Liver transplantation in patients with (PSC) and (IBD)

1-Timing, indication and allocation rules of LT (Eleonora De Martin, Paris)

PICO 1: Is the MELD allocation system suitable for patients with PSC?

Recommendations:

(1) MELD score, despite better performing in patients with secondary biliary cirrhosis, should be used to give priority to PSC liver transplantation candidates with or without IBD **(Quality of Evidence; Low | Grade of Recommendation; Strong).**
(2) Because MELD score underestimates the severity of PSC complicated by recurrent cholangitis, refractory pruritus and persistent jaundice, these events should be considered to give priority to PSC liver transplantation candidates despite the presence of IBD **(Quality of Evidence; Very Low | Grade of Recommendation; Strong**).
(3) IBD should be controlled at the time of liver transplantation **(Quality of Evidence; Low | Grade of Recommendation; Strong)**.

	Study type	**N of patients**	**Main outcomes**
Nagai, Transpl Int 2021;34: 499-513.	Observational comparative retrospective	ALD=6094 HCV=1653 NASH=3848 PBC=602 PSC=819	- Disease progression - Waitlist outcomes
Goet JC, Transpl Int. 2018 Jun;31(6):590-599	Observational comparative retrospective	Overall= 852 PSC=146	- Waitlist mortality - Post-transplant survival
Klose, Langenbecks Arch Surg 2014;399: 1021–1029.	Observational comparative retrospective	Overall = 1420 PSC = 126	- Post-transplant survival in pre- and post-MELD era
Suri, J Clin Med. 2020 Jan 23;9(2):319	Observational comparative retrospective	AIH=7412 PBC= 8119 PSC=10901	- Waitlist survival (composite death or removal for clinical deterioration)
Goldberg Liver Transpl. 2011 Nov;17(11):1355-63.	Observational comparative retrospective	Overall = 71976 PSC = 3165	- times to death or withdrawal from the waitlist

Brandsaeter . Liver Transpl. 2003 Sep;9(9):961-9	Observational comparative retrospective	PSC= 255 77% with IBD Control = 610	- Events on the waitlist - Events post-LT
Brandsaeter Scand J Gastroenterol. 2003 Nov;38(11):1176-83	Observational comparative retrospective	PSC=245 Control=618	- post-LT survival
Goldberg, Liver Transpl. 2013, 19, 250–258	Observational retrospective	PSC =171	- Waitlist survival (composite death or removal for clinical deterioration)

Outcomes:

1. Waitlist mortality (death or removal for deterioration)
2. Post-transplant survival

In the study of Brandsaeter et al. [1] the death rate on the waiting list was significantly lower for PSC patients (3.4%) than for control (7.3%) (p=0.003). If the MELD score was included in the analysis, it was a significant predictor of outcome from the waiting list (a higher MELD score predicts death without transplantation; p=0.025). There was no difference in post-acceptance survival between the two groups. This was confirmed by Goldberb and colleagues [2] in a study from the UNOS database. Over an 8-year period, 14,073 non-PSC patients (20.5%) and 432 PSC patients (13.6%) died or were removed from the waitlist (p< 0.0001). The adjusted hazard ratio (HR) for PSC was 0.72 [95% confidence interval (CI) = 0.66-0.79], which indicated that these patients had a lower time-dependent risk of death or removal from the waitlist in comparison with patients without PSC. More recently Goet et al. [3] showed that in the PSC group, a total of 18/146 (12.3%) died or were removed due to clinical deterioration on the LT waiting list compared to 141/706 (20.0%) in the non-PSC group. Although PSC patients had a significantly longer waiting time until delisting compared to non-PSC patients (HR 0.73; CI 0.61–0.88; P = 0.001), they had significant better waiting list survival (HRunivariate 0.48; CI: 0.29–0.78; P = 0.003) in the cumulative incidence curves of the competing risk analyses. There were no differences in the rate of LT between PSC and non-PSC candidates (HR 0.84; CI 0.69–1.03; P = 0.101. Not surprisingly, PSC patients with MELD Exception (ME) points had a significantly higher probability of LT than MELD PSC patients (HRME 9.86 CI 6.14–15.85; P < 0.001) and non-PSC patients with ME points (HRME in ME non-PSC patients 4.60 CI 3.78–5.61; P < 0.001). Nagai and colleagues [4] found that in comparison with ALD patients, risk of 90-day waitlist mortality was comparable for HCV and PSC patients (1.27, 95% CI 0.85–1.35 and 0.90–1.81, p= 0.2). Higher serum total bilirubin level was an independent risk factor for 90-day mortality in PSC and primary biliary cholangitis (PBC) patients. Hyponatremia was an independent risk factor for 90-day and 1-year mortality in PSC. Another study from the UNOS database [5] described better waitlist outcomes for patients with PSC compared with patients with autoimmune hepatitis (AIH) or PBC. this study found that patients with PBC and AIH were more likely to be removed from the waitlist for death or clinical deterioration (17.5% and 15%, respectively) than PSC (10.2%) patients. On competing risk analysis, AIH patients had a similar risk of being removed from the waitlist compared to those with PBC (subdistribution hazard ratio (SHR) 0.94, 95% CI 0.85-1.03) and

higher risk of removal compared to those with PSC (SHR 0.8, 95% CI 0.72 to 0.89). Klose at al. [6] found no difference in pre- and post-MELD eras. The mean time on the waiting list increased since introduction of MELD-based allocation from 1.6 to 2.3 years without reaching statistical significance (p=0.068). No improvement in means of short-term mortality could be shown in relation to alterations of allocation policy within the MELD era (p=0.375). Survival rates of the pre-MELD era did not differ significantly from those of the MELD era (p=0.097) in multivariate risk-adjusted analysis. Concerning post-LT survival Brandsaeter et al. [7] found no difference in 1-, 3- and 5-year patient survival rates for PSC and non-PSC patients; in PSC group year of transplantation, previous hepatobiliary surgery and MELD score are predictors of survival following transplantation.

Few studies addressed the questions of outcomes in patients with PSC and IBD. Brandsaeter et al. [1] found no difference in survival following LT between patients with and patients without IBD (p=0.451) and no difference in survival following LT between patients with ulcerative colitis and Crohn disease (p=0.149). The type of IBD (ulcerative colitis or Crohn disease) was not a predictor of outcome from the waiting list in the series of Goldberg et. al, nor does it affect the survival after LT. This is in contrast to what Neuberger et al. showed in their work, in which Crohn disease was an independent predictor of poor outcome [8]. An active IBD at the time of transplant has been identified as an independent predictive factor of graft failure post-LT [Joshi, Liver Transpl 2013]. However, this finding was recently questioned by a large Nordic Multicenter Study which found that neither high IBD activity nor the presence of IBD flare before LT was associated with PSC recurrence. On the other hand, in the same study colectomy before LT was associated with a reduced risk of PSC recurrence [Lindstrom, Scand J Gastroenterol 2018]. In clinical practice we try to avoid transplanting patients with active IBD while a prophylactic colectomy cannot be recommended.

In several allocation systems (including the French one) bacterial cholangitis allows PSC patients to have exception points as the severity of the disease is not reflected by the MELD score. The results of the study of Goldberg et al. [9] call into question this policy as the history of bacterial cholangitis was not associated with an increased risk of waitlist removal for death or clinical deterioration.

Moreover, also refractory pruritus and jaundice (with a perisisten bilirubine > 100 micromol/dL) gives priority to PSC liver transplantation candidates with a low MELD score (< 15).

We agree on the fact that PSC LT candidates require a different evaluation of disease's severity, which can be captured by the MELD score for those with secondary biliary cirrhosis, but is more complex to evaluate in those with biliary attempt and no fibrosis progression, who need a different prioritization.

RESEARCH AGENDA?

To develop a model PSC-specific to predict the risk of liver failure or complication requiring LT

References

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PICO 2: Is pre-emptive LT for high-grade dysplasia in suspicious strictures indicated and compatible with the overall demand of LT?

Recommendation:

Liver transplantation can be considered in people with PSC and high-grade biliary dysplasia confirmed by cytology or ductal histology (LoE 4, weak recommendation, 92% consensus).

	Study type	Number of patients	Main outcomes
Andersen Transpl Direct 2015;1:e39	Observational comparative retrospective	PSC= 138 Suspicion of malignancy 25/138 (18.1%)	Features of PSC LT recipients Post-LT outcomes

		PBC+AIH=84	
Majeed A Scand J Gastroenterol 2018;53:56–63	Observational comparative retrospective	PSC = 209 Benign lesions=169 CCA=16 HGD=12	Post-LT survival
Boberg KM J Hepatol 2006;45:568–574	Observational retrospective	PSC = 61 PSC with LGD or HGD/CCA=22 HGD LT = 7	results of brush cytology were compared with the final histopathology of the explanted liver
Vannas MJ Liver Int 2017;37:735–742	Observational comparative retrospective	PSC=126 Symptomatic= 96 Asymptomatic=35	results of brush cytology were compared with the final histopathology of the explanted liver

Liver transplantation for high grade dysplasia (HGD) is still controversial. HGD represents the prelude of CCA development as it has been clearly shown by the sequence metaplasia–low-grade dysplasia–high-grade dysplasia–carcinoma described by Lewis et al [1]. The policy of offering LT for HGD is routine practice in Nordic countries where a screening for dysplasia is systematically performed [2-4] and where the organ shortage is less marked compared to other countries. In the study of Andersen et al. 25 (18.1%) patients were transplanted for suspicion of malignancy and among them 5 (20%) had no malignancy in the explant liver [2]. Vannas et al. compared patients who underwent LT for symptomatic or asymptomatic PSC. In the symptomatic group (n=96), all patients had symptoms because of either end-stage liver disease, recurrent bacterial cholangitis, or refractory pruritus. The asymptomatic group (n=35) included patients with a high clinical suspicion of biliary neoplasia and with a rapid radiological progress of the disease but without clinical symptoms of liver disease. In the latter group 57.1% of patients had benign lesions on the explant [5].

One- and 5-year patient survival in this subgroup of patients were 95.8% and 83.3%, respectively, comparable to patients transplanted for impaired quality of life (97.4% and 94.9%, respectively) and for end-stage liver disease (91.4% and 88.6%, respectively).

In the series of Majeed at al., among 209 PSC transplant recipients, 30 (14%) patients were transplanted for biliary dysplasia while 179 (86%) patients for end stage liver disease. In the explant livers, 169 patients showed benign lesions, 16 CCA and 12 HGD. Mortality of patients with HGD in the explanted liver was similar to the one of patients with benign histopathology (log rank =0.87) [6].

In a descriptive study, 7 PSC patients with HGD confirmed in the explant liver, didn't show any signs of malignancy recurrence with median follow-up of 27 months (range 25–62 months) after the transplant [7].

The EASL guidelines recently published, recommend performing LT for HGD considering the strong association between HGD and CCA. On the other end LT for low grade dysplasia should not be considered due to the possible benign findings in the explant and the exposition to the risk of a transplant too early in the diseases' course [8].

On the other hand, based on the fact that the risk of HGD development in PSC patients is difficult to quantify, the ERCP screening is not systematic and the donor pool is limited in the majority of the countries, to recommend LT for HGD cannot t be made systematically but it should take into account countries' resources.

RESEARCH AGENDA?

To study the rate of HGD transforming in CCA in patients with PSC

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2-Management on WL (Annika Bergquist, Stockholm)

PICO 3: Is the prophylactic use of rotating antibiotic for recurrent cholangitis safe in view of liver transplantation (LT)?

Annika Bergquist, Christina Villard

Recommendation

Rotating antibiotics should only be considered following biliary cultures and multidisciplinary assessment in highly selected patients due to the risk for multidrug resistance (MDR). Available data on presence of MDR related adverse events after liver transplantation does not allow for a firmer recommendation.

Quality of Evidence: Low
Grade of Recommendation: Strong/Low

Bacterial cholangitis is common in patients with PSC due to bile flow obstruction associated with biliary stricturing (1, 2). High grade strictures increase the risk for colonization. The severity of bacterial cholangitis ranges from mild symptoms easily treated with antibiotics to severe symptoms with sepsis. Due to its variability, defining bacterial cholangitis in patients with PSC is challenging. A panel of PSC experts was unable to reach consensus through a Delphi process on its definition in the context of PSC (3). One suggested criterion is the presence of pus within the bile ducts at endoscopic retrograde cholangiopancreatography (ERCP) (4). Other suggested criteria include markers of inflammation (i.e. fever or elevated infection parameters), along with at least two of the following: upper right abdominal pain, positive microbiologic findings in bile culture, increase in total bilirubin or ALP level greater than twice the ULN, or exclusion of another foci of infection (4).

Biliary infections are often polymicrobial with Escherichia coli being the most frequently occurring pathogen (5). Other present pathogens include gram-negative bacteria (e.g., Klebsiella, Pseudomonas and Bacteroides) and gram-positive bacteria (e.g., Enterococci and Streptococci) (5). The selection of antibiotic therapy is based on the targeted organisms, local epidemiology, drug-resistance, renal/hepatic function, and severity of infection according to local routine (2). In addition to antibiotic treatment current guidelines recommend dilatation of relevant strictures after multidisciplinary assessment (2, 6, 7).

Long-term treatment with antibiotics and rotating antibiotics in PSC should be avoided when possible due to the apparent associated risk of multidrug-resistance (MDR)(2). The percentage of resistant organisms currently amounts to 28% of cirrhotic patients in Europe underscoring the importance of prudent antimicrobial usage (8). Recurrent episodes of severe bacterial cholangitis is an accepted indication for transplantation, even without presence of cirrhosis, and in these situations, close monitoring with repeated cultures and targeted therapy is important. One study assessed waitlist mortality in PSC transplant candidates and found no

increased risk of waitlist mortality for patients with recurrent bacterial cholangitis, yet this study did not address MDR (9).

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PICO 4: When should PSC patients on the waiting list be treated with biliary stents?

Recommendation

1. The indication for endoscopic intervention in PSC patients on the waiting list for liver transplantation should be based on a pre-interventional MRI/MRCP and discussion in a multidisciplinary team conference.

Quality of Evidence: 5
Grade of Recommendation: Strong

2. ERCP may be considered on the waiting list in PSC patients who present with aggravating and severe symptoms (itch, bacterial cholangitis) likely to improve following endoscopic treatment after pre-interventional MRI/MRCP and discussion in a multidisciplinary team conference

Quality of Evidence: 4
Grade of Recommendation: Weak

3. The choice between biliary balloon dilation with or without stenting should be left to the endoscopist's discretion

Quality of Evidence: 5
Grade of Recommendation: Weak

Introduction

Relief of biliary obstruction improves cholestatic symptoms and delays development of fibrosis (1-3). Evidence for the benefit of opening relevant strictures for long term prognosis in PSC is scarce but it may prolong liver transplant-free survival. Relevant strictures in PSC are defined as high-grade strictures on imaging in the common bile duct or hepatic ducts (4) together with signs or symptoms of obstructive cholestasis and/or bacterial cholangitis (3). These strictures are associated with worse outcomes even when CCA is excluded (5, 6) and are diagnosed in up to 50% of PSC patients (7).

Liver transplantation in PSC is recommended in patients with decompensated cirrhosis, confirmed high-grade biliary dysplasia, recurrent bacterial cholangitis and/or severe pruritus or jaundice (3). Endoscopic treatment options of biliary strictures with bile duct dilatation and/or stenting should be ruled out and/or deemed not beneficial long term, before considering transplantation.

Indications for endoscopic interventions

Decision-making about endoscopic intervention particularly for PSC patients on the waiting list for liver transplantation is complex and should be individualized. The evidence for benefit of endoscopic interventions in advanced PSC is lacking and ERCP is a high-risk procedure in the severely ill. Opening of strictures is most useful for well defined high-grade strictures in the larger bile ducts although a patient may sometimes benefit from the successful dilation of multiple or more peripheral strictures (3). Indications for ERCP include presence of relevant strictures, symptoms of obstructive cholestasis and/or bacterial cholangitis (1, 3). PSC patients with indication for endoscopic intervention should be investigated with a high quality MRI/MRCP (8) and discussed at a hepatopancreaticobiliary multidisciplinary conference before ERCP is performed (1, 3).

A reasonable approach to endoscopic treatment on the waiting list is to treat PSC patients with the aim to relieve symptoms in those with lower MELD and expected long waiting time.

However, there are no studies on the potential benefit or risk of endoscopic intervention in PSC patients on the waiting list. In the pretransplant setting in very advanced PSC, it may be difficult to decide whether a high or increasing bilirubin level is caused by increased stricturing

of the biliary tree available for dilatation or liver failure alone. The symptomatic relief is reported similar between patients with or without cirrhosis, while ALP and bilirubin levels do not significantly decline after ERC in cirrhotic patients(9). Endoscopic interventions for people with advanced PSC on the waiting list should therefore be reserved for treatment of unacceptable symptoms i.e. itch, or bacterial cholangitis in which ERCP is essential (6). Bacterial cholangitis does however not seem to increase waitlist mortality (10). In addition, some of the PSC patients listed for liver transplantation patients have previously been treated with repeated dilatations or stenting. In these cases, further treatment during the waiting time may be justified.

Risk for complications after ERCP

ERCP is associated with risks for complications such as perforation, cholangitis and pancreatitis(11). Preoperative prophylaxis with antiobiotics is generally recommended (1, 3). The risks for procedure related complications and aggravated liver failure need to be considered and ERCP in patients with very severe disease and high MELD scores should probably be avoided. The risk of complications in PSC patients with cirrhosis defined with histology elastography > 14.4 kPa or presence of liver failure has been investigated without showing increase in complication rates (9).

Stent or dilatation

There is no obvious additional benefit to balloon dilatations from stenting in the treatment of relevant strictures in PSC (12-14). Stenting is also associated with more complications (pancreatitis and cholangitis) (13, 14). Therefore, balloon dilatation is usually the first line treatment. Some strictures do not open satisfactorily with balloon dilatation alone and stent(s) may be inserted in these situations (15). If a plastic biliary stent is placed, it should generally be removed within 2-4 weeks to reduce the risk of adverse events (3, 13). Fully covered self-expandable metal stents may be used in selected cases, but there are no evidence to make a firm recommendation.

ESGE/EASL suggest in their guidelines from 2017, that the choice between stenting and balloon dilation should be left to the endoscopist's discretion (1). Ideally, such decisions are taken and supported by a multidisciplinary team, considering the patients´ history, previous response to balloon therapy and risk for complications. Since we know that biliary stenting should be avoided, if possible, a decision for a priori stenting is rarely taken. Often, a duct retaining contrast during ERCP even after dilatation, a difficult ductal access in combination with an expected necessity for a second ERCP or a contrast leakage play a role when a stent is placed. It might be therefore the decision in the end shall be left to the endoscopist, if there is no possibility for a "ad hoc" multidisciplinary discussion in the ERCP suite.

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3-Graft Selection and Technical issues (Pal Dag Line, Oslo)

PICO 5: Liver transplantation for primary sclerosing cholangitis (PSC): duct-to-duct anastomosis versus Roux-en-Y hepaticojejunostomy

Recommendation:

(1) Duct-to duct anastomosis should be used as biliary reconstruction technique in liver transplantation for PSC when feasible and technically possible **(Grade B, level 3a).**

(2) Compared to RY, DD anastomosis is associated with reduced incidence of cholangitis (grade B, level 3a) and late-onset non-anastomotic strictures **(grade B, level 3b)** and non-inferiority with respect to biliary leakage as well as graft and patient survival **(grade B level 3b).**

The following studies & guidelines have been considered;

Reference	Study type	No. of Patients/studies	Main outcomes
Montano-Loza, Aliment Pharmacol Ther 2017, 45: 485-500.	Systematic review	-	Recurrence
Sutton, Liver Transplant. 2014;20:457–463.	Retrospective, observational	98 patients 45 duct-to-duct, 53 Roux-en-Y	Patient and graft survival, biliary leakage, anastomotic strictures (AS), non-anastomotic strictures (NAS), cholangitis, cholangiocarcinoma
Pandanaboyana, Transpl Int. 2015;28(4):485-91	Systematic review & Meta analysis	10 studies, 910 patients 338 duct-to-duct 572 Roux-en-Y	Biliary strictures (AS/NAS) biliary leakage, cholangitis, cholangiocarcinoma
Wells, Transplant Proc. 2013 Jul-Aug;45(6):2263-71.	Systematic review & Meta analysis	7 studies, 692 patients 245 duct-to-duct, 447 Roux-en-Y	Patient and graft survival, biliary leak, disease recurrence, biliary stricture
Al-Judaibi, Hepat Mon. 2015;15(5):e18811	Retrospective observational	73 patients 15 duct-to-duct 58 Roux-en-Y	Patient and graft survival, biliary leak, stricture,
Shamsaeefar, Clin Transplant. 2017;31(6).	Retrospective observational	405 patients 143 duct-to-duct 260 Roux-en-Y	Patient and graft survival, biliary leak, stricture,
Chazouilleres ,*J Hepatol*. 2022;77:761–806.	EASL Clinical Practice Guidelines on sclerosing cholangitis		

There is a lack of consensus on the ideal biliary reconstruction technique in liver transplantation (LT) of patients with primary sclerosing cholangitis (PSC). In the current evidence report, the following outcomes have been compared in patients with Roux-en-Y (RY) and duct-to-duct biliary reconstruction:

Post-LT cholangitis, anastomotic strictures, late-onset Non AS (NAS), graft survival, patients survival, PSC recurrence, surgical and oncological complications (e.g. cholangiocarcinoma).
The largest study is a meta-analysis including 10 observational reports and over 900 patients[1]. The incidence of strictures was similar between RY and DD, but there was a reduced rate of ascending cholangitis in the DD patients. Moreover, patient and graft survival as well as incidence of cholangiocarcinoma was similar between the groups. In a retrospective single centre series from Holland 45 DD and 53 RY were compared. The incidence of biliary complication such as leaks and stricture within 1 year posttransplant were not different between the two groups, but cholangitis within the first year was more frequent in the RY group. In addition, RY was associated with significantly higher risk of NAS beyond the first post-transplant year compared to DD[2]. Other retrospective cohort studies and one meta-analysis of 7 retrospective cohort series have reported similar outcomes and thus non-inferiority when comparing DD and RY in LT for PSC[3–5] . In a systematic review on recurrent autoimmune liver disease after transplantation, it is recommended that DD anastomosis should be performed when feasible[6], and this is also in-line with the recent treatment guidelines from the European Association for Study of the Liver (EASL)[7].
Apart from the above outlined outcomes Duct-to-duct reconstruction confers certain advantages as compared to Roux-enY reconstruction. It maintains a normal anatomy with sphincter of oddi function after reconstruction and in addition provides easier endoscopic access to the biliary three after transplant. This is of particular relevance in PSC, since 10-30% of the patients may develop recurrent disease during the first 5-10 post-transplant years[8].

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PICO 6: Use of extended criteria donors (ECD) in primary sclerosing cholangitis

Recommendation

The use of ECD grafts in liver transplantation for PSC can be associated with increased risk of graft loss and recurrence in liver transplantation for PSC. **(Grade B, level 3b).**

The following studies have been included

Reference	Study type	No. of Patients	Main outcomes
Fleetwood, Exp Clin Transplant. 2021 Jun;19(6):563-569.	Retrospective observational study	95 patients, 28 DCD 67 DBD	Graft failure, graft and patient survival
Kitajima, American Journal of Transplantation 2021;21(suppl 4):782	Retrospective observational study	3099 DBD 151 DCD	Graft survival, biliary complications, PSC recurrence
Trivedi, J Hepatol. 2017 Nov;67(5):957-965.	Retrospective observational study	143 patients, 35 DCD 108 DBD	Graft and patient survival, Vascular complications, biliary strictures
Sundaram, Transplantation. 2015 May;99(5):973-978.	Retrospective registry study	1667 patients, 75 DCD 1592 DBD	Graft failure, graft and patient survival, biliary complications
Alabraba, Liver Transpl. 2009 Mar;15(3):330-340.	Retrospective observational study	263 patients, 73 ECD 1592 Normal risk	Recurrent PSC
El-Ghazaly Harb, ? Hepatology 2010; 52(SUPPL):846A.	Retrospective observational study	148 patients, outcomes compared with respect to graft type and donor risk index (DRI)	Recurrent PSC
Redfield, American Journal of Transplantation 2015;15(SUPPL):97.	Retrospective registry study	UOS dataset, PSC and non PSC LT stratified by DCD (3194) or DBD (103512). Exact group numbers not stated	Graft survival, biliary complications

Recurrent PSC is characterized by stenoses and dilations of the graft bile ducts. It has been shown that extended criteria donor (ECD) grafts, in particular grafts obtained from donation after circulatory arrest (DCD) are associated with an increased incidence of biliary complications. The implications of utilisation of ECD grafts in liver transplantation (LT) for PSC is not sufficiently clarified.

In the current PICO literature review was the use of ECD grafts for LT in PSC was compared with donation after brain death (DBD) with respect to the following outcomes:
Post-LT cholangitis, anastomotic strictures, late-onset non-anastomotic strictures (NAS), graft survival, patient survival, PSC recurrence, surgical and oncological complications (cholangiocarcinoma)
The number of relevant studies is low and the various reports inhomogeneous in terms of graft types and classifications. ECD grafts may be classified either by different scorings systems or graft type (DCD versus DBD). Within DCD, there are however difference in graft quality and risk of ischemic damage to the bile ducts depending on whether normothermic regional perfusion was utilised or not. Furthermore, the use of machine perfusion after organ retrieval has been shown to reduce the incidence of biliary strictures, but no study has reported specific outcomes in LT for PSC.
In the study by Alabraba et al, 73 of 263 transplants were done with ECD grafts according to a scoring system based on steatosis and donor age proposed by Tekin et al[1], and the use of ECD grafts was a risk factor for recurrent PSC[2]. The use of DCD grafts has been shown to be associated with higher risk of graft failure in PSC patients [3], Fleetwood et al also reports lower graft survival in the DCD group, but their findings suggest that if donors are scored according to the UKSS risk score system[4], low risk DCD donors have similar outcomes as DBD in LT for PSC[5], and it is likely that this can be attributed to the use of normothermic regional perfusion. In the report from Trivedi et al, DCD grafts were not associated with increased risk of biliary strictures overall, but ischemic type strictures were more frequent in DCD as compared to DBD, whereas the graft survival was similar in the two groups[6]. Three conference abstracts report similar results as the studies outlined above, but these are not published as peer reviewed articles.

The quality of evidence for the use of ECD grafts in LT for PSC is on this therefore low and more prospective studies are needed

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2. Alabraba E, Nightingale P, Gunson B, et al. A re-evaluation of the risk factors for the recurrence of primary sclerosing cholangitis in liver allografts. *Liver Transplant*. 2009;15:330–340.

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4. Oniscu GC, Randle LV, Muiesan P, et al. In Situ Normothermic Regional Perfusion for Controlled Donation After Circulatory Death—The United Kingdom Experience. *Am J Transplant*. 2014;14:2846–2854.

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4-Immunosuppression strategy: (James M. Neuberger, Birmingham)

PICO 7: Immunosuppression and PSC

Recommendations

1. The optimal immunosuppression regimen needs to be tailored to the need of the individual liver allograft recipient and will depend on many factors including the experience of the transplant team, the clinical state of the patient, access to medication and graft function. The optimal regimen is likely to be modified during the course of the patient's journey.
2. For patients grafted for PSC, there is little evidence to recommend any specific immunosuppression regimen in terms of overall survival.
3. Recurrent PSC is probably less frequently diagnosed when cyclosporin is used as the calcineurin inhibitor
4. With regard to IBD, use of tacrolimus may be associated with a worse outcome of IBD and azathioprine with a better outcome. Mycophenolate may increase the risk of de novo IBD pot transplant and azathioprine protect

The great majority of liver allograft recipients require immunosuppression to maintain good graft function. However, the benefits of immunosuppression need to be balanced against the consequences of immunosuppression, which may be inherent in suppressing the immune response (such as an increased risk of some malignancies and infections) or class or drug-specific (such as calcineurin inhibitor (CNI)- related renal impairment or corticosteroid induced osteopenia). As the number of immunosuppressive agents available for clinical use has increased, the clinician has a greater armentarium of drugs to select a drug-regimen that is appropriate for the individual. Over time, there has been a switch from cyclosporin-based immunosuppression to one based on tacrolimus, Current data suggest that the most commonly reported prescribed regimen to adult liver allograft recipients in the US is tacrolimus, corticosteroids and mycophenolate (around 65%), with tacrolimus and mycophenolate, and tacrolimus and corticosteroids less commonly used (SRTR). There is, however, a degree of variation between centres (Hussaini, Slowik, Nedredal).

There are available guidelines to help the clinician manage the immunosuppressive regimen (Charlton, Tan, Cillo). With regards to recipients grafted for PSC, the choice of immunosuppressive regimen will depend on many factors (see Table). This review will not consider all aspects of immunosuppression but will focus on those aspects specific to patients transplanted for PSC.

Although there are many studies evaluating the impact of different immunosuppressive regimens on a variety of outcomes, very few are randomised, prospective and long term and very few take into account variations in dose/levels of medications and changes in regimen over time. Furthermore, there are very few studies that evaluate the impact of newer agents (such as mTOR inhibitors) on PSC.

A further issue is that not all end-points are well defined: the diagnosis of recurrent PSC, based on a combination of imaging the biliary tree, demonstrating multiple non-anastomotic strictures and exclusion of other causes is often not carried out in a systemic way; it is usually clinically

simplistic to ascribe the cause of death to a single cause: for example, for a liver allograft recipient who reaches the age of 78 years and is taking triple immunosuppression, with tacrolimus associated diabetes and renal impairment, develops CMV-associated pneumonia, has immunosuppression reduced and dies following a myocardial infarct but because of the reduced immunosuppression, has allograft rejection, may have his death ascribed to several different causes.

A recent analysis of current clinical trials concluded that there was a 'a low number of trials, lack of variety in location and low publishing rates, with a focus mainly on the side effects and safety of immunosuppressants, and their withdrawal' (El Masri).

Thus, for all these reasons, any conclusions drawn from studies looking at outcomes related to immunosuppression will need to be cautious and limited.

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Immunosuppression and overall outcome

Outcome after liver transplantation is affected by many factors, pre-, peri- and post-transplant and may be related to donor as well as recipient factors. The major causes of premature death are related to cardiovascular disease, de novo malignancy, infection, renal failure and graft failure. Immunosuppression plays a variable role in all these causes of death (Neuberger). There is a complex interaction between the immunosuppressive regimen and the cause of death; furthermore, most studies looking at the cause of death in the liver transplant recipient fail to address the extent of pre-existing non-hepatic disease or the impact of age and other factors (such as obesity, smoking or alcohol use). There are relatively few prospective studies comparing long-term outcomes with different therapeutic regimens

One recent retrospective multi-centre study from 4 French centres (Irles-Depe 2020) found that, in 87 patients grafted for PSC, azathioprine was associated with a worse survival and mycophenolate with a better one, this was attributed to a chronological effect rather than a pharmacological one. However, in a later study of 72 Australian patients followed over 10 years, azathioprine use was associated with a significantly reduced mortality (RR 0.18) (Peverelle et al, 2021). Another review from the European Liver Transplant Registry found that the variables independently associated with worse survival were recipient male sex, donor and recipient age, cholangiocarcinoma at the time of transplant, non-donation after brain death donor, and reduced size of the graft; immunosuppression was not significantly associated with outcome. These findings were confirmed using a more recent liver transplant population closer to the current standard of care (transplant after 2000) (Berenguer).

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Immunosuppression and recurrent disease

As discussed below, there are several retrospective analyses and studies assessing the impact of immunosuppression on recurrent disease. It must be noted there are very few prospective randomised trials and conclusions are limited by several factors including the lack of randomisation and the variations in both the surveillance for and definition of recurrent disease.

Of the various meta-analysis, Chen (2020) analysed 13 retrospective studies reported until 2019 and found there was a significant association between rPSC and mycophenolate and cyclosporine in two studies each whereas neither azathioprine nor tacrolimus was related to rPSC. [I cannot find this on PubMed). An abstract published in 2020 reported on 14 studies and found the relative risk for rPSC was 1.773 on cyclosporine compared with tacrolimus. Another meta-analysis (Steenstraten) published in 2019 reviewed 21 studies and found no significant effect of immunosuppression on rPSC. Ratuapli (2014) suggested that use of prednisolone with tacrolimus was associated with a worse outcome of the IBD.

Of the observational studies, published after the dates covered by the meta-analyses above, Akamatsu (2021) concluded that monotherapy or no immunosuppression was an independent risk factor for rPSC, when using multivariate Cox regression modelling. Pellegrin (2019), in an abstract, found cyclosporin was associated with a greater risk of rPSC

Other agents such as mTORI have been less studied.

Immunosuppression and IBD

The impact of the choice of immunosuppressive regimen on the natural history of IBD is complex as the treatment of IBD may be affect the immunosuppressive burden and the regimen for immunosuppression of the liver may affect the natural history of IBD. Furthermore, the extent of IBD will depend not only on the presence of symptoms leading to further investigations or whether IBD surveillance is in place.

Furthermore, the course of IBD after liver transplantation is variable (Liu): for example, a longitudinal multi-centre Scandinavian study on 439 patients with PSC of whom 353 had IBD at the time of transplantation found that macroscopic colonic inflammation was more frequent after liver transplantation than before liver transplantation (153 vs 124 patients); the degree of inflammation decreased in 37 patients, was unchanged in 93 patients, and increased in 88 patients. The rate of relapse after transplantation was higher than that before transplantation, and overall clinical IBD activity also increased. Dual treatment with tacrolimus and mycophenolate mofetil was a significant risk factors for increased IBD activity after transplantation, whereas combination treatment with cyclosporin A and azathioprine had protective effects. Singh (2013) in a review of 14 studies on IBD post liver transplant for PSC concluded that use of tacrolimus was associated with an unfavourable course of IBD and azathioprine was associated with a better outcome. Similar conclusions were reached by Mouchli and colleagues from a retrospective analysis of 373 patients. They found that, despite baseline immunosuppression, 56 of 151 required escalation of therapy, whereas 87 had a stable course and 8 patients improved. On multivariate analysis, tacrolimus-based immunosuppression post-LT were associated with unfavourable course, and azathioprine use after transplant was associated with improved course post-LT. The finding that tacrolimus-based regimens are associated with a worse outcome was also found by Filipec and colleagues in a review.

Conversely, observational studies have shown conflicting results on whether control of IBD activity is associated with a better or worse graft or patient outcome; while Peverelle and colleagues in a French multi-centre study showed active bowel disease is associated with a worse graft outcome (Peverelle); similar conclusions were reached by Joshi and colleagues from a small retrospective study where they concluded active IBD at the time of transplant was

associated with a worse graft and patient outcome. In contrast, Irles in another French study concluded that there was no significant difference in either patient or graft survival in those with and without IBD at the time of transplantation.

De novo IBD: Montano-Loza (2017) in a general systematic review of recurrent autoimmune liver disease concluded that tacrolimus was associated with an increased risk of developing de novo IBD. Similarly, Mouchli noted that, of 84 patients with PSC but no evidence of IBD at the time of LT, 22 developed de novo IBD and, on univariate analysis, mycophenolate mofetil use was associated with increased risk of de novo IBD, but azathioprine use seemed to be protective.

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Table 1

Factors affecting choice of immunosuppressive regimen

Jurisdiction related: licenced drugs available

- Cost of drugs
- Availability of drugs
- Access to therapeutic drug monitoring (where appropriate)

Centre related: experience and standard of care

Patient
- impact of side-effects
- Wishing to conceive
- co-morbidities especially
  - renal impairment
  - diabetes mellitus
  - malignancies
  - osteopenia
- Indication

5- Management of IBD in PSC patients (Palak Trivedi, Birmingham)

Indications for colectomy

Patients with primary sclerosing cholangitis (PSC)-associated colitis harbour heightened lifetime risks of colonic dysplasia and colorectal cancer (CRC), as compared to their age- and sex-matched counterparts with UC alone, and against the general population.[1–5] Moreover, the majority of cancers tend to develop in the proximal colon.[6,7] Of note, colorectal cancer is among the leading causes of death in patients with PSC-IBD.[1,2]
Risks persist after liver transplantation,[8–10] with an estimated CRC incidence rate of 5.8-13.5 per 1,000 patient years.[11] The risk of progression of low-grade dysplasia in PSC-associated colitis is not fully quantified, but in a single-centre cohort of ten patients, three progressed to raised HGD over a mean follow-up of 13 ± 11 months. The investigators found that progression occurred within the first year of initial detection of LGD, and that flat lesions possessed the greatest risk;[12] similar to the background IBD population.[13] Thus, international guidelines prompt consideration of surgery (colectomy) with curative intent in patients with colitis and flat LGD, any degree of HGD, and in those with overt neoplasia that is deemed resectable provided patient fitness / comorbidities allow.[14,15]
In addition to CRC risk, colitis activity refractory to medical treatment is the commonest indication for colonic resection in PSC patients.[1,16–18] It is generally accepted that the definition of fulminant colitis is similar in PSC-associated colitis as it is in UC alone – the indication for colectomy herein is rarely debated.[19,20] However, for patients with steroid-dependent or steroid refractory chronic colitis, there is lack of consensus as to what stage colectomy should be performed. As PSC is an invariably progressive disease, with liver transplantation being the only life-extending intervention, there is premise for adopting a lower threshold with regards colonic resection compared to patients with IBD alone. One may also argue that colitis refractory to single (maximum two) biological agents warrants referral to (or at least discussion with) colorectal surgery. This is particularly relevant given the impact of persistent colitis activity on peri-/post-transplant complications (detailed in later section, below).

Recommendations:

(1) A diagnosis of colorectal carcinoma on colonoscopy and biopsy should prompt appropriate staging and multidisciplinary team discussion. For resectable disease in clinically appropriate candidates, colectomy is recommended (GRADE: strong recommendation, high quality evidence).
(2) Patients diagnosed with high grade dysplasia/neoplasia on colonic biopsies should be considered for sub-total colectomy (GRADE: strong recommendation, moderate quality evidence).
(3) Patients diagnosed with low grade dysplasia on colonic biopsies should be considered for colectomy, in the context of high-risk features, including flat and/or invisible dysplasia (GRADE: strong recommendation, low quality evidence).
(4) Patients who are not clinically fit to undergo colectomy should undergo regular surveillance colonoscopy with consideration of endoscopic resection if appropriate. (GRADE: weak recommendation, very low-quality evidence).
(5) PSC patients with fulminant colitis should be offered colectomy (GRADE: strong recommendation, high quality evidence).
(6) PSC patients with evidence of progressive liver disease (albeit well-compensated) and persistent colitis activity despite therapeutic trials of 5ASAs, azathioprine (thiopurines)

and a single biological agent, should be considered for early colectomy (GRADE: strong recommendation, low quality evidence).

What is the optimal timing for colectomy with regards native liver-related survival and overall survival?

Mortality: A systematic review and metanalysis of seven studies post-colectomy estimated a 2.11% per year mortality risk among patients with PSC (CI 0.03% to 4.18%, p=0.032 R^2= 0.722), un-stratified for indication and severity of liver disease.[21] Two/7 studies directly compare colectomy vs. no colectomy groups and show no difference in overall mortality across all evaluated time points (15.3% vs. 11.8% at 3 years in one study; and 17.4% vs. 20.4% over a median follow-up time of 5.9 years in another).[22,23] However, risk-stratified survival analysis of matched patient groups, who meet indications for colectomy and undergo resection, versus those meet indications but do not have surgery, has not been performed.

Native liver transplant-free survival: Early studies showed that patients with more aggressive PSC liver disease requiring transplantation had a milder clinical course of IBD, with less need of colectomy pre-transplant.[24,25] Reciprocally, patients in need of colectomy due to severe colitis can manifest less severe features of PSC liver disease.[26] The impact of colectomy on PSC-prognosis has been reported from a study of 45 PSC-IBD patients in whom colectomy did not affect liver function.[22] Other small studies, not primarily designed to investigate the effect of colectomy on PSC-prognosis, concluded that colectomy had no impact on liver-related prognosis.[27,28,29] However, emerging data from the paediatric literature indicates that late-onset colitis (>6 months following PSC diagnosis) is associated with higher rates of clinically significant portal hypertension (5/11 (45%) vs. 3/26 (12%); P = 0.007) and liver transplantation (5/11(45%) vs. 2/26 (8%); P = 0.02) over a median follow-up duration of 54 months.[30] Moreover, nationwide data from Sweden (N=2,594) shows that very early colectomy (prior to, or close to the onset of PSC) is associated with a lower risk of liver transplantation/death (hazard ratio [HR]: 0.71, 0.53-0.95), with a 5- and 10-year incidence of 14.0% and 25.5%, respectively. This was as compared to 20.7% and 33.0% among those without colectomy.[23]

Perhaps most striking, is the emerging body of data from population-based studies (published in abstract form) showing that patients who undergo colectomy and retain a permanent ileostomy are at a significantly lower risk of needing a liver transplant/dying over time (HR 0.47 (0.24-0.93)) compared to patients without colectomy. In turn, sensitivity analysis shows no beneficial effect for colectomy with a pouch (HR 0.95 (0.62-1.44)).[31] Taken together, this suggests that retention of an end ileostomy may be the preferred surgical method of choice in PSC patients. Very early studies in suggested that approximately 50% of patients may be at risk of developing ileostomal varices.[32] However, contemporary data is lacking, and there is no evidence to indicate such risk among individuals with non-cirrhotic PSC.[33]

There is no comparative data stratifying the benefits vs. risks of colectomy according to the extent of ductal disease involvement or liver disease stage. Nevertheless, data from chronic liver disease cohorts (including patients with PSC) highlight significant peri- and post-operative mortality following colectomy among patients with advanced liver disease compared to those with earlier stages (detailed in later sections, below).[34,35]

Recommendation:

(1) We recommend that colectomy is performed early in the clinical course of PSC, for patients with colitis who meet indication, and prior to the onset of advanced liver disease (GRADE: strong recommendation, moderate quality evidence).

(2) Evidence to suggest that colectomy prolongs transplant-free survival is limited, although colonic resection with ileostomy, early in the clinical course of PSC, may be associated with lower risks of liver disease progression (GRADE: weak recommendation, low quality evidence).

How does the timing of colectomy (pre-, peri- or post-transplant) affect the incidence and risk of developing recurrent PSC and/or other graft-related complications?

Large-scale studies from high-volume transplant programmes highlight that the risks of recurrent PSC are significantly lower among patients undergoing colectomy prior to transplantation; and greater in those with an intact colon. These include data from the Nordic liver transplant registry (HR 2.04),[36] the UK (HR 2.4) [37,38] and Germany (2.07-2.31).[39] In turn, persistence of active IBD and/or colectomy after liver transplant is seemingly associated with a 1.5 to 2-fold increased risk of recurrent PSC.[22,36–41] This body of evidence has been consolidated by systematic reviews and meta-analyses, yielding a pooled HR of 0.65 (95% CI: 0.42 – 0.99) favouring colectomy prior to liver transplantation as being protective against development of recurrent PSC.[42–44]

Vera et al also found that patients who undergo colectomy pre- or peri-transplant show better survival than those with an intact colon at the time of transplantation (10-year survival, 87% vs. 55%, not statistically significant), potentially reflecting that CRC- and colitis-related morbidity had been avoided. The investigators note that graft loss in the pre-transplant colectomy group occurred in 3 patients and was secondary to hepatic artery thrombosis in 2 and chronic rejection in 1.[8] Similar graft-related complications were also reported by Rowley et al.[45]

The principal aetiology of graft loss in PSC liver transplant recipients is hepatic artery thrombosis.[46,47] Data from a single UK centre indicates that only those with underlying IBD developed hepatic artery thrombosis over a median 5-year follow-up period.[46] Moreover, persistent active IBD at time of liver transplantation is associated with >3-fold greater risk of graft loss at 5 years compared to patients with quiescent disease.[48]

Recommendation:

(1) A lower threshold toward pre-transplant colectomy (compared to UC or Crohn's disease alone) should be considered in patients with PSC-associated colitis. This is because of the high likelihood of patients developing progressive liver disease, need for transplantation in later life, and associated risks of recurrent disease/graft loss with an intact colon (GRADE: moderate recommendation, moderate quality evidence).

Does the type of colonic resection (i.e. restorative vs. non-restorative colectomy; ileal pouch anal anastomosis (IPAA) vs. ileostomy alone) affect the outcomes listed in 1-3 above?

Data linking the type of colonic resection and liver-related outcomes are largely descriptive, with few comparative studies. Whilst the failure rate of IPAA and IRA in PSC-IBD may be no different to that of UC alone,[49] the cumulative incidence of acute pouchitis (31% vs. 14% at 10 years), overall pouch related dysfunction (Oresland score: 7.7 vs 5.4) and poor nocturnal pouch function is significantly greater.[50,51] Additionally, patients with large duct PSC and an IPAA exhibit a markedly lower quality of life compared to individuals with UC alone and an IPAA. Epidemiological data from the Netherlands show how patients that undergo colectomy and retain a permanent ileostomy are at a significantly lower risk of needing a liver transplant/dying over time (HR 0.47 (0.24-0.93)) compared to patients without colectomy. In turn, sensitivity analysis shows no beneficial effect for colectomy with a pouch (HR 0.95 (0.62-1.44)).[31] Taken together, this suggests that retention of an end ileostomy may be the surgical method of choice in PSC patients.

Very early studies suggest that approximately 50% of patients who undergo colonic resection may be at risk of developing ileostomal varices.[32] However, contemporary data is lacking, and there is no validating evidence to indicate such high risks in non-cirrhotic PSC.

In the post-transplant setting, there appears to be a significant difference in the incidence of graft loss between patient groups with an IPAA, end-ileostomy and those without a colectomy, with data from one large-volume centre (n=240) showing 10-year graft survival rates of 70%, 95% and 88%, respectively, P=0.038.[52] These differences were seen to persist on sub-analysis of patients undergoing colonic resection pre-transplant. With regards to graft-related complications, the rate of hepatic artery thrombosis was also elevated in the IPAA group by more than 4-fold compared to the end ileostomy group, whereas end-ileostomy appeared to have a protective effect including against non-anastomotic biliary stricturing disease.

Recommendation:

(1) Colectomy and retention of an end ileostomy is associated with lower risks of disease progression in the native liver compared to those having a restorative IPAA (GRADE: strong recommendation, moderate quality evidence).
(2) Colectomy and retention of an end ileostomy is associated with a lower risk of graft loss, non-anastomotic biliary structuring and hepatic artery thrombosis compared to IPAA and no colectomy (GRADE: strong recommendation, moderate quality evidence).
(3) Patients undergoing colectomy should be counselled about the risks of IPAA with regards to quality of life, acute pouchitis, pouch failure and liver/graft-related outcomes (GRADE: strong recommendation, moderate quality evidence).

How does the timing of colectomy (pre-, peri- or post-transplant) affect peri-operative outcomes with regards the colonic resection procedure itself?

At present, there is no data to support routine pre- vs. post-transplant colectomy timings, with regards the safety and efficacy of the colonic resection procedure itself. However, patients with advanced liver disease (cirrhosis) carry a greater risk of morbidity and mortality following any operation. Several scoring systems are available to help stratify risk,[34,35,53] although there is no robust comparative data to favour one scoring system to another.

Presently, there is no data to support the empirical use of transjugular intrahepatic portosystemic shunts (TIPSS) to mitigate peri-/post-operative risk among patients with

cirrhosis. In fact, data from a single retrospective study showed a heightened risk of complications among PSC patients undergoing TIPSS prior to colectomy (greater proportion with wound infections and wound dehiscence, longer hospital stays: 5d vs. 8d, and higher readmission rates).[54]

There is limited literature available comparing outcomes related to pre- vs. post-liver transplant colectomy, or to suggest the optimal timing of colonic resection post-transplant. Poritz et al. suggest that patients with PSC who require colectomy may undergo simultaneous liver transplant and total abdominal colectomy,[16] and other investigators have described this approach across their own respective practices.[8,37,43]

Recommendations:

(1) Risk stratification scores can be used to estimate the probability of peri-/post-operative mortality following colectomy in patients with cirrhosis (GRADE: Strong recommendation, moderate quality evidence).
(2) 'Empirical' use of TIPSS prior to colectomy in PSC patients with cirrhosis is not recommended, given the increased risk of complications (GRADE: weak recommendation, low quality evidence).

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What is the best screening strategy for IBD associated with PSC?

Approximately 70% of patients with primary sclerosing cholangitis (PSC) develop inflammatory bowel disease at some point.[1–3] Most patients (>60%) are diagnosed with IBD prior to PSC although 30-40% of patients are diagnosed after PSC.[4] The overall risk of *de novo* IBD in PSC is estimated to be >25% at 10 years post-LT.[5] Pooled cohorts from 3 studies found that out of 398 patients transplanted for PSC, 29 proceeded to develop *de novo* IBD.[5–7]

Phenotypically, IBD in PSC is most often classified as ulcerative colitis (60-66%; UC), and less commonly Crohn's disease (18-30%; CD), or IBD unclassified/indeterminate colitis (21%).[2,4] Inflammation is typically colonic (83%; pancolitis), predominantly affecting the ascending colon

(85%).[2,8] Phenotypic descriptors of CD are ill-defined, with isolated small bowel involvement being a rare occurrence and lower rates of fibrostenotic and penetrating disease.[9,10] However, in children, approximately 40% of patients without colonic disease have small bowel aphthous ulcers.[11] Isolated rectal involvement or left-sided colitis is uncommon (2-4% of patients with PSC-UC).

Children can present with milder clinical features of IBD (median paediatric ulcerative colitis activity indices [PUCAI] 25 vs. 55, P<0.001).[8] However, underlying IBD activity associates poorly with symptoms, and the probability of sub-clinical disease (inflammation in the absence of symptoms) is threefold greater than that of IBD alone: odds ratio (OR) 2.94.[12] In adults, the presence of subclinical endoscopic and histologic activity is greater particularly in the right colon compared to that seen in UC alone (OR 4.21 and 5.13, respectively). By contrast, histological disease activity is lower in the rectum (OR 0.24).[13]

Data from retrospective observational cohort studies also suggests that patients with PSC-associated IBD are offered biological therapies less readily than those with IBD alone; and that the incidence of colonic resection (for non-cancer-related indications) is also significantly greater.[4,8,12,14] Thus, historic perceptions of PSC-associated IBD being milder in clinical course than IBD alone are no longer valid.

One-third of patients with PSC-associated-colitis develop dysplastic colonic lesions, with the cumulative lifetime incidence of neoplasia/colorectal cancer estimated at 15%.[15,16] Approximately 60% of patients who develop dysplastic/neoplastic lesions have right-sided/proximal lesions, with >65% being endoscopically/grossly invisible.[16] Presently, there is insufficient data to connect the extent of colitis involvement and/or the duration of IBD, to the risks of developing colorectal dysplasia/neoplasia. However, the majority of colorectal cancers are diagnosed close to the time of PSC diagnosis.[4,14]

The presence of IBD, its specific subtype, and the severity of inflammation on the course of liver disease (pre- and post-transplantation) has been studied extensively, and will be detailed across later sections.[1,4,15,17–24] In brief, retrospective series show that ongoing IBD activity at the time of transplantation is associated with heightened rates of graft loss in adults (compared to quiescent IBD),[25,26] emphasising the importance of mucosal healing pre-operatively. These findings are less evident in children undergoing transplantation for PSC,[27] although data from a single centre indicates that onset of UC >6 months after PSC diagnosis is associated greater risks of portal hypertension and need for transplantation of the native liver.[28]

Taken together, screening for colitis (if not already evident) is recommended for all patients at time of PSC diagnosis, irrespective of age. Given the predominant disease distribution, both with regards colitis extent and location of dysplasia/neoplasia, the recommendation is for screening to be via colonoscopy, including pan-colonic biopsies (even in the absence of endoscopically overt inflammation), provided the procedure is safe to do so. The safety of colonoscopy in advanced cirrhosis was evaluated by Oey et al. (n=808, median model for end stage liver disease score (MELD) of 15 (range 6-40)). Compared to a control time-frame (30 days prior to or 30 days after colonoscopy) 14.9% vs. 8.6% experienced a clinical event, with principal differences between groups relating to acute kidney injury (3.8% vs. 1.2%) and the incidence of gastrointestinal bleeding (2.9% vs. 1.3%).[29] Principal risks for post-colonoscopy clinical events were ascites (OR 1.20 if diuretic responsive and 5.38 if diuretic intolerant) and an elevated MELD score (OR 1.27 per point increase).

Screening for IBD via flexible sigmoidoscopy is not recommended for PSC patients, given that predominant disease distributions are colonic with right-sided inflammation. The utility of stool biomarkers (faecal calprotectin) as a diagnostic screening tool unproven. Additionally, there is little evidence to guide (a) which patients require screening for small bowel IBD, (b) when to repeat colonoscopy among those without evidence of colitis at their index investigation. Data from one large population-based study indicates that the majority (>80%) of patients who develop IBD after PSC diagnosis do so within 5 years. Thus, a repeat colonoscopy may be performed after this interval, or sooner should symptoms or signs of IBD manifest *de novo.*

Recommendations:

(1) All patients with a new diagnosis PSC should be screened for IBD at the point of diagnosis, irrespective of bowel symptoms (GRADE: strong recommendation, high quality evidence).
(2) Ileocolonoscopy is recommended as the screening method of choice (GRADE: strong recommendation, high quality evidence).
(3) Pan-colonic biopsies are recommended at the time of screening ileocolonoscopy, even in the absence of endoscopically overt IBD activity (GRADE: strong recommendation, high quality evidence).
(4) The risks and timings of screening colonoscopy must be weighed against the severity of liver disease. In the absence of symptoms and/or suspicion of colorectal cancer, screening colonoscopy should be deferred in patients with a MELD score >15 or those with ascites (GRADE: strong recommendation, low quality evidence).
(5) In patients without colitis on screening endoscopy, repeat endoscopy at a 5-year interval (or sooner if new symptoms / signs suggestive with IBD emerge (GRADE: strong recommendation, weak quality evidence).
(6) In patients without colitis, evaluation of small bowel involvement is recommended via capsule endoscopy (GRADE: weak recommendation, moderate quality evidence).

What is the Optimum Interval and Monitoring Strategy for IBD activity in PSC?

Among transplant recipients, the cumulative probability of deterioration in colitis activity at 10 years is estimated to range between 25.5% to 40%, despite ongoing use of anti-rejection/immunosuppression.[5,30,31] However, there is poor correlation between symptoms and underlying IBD activity in PSC, meaning that disease may be active endoscopically/histologically in the absence of symptoms.[8,12,13,32] Additionally, no health-related quality of life or patient reported outcome measure for IBD has been validated for PSC-IBD specifically. With regards faecal calprotectin (fCAL), data from one study of twenty PSC patients showed weak correlation with the UC endoscopic index of severity (UCEIS, rho=0.596), and falsely elevated fCAL values in the context of quiescent colitis compared to those with UC alone (279 microg/g vs. 30 microg/g). Of note, elevated fCAL was also observed among patients that have biliary complications or intervention, irrespective of colitis activity (e.g., acute cholangitis, and those undergoing ERCP).[33] However, data from a large Finnish cohort (n=4289 colonoscopies in n=982 patients) showed that the histological inflammatory burden was significantly higher in PSC patients with fCAL values consistently >500 microg/g than those with FC <500 µg/g.[34] This suggests that fCAL may have a role in monitoring colonic inflammatory activity in PSC, albeit with different cut-off values to stratify risk compared to IBD alone.[34]

Given the phenotypic distribution of IBD in PSC, and the fact that sub-clinical inflammatory activity most often occurs in the ascending colon (above), the current gold standard for assessing disease activity remains via colonoscopy and pan-colonic biopsies. Novel colonoscopic scoring systems for IBD (e.g., PICASSO) may allow better clarification of inflammatory burden in UC alone,[35,36] however there is no evidence that they correlate better with histology compared to standard high-definition white light endoscopy in PSC-IBD. At present, surveillance of IBD activity is largely performed in parallel to colorectal cancer surveillance, and there is no evidence to suggest that shorter monitoring intervals add value. Additionally, there is no evidence to support a particular modality or interval for monitoring small bowel, peri-anal, or stricturing/penetrating IBD in PSC.

Recommendations:

(1) We recommend that the minimum interval for routine monitoring of PSC-associated colitis is every twelve months, in line with cancer surveillance (GRADE: low quality evidence; strong recommendation).
(2) In patients with PSC-associated colitis, routine monitoring of IBD activity must include colonoscopic evaluation (with pan-colonic biopsies, even in the absence of inflammation): (GRADE: high quality evidence; strong recommendation).
(3) Routine monitoring of small bowel, peri-anal, or stricturing/penetrating IBD activity in PSC patients should follow established clinical pathways set out by the European Crohn's and Colitis Organisation (or equivalent) (GRADE: low quality evidence; weak recommendation).
(4) Health-related quality of life tools, patient-reported outcome measures and fCAL may serve as adjunctive measures in the routine monitoring of IBD activity in patients with PSC-associated colitis (GRADE: low quality evidence; weak recommendation).

What is the Optimum Interval and Modality for Bowel Cancer Surveillance in PSC?

Colitis associated with PSC imparts a heightened lifetime risk of colorectal cancer, approximately 4-fold greater than that of IBD alone.[4] Observational studies suggest cumulative risks ranging 2-14%, 8-31%, and 18-50% at 10, 20 and 25 years, respectively.[37,38] Retrospective series indicate that cancer risk persists post-transplant, with one study estimating a 4.4-fold greater risk compared to non-transplanted PSC patients.[39] Data from large volume centres indicates that the cumulative inflammatory burden and extent of IBD do not seemingly associate with risk, as the prevalence of dysplasia in patients with moderate to severe histological inflammatory appears to be similar to those in remission or with mild inflammatory activity.[34] Moreover, there is seemingly no association between the long-time histological inflammatory activity burden and development of cancer over time.[34] However, there is no evidence that the risks of colorectal cancer are elevated in PSC without IBD, compared to the general population.[15]

To this effect, annual (1-2 yearly) international guidelines advocate annual colonoscopic surveillance for all patients diagnosed with PSC-associated colitis, pre- and post-transplantation.[40–42] The goal of annual surveillance colonoscopy is to detect lesions early, at a more resectable/curable stage. Indeed, large-scale population-based data indicate improved post-cancer survivorship among patients undergoing annual surveillance colonoscopy who are diagnosed with CRC compared to those who do not partake in a surveillance program.[15] There is no current evidence to support more (or less) frequent colorectal cancer surveillance intervals than 1-2 yearly.

Lesions that develop in the PSC colon often bear atypical features and may not be visible macroscopically.[16] Therefore guideline recommendations support the use of systematic pan-colonic biopsies. The use of adjunctive techniques, such as dye spray chromoendoscopy and virtual chromoendoscopy, can highlight dysplastic lesions, although the added value in PSC-associated colitis is still being explored. Additionally, decisions regarding annual colonoscopic surveillance in patients with advanced liver disease must be guided by the clinical and performance status, and the overall perceived benefit of undergoing surveillance.[29] The accuracy of detecting dysplastic lesions is hampered by poor bowel preparation and/or active inflammation. Therefore, CRC surveillance should be repeated in those with endoscopically active disease once IBD is in remission.[43,44] Presently, there is no evidence to support the use of faecal immunochemical test (FIT) and faecal occult blood (FOB) testing for bowel cancer surveillance in PSC-IBD. Faecal volatile organic compounds also remain under ongoing investigation.[45]

Recommendation:

(1) Annual colonoscopy should be performed in patients with PSC-associated colitis to survey for colorectal cancer and colorectal dysplasia (GRADE: strong recommendation, moderate quality evidence).
(2) Annual colonoscopy should be performed when colitis activity is in remission, and in the presence of good bowel preparation (GRADE: strong recommendation, high quality evidence).
(3) Annual surveillance colonoscopy should include systematic pan-colonic biopsies, even in the absence of inflammation (GRADE: strong recommendation, moderate quality evidence).
(4) Annual surveillance colonoscopy should encompass techniques that enhance the detection of dysplastic/neoplastic lesions, such as chromoendoscopy and virtual chromoendoscopy (GRADE: strong recommendation, weak quality evidence).

(5) Annual colonoscopy is recommended for PSC-IBD patients pre- and post-liver transplant. (GRADE: strong recommendation, high quality evidence).
(6) In PSC patients without colitis, colonoscopic surveillance can follow that of the general population (GRADE: weak recommendation, low quality evidence).
(7) There is no evidence to support the use of faecal immunochemical test (FIT) and faecal occult blood (FOB) testing for bowel cancer surveillance. (GRADE: strong recommendation, very low quality evidence).
(8) The use of MELD score, performance status and comorbidity indices (and other indices of liver disease severity) should guide the decision to continue annual colonoscopic surveillance in patients with cirrhosis (GRADE: strong recommendation, low quality evidence).

What is the optimum (safety/efficacy) therapeutic approach for maintaining remission in IBD associated with PSC pre-, peri- and post-LT?

Despite the advent of immunosuppression, biologics and microbial therapies, there have been no randomised controlled clinical trials specifically addressing IBD activity in PSC. Thus, clinical data is limited to (largely retrospective) case series and observational cohort studies. Nevertheless, therapeutic paradigms in IBD have evolved with complete mucosal healing being the desired treatment target. This is particularly relevant given that (a) PSC is invariably a progressive liver disease, (b) liver transplantation is the only life-extending intervention for patients, and (c) ongoing IBD activity is associated with a heightened risk of peri- and post-transplant complications including hepatic artery thrombosis, recurrent PSC and overall rates of graft loss. Macroscopic colonic inflammation can be more evident post- compared to pre-transplantation.[31] However, persistent inflammatory activity pre-transplant can affect IBD behaviour post, with some studies indicating a 3-fold greater risk of acute 'flare-ups.'[46] To this effect, there is a view that all efforts to attain mucosal healing in PSC should be pursued, particularly for patients with evidence of progressive liver disease over time that will ultimately require liver transplantation.

5-aminosalicylates (5-ASA) are generally considered safe and have been used as a principal agent for inducing and maintaining remission in 6 retrospective cohort studies.[7,25,46–49] These studies, however, do not comment on 5-ASA use in the context of disease severity. With regards peri-operative safety, 5-ASAs can be continued up until transplantation, and then resumed on discharge. Combination 5-ASAs and corticosteroids have also been studied.[7,25,46,48,49] However, the implications of long-term steroid use on post-surgical outcomes are well-described, with extensive literature highlighting the negative impacts on wound healing, sepsis and glycaemic control.[50–53] In patients who are steroid dependent treatment escalation should be considered, by optimising 5-ASA dose or introducing an immunomodulatory/steroid-sparing agent to reduce the risk of steroid-related complications pre-transplant.[44]

Thiopurines, principally azathioprine, can been used to maintain remission from IBD pre- and post- transplantation, and does not adversely affect post-operative outcomes nor the risks of PSC-associated cancers.[50,51,54] Moreover, data from the Nordic liver transplant registry collected over 21 years (N=353) shows that ciclosporin and azathioprine-based immunosuppression is associated with significantly lower risks of deterioration in IBD activity compared to tacrolimus and mycophenolate (hazard ratio [HR]: 0.2; P<0.001).[31] Whilst differences in ciclosporin vs. tacrolimus may reflect an era effect in transplant practice, this is less apparent for azathioprine vs. mycophenolate treatment paradigms which are both still commonplace. Moreover, the merits of ciclosporin vs. tacrolimus use must be

counterbalanced with risks of allograft rejection and acute kidney injury in immune-mediated liver diseases.

The two most commonly used anti-TNFa agents are infliximab and adalimumab. In a multi-centre study of 141 PSC patients across 20 sites, 3-month clinical response and remission rates were reported at 48% and 23%, respectively.[55] Four/7 patients treated with anti-TNFa therapy post-transplantation were reported to have responded at three months. However, use of anti-TNF agents has been associated with an increased likelihood of acute cholangitis in PSC-IBD specifically (OR, 7.29; 95% CI, 2.63-12.43).[56] Safety outcomes in relation to biologics mostly concern opportunistic infections, particularly when used in combination with other immunosuppressive agents. One study noted that six/18 patients receiving anti-TNFα treatment developed serious infections including cytomegalovirus (CMV) colitis, *C. difficile*, cryptosporidiosis and enterococcus faecalis bacteramia. Similar adverse events are reported in 3 other studies which also report an increased incidence of oral and oesophageal candidiasis.[5,48,49,57] Contemporary guidelines in the IBD literature currently advocate for prophylaxis against *pneumocystis jirovecii* in heavily immunosuppressed individuals. Pragmatically, these would include patients on triple immunosuppression (corticosteroids, calcineurin inhibitors and anti-proliferative agents). In a similar vein, there is rationale from a safety point of view to minimise immunosuppression among transplant recipients commencing anti-TNFa therapy, whilst balancing the risks of allograft rejection and recurrent disease. For instance, this may include cessation of corticosteroids and antiproliferative agents in patients who are being treated with calcineurin inhibitors and anti-TNFa therapy simultaneously. At present, there is no published data studying the safety and efficacy of newer biological agents such as those directed toward Janus Kinase and/or IL12/23.

Given its comparative safety profile and limited off-target effects, retrospective studies favouring vedolizumab have also been presented. Data from the International PSC Study Group (n=36) showed a reduction in mean Mayo Endoscopic Subscore from 2.2 to 1.4 over a median treatment duration of 36 days, without any appreciable safety signals across a non-transplant cohort of patients. These findings were mirrored by another multicentre cohort of 16 and 14 PSC patients with Crohn's disease and UC, respectively. Over a median follow-up of 9 months, clinical remission was evident in 29% (PSC-UC) and 55% (PSC-Crohn's disease) of patients following 30 weeks of therapy. 21% of patients stopped therapy due to persistent IBD activity. The paediatric PSC consortium have validated these findings, wherein 37 patients from 19 centres were treated with vedolizumab for 9-12 months. Therein, 32% achieved remission, 30% experienced clinical response and 38% were non-responders over 9-12 months. A systematic review of vedolizumab use among liver transplant recipients (eight studies) indicates greater response rates than pre-transplant studies, with 20/27 patients reporting clinical improvement over a mean follow-up of 5-20 months. However, seven/31 patients experienced an infectious event after a mean-time vedolizumab exposure of 11.4 months.[61]

Lastly, oral vancomycin has been used as an open label therapy to induce remission from colitis across several medium-large-sized PSC cohorts.[62–65] Perhaps most striking, is the ability to induce rapid clinical, biochemical (faecal calprotectin) and endoscopic remission in children and adults, pre- and post-transplantation, with near immediate relapse on stopping therapy.[62–65] Moreover, no emergent safety signals or anti-microbial resistance has been reported thus far, and the effects appear independent of prior biologic exposure.[66] Data from randomised controlled clinical trials are currently awaited.

Recommendations:

(1) 5-ASAs may be used in the pre- and post-transplantation period for the induction and maintenance of remission in IBD associated with PSC. (GRADE: strong recommendation, low quality evidence).
(2) Corticosteroids may be used for the induction of remission in PSC-associated IBD, and as a bridge to escalating treatment. (GRADE: strong recommendation, low quality evidence).
(3) Azathioprine is favoured as immunosuppressive maintenance therapy in the pre- and post-liver transplantation period, over mycophenolate-based regimens (GRADE: strong recommendation, low quality evidence).
(4) Vedolizumab is recommended as the first-line biological agent of choice to induce and maintain remission of moderate to severe luminal IBD pre and post-liver transplant (GRADE: weak recommendation, very low quality evidence).
(5) Infliximab and adalimumab are to be avoided in patients with a history of recurrent cholangitis (GRADE: strong recommendation, moderate quality evidence).
(6) Infliximab and adalimumab may be administered post-transplantation, alongside calcineurin inhibitors, provided azathioprine/mycophenolate have been stopped (GRADE: strong recommendation, low quality evidence).
(7) Empirical switching of tacrolimus to ciclosporin is not recommended to induce or maintain remission from IBD post-transplant (GRADE: weak recommendation, very low-quality evidence).
(8) Patients on 2 or more immunosuppressive agent should receive prophylaxis against *pneumocystis jirovecii* (GRADE: strong recommendation, moderate quality evidence).
(9) Oral vancomycin may be used to induce remission from PSC-associated colitis (GRADE: strong recommendation, moderate quality evidence).

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6-Avoiding PSC recurrence (strategies) (Marco Carbone, Milan)

Should LT recipients for PSC/IBD be monitored with regular histological follow up (liver and intestine) to capture the first signs of disease reactivation which could be potentially treated with experimental drugs in appropriately designed studies?

Recommendations:

(1) A diagnosis of rPSC can be made based on progressive biliary strictures on cholangiography and/or histological findings compatible with PSC more than 90 days (more than 12 months to distinguish from ITBL) after LT upon exclusion of other identifiable causes), in particular, given the rise in the usage of DCD grafts, it is necessary a distinction between ITBL and rPSC

Quality of Evidence: Moderate
Grade of Recommendation: Strong

(2) MRCP and/or liver biopsy should be introduced to investigate at an early stage the onset of rPSC;

Quality of Evidence: Very Low
Grade of Recommendation: Weak

(3) Protocol biopsies and protocol MRCP, performed within clinical trials, would help earlier, more accurate diagnosis of recurrence, and test efficacy and safety of novel drugs and potentially allow immunosuppression treatment optimization;

Quality of Evidence: Very Low
Grade of Recommendation: Weak

The diagnosis of PSC is based on well-defined cholangiographic features combined with biochemical and histological findings (Mayo Clinic criteria). However, none of these is pathognomonic for PSC, particularly after LT, when biliary strictures in the liver allograft can occur from a variety of causes other than recurrence. rPSC has been described in 10-50% of patients, with broad variability. This gap reflects the lack of standard diagnostic or management practices in published clinical cohort, particularly in the surveillance (e.g. the use of protocol biopsies), in the workup for rPSC and IBD activity, the time-frame analyzed, and the cohort size. The median time to recurrence ranges between 80 months in mild cases, to 41 months in progressive forms. rPSC is reported to have a faster disease progression compared to the disease in the native liver and affects graft survival with a probability at 15-years of 25% in case of early recurrence (<5 years) to 38% in the late presentation (> 5 years). The relationship between IBD activity and/or gut microbiota and risk of recPSC has not beed assessed.

Considerable bile duct irregularities might be present for a long time before the patients show symptoms or even a cholestatic biochemical profile. Early, confident detection of rPSC, for example by protocol MRC or protocol biopsies, may lead to an earlier diagnosis, enabling timely multidisciplinary team (MDT) discussion to adopt strategies aimed at hindering

progression to advanced disease and graft loss. Of note, in the past, there was no immediate impact of making the diagnosis of recurrent disease because no treatment was available. Nowadays, several experimental molecules are being tested in PSC in the native liver (e.g. fibrates, IBAT inhibitors, oral antibiotics). It is of utmost importance to extend these strategies to the post-transplant setting with rPSC in order to improve the outcomes for these patients and to reduce the demand on scarce donor organs. Moreover, advances in multiplex tissue staining, automated image analysis, quantitative MRCP technology enable today even more objective data extraction from spatial analysis of tissue specimens and imaging opening avenues for translational research in this setting. Furthermore, with the scarcity of organs available for LT, understanding the factors and phenotype of patients associated with improved survival after re-LT is important in order to limit futility.

This paragraph focused on the evidences supporting a standardised monitoring with regular histological and radiological follow-up to capture the first signs of disease reactivation which could be potentially treated with experimental drugs in appropriately designed studies. And explore the outcome of retransplant to justify the use of a limited resource for a recurrent disease.

Rates of PSC recurrence

The reported rate of recurrence of 10-50% with a median time to recurrence of 41-80 months might be underestimated. The actual rate of rPSC may even be higher, had all patients undergone protocol liver biopsy and/or cholangiography at set time points.

Several studies have demonstrated that liver allograft histology is rarely normal when assessed in recipients with normal LFTs. Abnormalities in histology increase with time after LT from 65% at the 10-year biopsy to 90% at the 20-year biopsy (Slapak et al.).

Another overlooked issue is mild cholestasis after LT. Authors from Alberta, using a definition of mild cholestasis of alkaline phosphatase level >2 times the upper limit of normal or a combined elevation of both bilirubin and alkaline phosphatase levels, described that approximately 1 in 4 patients in a review of > 900 adult in the LT program at the University of Alberta Hospital, met the criteria for cholestasis in the third month after LT. The probability of rPSC was higher for patients with PSC (n=92) and cholestasis at 3 months versus PSC patients without cholestasis with median times to recurrence of 115 versus 155 months; patients with PSC and cholestasis at 3 months had a hazard ratio of 2.62 for rPSC. (Mason, Montano-Loza) These data suggest that rPSC might have a mild and insidious onset and rPSC could be highlighted even only based on a raised alkaline phosphatase, with no ischemic biliary insult or other cause – however this non-invasive approach, without liver biopsy and/or MRCP, may miss other graft issues.

The rate of rPSC reported in the literature is broad and mainly influenced by the heterogeneity in the standard diagnostic or management practices. In the seminal paper of Graziadei et al. from the Mayo clinic, liver biopsies were performed on day 7, day 21, 4 months, annually, and whenever graft dysfunction occurred. To assess biliary strictures, protocol cholangiograms were performed on day 7 and day 21 using a biliary tube placed at the time of transplantation. Percutaneous transhepatic cholangiography was performed when visualization of the biliary tree was clinically indicated and access by means of the biliary tube was no longer available. Cholangiography was also performed for patients who had persistent abnormal liver function tests of undetermined cause. Non-anastomotic strictures were described in 47 PSC hepatic

allografts (27.2%) with a mean time to diagnosis of 223-326 days (range, 11-3.240 days) after LT. After excluding patients who experienced hepatic artery thrombosis/stenosis and ductopenic rejection, 20% of PSC patients were diagnosed with rPSC. In this group, 8.3% had both histological and cholangiographic features, strongly suggestive of rPSC. Recurrence of PSC did not have a negative influence on short-term patient and graft survival; however, longer follow-up was not reported at the time these data were published (Graziadei et al.)

A multicentre UK observational cohort study in 2015, across six of the seven national LT units between 1990 and 2010 was reported. They identified 679 first transplants for PSC, 347 patients (61.4%) having IBD. After LT, patients were investigated by Doppler ultrasonography, CT or MRI, magnetic resonance cholangiography (MRCP) or liver biopsy if indicated by abnormal liver function tests. Routine/protocol cholangiographic imaging or liver biopsies for the diagnosis of rPSC were not performed in patients with normal liver function tests in the absence of clinical indications. The diagnosis of rPSC was guided by the Mayo Clinic criteria. Out of 679, 81 (14.3%) patients developed rPSC and 37 (48.7%) of them developed graft failure from rPSC. Presence of UC post-liver transplant (HR=2.40, 95% CI 1.44-4.02) and younger age (HR=0.78, 95% CI 0.66-0.93) were the only factors significantly associated with rPSC. The lack of utilisation of protocol biopsies and/or MRCP may have resulted in fewer cases of rPSC reported, in line with case series in which liver biopsy and MRCP were performed on demand (Ravikumar et al.).

A higher rate of rPSC of 20% has been reported by a multicentre study from Germany in 2016, in the period 1990-2006, in 335 recipients after 4.6 years of follow-up. Since this was a retrospective study, there was no standardized follow-up protocol. Nevertheless, all participating centres performed regular follow-up visits of their LT recipients (up to 4 times a year during the first 2 years after LT and yearly in the late posttransplant period).

A recent cross-sectional study from Helsinki, Finland, examined 250 protocol liver biopsies (at 1 year and every 5 years) from 82 PBC and 100 PSC patients performed since 2009 (Vannas). Overall histopathological findings and those leading to changes in immunosuppression therapy were retrospectively analysed. 43% of PSC patients had two or more abnormal histopathological parameters, but the follow-up time from LT to biopsy was relatively short (8 years). Primary recurrence of PSC was fairly low in this study, of only 3%. However, these numbers are based on histological findings in protocol biopsies only, and no other considerations for recurrence were taken into account. Since PSC recurrence diagnoses are usually based on radiological findings, an actual diagnosis of recurrent PSC was underestimated. All the protocol biopsy results were discussed in MDT meetings, and thus, possible changes in medication were reviewed by a larger audience of experts. No specific cut-off values were identified for protocol biopsies either for reducing or increasing immunosuppression therapy. Mild histopathological findings were frequently found in the protocol biopsies despite the normal biochemistry. Overall, findings in protocol biopsies caused medication changes in 19% of PSC patients. These data suggest that protocol biopsy may be useful in the decision-making of immunosuppression therapy in patients with PSC, among the others, therefore a longitudinal study of protocol biopsies in PSC recipient is warranted. Moreover, protocol liver biopsies might enable to diagnose an early process of recurrence when the macroscopic biliary tree is still normal. An important caveat to this statement is, though, that while onion skin fibrosis is thypical for PSC in the native liver and sought to assess recurrence after LT, it is not known its prevalence in other conditions after LT.

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PICO 11: Are there criteria of futility for re-OLT?

Recommendations:

(1) Patients with rPSC and graft failure should be offered re-transplant until further prospective studies demonstrate otherwise.

(Quality of Evidence; very low | Grade of Recommendation; strong).

When graft failure occurs secondary to disease recurrence, LT may be the only alternative to death. Re-transplantation in PSC is controversial, because of the historical lower patient and graft survival rates compared with primary transplantation, due to surgical challenges and septic complications. This raises ethical concerns on utility and equity in the use of a scarce resource (liver organ) for a disease that will tend to recur, sometimes more than once.

Several studies have explored the impact of rPSC on patient survival showing conflicting results. Some studies reported no effect on patient survival [Dekkers, Egawa, Moncrief, Campsen, Goss]. Others reported a negative effect on both graft and patient survival [Ravikumar, Lindstrom]. The inconsistency in results might be related to the different study design and study limitations, e.g. small sample size, short follow-up time, single vs combined endpoints used, selection bias in patient selection. In some studies, the evidence of recurrence was not included as time-varying covariate, therefore disregarding the impact of survived time until rPSC development on the overall.

A recent analysis of the European Liver Transplant Registry (ELTR) data by Visseren et al. on 1.549 patients undergoing LT for PSC over a period of 35 years (1980– 2015) reported a graft survival (including re-transplants) at 1, 5, 10 and 20 years of 80%, 70%, 60% and 41%, respectively. This survival rate is far superior to the expectation of at least 50% at 5 years that has been proposed by the transplant community as a minimum threshold to avoid futility (Neuberger et al.). The rate of rPSC was 17%, including re-transplants, after a median of 5.1 years. In 48% of the cohort, rPSC occurred within 5 years after LT, in 32% between 5 years and 10 years after LT, and in 20% more than 10 years after LT. Authors reported a negative impact of rPSC on patient survival (HR=2.3) independent of other transplant related co-variates. Patients with rPSC underwent significantly more re-transplants than those without rPSC (OR 3.6). Notably, patients affected by rPSC did benefit from re-transplantation, showing a patient survival similar to that of patients without rPSC but re-transplanted for other causes. Moreover, in patients with and without rPSC, 5-year graft survival for second graft was noted to be 77% vs. 79%, with no difference in patient survival.

Similar results come from the analysis of the UNOS/OPTN database (Henson) of 5.080 PSC patients who received LT in the US. Authors reported graft failure in 1803 patients (35.5%), of which 762 (42%) were listed for a second LT. rPSC was the cause of graft failure in 32% of these. When compared with primary LT, the recipients of re-LT for rPSC were more likely to be in the ICU or on mechanical ventilation at LT, and they also had a greater degree of hepatic and renal dysfunction. However, their outcomes were similar at 5 years. The graft and patient survival remained similar after adjusting for recipient and donor factors and the time period in which the transplant was performed. Furthermore, the majority of wait-list mortalities for rPSC occurred within 6 months, highlighting the risk of not receiving re-LT. Putting together these data, considering the favourable post-re-LT outcomes and the high proportion of waitlist

mortalities occurring soon after relisting, support the consideration of re-LT in patients with rPSC.

While these are the largest multicentre study on rPSC post-transplant, granular patient data, such as imaging and biopsy, were only available for a minority (approximately one third of all the transplant centre included in the ELTR and not available in the UNOS/OPTN database). It must be noted there are no prospective randomised trials and conclusions are limited by several factors inherent with retrospective review of a large administrative database, including missing, incomplete, or potentially inaccurate data. In the UNOS/OPTN database a bias might also be introduce in the outcome of retransplanted since, by virtue of being relisted, these individuals had already been deemed fit to undergo re-LT and may have been predisposed to better outcomes.

The ethical principle of fair and equitable distribution of organs based on long-term outcomes is on the front line when considering listing patients for retransplantation. If the focus of allocation is based on most efficient use of organs, then the prime outcome should be graft survival. A major message from this systematic review is that patients who undergo a second liver transplant for rPSC do no worse than PSC patients who undergo a second liver transplant for other causes, with similar graft and patient survival. An important caveat to this statement though is that the patients included in this analysis were likely highly selected to undergo re-LT for their favourable pre-LT characteristics. Future research should be performed to identify the individuals who may benefit from retransplant. At the time being, based on a pure needs and outcomes standpoint, it seems reasonable to continue offering re-transplant to patients with rPSC until further prospective studies demonstrate otherwise. An ad-hoc strategy for regrafting in rPSC, including the avoidance of DCD, pre-emptive colectomy, HLA/ABO match or mismatch, change of IMS, should be developed.

I would mention the issue of possible activation of specific B and T limpho clones which may favor rPSC at least in some cases. This would justify major manipulation of IS soon after reTX for r PSC. Very poor evidence but attractive prospects for future research

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Cynthia Tsien & Nazia Selzner. Comment 2021

7-PSC & IBD in Paediatrics (Ulrich Baumann, Hannover)

PICO: Is the prophylactic use of rotating antibiotic for recurrent cholangitis safe in patients waitlisted for liver transplantation?

P	Adult and paediatric waitlisted patients with primary sclerosing cholangitis (PSC) and bacterial cholangitis
I	Continuous prophylactic rotating treatment with antibiotics
C	Treatment with antibiotics in case of infection (bacterial cholangitis/sepsis)
O	Presence of multi-drug-resistant bacteria (MDR) posttransplant, MDR related infections posttransplant, adverse events posttransplant

Recommendation

Rotating antibiotics for children with bacterial cholangitis listed for liver transplantation cannot generally be recommended	
Level of evidence	Very low
Grade of recommendation	Weak for

PICO: When should PSC patients on the waiting list be treated with biliary stents?

P	Liver transplantation (paediatric and adult) for primary sclerosing cholangitis with jaundice
I	Biliary stenting (percutaneous transhepatic cholangiography (PTC) or endoscopic retrograde cholangiography)
C	No stenting or dilatation
O	No stenting or dilatation

Recommendation

Children with large duct disease and biliary obstruction listed for liver transplantation may be stented to bridge to transplantation.	
Level of evidence	Very low
Grade of recommendation	Weak for

PICO: Can we identify parameters that support the decision making process of liver re-transplantation for PSC recurrence?

P	Paediatric or adult liver transplant recipients who received their transplant for PSC.
I	Re-transplantation
C	No Re-transplantation
O	Patient and graft survival, and retransplant rate.

Recommendation

Paediatric patients after liver transplantation for PSC should be considered for re-transplantation in case of persistent jaundice.	
Level of evidence	Very low
Grade of recommendation	Strong for

PICO: Can we develop a strategy to monitor PSC recipient of LT for disease recurrence?

P	Paediatric or adult liver transplant recipients who received their transplant for PSC.
I	Protocol Liver biopsy Protocol Magnetic resonance cholangiopancreatography
C	Liver transplant recipients who do not undergo investigation nor experimental therapy
O	End-stage liver failure secondary to PSC recurrence, overall mortality

Recommendation

Paediatric patients transplanted for PSC should undergo regular imaging like MRCP. Liver histology should be performed when clinically indicated.	
Level of evidence	Very low
Grade of recommendation	Strong for

PICO: Is the MELD allocation system suitable for patients with PSC ?

P	Adult liver transplant recipients for PSC and PSC patients waitlisted for adult LT
I	
C	
O	

Recommendation

The MELD system is not suitable for paediatric patients with PSC awaiting liver transplantation.

Level of evidence	Very low
Grade of recommendation	Strong for

PICO: What is the optimal immunosuppressive regimen for patients transplanted with PSC?

P	PSC recipients (Liver alone, Paediatric, Adult, With/without IBD, With intact colon at time of transplant)
I	Immunosuppression
C	Calcineurin inhibitor: Cyclosporin (CyA) vs Tacrolimus (Tac) Antimetabolic: Azathioprine (Aza) vs mycophenolate (MMF) Induction YES/NO (If YES what? e.g. IL2R vs anti-TG)
O	*Outcomes:* - PSC recurrence - ITT survival - Perioperative mortality (intraop. M., 30 days M. 90 days M. in-hospital M.) - Posttransplant survival (1,5,10 yr survival) - Quality adjusted ITT survival benefit - Graft loss from recurrent disease - Hypertension - Renal failure - De novo malignancy

Recommendation

Paediatric patients liver transplanted for PSC should receive standard immunosuppression.

Level of evidence	Very low
Grade of recommendation	Weak for

PICO: Do clinical outcomes differ between duct-to-duct anastomosis versus Roux-en-Y hepaticojejunostomy in liver transplant recipients who were transplanted for primary sclerosing cholangitis (PSC)?

P	Adult and paediatric liver transplant recipients who were transplanted for PSC
I	Duct-to duct anastomosis
C	Roux-en-Y hepaticojejunostomy
O	Post-LT cholangitis, anastomotic strictures, late-onset Non AS (NAS), graft survival, patients survival, PSC recurrence, surgical and oncological complications (e.g. cholangiocarcinoma of the remnant bile duct)

Recommendation

No recommendation can be made for the biliary anastomosis in paediatric patients undergoing liver transplantation for PSC	
Level of evidence	Very low
Grade of recommendation	Weak for

PICO: Is the use of extended criteria donors (ECD), including donation after circulatory death (DCD) in PSC associated with higher rate of non-anastomotic strictures (NAS) compared to other LT indications?

P	Liver transplantation (Adult and paediatric, PSC)
I	DBD liver transplantation

C	ECD liver transplantation
O	Post-LT cholangitis, anastomotic strictures, late-onset non-anastomotic strictures (NAS), graft survival, patients survival, PSC recurrence, surgical and oncological complications (e.g. cholangiocarcinoma of the remnant bile duct)

Recommendation

No recommendation can be made for the use of extended criteria donors (marginal donors) in paediatric patients undergoing liver transplantation for PSC	
Level of evidence	Very low
Grade of recommendation	Weak for

PICO: What are the best screening and surveillance strategies for IBD associated with PSC? (Screening for the presence of IBD, monitoring activity of IBD, bowel cancer surveillance in IBD in pre-, peri- and post-LT).

PICO: What is the optimum therapeutic approach for maintaining remission in IBD associated with PSC; pre-, peri- and post-transplant? (Safety and efficacy profiles of biologics, calcineurin inhibitors, anti-proliferatives and corticosteroids)

P	Liver transplantation (Adult and paediatric, PSC with / without IBD, Individuals with / without intact colon, either large bowel (colitis) or small bowel involvement from IBD)
I	• IBD screening, disease activity monitoring, bowel cancer surveillance in patients with/without an intact colon pre/post LT. • Treatment with biologics and microbial therapy (including oral vancomycin, faecal microbiota transplantation, pre-biotics and/or exclusive enteral nutrition) pre-, peri- and/or post-transplant
C	• No IBD screening or surveillance • No CRC screening or • No IBD-specific therapy • Non-biologic IBD treatment • Non-microbial therapy for IBD

O	Incidence and/or risk of 1. Acute colitis flares 2. Sub-total colectomy (or other colonic / bowel resection) 3. CRC and cancer-related death 4. IBD activity (e.g. Mayo/CDAI) 5. Complications/side effects of treatment. 6. HPB cancer and cancer-related death 7. Hepatic decompensations 8. Liver transplant-free survival (native liver) 9. Post-transplant graft loss 10. Post-transplant survival (overall, liver-related) 11. Post-transplant graft loss or mortality (combined endpoint) 12. PSC recurrence post-transplant 13. Non-anastomotic biliary strictures (aetiology specific and combined) 14. Post-transplant hepatic artery thrombosis / stenosis

Recommendation

Children liver transplanted for PSC should undergo standard paediatric management of their underlying inflammatory bowel disease.	
Level of evidence	Very weak
Grade of recommendation	Weak for

PICO:
1. When the colectomy is indicated?
2. What is the optimal timing for colectomy with regards native liver-related, graft-related, and overall survival?
3. How does the timing of colectomy (pre-, peri- or post-transplant) affect the incidence and risk of developing recurrent PSC and/or other graft-related complications?
4. What is the optimal timing for colectomy (pre-, peri- or post-transplant) with regards minimising peri-operative (peri-transplant) complications?
5. Does the type of colonic resection (i.e. restorative vs. non-restorative colectomy; ileal pouch anal anastomosis vs. ileorectal anastomosis vs. ileostomy alone) affect the outcomes listed in 1-3 above?
6. How does the timing of colectomy (pre-, peri- or post-transplant) affect peri-operative outcomes with regards the colonic resection procedure itself?

P	Liver transplantation (Adult and paediatric, PSC +/- autoimmune hepatitis overlap or autoimmune sclerosing cholangitis with / without IBD, Colonic resection (colectomy), Colectomy with/without an ileostomy, with/without a restorative IPAA / pouch, with/without a restorative ileorectal anastomosis (IRA))
I	· Colonic resection / colectomy · Timing of colectomy · Type of colectomy
C	· Colectomy for colorectal cancer vs. for active colitis · No colectomy vs. colectomy · Colectomy pre-transplant vs. colectomy post-transplant · Colectomy pre-transplant vs. no colectomy · Colectomy post-transplant vs. no colectomy · Ileostomy alone vs. no colectomy · IRA vs no colectomy · IPAA vs. no colectomy · Ileostomy alone vs. IPAA · Ileostomy alone vs. IRA · IPAA vs. IRA
O	Incidence and/or risk of: · Peri-operative complications/side effects of interventions · HPB cancer and cancer-related death · Hepatic decompensations (including stomal variceal bleeding) · Kidney injury · Liver transplant-free survival (native liver) · Post-transplant graft loss / regrafting · Post-transplant survival (overall, liver-related) · Post-transplant graft loss or mortality (combined endpoint) · PSC recurrence post-transplant · Non-anastomotic biliary strictures (aetiology specific and combined) · Post-transplant hepatic artery thrombosis / stenosis · Fertility · Pouchitis · IPAA reversal · IRA reversal · Overall survival · Health-related quality of life

Recommendation

No recommendation can be made