Chronic Hepatitis

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Review

Primary sclerosing cholangitis: an update

JD Feuerstein*, EB Tapper

Abstract

Introduction

Primary sclerosing cholangitis is a chronic and progressive liver disorder. The disease is characterized by progressive inflammation leading to stricturing and fibrosis of the medium and large biliary ducts in intra and/or extrahepatic ductal system. Primary sclerosing cholangitis is more common in men. It is classically associated with inflammatory bowel disease, specifically ulcerative colitis. The disease is progressive resulting in complications, including cholestasis, malignancy and hepatic failure, necessitating a liver transplantation. The median survival following diagnosis is 10–12 years, but shorter when disease is advanced at the time of diagnosis. Approximately 50% of patients meet the criteria for liver transplantation within 10–15 years of becoming symptomatic. Unfortunately, primary sclerosing cholangitis can recur after transplantation. Herein we present a review for the clinicians of this fascinating and difficult disease.

Conclusion

Therapies are still lacking to cure the disease or to halt its progression. Further studies are necessary to answer these questions.

Introduction

Epidemiology

The prevalence of primary sclerosing cholangitis (PSC) ranges from 6 to 16 cases per 100,000 individuals and an incidence of 1 per 100,000 individuals in North America and Europe[1]. Globally, there is geographical variation in the prevalence of primary sclerosing cholangitis (PSC) with similar rates in North American and Northern European countries but less in Asia and Southern Europe[2]. However, overall incidence does seem to be increasing[1]. PSC is slightly more common in men than women. The median age at diagnosis is 41 years, though notably when it is diagnosed at an older age, PSC is slightly more common in women. Approximately 60%--80% of patients with PSC have concomitant inflammatory bowel disease (IBD), most often ulcerative colitis (UC)[3]. The aim of this review was to provide an update for PSC.

Discussion

Risk factors

A few risk factors have been associated with the development of PSC. However, family history is the only significant risk factor. Individuals with a first-degree relative have a 9–39 fold increased risk of PSC[4]. In addition, patients with IBD are also at increased risk of PSC[3,5,6]. Interestingly, cigarette smoking appears to have a protective effect against PSC. Tonsillectomy may also portend a protective affect as well[7].

Pathophysiology

The exact pathogenesis of PSC is unclear but is presumed to be a multifactorial immune-mediated process. PSC develops in genetically susceptible individuals after exposure to some unknown environmental trigger[8]. Multiple candidate genes have been associated with PSC, including HLA-DRB1*1501-DQB1*602, HLA-DRB1*1301-DQB1*0603 and HLA-A1-B8-DRB1*0301-DQB1*0201[9]. Weaker associations have been made with non-HLA genes including those encoding intracellular adhesion molecule 1, tumour necrosis factor and matrix metalloproteinase-3[7].

Once the 'second hit'—environmental trigger, toxin or infectious exposure—occurs, the immune system is activated, resulting in interactions between innate and adaptive immune systems, which, in turn, lead to lymphocyte migration, cholangiocyte damage and, ultimately, fibrosis[10,11]. Other theories have included portal bacteraemia whereby gut flora translocates and triggers the cascade of events causing PSC[11]. An ischaemic bile duct injury theory has been postulated but is supported by very little evidence[11]. Another theory involving mutations in the cystic fibrosis transmembrane conductance regulator has been supported by a single study[12].

Clinical presentations

The majority of patients are asymptomatic at the time of diagnosis[1]. PSC is usually diagnosed in the setting of incidentally elevated alkaline phosphatase or suggestive findings on cross-sectional imaging[1,3]. Even when presenting asymptomatically, patients can present with advanced disease. In fact, 17% of patients will already have cirrhosis at the time of diagnosis[13]. By 6 years, ~75% will have evidence of disease progression[14].

In more advanced cases, patients present with often non-specific symptoms. Most commonly, patients present with fatigue, followed by pruritus and jaundice and, in very advanced disease, weight loss[15]. The

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exact cause of fatigue is unclear. Pruritus, which can occur even with a normal bilirubin, is believed to be due to either bile acid accumulation or endogenous opioids. Less common are fever, chill, night sweat and abdominal pain, all of which are usual symptoms of episodic cholangitis. In around 50% of cases, physical examination is most often normal at the time of diagnosis. In other cases, jaundice may be present, along with hepatomegaly, splenomegaly, and, when pruritus is present, excoriations on the skin[3]. Laboratory testing is most often notable for an elevated alkaline phosphatase which is usually the trigger for the initial workup leading to the diagnosis of PSC. Other findings in more advanced disease include elevated bilirubin. Bilirubin may rise and fall during episodes of transient cholangitis. Serum aminotransferases are typically normal or mildly elevated. Rarely do they ever exceed 2–3 fold above the upper limits of normal. Synthetic function (albumin, platelets and international normalized ratio) are only altered in advanced disease associated with hepatic failure[3].

Radiologically, the disease classically shows wall thickening, dilation and strictures of the biliary ductal system. Magnetic resonance cholangiopancreatography (MRCP) is the most sensitive and specific imaging modality for the diagnosis of PSC[16,17]. Classically, MRCP shows a "beaded" appearance formed by multifocal short annular strictures that alternatebetween normal and dilated segments[18]. The presence of any long stricture is concerning for cholangiocarcinoma. Ultrasound is not very sensitive or specific for the making the diagnosis. Ultrasound may show ductal wall thickening and focal bile duct dilations. Other findings may include gallbladder wall thickening, distention, gallstones and mass lesion. Computer tomography may show thickened and inflamed bile ducts, saccular dilation of the intrahepatic ducts and, occasionally, mass lesions in the gallbladder[3,7].

Diagnosis

The diagnosis of PSC should be considered in any patient with an unexplained elevated alkaline phosphatase or cholestatic pattern of liver abnormalities, especially in patients with IBD[3,5,6,13]. The gold standard for diagnosis is cholangiography, preferably using magnetic resonance imaging (MRI) or, if non-diagnostic, then endoscopic retrograde cholangiopancreatography (ERCP)[16]. Diagnostic cholangiography of classic PSC includes multifocal annular strictures alternating with segments of normal or dilated bile ducts of the intrahepatic and/or extrahepatic bile ducts—the so-called 'bead on a string appearance[3,18,19].' Less often, the disease may present with long confluent strictures which is worrisome for cholangiocarcinoma. While it is most common to have diffuse involvement of the biliary system, 25% of patients may only have intrahepatic involvement[3]. All other causes of sclerosing cholangitis, like IgG-4 associated sclerosing cholangitis must be excluded. Some advocate checking IgG-4 and performing pancreatic imaging to definitively rule out IgG-4 associated disease prior to diagnosing PSC[10].

MRCP has become the test of choice over ERCP or percutaneous cholangiography[16]. MRCP offers improved diagnostic accuracy and, furthermore, it is non-invasive, does not involve radiation exposure and is cost-effective[10,16,20]. A meta-analysis of six studies showed MRCP to have a sensitivity of 86% and specificity of 94% in diagnosing PSC[17]. Liver biopsy is rarely helpful in making the diagnosis safe for those patients with normal imaging yet a high suspicion for small duct associated PSC. In most cases, the histology from a liver biopsy is nonspecific. The disease is usually heterogeneous and random biopsy is prone to false negative sampling error. The classic histologic findings are fibrosis and destruction of the small bile ducts with concentric replacement by connective tissue[21]. This classic "onion skin" pattern associated with PSC is seen in <25% of liver biopsies[22]. The stage of liver fibrosis is determined using the Batts–Ludwig scoring system[23].

Imaging findings in PSC tend to fall into two categories. The first is classic PSC, defined by biliary strictures with normal intervening segments or diffusely involved long segments. Strictures may occur in any part of the biliary system. Eighty-seven percent of cases involve intrahepatic and extrahepatic bile ducts; 11% involve intrahepatic bile ducts alone and 2% involve extrahepatic ductal systems only[24]. In many cases, the gallbladder and cystic duct may also be involved[25]. The second major category of PSC is radio-occult disease. In early PSC, strictures may not be present on cholangiographic imaging. The only finding may be shallow ulcerations of the bile duct. As a result, in these cases, ERCP is usually necessary to make the diagnosis. Small duct PSC is a more difficult diagnosis to make. In this variant, cholangiography is often normal even when repeated, but the patients have a persistently elevated alkaline phosphatase because the disease involves the small calibre bile ducts. In this case, the diagnosis of small duct PSC is made after liver biopsy confirms the diagnosis. The prognosis is usually better than classic PSC. However, up to 20% will evolve into large duct PSC over the ensuing 7–10 years[7,8,10].

Many antibodies have been studied in PSC but all are non-specific[26]. As such, serologic testing is rarely helpful in the diagnosis of PSC. In some cases, increased IgG (30%) and IgM (40%–50%) levels have been seen. Similarly, studies have also found antinuclear antibodies, atypical perinuclear anti-neutrophil cytoplasmic antibodies, anti-smooth

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muscle antibodies, anti-cardiolipin antibodies and rheumatoid factor, all with unclear significance[26]. Additionally, the antibodies, even when positive, do not correlate with disease severity or progression of disease.

Differential diagnosis in cases of PSC is quite broad. All secondary causes of cholangiographic findings similar to PSC must be excluded. The most similar presenting disease is IgG-4 related sclerosing cholangitis. Other possible causes include bacterial or eosinophilic cholangitis, ischaemic or mast cell cholangiopathy, cholangiocarcinoma, choledocholithiasis, hepatic metastasis, portal hypertensive biliopathy, recurrent pyogenic cholangitis and surgical biliary trauma.

Associated conditions

PSC has been associated with IBD and autoimmune hepatitis (AIH)[5,27]. AIH-PSC overlap syndrome is more commonly seen in children and in young adults under the age of 25. These patients have classic findings associated with AIH and the cholangiographic findings associated with PSC. AIH-PSC occurs in ≤6% of patients with PSC. These patients typically have shorter survival and shorter times to liver transplantation compared with patients with either disease alone[7,10,27]. In IBD, PSC is more common with UC, occurring in ~4% of patients with UC, but can occur with Crohn's disease as well. In patients with IBD-PSC, the risk of colorectal cancer is significantly increased. These patients should undergo indefinite yearly screening colonoscopy at the time of PSC diagnosis even if IBD disease duration is under 8 years. In addition, while colectomy treats underlying UC, PSC can still develop in these patients[5,19,23].

Treatments

Ideal treatment goals are to cure the disease, prevent progression of disease and prevent complications. Currently, there is no cure for PSC. Liver transplantation is temporarily effective but disease recurrence occurs. In addition, no treatment effectively prevents disease progression. While there are effective therapies for complications, there are no proven strategies for prevention[28].

Although recent studies are not as promising, the most commonly used agent is ursodeoxycholic acid (UCDA)[29]. A European study did not show any survival benefit in doses of 17–23 mg/kg/day compared with placebo[30]. A North American study using 28–30 mg/kg/day was stopped early due to an increased risk of disease progression, formation of varices, liver transplantation, colorectal cancer and death compared with placebo[31]. The adverse events were most common in those with early stage disease. Furthermore, a meta-analysis did not show any benefit of UDCA in PSC on survival or delaying liver transplantation[32]. However, in doses up to 15 mg/kg/day, UCDA is presumed to be safe and may improve biochemical markers and stabilize hepatic inflammation[29]. The current guidelines are mixed regarding the recommended use of UDCA. The AASLD does not recommend UDCA use[3], but the European Association for the Study for Liver Diseases makes no recommendation regarding UDCA[33].

Multiple other drugs have been studied in PSC with limited or adverse results. Immunosuppresive agents including anti-tumour necrosis factors (etanercept, infliximab), thiopurines (azathioprine, 6-meracaptopurine), methotrexate, calcineurin inhibitors (cyclosporine, tacrlomus), antibiotics (e.g. vancomycin, metronidazole) and corticosteroids have all been ineffective in delaying progression of PSC. Some of the agents have shown an improvement in biochemical markers in small studies, but given the toxicity associated with these agents, none are recommended[10,28,34].

Liver transplantation is indicated for end-stage liver disease and complications of portal hypertension refractory to medical therapy. In addition, liver transplantation is considered in cases of PSC-specific complications, including intractable pruritus and recurrent cholangitis. Given that patients with PSC often have a relatively low model for end-stage liver disease (MELD) score, many pursue to living donor transplants. Liver transplantation has a high success rate with a 1-year survival exceeding 90%, 5-year survival exceeding 80% and 10-year survival of 70%. However, early acute cellular rejection within 30 days of transplantation is higher in patients with PSC[3,35].

Complications

The complications of PSC are a result of the progressive nature of the disease. Cholangitis occurs in 10%–15% of patients. It is typically treated with recurrent courses of antibiotic therapy. In some cases of recurrent cholangitis, continuous suppressive antibiotic therapy may be used[3,7,10,16,25].

The complications of PSC can be devastating. First, dominant strictures (e.g. stenosis of ≤1.5 mm in the common bile duct or ≤1 mm in the hepatic duct) may result in obstructive symptoms, cholangitis or harbour a cholangiocarcinoma. More than 60% of patients with PSC develop dominant strictures in either the intra or extrahepatic biliary system. When present, an ERCP with cytologic brushings are warranted to exclude malignancy. If obstructive symptoms are present,endoscopic dilation can be attempted. If endoscopic dilation fails to maintain patency of the lumen, temporary placement of a biliary stent for 6–8 weeks can be utilized. However, superimposed cholangitis secondary to stent placement is a concern. Whenever an ERCP is performed in patients with PSC, prophylactic antibiotics are warranted to reduce the risk of cholangitis with any biliary tract manipulation[3,7,10,16,25,36].

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Second, as the disease progresses, the patient may develop cirrhosis. Once cirrhosis develops, the patient is vulnerable to any of the classic complications related to cirrhosis, including portal hypertension with varices or ascites and hepatic encephalopathy[3,7].

Third, the risk of several malignancies is also increased, including cholangiocarcinoma, hepatocellular carcinoma (when cirrhosis is present), colorectal cancer and gallbladder carcinoma[3,7,10,16,25,37]. Patients with PSC have a 10%–15% lifetime risk of developing cholangiocarcinoma with an annual incidence of ~1.5%. When present, 1/3 of cholangiocarcinoma develops within 1–3 years after the initial diagnosis. Prolonged duration of IBD, variceal bleeding, presence of a dominant stricture and alcohol abuse increase the risk of cholangiocarcinoma. There are no data that screening for cholangiocarcinoma decreases the risk. Furthermore, diagnosing cholangiocarcinoma is difficult. Tests that are employed include endoscopic brushing for cytology, endobiliary biopsy, computed tomography, MRCP and tumour markers including CEA and CA19-9. Some centres, ours included, perform annual surveillance for cholangiocarcinoma with MRCP or ultrasound imaging along with CA19-9. However, the current AASLD guidelines do not specifically recommend for or against screening[3]. One critical feature in favour of screening is that early cholangiocarcinoma may be surgically resected. In cases where surgery is not feasible, liver transplantation can be considered at specialized centres for stage I–II disease and perihilar cholangiocarcinoma under ≤3 cm. If the patient is cirrhotic, screening for hepatocellular carcinoma is indicated irrespective of PSC. However, given the risk for cholangiocarcinoma, we use MRCP in place of the conventional ultrasound.

Colorectal cancer is similarly increased, especially in patients with underlying IBD who have a 4-fold increased risk compared with IBD alone. Therefore, patients with PSC should have a colonoscopy at diagnosis of PSC with random biopsies to exclude IBD. If IBD is present, yearly colonoscopy should be continued indefinitely. Liver transplantation does not reduce the risk of colon cancer. Similarly, even after colectomy, there is still a risk of cancer developing in the pouch, and a continued pouchoscopy is warranted. Given this increased risk of cancer in the subset of IBD-associated PSC, studies have evaluated the use of UDCA as a chemopreventative agent. Studies have been inconclusive and guidelines do not recommend for the drug[3]. However, it is still used by some in practice[3,7,8,19,29,37,38].

Gallbladder cancer is also increased with a prevalence ranging from 3% to 14%. More than 50% of gallbladder polyps identified incidentally in patients with PSC may harbour a malignancy. Due to the increased risk, AASLD guidelines recommend yearly ultrasound to assess for malignancy[3]. Cholecystectomy is recommended whenever a lesion is found regardless of the size. However, cholecystectomy in patients with advanced PSC may carry higher morbidity and careful decision-making should be made regarding cholecystectomy for very small lesions in patients with advanced liver disease[3,7,8,25,37].

Other associated complications include cholelithiasis, fat-soluble vitamin deficiencies and osteoporosis[7]. Fat-soluble vitamin deficiencies presumably result from a decreased secretion of conjugated bile acids in the small intestine. Bone disease usually occurs in advanced disease. The current guidelines recommend screening for osteoporosis at diagnosis and then every two to three years[3]. Risk factors for bone disease include age over 54, body mass index ≤24 kg/m and IBD for >19 years[3,7,8].

Prognosis

Prognosis is best when patients are asymptomatic and without any comorbid IBD at the time of presentation. The median time to death or liver transplantation in these cases is 12–18 years. However, when patients are already symptomatic at presentation, the median time to death or liver transplantation is 9 years. Prognosis is best estimated using the Mayo Risk Score: $R = 0.03$ (age [years]) + 0.54 loge (bilirubin [mg/dL]) + 0.54 loge (AST [UIL]) + 1.24 (variceal bleeding [0/1]) – 0.84 (albumin [g/dL]) (Table 2)[39]. This score includes patient's age, bilirubin, albumin, aspartate aminotransferase and any history of variceal bleeding. When concomitant IBD is present, the prognosis is poorer. Unfortunately, even if liver transplantation is performed, disease recurrence occurs in 14%–20% of patients. Male sex and presence of IBD with an intact colon may increase the risk of recurrence.The prognosis following disease recurrence after liver transplantation is similar to the pre-transplant prognosis. Approximately 1/3 of patients develop progressive disease, resulting in need for liver transplantation or death[3,7,8,13,15,19,35,40].

Conclusion

PSC is a chronic and progressive disease. Little is still known regarding the actual pathogenesis of disease. Therapies are still lacking to cure the disease or to halt its progression. Further studies are necessary to answer these questions.

References

1. Bambha K, Kim W, Talwalkar J, Torgerson H, Benson JT, Therneau TM, et al. Incidence, clinical spectrum, and outcomes of primary sclerosing cholangitis in a united states community. Gastroenterology. 2003 Nov;125(5):1364–9.

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All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

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2. Boonstra K, Beuers U, Ponsioen CY. Epidemiology of primary sclerosing cholangitis and primary biliary cirrhosis: a systematic review. Journal of hepatology. 2012 Apr;56(5):1181–8.
3. Chapman R, Fevery J, Kalloo A, Nagorney DM, Boberg KM, Shneider B, et al. Diagnosis and management of primary sclerosing cholangitis. Hepatology. 2010 Feb;51(2):660–78.
4. Bergquist A, Lindberg G, Saarinen S, Broomé U. Increased prevalence of primary sclerosing cholangitis among first-degree relatives. Journal of hepatology. 2005 Feb;42(2):252–6.
5. O'Toole A, Alakkari A, Keegan D, Doherty G, Mulcahy H, O'Donoghue D. Primary sclerosing cholangitis and disease distribution in inflammatory bowel disease. Clinical Gastroenterology and Hepatology. 2012 Apr;10(4):439–41.
6. Tung B, Brentnall T, Kowdley K, Emond M, Kimmey M, Stevens A, et al. Diagnosis and prevalence of ulcerative colitis in patients with primary sclerosing cholangitis. Paper presented at: Hepatology; May, 1996.
7. Singh S, Talwalkar JA. Primary sclerosing cholangitis–diagnosis, prognosis and management. Clinical Gastroenterology and Hepatology. 2013 Aug(11):898–907.
8. Hirschfield GM, Karlsen TH, Lindor KD, Adams DH. Primary sclerosing cholangitis. The Lancet. 2013 Nov;382(9904):1587–99.
9. Karlsen TH, Franke A, Melum E, Kaser A, Hov JR, Balschun T, et al. Genome-wide association analysis in primary sclerosing cholangitis. Gastroenterology. 2010 March;138(3):1102–11.
10. Eaton JE, Talwalkar JA, Lazaridis KN, Gores GJ, Lindor KD. Pathogenesis of primary sclerosing cholangitis and advances in diagnosis and management. Gastroenterology. 2013 Sep;145(3):521-–36.
11. Pollheimer MJ, Halilbasic E, Fickert P, Trauner M. Pathogenesis of primary sclerosing cholangitis. Best Practice & Research Clinical Gastroenterology. 2011 Dec;25(6):727–39.
12. Sheth S, Shea JC, Bishop MD, Chopra S, Regan MM, Malmberg E, et al. Increased prevalence of cftr mutations and variants and decreased chloride secretion in primary sclerosing cholangitis. Human genetics. 2003 Aug;113(3):286–92.
13. Okolicsanyi L, Fabris L, Viaggi S, Carulli N, Podda M, Ricci G. Primary sclerosing cholangitis: clinical presentation, natural history and prognostic variables: an italian multicentre study. the italian psc study group. Eur J Gastroenterol Hepatol. 1996 Jul;8(7):685–91.
14. Porayko MK, Wiesner RH, LaRusso NF, Ludwig J, MacCarty R, Steiner B, et al. Patients with asymptomatic primary sclerosing cholangitis frequently have progressive disease. Gastroenterology. 1990 Jun;98(6):1594–1602.
15. Wiesner RH, Grambsch PM, Dickson ER, Ludwig J, Maccarty RL, Hunter EB, et al. Primary sclerosing cholangitis: natural history, prognostic factors and survival analysis.Hepatology.1989Oct;10(4):430–36.
16. LaRusso NF, Shneider BL, Black D, Gores GJ, James SP, Doo E, et al. Primary sclerosing cholangitis: summary of a workshop. Hepatology. 2006 Sept;44(3):746–64.
17. Dave M, Elmunzer BJ, Dwamena BA, Higgins PD. Primary sclerosing cholangitis: meta-analysis of diagnostic performance of mr cholangiopancreatography. Radiology. 2010 Aug;256(2):387–96.
18. MacCarty R, LaRusso N, Wiesner R, Ludwig J. Primary sclerosing cholangitis: findings on cholangiography and pancreatography. Radiology. 1983 Oct;149(1):39–44.
19. Talwalkar JA, Lindor KD. Primary sclerosing cholangitis. Inflammatory Bowel Diseases. 2005 Jul;11(1):62–72.
20. Talwalkar JA, Angulo P, Johnson CD, Petersen BT, Lindor KD. Cost-minimization analysis of mrc versus ercp for the diagnosis of primary sclerosing cholangitis. Hepatology. 2004 Jul;40(1):39–45.
21. Burak KW, Angulo P, Lindor KD. Is there a role for liver biopsy in primary sclerosing cholangitis? Am J Gastroenterol. 2003 May;98(5):1155–58.
22. Ludwig J. Surgical pathology of the syndrome of primary sclerosing cholangitis. The American journal of surgical pathology. 1989;13:43.
23. Ludwig J, Barham SS, Larusso NF, Elveback LR, Wiesner RH, McCall JT. Morphologic features of chronic hepatitis associated with primary sclerosing cholangitis and chronic ulcerative colitis. Hepatology. 1981 Nov;1(6):632–40.
24. Lee YM, Kaplan MM. Primary sclerosing cholangitis. N Engl J Med.1995 Apr;332(14):924–33.
25. Said K, Glaumann H, Bergquist A. Gallbladder disease in patients with primary sclerosing cholangitis. J Hepatol. 2008 Apr;48(4):598–605.
26. Angulo P, Peter JB, Gershwin ME, DeSotel CK, Shoenfeld Y, Ahmed AE, et al. Serum autoantibodies in patients with primary sclerosing cholangitis. Journal of hepatology. 2000 Feb;32(2):182–7.
27. Boberg KM, Fausa O, Haaland T, Holter E, Mellbye OJ, Spurkland A, et al. Features of autoimmune hepatitis in primary sclerosing cholangitis: an evaluation of 114 primary sclerosing cholangitis patients according to a scoring system for the diagnosis of autoimmune hepatitis. Hepatology. 1996 Jun;23(6):1369–76.
28. Barnabas A, Chapman RW. Primary sclerosing cholangitis: is any treatment worthwhile? Current gastroenterology reports. 2012 Feb;14(1):17–24.
29. Triantos C, Koukias N, Nikolopoulou V, Burroughs A. Ursodeoxycholic acid in primary sclerosing cholangitis. Aliment Pharmacol Ther.2012 Nov;35(5):622–23.
30. Olsson R, Boberg KM, de Muckadell OS, Lindgren S, Hultcrantz R, Folvik G, et al. High-dose ursodeoxycholic acid in primary sclerosing cholangitis: a 5-year multicenter, randomized, controlled study. Gastroenterology. 2005 Nov;129(5):1464–72.
31. Lindor KD, Kowdley KV, Luketic VA, Harrison ME, McCashland T, Befeler AS, et al. High-dose ursodeoxycholic acid for the treatment of primary sclerosing cholangitis.Hepatology.2009 Sept;50(3):808–14.
32. Triantos CK, Koukias NM, Nikolopoulou VN, Burroughs AK. Meta-analysis: ursodeoxycholic acid for primary sclerosing cholangitis. Aliment Pharmacol Ther. 2011 Oct;34(8):901–10.
33. European Association for the Study of the L. Easl clinical practice guidelines: management of cholestatic liver diseases. Journal of hepatology. 2009;51(2):237–67.
34. Tabibian J, Weeding E, Jorgensen R, Petz J, Keach J, Talwalkar J, et al. Randomised clinical trial: vancomycin or metronidazole in patients with primary sclerosing cholangitis-a pilot study. Aliment Pharmacol Ther. 2013 Mar;37(6):604–12.
35. Dickson ER, Murtaugh PA, Wiesner RH, Grambsch PM, Fleming TR, Ludwig J, et al. Primary sclerosing cholangitis: refinement and validation of survival

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All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

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models. Gastroenterology. 1992 Dec;103(6):1893–1901.
36. Bangarulingam SY, Gossard AA, Petersen BT, Ott BJ, Lindor KD. Complications of endoscopic retrograde cholangiopancreatography in primary sclerosing cholangitis. Am J Gastroenterol. 2009 Apr;104(4):855–60.
37. Razumilava N, Gores GJ, Lindor KD. Cancer surveillance in patients with primary sclerosing cholangitis. Hepatology. 2011 Nov;54(5):1842–52.
38. Treeprasertsuk S, Björnsson E, Sinakos E, Weeding E, Lindor KD. Outcome of patients with primary sclerosing cholangitis and ulcerative colitis undergoing colectomy. World Journal Of Gastrointestinal Pharmacology And Therapeutics. 2013 Aug;4(3):61.
39. Kim W, Therneau TM, Wiesner RH, Poterucha JJ, Benson JT, Malinchoc M, et al. A revised natural history model for primary sclerosing cholangitis. Mayo Clinic Proceedings. 2000 Jul;75(7):688–94.
40. Boonstra K, Weersma RK, van Erpecum KJ, Rauws EA, Spanier B, Poen AC, et al. Population-based epidemiology, malignancy risk and outcome of primary sclerosing cholangitis. Hepatology. 2013 Dec;58(6):2045–55.

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