declare. Open access publishing facilitated by The University of Adelaide, as part of the Wiley - The University of Adelaide agreement via the Council of Australian University Librarians.

AUTHORSHIP

Guarantor of the article: Samuel P Costello.

ORCID

Damjana Bogatic https://orcid.org/0000-0001-9207-563X
Samuel P. Costello https://orcid.org/0000-0002-2857-1812

REFERENCES

1. Boonstra K, Weersma RK, van Erpecum KJ, Rauws EA, Spanier BWM, Poen AC, et al. Population-based epidemiology, malignancy risk, and outcome of primary sclerosing cholangitis. Hepatology. 2013;58(6):2045–55.
2. Bergquist A, Ekbom A, Olsson R, Kornfeldt D, Lööf L, Danielsson Å, et al. Hepatic and extrahepatic malignancies in primary sclerosing cholangitis. J Hepatol. 2002;36(3):321–7.
3. Mertz A, Nguyen NA, Katsanos KH, Kwok RM. Primary sclerosing cholangitis and inflammatory bowel disease comorbidity: an update of the evidence. Ann Gastroenterol. 2019;32(2):124–33.
4. Poropat G, Giljaca V, Stimac D, Gluud C. Bile acids for primary sclerosing cholangitis. Cochrane Database Syst Rev. 2011;1.
5. Othman MO, Dunkelberg J, Roy PK. Urosdeoxycholic acid in primary sclerosing cholangitis: a meta-analysis and systematic review. Arab J Gastroenterol. 2012;13(3):103–10.
6. Saffioti F, Gurusamy KS, Hawkins N, Toon CD, Tsochatzis E, Davidson B, et al. Pharmacological interventions for primary sclerosing cholangitis: an attempted network meta-analysis. Cochrane Database Syst Rev. 2017;3:Cd011343.
7. Baluyut AR, Sherman S, Lehman GA, Hoen H, Chalasani N. Impact of endoscopic therapy on the survival of patients with primary sclerosing cholangitis. Gastrointest Endosc. 2001;53(3):308–12.
8. Ponsioen CY, Arnelo U, Bergquist A, Rauws EA, Paulsen V, Cantú P, et al. No superiority of stents vs balloon dilatation for dominant strictures in patients with primary sclerosing cholangitis. Gastroenterology 2018;155(3):752-759.e755.
9. Hildebrand T, Pannicke N, Dechene A, Gotthardt DN, Kirchner G, Reiter FP, et al. Biliary strictures and recurrence after liver transplantation for primary sclerosing cholangitis: a retrospective multicenter analysis. Liver Transpl. 2016;22(1):42–52.
10. Gidwaney NG, Pawa S, Das KM. Pathogenesis and clinical spectrum of primary sclerosing cholangitis. World J Gastroenterol. 2017;23(14):2459–69.
11. Kummen M, Holm K, Anmarkrud JA, Nygard S, Vesterhus M, Hoivik M, et al. The gut microbial profile in patients with primary sclerosing cholangitis is distinct from patients with ulcerative colitis without biliary disease and healthy controls. Gut. 2016;66:611–9.
12. Bajer L, Kverka M, Kostovcik M, Macinga P, Dvorak J, Stehlikova Z, et al. Distinct gut microbiota profiles in patients with primary sclerosing cholangitis and ulcerative colitis. World J Gastroenterol. 2017;23(25):4548–58.
13. Lemoinne S, Kemgang A, Ben Belkacem K, Straube M, Jegou S, Corpechot C, et al. Fungi participate in the dysbiosis of gut microbiota in patients with primary sclerosing cholangitis. Gut. 2020;69(1):92–102.
14. Rühlemann M, Liwinski T, Heinsen F-A, Bang C, Zenouzi R, Kummen M, et al. Consistent alterations in faecal microbiomes of patients with primary sclerosing cholangitis independent of associated colitis. Aliment Pharmacol Ther. 2019;50(5):580–9.
15. Lichtman SN, Keku J, Clark RL, Schwab JH, Sartor RB. Biliary tract disease in rats with experimental small bowel bacterial overgrowth. Hepatology. 1991;13(4):766–72.
16. Hole MJ, Kaasen Jørgensen K, Holm K, Braadland PR, Meyer-Myklestad MH, Medhus AW, et al. A shared mucosal gut microbiota signature in primary sclerosing cholangitis before and after liver transplantation. Hepatology. 2022. https://doi.org/10.1002/hep.32773
17. Shah A, Crawford D, Burger D, Martin N, Walker M, Talley NJ, et al. Effects of antibiotic therapy in primary sclerosing cholangitis with and without inflammatory bowel disease: A systematic review and meta-analysis. Semin Liver Dis. 2019;39(4):432–41.
18. Chapman MH, Thorburn D, Hirschfield GM, Webster GGJ, Rushbrook SM, Alexander G, et al. British Society of Gastroenterology and UK-PSC guidelines for the diagnosis and management of primary sclerosing cholangitis. Gut. 2019;68(8):1356–78.
19. Ponsioen CY, Chapman RW, Chazouillères O, Hirschfield GM, Karlsen TH, Lohse AW, et al. Surrogate endpoints for clinical trials in primary sclerosing cholangitis: review and results from an international PSC study group consensus process. Hepatology. 2016;63(4):1357–67.
20. Williamson KD, Chapman RW. Editorial: further evidence for the role of serum alkaline phosphatase as a useful surrogate marker of prognosis in PSC. Aliment Pharmacol Ther. 2015;41(1):149–51.
21. Kim WR, Therneau TM, Wiesner RH, Poterucha JJ, Benson JT, Malinchoc M, et al. A revised natural history model for primary sclerosing cholangitis. Mayo Clin Proc. 2000;75(7):688–94.

22. de Vries EM, Wang J, Williamson KD, Leeflang MM, Boonstra K, Weersma RK, et al. A novel prognostic model for transplant-free survival in primary sclerosing cholangitis. Gut. 2018;67(10):1864–9.
23. Goode EC, Clark AB, Mells GF, Srivastava B, Spiess K, Gelson WTH, et al. Factors associated with outcomes of patients with primary sclerosing cholangitis and development and validation of a risk scoring system. Hepatology. 2019;69(5):2120–35.
24. Tan LZ, Reilly CR, Steward-Harrison LC, Balouch F, Muir R, Lewindon PJ. Oral vancomycin induces clinical and mucosal remission of colitis in children with primary sclerosing cholangitis-ulcerative colitis. Gut. 2019;68(8):1533–5.
25. Fahad L, Charoen M, Daniel G, Aline C. Therapeutic effect of vancomycin in UC patients associated with PSC: case series: P-020. Am J Gastroenterol. 2018;113:S6.
26. Dao A, Abidian M, Lestrange A, Mattar M, Rangnekar A, Charabaty A. Oral vancomycin induces and maintains remission of ulcerative colitis in the subset of patients with associated primary sclerosing cholangitis. Inflamm Bowel Dis. 2019;25(7):e90–1.
27. Vaughn BP, Kaiser T, Staley C, Hamilton MJ, Reich J, Graiziger C, et al. A pilot study of fecal bile acid and microbiota profiles in inflammatory bowel disease and primary sclerosing cholangitis. Clin Exp Gastroenterol. 2019;12:9–19.
28. Cox KL, Cox KM. Oral vancomycin: treatment of primary sclerosing cholangitis in children with inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 1998;27(5):580–3.
29. Davies YK, Tsay CJ, Caccamo DV, Cox KM, Castillo RO, Cox KL. Successful treatment of recurrent primary sclerosing cholangitis after orthotopic liver transplantation with oral vancomycin. Case Rep Transplant. 2013;2013:314292–5.
30. Buness C, Lindor KD, Miloh T. Oral vancomycin therapy in a child with primary sclerosing cholangitis and severe ulcerative colitis. Pediatr Gastroenterol Hepatol Nutr. 2016;19(3):210–3.
31. Hey P, Lokan J, Johnson P, Gow P. Efficacy of oral vancomycin in recurrent primary sclerosing cholangitis following liver transplantation. BMJ Case Rep 2017;bcr2017221165, 2017.
32. de Chambrun GP, Nachury M, Funakoshi N, Gerard R, Bismuth M, Valats JC, et al. Oral vancomycin induces sustained deep remission in adult patients with ulcerative colitis and primary sclerosing cholangitis. Eur J Gastroenterol Hepatol. 2018;30(10):1247–52.
33. Rahimpour S, Nasiri-Toosi M, Khalili H, Ebrahimi-Daryani N, Nouri-Taromlou MK, Azizi Z. A triple blinded, randomized, placebo-controlled clinical trial to evaluate the efficacy and safety of Oral vancomycin in primary sclerosing cholangitis: a pilot study. J Gastrointestin Liver Dis. 2016;25(4):457–64.
34. Fisk JD, Ritvo PG, Ross L, Haase DA, Marrie TJ, Schlech WF. Measuring the functional impact of fatigue: initial validation of the fatigue impact scale. Clin Infect Dis. 1994;18(Suppl 1):S79–83.
35. Tabibian JH, Weeding E, Jorgensen RA, Petz JL, Keach JC, Talwalkar JA, et al. Randomised clinical trial: vancomycin or metronidazole in patients with primary sclerosing cholangitis – a pilot study. Aliment Pharmacol Ther. 2013;37(6):604–12.
36. Deneau MR, Mack C, Mogul D, Perito ER, Valentino PL, Amir AZ, et al. Oral vancomycin, ursodeoxycholic acid or no therapy for pediatric primary sclerosing cholangitis: a matched analysis. Hepatology. 2021;73(3):1061–73.
37. Davies YK, Cox KM, Abdullah BA, Safta A, Terry AB, Cox KL. Long-term treatment of primary sclerosing cholangitis in children with oral vancomycin: an immunomodulating antibiotic. J Pediatr Gastroenterol Nutr. 2008;47(1):61–7.
38. Abarbanel DN, Seki SM, Davies Y, Marlen N, Benavides JA, Cox K, et al. Immunomodulatory effect of vancomycin on Treg in pediatric inflammatory bowel disease and primary sclerosing cholangitis. J Clin Immunol. 2013;33(2):397–406.
39. Nitzan O, Elias M, Peretz A, Saliba W. Role of antibiotics for treatment of inflammatory bowel disease. World J Gastroenterol. 2016;22(3):1078–87.
40. Cheifetz A, Itzkowitz S. The diagnosis and treatment of pouchitis in inflammatory bowel disease. J Clin Gastroenterol. 2004;38(5 Suppl 1):S44–50.
41. Leite AZ, Sipahi AM, Damião AO, Coelho AM, Garcez AT, Machado MC, et al. Protective effect of metronidazole on uncoupling mitochondrial oxidative phosphorylation induced by NSAID: a new mechanism. Gut. 2001;48(2):163–7.
42. Pélissier M-A, Vasquez N, Balamurugan R, Pereira E, Dossou-Yovo F, Suau A, et al. Metronidazole effects on microbiota and mucus layer thickness in the rat gut. FEMS Microbiol Ecol. 2010;73(3):601–10.
43. Färkkilä M, Karvonen A-L, Nurmi H, Nuutinen H, Taavitsainen M, Pikkarainen P, et al. Metronidazole and ursodeoxycholic acid for primary sclerosing cholangitis: A randomized placebo-controlled trial. Hepatology. 2004;40(6):1379–86.
44. Bass NM, Mullen KD, Sanyal A, Poordad F, Neff G, Leevy CB, et al. Rifaximin treatment in hepatic encephalopathy. N Engl J Med. 2010;362(12):1071–81.
45. Kang DJ, Kakiyama G, Betrapally NS, Herzog J, Nittono H, Hylemon PB, et al. Rifaximin exerts beneficial effects independent of its ability to Alter microbiota composition. Clin Transl Gastroenterol. 2016;7(8):e187–7.
46. Bajaj JS, Heuman DM, Sanyal AJ, Hylemon PB, Sterling RK, Stravitz RT, et al. Modulation of the metabiome by rifaximin in patients with cirrhosis and minimal hepatic encephalopathy. PLoS One. 2013;8(4):e60042–2.
47. Xu D, Gao J, Gillilland M, III, Wu X, Song I, Kao JY, Owyang C Rifaximin alters intestinal bacteria and prevents stress-induced gut inflammation and visceral hyperalgesia in rats. Gastroenterology 2014;146(2):484-496.e484.
48. Tabibian JH, Gossard A, el-Youssef M, Eaton JE, Petz J, Jorgensen R, et al. Prospective clinical trial of rifaximin therapy for patients with primary sclerosing cholangitis. Am J Ther. 2017;24(1):e56–63.
49. Silveira MG, Torok NJ, Gossard AA, Keach JC, Jorgensen, RN RA, Petz, RN JL, et al. Minocycline in the treatment of patients with primary sclerosing cholangitis: results of a pilot study. Am J Gastroenterol. 2009;104(1):83–8.
50. Boner AL, Peroni D, Bodini A, Delaini G, Piacentini G. Azithromycin may reduce cholestasis in primary sclerosing cholangitis: a case report and serendipitous observation. Int J Immunopathol Pharmacol. 2007;20(4):847–9.
51. Oldenburg CE, Sié A, Coulibaly B, Ouermi L, Dah C, Tapsoba C, et al. Effect of commonly used pediatric antibiotics on gut microbial diversity in preschool children in Burkina Faso: A randomized clinical trial. *Open forum*. Infect Dis. 2018;5(11).
52. Wei S, Mortensen MS, Stokholm J, Brejnrod AD, Thorsen J, Rasmussen MA, et al. Short- and long-term impacts of azithromycin treatment on the gut microbiota in children: a double-blind, randomized, placebo-controlled trial. EBioMedicine. 2018;38:265–72.
53. Li R, Wang H, Shi Q, Wang N, Zhang Z, Xiong C, et al. Effects of oral florfenicol and azithromycin on gut microbiota and adipogenesis in mice. PLoS ONE. 2017;12(7):e0181690.
54. Swaminath A, Feathers A, Ananthakrishnan AN, Falzon L, Li Ferry S. Systematic review with meta-analysis: enteral nutrition therapy for the induction of remission in paediatric Crohn's disease. Aliment Pharmacol Ther. 2017;46(7):645–56.
55. Suskind DL, Wu B, Braly K, Pacheco MC, Wahbeh G, Lee D. Clinical remission and normalization of laboratory studies in a patient with ulcerative colitis and primary sclerosing cholangitis using dietary therapy. J Pediatr Gastroenterol Nutr. 2018;67(1):e15–8.

56. Tetzlaff M. Gluten-free diet in patients with primary sclerosing cholangitis (PSC) (PSt-GFD). 2019; https://clinicaltrials.gov/ct2/show/NCT04006886.
57. Vleggaar FP, Monkelbaan JF, van Erpecum KJ. Probiotics in primary sclerosing cholangitis: a randomized placebo-controlled crossover pilot study. Eur J Gastroenterol Hepatol. 2008;20(7):688–92.
58. Fujiya M, Ueno N, Kohgo Y. Probiotic treatments for induction and maintenance of remission in inflammatory bowel diseases: a meta-analysis of randomized controlled trials. Clin J Gastroenterol. 2014;7(1):1–13.
59. Gionchetti P, Calafiore A, Riso D, Liguori G, Calabrese C, Vitali G, et al. The role of antibiotics and probiotics in pouchitis. Ann Gastroenterol. 2012;25(2):100–5.
60. Lavekar AS, Raje DV, Manohar T, Lavekar AA. Role of probiotics in the treatment of nonalcoholic fatty liver disease: A meta-analysis. Euroasian J Hepatogastroenterol. 2017;7(2):130–7.
61. Bomhof MR, Parnell JA, Ramay HR, Crotty P, Rioux KP, Probert CS, et al. Histological improvement of non-alcoholic steatohepatitis with a prebiotic: a pilot clinical trial. Eur J Nutr. 2019;58(4):1735–45.
62. van Nood E, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal EG, de Vos WM, et al. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. N Engl J Med. 2013;368(5):407–15.
63. Cammarota G, Masucci L, Ianiro G, Bibbò S, Dinoi G, Costamagna G, et al. Randomised clinical trial: faecal microbiota transplantation by colonoscopy vs. vancomycin for the treatment of recurrent *Clostridium difficile* infection. Aliment Pharmacol Ther. 2015;41(9):835–43.
64. Quraishi MN, Widlak M, Bhala N, Moore D, Price M, Sharma N, et al. Systematic review with meta-analysis: the efficacy of faecal microbiota transplantation for the treatment of recurrent and refractory *Clostridium difficile* infection. Aliment Pharmacol Ther. 2017;46(5):479–93.
65. Paramsothy S, Paramsothy R, Rubin DT, Kamm MA, Kaakoush NO, Mitchell HM, et al. Faecal microbiota transplantation for inflammatory bowel disease: A systematic review and meta-analysis. J Crohns Colitis. 2017;11(10):1180–99.
66. Costello SP, Soo W, Bryant RV, Jairath V, Hart AL, Andrews JM. Systematic review with meta-analysis: faecal microbiota transplantation for the induction of remission for active ulcerative colitis. Aliment Pharmacol Ther. 2017;46(3):213–24.
67. Philips CA, Augustine P, Phadke N. Healthy donor fecal microbiota transplantation for recurrent bacterial cholangitis in primary sclerosing cholangitis – a single case report. J Clin Transl Hepatol. 2018;6(4):438–41.
68. Allegretti JR, Kassam Z, Carrellas M, Mullish BH, Marchesi JR, Pechlivanis A, et al. Fecal microbiota transplantation in patients with primary sclerosing cholangitis: A pilot clinical trial. Am J Gastroenterol. 2019;114(7):1071–9.
69. Ejim L, Farha MA, Falconer SB, Wildenhain J, Coombes BK, Tyers M, et al. Combinations of antibiotics and nonantibiotic drugs enhance antimicrobial efficacy. Nat Chem Biol. 2011;7(6):348–50.
70. Rossen NG, Fuentes S, Boonstra K, D'Haens GR, Heilig HG, Zoetendal EG, et al. The mucosa-associated microbiota of PSC patients is characterized by low diversity and low abundance of uncultured Clostridiales II. J Crohns Colitis. 2014;9(4):342–8.
71. Torres J, Bao X, Goel A, Colombel JF, Pekow J, Jabri B, et al. The features of mucosa-associated microbiota in primary sclerosing cholangitis. Aliment Pharmacol Ther. 2016;43(7):790–801.
72. Kevans D, Tyler AD, Holm K, Jørgensen KK, Vatn MH, Karlsen TH, et al. Characterization of intestinal microbiota in ulcerative colitis patients with and without primary sclerosing cholangitis. J Crohns Colitis. 2016;10(3):330–7.
73. Sabino J, Vieira-Silva S, Machiels K, Joossens M, Falony G, Ballet V, et al. Primary sclerosing cholangitis is characterised by intestinal dysbiosis independent from IBD. Gut. 2016;65(10):1681–9.
74. Torres J, Palmela C, Brito H, Bao X, Ruiqi H, Moura-Santos P, et al. The gut microbiota, bile acids and their correlation in primary sclerosing cholangitis associated with inflammatory bowel disease. United Eur Gastroenterol J. 2018;6(1):112–22.
75. Lapidot Y, Amir A, Ben-Simon S, Veitsman E, Cohen-Ezra O, Davidov Y, et al. Alterations of the salivary and fecal microbiome in patients with primary sclerosing cholangitis. Hepatol Int. 2021;15(1):191–201.
76. Denoth L, Juillerat P, Kremer AE, Rogler G, Scharl M, Yilmaz B, et al. Modulation of the mucosa-associated microbiome linked to the PTPN2 risk gene in patients with primary sclerosing cholangitis and ulcerative colitis. Microorganisms. 2021;9(8):1752.
77. Ostadmohammadi S, Azimirad M, Houri H, Naseri K, Javanmard E, Mirjalali H, et al. Characterization of the gut microbiota in patients with primary sclerosing cholangitis compared to inflammatory bowel disease and healthy controls. Mol Biol Rep. 2021;48(7):5519–29.
78. Dubrovsky A, Kitts CL. Effect of the specific carbohydrate diet on the microbiome of a primary sclerosing cholangitis and ulcerative colitis patient. Cureus. 2018;10(2):e2177–7.
79. Buness CW, Johnson KM, Ali AH, Alrabadi L, Lindor K, Miloh T, et al. Successful response of primary sclerosing cholangitis and associated ulcerative colitis to oral vancomycin may depend on brand and personalized dose: report in an adolescent. Clin J Gastroenterol. 2021;14(2):684–9.

How to cite this article: Bogatic D, Bryant RV, Lynch KD, Costello SP. Systematic review: microbial manipulation as therapy for primary sclerosing cholangitis. Aliment Pharmacol Ther. 2023;57:23–36. https://doi.org/10.1111/apt.17251

APPENDIX A

PubMed and Cochrane Library were searched using the following search terms

An initial database search using the keywords “antibiotic” or “vancomycin” or “metronidazole” or “rifaximin” or “minocycline” or “azithromycin” or “diet” or “tacrolimus” or “sulfasalazine” or “infliximab” or “adalimumab” or “probiotic” or “faecal microbiota transplant” or “FMT.” Subsequently, each key word was combined with the term “Primary sclerosing cholangitis” using the Boolean term “AND.” This strategy was used both as Medical Subject Headings (MeSH) terms if available and as free text.