Chapter 8
Recurrence of Primary Sclerosing Cholangitis After Liver Transplantation

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Abbreviations

ACR	Acute cellular rejection
CMV	Cytomegalovirus
GWAS	Genome-wide association study
HLA	Human leukocyte antigen
IBD	Inflammatory bowel disease
OKT3	Orthoclone
PBC	Primary biliary cirrhosis
PSC	Primary sclerosing cholangitis

Primary sclerosing cholangitis (PSC) is a progressive cholestatic liver disease characterized by diffuse inflammation and fibrosis that can involve the entire biliary tree. Population-based studies observed annual incidence rates ranging from 0.9 to 1.3 per 100,000 population [1–3]. The pathogenesis of PSC remains unknown, but it is established as being immune mediated, occurring in genetically predisposed individuals and strongly associated with inflammatory bowel disease (IBD), which often runs an independent course from the liver disease [4]. The clinical presentation of PSC is variable. Patients frequently present without symptoms, but many develop progressive biliary strictures, leading to recurrent cholangitis and

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P.J. Thuluvath (ed.), *Disease Recurrence After Liver Transplantation*,
DOI 10.1007/978-1-4939-2947-4_8

ultimately end-stage liver disease. To date, no medical therapy has yet been proven to prolong survival or improve outcome of PSC [5]. Liver transplantation remains the only effective therapeutic option for patients with advanced liver disease from PSC. It is estimated that PSC accounts for approximately 4–5 % of adult liver transplantations performed each year in Europe and the United States [6, 7]. As the long-term outcome of PSC patients following liver transplantation continues to improve, reaching over 80 % at 5 years [7], there appears to be an increase in the number of patients developing recurrent PSC, which has emerged as clinically and academically important. In this chapter, the authors review diagnostic criteria, epidemiology, risk factors, graft and patient survival, and treatment of recurrent PSC after liver transplantation.

8.1 Diagnostic Criteria and Epidemiology of Recurrent PSC

Recurrent PSC usually manifests more than 1 year after liver transplantation as elevation of alkaline phosphatase and gamma glutamyl transpeptidase. The diagnosis of recurrent PSC can be challenging, as biliary strictures in the allograft suggesting recurrent disease are nonspecific and a variety of potential insults to the hepatic graft may result in biliary injury and stricturing. In particular, nonanastomotic biliary strictures in the liver allograft can occur because of the use of an ABO-incompatible allograft, chronic rejection, biliary tract infection, hepatic artery thrombosis, preservation injury, and prolonged cold ischemic time [8, 9]. Nonanastomotic intrahepatic strictures developing before 90 days after transplantation are usually not attributable to recurrent disease. The diagnosis of recurrent PSC can be difficult to establish with certainty and is therefore dependent on extensive histological and radiographic evaluation. Previously, a set of criteria has been proposed by a group of investigators from the Mayo Clinic [10] to serve as a uniform clinicopathologic standard for the diagnosis of recurrent PSC as shown in Table 8.1. The diagnostic criteria consist of a confirmed diagnosis of PSC before liver transplantation; cholangiogram showing nonanastomotic biliary strictures occurring 90 days after liver transplantation; exclusion of other conditions associated with biliary strictures; and/or liver biopsy showing fibrous cholangitis and/or fibro-obliterative lesions. Thereafter, these diagnostic criteria have been increasingly used as the standard tool for diagnosis of recurrent PSC.

A diagnosis of recurrent PSC can be made by means of cholangiography revealing nonanastomotic biliary strictures of the intrahepatic and/or extrahepatic biliary tree with beading and irregularity, occurring more than 90 days post-transplantation. However, assessing the bile ducts via the endoscopic route after liver transplantation for PSC is usually not feasible because most recipients have a Roux-en-Y loop rather than a duct-to-duct anastomosis. Given recent and considerable improvement of magnetic resonance imaging technique with its noninvasive nature, magnetic resonance cholangiography (MRC) has become the first choice to evaluate abnormalities of the biliary tract following liver transplantation, instead of percutaneous

Table 8.1 Diagnostic criterion for recurrent primary sclerosing cholangitis after liver transplantation

Inclusion criteria	Exclusion criteria
Confirmed diagnosis of primary sclerosing cholangitis before liver transplantation	Hepatic artery thrombosis or stenosis
And	Chronic ductopenic rejection
Cholangiographic evidence of intrahepatic and/or extrahepatic biliary stricturing, beading, and irregularities more than 90 days after liver transplantation	Anastomotic strictures
Or	Nonanastomotic strictures less than 90 days after liver transplantation
Histological evidence of fibrous cholangitis and/or fibro-obliterative lesions with or without ductopenia, biliary fibrosis, or biliary cirrhosis	ABO incompatibility between donor and recipient

Note: This table has been adapted from Graziadei et al. Recurrence of primary sclerosing cholangitis following liver transplantation. *Hepatology*. 1999; 29: 1050–1056

transhepatic cholangiography. MRC has been validated as an imaging modality to accurately assess the degree of biliary strictures with identification of mural irregularities and diverticulum-like outpouchings specific of PSC [11]. However, in the transplant setting, emphasis must be put on exclusion of other etiologies that can cause similar cholangiographic change. In a published series by Brandsaeter et al., a thorough examination with magnetic resonance angiography revealed a high rate of hepatic artery thrombosis and hepatic artery stenosis that explain some of the biliary stricture after liver transplantation in the non-PSC cohort [12]. Thus, apart from its assistance in diagnosing recurrent PSC, magnetic resonance imaging is of value for identifying a differential diagnosis of vascular complications.

Histopathological findings suggestive of PSC recurrence are identical to those described in the native liver with PSC. The early features in recurrent PSC are characterized by mild nonspecific cholangitis; acute and chronic "pericholangitis" often accompanied by a mild type 1 ductular reaction involving a variable percentage of portal tracts. As the disease progresses, increased ductal proliferation and neutrophilic and eosinophilic inflammation in the portal tract and periportal edema become apparent [13]. Other chronic cholangiopathic features including intralobular foam cell clusters and marked deposits of copper with Mallory's hyaline in periportal hepatocytes may be visualized [13]. In the late stage, the typical features of fibro-obliterative lesions may be observed with focal loss of medium and small bile ducts. However, similar changes can be seen with other causes of bile duct injuries in the allograft. Such an overlap particularly with chronic rejection questions the validity of liver histopathology as a sole definition of PSC recurrence. Histologically, the diagnostic criteria for chronic rejection are as follows: (1) senescent changes (including cytoplasmic eosinophilia, cell enlargement and multinucleation, uneven nuclear spacing, loss of polarity), affecting a majority of the bile ducts with or without bile duct loss; (2) convincing foam cell obliterative arteriopathy; or (3) bile duct

loss affecting greater than 50 % of the portal tracts [14]. In a transplant study by Jeyarajah et al., histopathologic analysis suggests that chronic rejection and recurrent PSC represent a spectrum of indistinguishable disease [15]. However, the distinct difference in clinical outcome, as evidenced by an increased repeat transplantation rate and lower graft and patient survival in PSC recipients with chronic rejection, clearly suggests that they are two distinct entities that require very different treatment strategies [15]. A history of suboptimal immunosuppression and severe or unresolved acute rejection constitute strong arguments in favor of diagnosing chronic rejection. Therefore, a definitive diagnosis of recurrent PSC mandates documentation of the characteristic cholangiographic findings combined with compatible histological features after exclusion of the other possible causes of biliary strictures.

Recurrence of PSC in the hepatic graft was first reported by Lerut et al., in 1988 [16]. Despite controversy that followed shortly after this concept was introduced; the recognition of recurrent PSC is now firmly established in the liver transplant community. The reported cumulative incidence of recurrent PSC has ranged from 10 to 55 % of the transplanted grafts with a median time to recurrence ranging from 8 to 68 months as shown in Table 8.2 [10, 12, 15, 17–25]. The variation is related in part to differences in diagnostic criteria and duration of follow-up. The use and timing of the protocol applied to detect biliary strictures and/or liver histology appears to be the most important factor for the disparity in the reported cumulative incidence of recurrent PSC. Considering that cholangiographic and histologic features of recurrent PSC are not correlated with biochemical indices, protocol liver biopsies, and cholangiography with a magnetic resonance technique may allow systemic and noninvasive evaluation of recipients with possibly full documentation of disease recurrence.

8.2 Risk Factors Related to Pathogenesis for Recurrent PSC

Reappearance of PSC in the liver allograft suggests that the mechanisms that lead to the initial development of the disease persist after liver transplantation. This would provide a wonderful opportunity to learn about the pathogenesis of the disease. However, factors determining disease development in the post-transplantation situation have been studied only to a limited extent. Several transplant groups have attempted to identify peritransplantation variables that may predict patients who will develop recurrent PSC. The results in general have been heterogeneous. Potential risk factors associated with disease recurrence included recipient age [15], male gender [26], donor-recipient gender mismatch [17], human leukocyte antigen (HLA)-DR1*08 [21], coexistent IBD [20], intact colon before transplantation [22, 26], episodes of acute cellular rejection (ACR) [21, 24], steroid-resistant ACR [12], orthoclone (OKT3) therapy for steroid-resistant ACR [18], maintenance steroid therapy for greater than 3 months post-transplantation [20], the presence of cholangiocarcinoma before transplantation [19], and concurrent cytomegalovirus (CMV)

Table 8.2 Cumulative incidence, risk factors, and outcomes of recurrent primary sclerosing cholangitis after liver transplantation

Authors, year	Cohort size	Follow-up period	Cumulative incidence	Risk factors for recurrence	Outcomes of PSC recurrence		
					5-year patient survival (PSC recurrence vs. non-recurrence)	5-year graft survival (PSC recurrence vs. non-recurrence)	Re-OLT
Jeyarajah et al. (1998) [15]	100	21 months (mean)	18 (18 %)	ACR	76 % vs. 89 %	65 % vs. 76 %	5/18
Graziadei et al. (1999) [10]	120	55 months (mean)	24 (20 %)	NA	Unchanged (86 % vs. 91 %)	Unchanged (79 % vs. 82 %)	2/24
Khettry et al. (2003) [17]	42	24–168 months (range)	6 (14.3 %)	Recipient-donor mismatch	NA	NA	None
Kugelmas et al. (2003) [18]	71	14–91 months (range)	15 (21.1 %)	OKT3 use	Unchanged (92 % vs. 86 %)	NA	NA
Brandsaeter et al. (2005) [12]	49	77 months (median)	9 (18 %)	Steroid-resistant ACR	NA	NA	NA
Campsen et al. (2008) [19]	130	66 months (median)	22 (16.9 %)	Cholangiocarcinoma before OLT	45 % without re-OLT	NA	7/22
Cholangitas et al. (2008) [20]	53	11 months (median)	7 (13.2 %)	Steroid use for ulcerative colitis >3 months post-OLT	Unchanged (85 % vs. 76 %)	NA	3/7
Alexander et al. (2008) [21]	69	50 months (median)	7 (10 %)	ACR, steroid-resistant ACR, HLA-DRB1*08	NA	NA	NA
Alabraba et al. (2009) [22]	230	82.5 months (median)	54 (23.5 %)	Intact colon at the time of OLT	Decreased in PSC recurrence	NA	11/54

(continued)

Table 8.2 (continued)

Authors, year	Cohort size	Follow-up period	Cumulative incidence	Risk factors for recurrence	Outcomes of PSC recurrence		
					5-year patient survival (PSC recurrence vs. non-recurrence)	5-year graft survival (PSC recurrence vs. non-recurrence)	Re-OLT
Egawa et al. (2009) [23]	20	63 months (median)	11 (55 %)	CMV injection within 3 months	NA	NA	6/20
Moncrief et al. (2010) [24]	59	68 months (median)	15 (25 %)	ACR, CMV mismatch	Unchanged	Unchanged	4/15
Egawa et al. (2011) [25]	114	42 months (median)	26 (27 %)	High MELD score, first-degree-relative donors, CMV infection, early biliary anastomosis complication	NA	39 % vs. 74 %	11/26

PSC primary sclerosing cholangitis, *ACR* acute cellular rejection, *NA* not assessed, *OKT3* orthoclone, *HLA* human leukocyte antigen, *CMV* cytomegalovirus, *MELD* model for end-stage liver disease

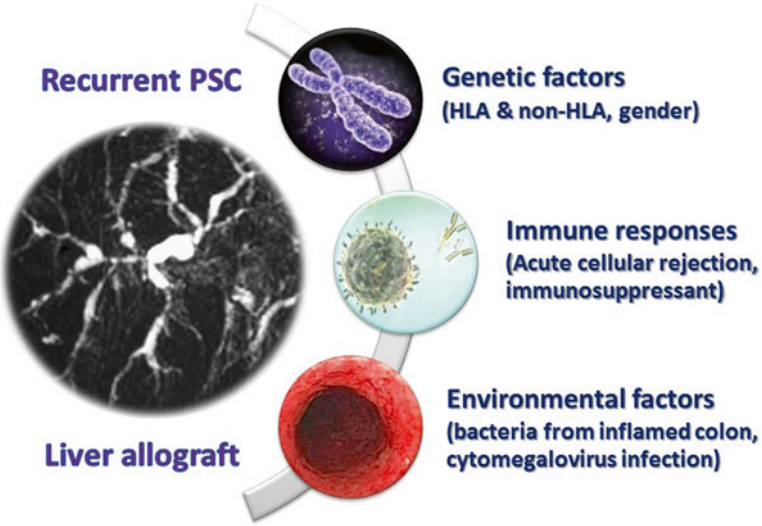

Fig. 8.1 Risk factors related to pathogenesis of recurrent primary sclerosing cholangitis

infection in the recipient [24]. The reasons for these discrepant findings among these studies may be due to the small number of patients with recurrent disease as well as the differences in the study design, the diagnostic criteria, and the interesting and confounding variables considered in the regression model.

Although the pathogenesis of PSC remains unclear, epidemiological and laboratory studies consistently indicate that PSC is a complex autoimmune disorder resulting from the interaction between genetic and environmental factors [27] as proposed in Fig. 8.1. In the last decade, there have been major efforts to delineate the genetic architecture of this condition. Recently, genome-wide association studies (GWAS) and immunochip-based studies identified numerous risk loci for PSC that host genes involved in innate or acquired immune responses [28–34], consistent with an autoimmune component to pathogenesis. Also, GWAS have clearly demonstrated that the major component of the genetic architecture of PSC is within the HLA region. To some extent, the genetic findings from non-transplant setting may guide the discovery of interacting and coexisting environmental susceptibility in PSC patients who developed recurrent disease after liver transplantation. The prognostic relevance of the particular HLA genes that confer recurrent PSC after liver transplantation was investigated by many investigators [15, 21]. In a report from the University of Washington transplant group, the overall frequency of the HLA-DRB1*03, DQB1*02 haplotypes among their PSC recipients was higher than that among donor populations, and this confirms that this genotype is more commonly expressed in patients who have PSC [21]. However, there was no difference in the frequency of this HLA haplotype between patients with recurrent PSC and those not having recurrence, and this suggests that the recipient HLA-specific haplotype represents a genetic predisposing factor rather than an antigen for immune

recognition in disease development. Interestingly, there was a higher incidence of HLA-DRB1*08, particularly in the absence of HLA-DQB1*04, in their recipients that eventually developed recurrent disease than in those that did not [21]. However, more work is required to confirm candidate genes, to evaluate the functional consequences of risk variants, and to understand how functional changes contribute to disease-specific pathologies. If the association between HLA haplotypes and risk of disease recurrence is validated in further studies, HLA typing would be useful in donor selection as well as to provide valuable prognostic information at the time of transplantation.

Of great interest is the reported higher rate of disease recurrence in 114 Japanese recipients of grafts from living-related donors, with recurrent PSC occurring in 32 % at 5 years and 52 % at 10 years after transplantation [25]. A potential explanation may be the first-degree-relatives and sibling have a prevalence of PSC about 100-fold that of nonrelatives [35]. Another possible mechanism contributing to the effect of first-degree-related donors might be linked to the effect of a shared genetic disposition in blood-related recipient and donor pairs including the HLA system. However, the incidence of recurrent PSC in recipients with grafts from related donors other than parents as well as nonrelated donors was similar to those reported for deceased donor liver transplantation [10, 12, 17–22, 26].

The pathogenesis of recurrent PSC could hypothetically be linked to autoimmunity, cross-sensitization between biliary and colonic antigens due to common epithelial epitopes, or leak of bacterial toxins from the inflamed colon with genetic predisposition [36]. The leaky theory is supported by observation of the absence of inflammation in the colon, either due to the absence of concurrent IBD or colectomy before or at the time of liver transplantation has a protective effect against disease recurrence [20, 22, 26]. This was first reported in a study by Vera et al., which demonstrated a dramatic reduction in the risk of PSC recurrence if the colon was removed before or during transplantation [26]. This finding was considerably strengthened in a study by Cholangitas et al., in which no PSC patients without ulcerative colitis or those undergoing pretransplant colectomy developed recurrent PSC [20]. The protective effect of colectomy before or during liver transplantation on the risk of developing recurrent PSC was confirmed in the largest prognostic study of recurrent PSC involved 230 consecutive adult patients who underwent liver transplantation for PSC [22]. Taken together, these findings are consistent with the hypothesis of aberrant homing of mucosal lymphocytes to the liver in the development of PSC [36] that may also be relevant in recurrent PSC. Importantly, these data should not be interpreted as an advocation for pretransplant colectomy but rather as input to understanding the mechanism of developing recurrent PSC.

The susceptibility of the transplanted liver to recurrent PSC may be influenced by the use of immunosuppression. A previous study by Kugelmas et al. [18] of immunosuppression after liver transplantation showed that disease recurrence was often seen in recipients who received maintenance corticosteroids, but the time to recurrence was not associated with length of corticosteroid administration. This was emphasized by published observation from the Royal Free Hospital transplant group showing that maintenance corticosteroids after liver transplantation were

associated with an increased risk of recurrent PSC [20]. The reason for this correlation remains unclear, whether it is greater immunosuppression, associated with graft rejection, or opportunistic (yet undefined) biliary infections, which may be from a leaky mucosa in IBD that leads to recurrence. On the basis of a higher likelihood of recurrent PSC and adverse metabolic consequences in patients exposed to corticosteroids chronically, early corticosteroid withdrawal should be recommended in the management of these recipients. This, however, must be weighed against the need for corticosteroids for control of graft rejection or colitis in patients with coexistent IBD. Furthermore, differences in the type of immunosuppression used after transplantation have been hypothesized to be related to the risk of recurrent PSC; however, no such effect has been observed [20, 22]. Also, no beneficial effect has been found according to post-transplant use of ursodeoxycholic acid (UDCA) [22].

The association between ACR and recurrent PSC has arisen because ACR may increase autoimmune epitopes that can lead to ductal damage. In a reported transplant series by Jeyarajah et al., they found a significantly higher incidence of ACR in recipients that later developed recurrent PSC [15]. Also, the University of Washington transplant group found ACR, particularly steroid-resistant ACR, as an increased risk for recurrent PSC [21]. However, it is unclear whether recurrent PSC results from a response to an immunogenically damaged biliary system due to ACR, or the existence of a common factor predisposing to both ACR and recurrent disease. Furthermore, OKT3 monoclonal antibody therapy for refractory ACR has been noted to be associated with a greater incidence of recurrent PSC [15]. This observation, rather than indicating an adverse effect of OKT3, is more likely to represent an increased risk of recurrent PSC as a by-product of ACR.

CMV infection has been reported as a risk factor for recurrent PSC, although the mechanism has not yet been clarified [37–39]. In the experimental studies, there is increasing evidence that CMV could provoke inflammation leading to biliary damage through ischemic insults or immune reaction activation [40–42]. Thus, CMV prophylaxis might be important to reduce the recurrence of PSC after liver transplantation. Valganciclovir, an oral pro-drug of ganciclovir, is an attractive agent for both antiviral prophylaxis and the preemptive treatment of CMV viremia [43].

8.3 Impact of Recurrent PSC on Graft and Patient Survival

Based on the analysis of the United Network for Organ Sharing (UNOS) database of 3309 PSC patients compared to 3254 patients with primary biliary cirrhosis (PBC) who had liver transplantation during 1987–2001, retransplantation rate was significantly higher in PSC (12.4 % vs. 8.5 %) than in PBC, and PSC was an independent predictor for retransplantation [44]. PSC patients had significantly lower graft and patient survival during the 10-year period of follow-up compared to PBC patients after adjusting for age, serum creatinine, UNOS status, ABO compatibility, and donor age. Importantly, the reduced survival in PSC did not become evident until 7 year after the primary transplantation [44]. The reasons for higher

retransplantation rate in PSC patients could not be determined from the database due to insufficient information. However, based on previous publications, it was probably due to a number of reasons including a higher rate of biliary complications, disease recurrence, and chronic rejection.

Earlier studies reported that recurrent PSC had no impact on graft and patient survival in the intermediate term of follow-up [10, 45]. However, there is increasing evidence that disease recurrence might lead to graft dysfunction and need for retransplantation related to recurrent PSC as longer follow-up became available [23, 46]. Campsen et al. reported that once a patient was diagnosed with recurrent disease, the median survival time without receiving a second transplant was 39.1 months [19]. Though most published studies failed to demonstrate a significant decrease in patient survival of recurrent PSC as shown in Table 8.2 [10, 15, 18, 20, 24], in the largest series of 230 patients transplanted for PSC, there was a trend toward reduced patient survival in patients with disease recurrence compared with those did not [22]. However, after exclusion of all patients who died before 6 months post-liver transplant, restriction to single-transplant patients and adjustment for age, patient survival was significantly better in patients without recurrent PSC [22]. This is not surprising, considering that retransplantation usually is a much more complicated procedure than the primary operation. The risk of perioperative death increases significantly from less than 5 % in the primary procedure to almost 20 % in retransplantation [47, 48].

8.4 Treatment for Recurrent PSC

As for PSC in the native liver, there is no established treatment for recurrent PSC. Several trials have been performed in PSC patients before transplantation to evaluate whether immunosuppressive or immunomodulating drugs could halt the progressive course of PSC and prolong transplant-free survival [4, 5, 7]. So far the trials have not shown conclusive results. One of the proposed theories for the lack of effect has been that the therapy is initiated too late. When the PSC diagnosis has been established and immunosuppressive drugs administered, the disease process is already advanced. Hence, if immunosuppressive treatment could be started earlier, the patients would possibly have a better chance of responding to such therapy. In PSC patients undergoing transplantation, immunosuppressive therapy was started during transplant surgery and all receive lifelong immunosuppression. Still, a group of patients developed recurrent PSC in presumably healthy liver graft. Furthermore, UDCA has been advocated in the majority of transplant centers for PSC recipients; however, there is no supporting evidence that the use of UDCA is beneficial in preventing or treating recurrent PSC [49]. UDCA may be of benefit in those with coexisting ulcerative colitis, as some suggest it reduces the risk of colon cancer [50]. Patients with end-stage liver disease from recurrent PSC should be considered for retransplantation.

Interventional cholangiographic treatment of biliary strictures should be considered when dominant strictures or their complications, such as cholangitis or choledocholithiasis are present. However, such approaches are rarely feasible since most strictures are multiple and most recipients have a Roux loop. Some centers have addressed this challenge using single or double balloon enteroscopy to perform endoscopic retrograde cholangiography in patients with complex postsurgical gastrointestinal anatomy [51, 52]. These experienced groups illustrated the usefulness and feasibility of an endoscopic approach using an enteroscope for diagnosis and treatment of biliary strictures in liver transplant patients with biliary-enteric anastomosis. However, development of a therapeutic channel of enteroscope for delivery of larger-diameter stents as well as longer-length accessories is needed. In the native liver, three retrospective studies evaluating the beneficial effect of endoscopic treatment of dominant strictures in PSC patients have suggested the improvement of 3- and 5-year patient survival rates [53–55]. Whether endoscopic treatment influences the progression of recurrent PSC is currently unknown. Therefore, further studies of endoscopic treatment modalities in patients with recurrent PSC should be encouraged.

8.5 Conclusion

Recurrent PSC is now established as an important clinical outcome after liver transplantation. Over time, this problem is likely to increase and exert more impact on patients and graft survival. Several transplant groups have tried to identify risk factors for recurrent disease; however, reported predictors in general have not been confirmed across different studies. Current available data lend support to an association of the inflamed colon with recurrence of PSC in susceptible patients. Treatment of this condition relies mainly on relief of symptomatic biliary strictures, but no evidence of medical or endoscopic therapy has been able to alter the disease course. Although the rarity of the disease has made observational and treatment studies difficult to perform, the future looks bright with the ongoing international collaborations and strong support from patients for research efforts.

References

1. Boberg KM, Aadland E, Jahnsen J, et al. Incidence and prevalence of primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis in a Norwegian population. Scand J Gastroenterol. 1998;33:99–103.
2. Bambha K, Kim WR, Talwalkar J, et al. Incidence, clinical spectrum, and outcomes of primary sclerosing cholangitis in a United States community. Gastroenterology. 2003;125:1364–9.
3. Kingham JG, Kochar N, Gravenor MB. Incidence, clinical patterns, and outcomes of primary sclerosing cholangitis in South Wales, United Kingdom. Gastroenterology. 2004;126:1929–30.

4. Charatcharoenwitthaya P, Lindor KD. Primary sclerosing cholangitis: diagnosis and management. Curr Gastroenterol Rep. 2006;8:75–82.
5. Lindor KD. New treatment strategies for primary sclerosing cholangitis. Dig Dis. 2011;29: 113–6.
6. Duclos-Vallee JC, Sebagh M. Recurrence of autoimmune disease, primary sclerosing cholangitis, primary biliary cirrhosis, and autoimmune hepatitis after liver transplantation. Liver Transpl. 2009;15 Suppl 2:S25–34.
7. LaRusso NF, Shneider BL, Black D, et al. Primary sclerosing cholangitis: summary of a workshop. Hepatology. 2006;44:746–64.
8. Gautam M, Cheruvattath R, Balan V. Recurrence of autoimmune liver disease after liver transplantation: a systematic review. Liver Transpl. 2006;12:1813–24.
9. Graziadei IW. Recurrence of primary sclerosing cholangitis after liver transplantation. Liver Transpl. 2002;8:575–81.
10. Graziadei IW, Wiesner RH, Marotta PJ, et al. Long-term results of patients undergoing liver transplantation for primary sclerosing cholangitis. Hepatology. 1999;30:1121–7.
11. Sheng R, Campbell WL, Zajko AB, et al. Cholangiographic features of biliary strictures after liver transplantation for primary sclerosing cholangitis: evidence of recurrent disease. AJR Am J Roentgenol. 1996;166:1109–13.
12. Brandsaeter B, Schrumpf E, Bentdal O, et al. Recurrent primary sclerosing cholangitis after liver transplantation: a magnetic resonance cholangiography study with analyses of predictive factors. Liver Transpl. 2005;11:1361–9.
13. Demetris AJ. Distinguishing between recurrent primary sclerosing cholangitis and chronic rejection. Liver Transpl. 2006;12:S68–72.
14. Demetris A, Adams D, Bellamy C, et al. Update of the International Banff Schema for Liver Allograft Rejection: working recommendations for the histopathologic staging and reporting of chronic rejection. An International Panel. Hepatology. 2000;31:792–9.
15. Jeyarajah DR, Netto GJ, Lee SP, et al. Recurrent primary sclerosing cholangitis after orthotopic liver transplantation: is chronic rejection part of the disease process? Transplantation. 1998;66:1300–6.
16. Lerut J, Demetris AJ, Stieber AC, et al. Intrahepatic bile duct strictures after human orthotopic liver transplantation. Recurrence of primary sclerosing cholangitis or unusual presentation of allograft rejection? Transpl Int. 1988;1:127–30.
17. Khettry U, Keaveny A, Goldar-Najafi A, et al. Liver transplantation for primary sclerosing cholangitis: a long-term clinicopathologic study. Hum Pathol. 2003;34:1127–36.
18. Kugelmas M, Spiegelman P, Osgood MJ, et al. Different immunosuppressive regimens and recurrence of primary sclerosing cholangitis after liver transplantation. Liver Transpl. 2003;9:727–32.
19. Campsen J, Zimmerman MA, Trotter JF, et al. Clinically recurrent primary sclerosing cholangitis following liver transplantation: a time course. Liver Transpl. 2008;14:181–5.
20. Cholongitas E, Shusang V, Papatheodoridis GV, et al. Risk factors for recurrence of primary sclerosing cholangitis after liver transplantation. Liver Transpl. 2008;14:138–43.
21. Alexander J, Lord JD, Yeh MM, et al. Risk factors for recurrence of primary sclerosing cholangitis after liver transplantation. Liver Transpl. 2008;14:245–51.
22. 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 Transpl. 2009;15:330–40.
23. Egawa H, Taira K, Teramukai S, et al. Risk factors for recurrence of primary sclerosing cholangitis after living donor liver transplantation: a single center experience. Dig Dis Sci. 2009;54:1347–54.
24. Moncrief KJ, Savu A, Ma MM, et al. The natural history of inflammatory bowel disease and primary sclerosing cholangitis after liver transplantation–a single-centre experience. Can J Gastroenterol. 2010;24:40–6.
25. Egawa H, Ueda Y, Ichida T, et al. Risk factors for recurrence of primary sclerosing cholangitis after living donor liver transplantation in Japanese registry. Am J Transplant. 2011;11: 518–27.

26. Vera A, Moledina S, Gunson B, et al. Risk factors for recurrence of primary sclerosing cholangitis of liver allograft. Lancet. 2002;360:1943–4.
27. Hirschfield GM, Karlsen TH, Lindor KD, et al. Primary sclerosing cholangitis. Lancet. 2013;382:1587–99.
28. Karlsen TH, Franke A, Melum E, et al. Genome-wide association analysis in primary sclerosing cholangitis. Gastroenterology. 2010;138:1102–11.
29. Liu JZ, Hov JR, Folseraas T, et al. Dense genotyping of immune-related disease regions identifies nine new risk loci for primary sclerosing cholangitis. Nat Genet. 2013;45:670–5.
30. Srivastava B, Mells GF, Cordell HJ, et al. Fine mapping and replication of genetic risk loci in primary sclerosing cholangitis. Scand J Gastroenterol. 2012;47:820–6.
31. Melum E, Franke A, Schramm C, et al. Genome-wide association analysis in primary sclerosing cholangitis identifies two non-HLA susceptibility loci. Nat Genet. 2011;43:17–9.
32. Janse M, Lamberts LE, Franke L, et al. Three ulcerative colitis susceptibility loci are associated with primary sclerosing cholangitis and indicate a role for IL2, REL, and CARD9. Hepatology. 2011;53:1977–85.
33. Folseraas T, Melum E, Rausch P, et al. Extended analysis of a genome-wide association study in primary sclerosing cholangitis detects multiple novel risk loci. J Hepatol. 2012;57:366–75.
34. Ellinghaus D, Folseraas T, Holm K, et al. Genome-wide association analysis in sclerosing cholangitis and ulcerative colitis identifies risk loci at GPR35 and TCF4. Hepatology. 2013;58:1074–83.
35. Bergquist A, Lindberg G, Saarinen S, et al. Increased prevalence of primary sclerosing cholangitis among first-degree relatives. J Hepatol. 2005;42:252–6.
36. Grant AJ, Lalor PF, Salmi M, et al. Homing of mucosal lymphocytes to the liver in the pathogenesis of hepatic complications of inflammatory bowel disease. Lancet. 2002;359:150–7.
37. Kasahara M, Egawa H, Takada Y, et al. Biliary reconstruction in right lobe living-donor liver transplantation: comparison of different techniques in 321 recipients. Ann Surg. 2006;243:559–66.
38. Halme L, Hockerstedt K, Lautenschlager I. Cytomegalovirus infection and development of biliary complications after liver transplantation. Transplantation. 2003;75:1853–8.
39. Egawa H, Inomata Y, Uemoto S, et al. Biliary anastomotic complications in 400 living related liver transplantations. World J Surg. 2001;25:1300–7.
40. Melnick JI, Adam E, De Bakey ME. Possible role of cytomegalovirus infection in atherosclerosis. JAMA. 1990;263:2204–7.
41. Bolovan-Fritts CA, Spector SA. Endothelial damage from cytomegalovirus-specific host immune response can be prevented by targeted disruption of fractalkine-CX3CR1 interaction. Blood. 2008;111:175–82.
42. Streblow DN, Kreklywich C, Yin Q, et al. Cytomegalovirus-mediated upregulation of chemokine expression correlates with the acceleration of chronic rejection in rat heart transplants. J Virol. 2003;77:2182–94.
43. Levitsky J, Singh N, Wagener MM, et al. A survey of CMV prevention strategies after liver transplantation. Am J Transplant. 2008;8:158–61.
44. Maheshwari A, Yoo HY, Thuluvath PJ. Long-term outcome of liver transplantation in patients with PSC: a comparative analysis with PBC. Am J Gastroenterol. 2004;99:538–42.
45. Goss JA, Shackleton CR, Farmer DG, et al. Orthotopic liver transplantation for primary sclerosing cholangitis. A 12-year single center experience. Ann Surg. 1997;225:472–81.
46. Rowe IA, Webb K, Gunson BK, et al. The impact of disease recurrence on graft survival following liver transplantation: a single centre experience. Transpl Int. 2008;21:459–65.
47. Reese PP, Yeh H, Thomasson AM, et al. Transplant center volume and outcomes after liver retransplantation. Am J Transplant. 2009;9:309–17.
48. Akpinar E, Selvaggi G, Levi D, et al. Liver retransplantation of more than two grafts for recurrent failure. Transplantation. 2009;88:884–90.
49. Schreuder TC, Hübscher SG, Neuberger J. Autoimmune liver diseases and recurrence after orthotopic liver transplantation: what have we learned so far? Transpl Int. 2009;22:144–52.

50. Pardi DS, Loftus EV, Kremers WK, et al. Ursodeoxycholic acid as a chemopreventive agent in patients with ulcerative colitis and primary sclerosing cholangitis. Gastroenterology. 2003;124:889–93.
51. Koornstra JJ. Double balloon enteroscopy for endoscopic retrograde cholangiopancreaticography after Roux-en-Y reconstruction: case series and review of the literature. Neth J Med. 2008;66:275–9.
52. Saleem A, Baron TH, Gostout CJ, et al. Endoscopic retrograde cholangiopancreatography using a single-balloon enteroscope in patients with altered Roux-en-Y anatomy. Endoscopy. 2010;42:656–60.
53. Stiehl A, Rudolph G, Klöters-Plachky P, et al. Development of dominant bile duct stenoses in patients with primary sclerosing cholangitis treated with ursodeoxycholic acid: outcome after endoscopic treatment. J Hepatol. 2002;36:151–6.
54. Baluyut AR, Sherman S, Lehman GA, et al. Impact of endoscopic therapy on the survival of patients with primary sclerosing cholangitis. Gastrointest Endosc. 2001;53:308–12.
55. Gluck M, Cantone NR, Brandabur JJ, et al. A twenty-year experience with endoscopic therapy for symptomatic primary sclerosing cholangitis. J Clin Gastroenterol. 2008;42:1032–9.