SPECIAL ARTICLE

Primary Sclerosing Cholangitis: Summary of a Workshop

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Primary sclerosing cholangitis (PSC) is a rare but important liver disease that leads to cirrhosis and need for liver transplantation in a high proportion of cases. The disease occurs in approximately 1 per 100,000 population per year, usually presents in adulthood, and affects men more often than women. Typical serum biochemical results, autoantibodies and liver biopsy are suggestive but not diagnostic of PSC, the diagnosis requiring cholangiographic demonstration of stricturing and dilatation of the intra- and/or extra-hepatic bile ducts. The natural history of PSC is variable, the average survival being 12 to 17 years. The cause of PSC is still unknown. Although considered an autoimmune disease, PSC has several atypical features and a strong genetic component. The therapy of PSC is unsatisfactory. Standard doses of ursodeoxycholic acid (UDCA) lead to improvements in biochemical abnormalities but not in histology, cholangiographic appearance or survival. Several innovative therapies have been tried in PSC, but with scant evidence of benefit. For patients with high grade strictures, endoscopic dilatation is beneficial. Liver transplantation is successful for end-stage liver disease due to PSC and improves survival. PSC may recur after transplantation but is rarely progressive. The most dreaded complication of PSC is cholangiocarcinoma. Diagnosis of this highly malignant tumor is difficult, and there are no biomarkers for its early detection. Liver transplantation for cholangiocarcinoma has an exceedingly poor outcome, although transplantation with neoadjuvant chemoirradiation holds promise in selected patients. Thus, significant opportunities remain for basic and clinical research into the cause, natural history, and therapy of PSC. (HEPATOLOGY **2006;44:746-764.**)

Primary sclerosing cholangitis (PSC) is a rare but important cause of chronic liver disease. The disease is characterized by chronic inflammation and obliterative fibrosis of the intra- and/or extra-hepatic biliary tree which leads to bile stasis, hepatic fibrosis, and ultimately to cirrhosis, end-stage liver disease, and need for liver transplantation. PSC can also lead to cholangiocarcinoma, a highly malignant tumor. The cause of PSC is unknown. While often associated with autoantibodies and closely linked to inflammatory bowel disease (IBD), PSC is not a typical autoimmune disease and responds poorly, if at all, to typical immunosuppressive therapies. Indeed, no therapies have been proven to improve survival or ameliorate the natural history of PSC. Liver transplantation is successful for patients with end-stage liver disease, and PSC now accounts for 5% of liver transplants done in the United States.

Despite its importance, there have been few advances in understanding the pathogenesis of PSC. Furthermore, there are uncertainties regarding optimal means of diagnosis, monitoring, and therapy. These needs led the Liver Disease Research Branch of the NIDDK to organize a 2-day research workshop on PSC, focusing on summarizing current knowledge and defining needs for future research. The meeting was cosponsored by the Office on Rare Diseases in the Office of the Director, NIH, and the Musette and Allen Morgan Jr. Foundation for Study of PSC. This review summarizes that workshop, which is available as a videocast at www.videocast.nih.gov

Session One. Clinical Features and Epidemiology

Dr. Russell Wiesner (Mayo Clinic, Rochester, MD) described the clinical features and modes of presentation

Abbrevations: PSC, primary sclerosing cholangitis; IBD, inflammatory bowel disease; ALT, alanine aminotransferase; ANA, antinuclear antibody; SMA, smooth muscle antibody; GGT, gamma-glutamyl transpeptidase; CPT, Child-Pugh-Turcotte score; MELD, Model for End-Stage Liver Disease; ERCP, endoscopic retrograde cholangio-pancreatography; MRCP, magnetic resonance cholangio-pancreatography; pANCA, antibody to perinuclear neutrophil cytoplasmic antigen; PBC, primary biliary cirrhosis; IL, interleukin; TNF, tumor necrosis factor; TGF, transforming growth factor; MHC, major histocompatibility complex; HLA, human leukocyte antigen; NK, natural killer; PFIC, progressive familial intrahepatic cholestasis; MDR, multi-drug resistance; CFTR, cystic fibrosis transmembrane conductance regulator; BSEP, bile salt export protein; UDCA, ursodeoxycholic acid; TLR, toll-like receptor; NF, nuclear factor; iNOS, inducible nitric oxide synthetase; SPLIT, Study of Pediatric Liver Transplantation; PELD, Pediatric Model for End-Stage Liver Disease; SEER, Surveillance, Epidemiology and End Results; CEA, carcinoembryonic antigen.

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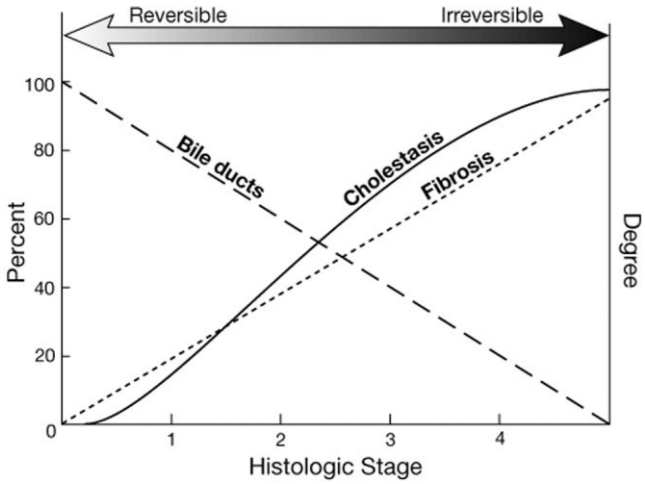

Fig. 1. Concept of the natural history of PSC. A gradual loss of bile ducts causes a progressive cholestasis followed by fibrosis. Early stages are reversible, whereas later stages are not. Modified with permission from Dr. Russell Wiesner.

of PSC in adults. PSC typically presents during the 4th or 5th decade, the average age of onset being 42 years.[1-4] The disease is more common in men than women and among Caucasians and Northern Europeans, than in Southern Europeans, Asians, or Africans. Typical symptoms of PSC are pruritus and fatigue, but some patients are diagnosed before the onset of symptoms on the basis of abnormal liver enzymes. PSC is closely linked to IBD, and some cases come to medical attention when patients with IBD are screened for liver disease.[5] A rare presentation is with variceal hemorrhage, end-stage liver disease, or cholangiocarcinoma.

The clinical course of PSC is typically one of insidious worsening of cholestasis and eventual development of jaundice and end-stage liver disease (Fig. 1).[2,6] About one-third of patients have episodes of bacterial cholangitis especially following biliary interventions, during which the disease can materially progress. Cholangiocarcinoma develops in 10% of patients and can occur relatively early and before onset of cirrhosis. Patients with PSC are frequently categorized as symptomatic versus asymptomatic, with small versus large duct disease, with IBD versus without, and with features of autoimmune hepatitis versus without.

PSC typically affects both intra- and extra-hepatic bile ducts. "Small duct PSC" refers to disease that affects bile ducts that are too small to be identified by endoscopic retrograde cholangiopancreatography (ERCP).[7,8] Among adults with PSC, 75% have involvement of both small and large ducts, 15% small ducts only, and 10% large ducts only. Small duct PSC typically presents with insidious onset of symptoms or with end-stage liver disease. Episodes of cholangitis are rare. Small duct PSC can be associated with IBD, has a more favorable prognosis, and is less likely than large duct PSC to lead to cholangiocarcinoma.[9]

Many patients with PSC have IBD as well, typically ulcerative colitis and less commonly Crohn's disease with colonic involvement.[10] IBD is diagnosed before PSC in 75% of cases and afterward in the remainder. Indeed, the diagnosis of IBD may not become evident until after liver transplantation for end-stage PSC; and conversely, PSC may not become apparent in patients with ulcerative colitis until after colectomy. There is little or no correlation between the severity of PSC and that of the associated IBD. Furthermore, therapy of IBD has little effect on the course of PSC, and *vice versa*. Other less common disease associations are thyroiditis, ankylosing spondylitis, and celiac disease.

PSC with autoimmune hepatitis-like features has been referred to as autoimmune cholangitis.[11,12] These patients usually present with high serum alanine aminotransferase (ALT) levels, modest or no elevations in serum alkaline phosphatase, high titers of antinuclear (ANA) and anti-smooth muscle antibodies (SMA) and liver histology typical of autoimmune hepatitis. Corticosteroid therapy may lead to improvements in symptoms and liver enzyme abnormalities. Eventually, however, patients become resistant to therapy and serum enzymes rise again, with prominent elevations in alkaline phosphatase and gamma glutamyl transpeptidase (GGT). Thus, PSC is a heterogeneous condition that can present with distinct clinical patterns that may have important implications for pathogenesis, prognosis and therapy.

Dr. Eve Roberts (Hospital for Sick Children, Toronto, Canada) described the clinical features of PSC in children. PSC is uncommon in children and must be separated from secondary forms of sclerosing cholangitis.[13-16] Neonatal sclerosing cholangitis is likely a separate disease process.[17,18] In children, PSC usually presents with nonspecific symptoms and pruritus, and rarely with jaundice.[11,13,18-22] An autoimmune hepatitis-like presentation is common.[11,22] ERCP may demonstrate bile duct abnormalities in these children,[23] but their course is typical of autoimmune hepatitis, although with time, features of PSC become prominent. A rare mode of presentation is with advanced disease as shown by marked splenomegaly or gastrointestinal hemorrhage. Most case series of PSC in children show a male predominance with an average age of onset in preteens (Table 1). Rarely, PSC presents before the age of two. IBD (usually ulcerative colitis) is found in 33% to 81% of children, but often not at initial presentation; up to 5% of children with IBD will develop PSC.

Table 1. Five Published Case Series on PSC in Children

Author[Ref](year)	No. of Patients	Percent Male	Mean Age (years)	Percent With IBD	Percent With AIH features	Jaundice	Elevated Alk P
Debray[18](1994)	19	53%	7.1	37%	11%	32%	84%
Wilschanski[19](1995)	32	72%	11.2	53%	28%	25%	53%
Gregorio[11](2001)	27	44%	11.8	44%	100%	56%	NA
Feldstein[20](2003)	52	65%	13.8	81%	27%	19%	75%
Floreani[21](2005)	3	0%	15.3	33%	100%	NA	NA

Abbreviations: IBD, inflammatory bowel disease; AIH, autoimmune hepatitis-like features; Alk P, serum alkaline phosphatase levels; NA, not available.

The natural history of PSC in children is only partially defined. Dominant strictures and recurrent cholangitis are uncommon. The prognosis is only fair, survival being better than in adults, but resulting in need for liver transplantation in up to one-third of patients by early adulthood. The risk of cholangiocarcinoma is not well defined, but appears to be rare. Thus, PSC is uncommon in children but is clinically distinct and challenging.

Dr. W. Ray Kim (Mayo Clinic, Rochester, MN) described current understanding of the natural history of PSC. PSC is a life-long disease that limits the life span.[2] While this disease is typically insidious and progresses slowly, spontaneous resolution does not occur. The median time from diagnosis to death or liver transplantation is only 8 years (Fig. 2), but the actual time varies due to three factors: (1) the stage of disease at time of diagnosis; (2) interpatient variability in the rate of progression; and (3) the possibility that PSC represents several diseases with different natural histories.

Defining the natural history of PSC is difficult. PSC is often separated into four phases: (1) small duct cholangitis, (2) progressive cholestasis, (3) cirrhosis, (4) decompensation. In only a small number of patients can these four phases be distinctly demarcated. Large duct lesions developing during the second phase may speed progression. Furthermore, cholangiocarcinoma can develop at any time. Some of the variability in disease progression can be resolved by categorizing patients as symptomatic versus asymptomatic, with small duct versus large duct PSC, and with versus without IBD.

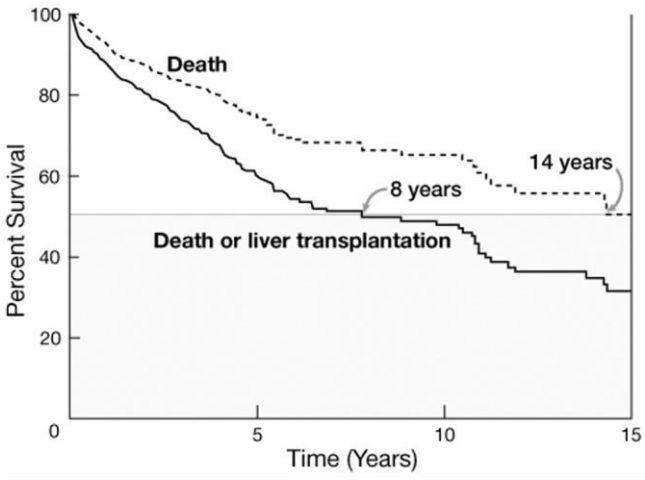

Fig. 2. Survival in PSC, as measured by time to death or time to either death or liver transplantation. Modified with permission from Dr. W. Ray Kim.

Asymptomatic patients may have a better prognosis than those with symptoms. This distinction, however, may be due to "lead time bias", patients without symptoms being those with earlier stages of disease. Asymptomatic patients are usually younger and have fewer biochemical abnormalities than symptomatic patients. Ultimately, asymptomatic patients usually develop symptoms.

Small duct PSC has been reported to be less rapidly progressive than large duct PSC.[8,9,24] This pattern is probably not due to lead time bias, in that only 12% to 16% of patients with small duct PSC progress to large duct disease (in 5- to 6-year follow up). Furthermore, some patients develop cirrhosis without obvious large duct involvement. Thus, small duct PSC may present a distinct clinical entity.

Several prognostic models for PSC have been developed (Table 2).[2,25-29] Most models include age and serum bilirubin, but not symptoms. A revised Mayo Model has been developed based upon the course of disease in 468 patients seen at three large referral centers in the last 20 years. The risk score is calculated as follows: 0.30 age (years) + 0.54 $\log_e$ bilirubin (mg/dL) + 0.54 $\log_e$ AST (U/L) + 1.24 history of variceal bleeding (0 = no, 1= yes) – 0.84 albumin (g/dL) (web-based calculator available at http://www.mayoclinic.org/gi-rst/ mayomodel3.html). The advantage of the revised model over the Child-Pugh-Turcotte (CPT) score or Mathematical Model for End-stage Liver Disease (MELD) is in capturing earlier stages of PSC before onset of cirrhosis.[30,31] Once decompensated cirrhosis is present, the MELD score more accurately predicts survival and is more appropriately used in listing for liver transplantation.

Dr. Kirsten Muri Boberg (Rikshospitalet, Oslo, Norway) described the epidemiology of PSC. With better

Table 2. Prognostic Models in PSC: Factors

Reference (year)	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
Wiesner[2] (1989)	Age	Bilirubin	Histology	Hemoglobin	IBD
Farrant[25] (1991)	Age	Alkaline Phosphatase	Histology	Splenomegaly	Hepatomegaly
Dickson[26] (1992)	Age	Bilirubin	Histology	Splenomegaly	
Broome[27] (1996)	Age	Bilirubin	Histology		
Okolicanyi[28] (1996)		Cholesterol	ALT		
Kim[29] (2000)	Age	Bilirubin	AST	Albumin	Variceal Bleeding

Abbreviations: Alk Phos, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IBD, inflammatory bowel disease.

diagnostic tests, PSC has been found to be more common than previously believed. In Scandinavian countries, PSC is the single leading cause for liver transplantation.[10]

There have been few population-based epidemiological studies of PSC (Table 3). The incidence is 0.9 to 1.3 per 100,000 in Northern Europe[10,32,33] and the United States[6] but less than 0.1 per 100,000 in Southern Europe[34] and Asia.[35] Patients with PSC survive for an average of 12 to 17 years, so that the prevalence of this disease in these same surveys ranges from 8 to 14 per 100,000 persons in Northern Europe and the United States, but is 1.3 or less in Southern Europe and Asia. The frequency of PSC in Africa is unknown and there have been no large studies of PSC in minority U.S. populations (Asians and African Americans). PSC appears to be rare among Native Alaskans.[36] The incidence and prevalence of PSC (1.3 and 8.5 per 100,000 in Oslo, Norway) is somewhat less than that for primary biliary cirrhosis (1.6 and 14.6 per 100,000) and autoimmune hepatitis (1.9 and 16.9 per 100,000).[32]

PSC is frequently associated with IBD. In Northern Europe and the United States, 70% to 80% of patients with PSC have or will develop IBD. In contrast, IBD is found in 54% or less of patients with PSC in Spain,[34] Italy,[28] and India[37] and in only 20% of PSC patients in Asian countries.[38] In Western countries, 2.4% to 4% of patients with IBD have PSC.[39-41] Of course, the frequency of these associations depends on diagnostic rigor. Thus, in some studies, patients with IBD are routinely evaluated for liver disease (serum enzymes) or biliary abnormalities [ERCP or magnetic resonance cholangiopancreatography (MRCP)]. Furthermore, patients with PSC in these series are frequently screened for IBD using colonoscopy with biopsies. Thus, the epidemiology of PSC is not well defined. Better studies are needed in larger, more representative populations, using standardized means of screening and diagnosis.

Session Two. Diagnosis and Assessment of Primary Sclerosing Cholangitis

Dr. Paul Angulo (Mayo Clinic, Rochester, MN) discussed the differential diagnosis of PSC in adults. The major criteria for diagnosis are (1) cholangiographic findings of multifocal strictures and beading of the intra- and/or extra-hepatic bile ducts with (2) compatible biochemical abnormalities and (3) exclusion of secondary causes.[1,3,42] Secondary causes of bile duct abnormalities that should be excluded in adults include strictures due to surgery, trauma, ischemia, tumors and infections, such as cryptosporidiosis and cytomegalovirus (particularly in patients with immunodeficiency).

PSC can be suspected from typical biochemical abnormalities such as elevations in serum alkaline phosphatase and GGT with lesser increases in ALT and AST levels. The mainstay of diagnosis is ERCP demonstrating multiple strictures and focal dilatation of bile ducts.[1] Most diagnostic are changes found in the extra-hepatic biliary tree, because focal narrowing and a "pruned tree" appearance can occur advanced cirrhosis without PSC. Recently, MRCP has been increasingly used for imaging of the bil-

Table 3. Epidemiology of PSC

Region (reference)	Time	Population	No. Cases of PSC	Incidence (per 100,000/year)	Prevalence (per 100,000)
Norway[32]	1986-1995	130,000	17	1.3	8.5
Wales, U.K.[33]	1984-2003	NA	46	0.9	12.7
Minnesota, U.S.[6]	1976-2000	NA	22	0.9	13.6
Spain[34]*	1984-1988	19,200,000	43	0.07	0.22
Singapore[35]†	1989-1998	750,000	10	NA	1.3
Alaska, U.S.[36]	1983-2000	100,312	0	0	0

Abbreviation: NA, not available.

*Based on a questionnaire sent to gastroenterologists in parts of the country. †10 cases diagnosed over a 10-year period, giving a maximum prevalence of 1.3.

Table 4. Autoimmune Cholangitis Versus Autoimmune Hepatitis Versus Primary Sclerosing Cholangitis in Children.[11]Clinical and Laboratory Features at Presentation

Feature	PSC n = 9	AC n = 27	AIH n = 28
Male Sex	67%	45%	25%
Age at Onset (years)*	6.6 (2-14.5)	11.8 (2.3-16)	10.5 (2.2-14)
Jaundice at Onset	13%	56%	68%
Bilirubin (mg%)*	0.9 (0.3-1.5)	1.2 (0.3-10.5)	2.1 (0.3-18.0)
AST (U/L)*	90 (26-760)	102 (18-1215)	333 (24-4830)
Alk Phos (U/L)*	474 (23-688)	303 (104-1710)	356 (131-878)
GGT (U/L)*	141 (23-688)	129 (13-948)	76 (29-383)
Alk Phos/AST ratio*	5.5 (1.4-9.9)	4.0 (0.2-14.2)	1.14 (0.1-14.8)
pANCA	44%	74%	36%
Response to Corticosteroids	Uncommon	89%	94%
Presence of IBD	33%	44%	18%

Abbreviations: PSC, primary sclerosing cholangitis; AC, autoimmune cholangitis; AIH, autoimmune hepatitis; AST, aspartate aminotransferase; Alk Phos, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; pANCA, perinuclear antineutrophil cytoplasmic antibody; IBD, inflammatory bowel disease. *Median (range).

iary tree.[43,44] Liver biopsy is usually not needed for diagnosis, although it may help in excluding other diseases.[45]

There are no standardized and widely accepted diagnostic criteria for the different forms of PSC. Small-duct PSC is diagnosed on the basis of cholangiography, but excellent technique is needed to exclude mild extrahepatic biliary involvement. Autoimmune features are common in patients with PSC, antinuclear antibody being present in up to 50% and perinuclear antineutrophil cytoplasmic antibody (pANCA) in 80% of cases.[46] Autoimmune cholangitis is a term used to describe patients with ERCP changes consistent with PSC who have serological and histologic features of autoimmune hepatitis.[11,47] Thus, the diagnosis of PSC relies on excellent cholangiography and the exclusion of other diseases, autoimmune hepatitis being the most challenging.

Dr. Giorgina Mieli-Vergani (King's College Hospital, London, UK) discussed the special challenges to diagnosis of PSC in children. The diagnostic criteria for PSC are similar in children as adults, although a different group of secondary causes need to be excluded, including neonatal sclerosing cholangitis, Langerhans cell histiocytosis, primary and secondary immunodeficiences, and cystic fibrosis.[13,19,22] A major differential diagnosis in children is between autoimmune hepatitis and autoimmune cholangitis (Table 4). At issue is whether these are different diseases; whether one evolves into the other; whether the prognosis and natural history of each are different; and whether different approaches to therapy should be used in these different clinical patterns of disease.

Dr. Ann S. Fulcher (Virginia Commonwealth University, Richmond, VA) reviewed the current role of imaging tests in PSC. The gold standard for diagnosis has been ERCP,[1,2,48] which in experienced hands is successful in demonstrating the intra- and extra-hepatic biliary tree in 95% of cases. Shortcomings of ERCP include its discomforts and risks, including pancreatitis, cholangitis, intestinal or bile duct perforation, and bleeding. The risks are probably greater in patients with PSC than those with other diagnoses, and instances of life-threatening and even fatal cholangitis have been reported. In recent years, MR techniques have been developed and improved such that MRCP has replaced ERCP for diagnosis of PSC in many centers[43,44,49,50] (Fig. 3). MRCP is done without the need for endoscopy, catheterization of the biliary tree, contrast material, sedation, or radiation exposure. MRCP has the advantage of depicting ducts proximal to high-grade strictures and allowing visualization in patients with biliary-enteric anastamoses and gastric bypass procedures. In addition, MR provides imaging of the rest of the abdomen, which may yield important information. The shortcomings of MRCP are that it is purely diagnostic, not allowing intervention. In addition, in some instances, MRCP may be less sensitive in demonstrating bile duct abnormalities and provide equivocal results that would call for follow up ERCP. Overall, in routine cases, MRCP is probably the best initial approach to diagnosis of PSC[51] and can be used for screening, such as in patients with IBD or patients with new onset autoimmune hepatitis to rule out PSC. ERCP and percutaneous transhepatic cholangiography will remain useful adjunctive procedures when MRCP is nondiagnostic or when acquisition of tissue samples or intervention is necessary.

Dr. Swan N. Thung (Mount Sinai School of Medicine, New York, NY) discussed the role of liver biopsy in the diagnosis and staging of PSC. The primary injury in PSC is not to hepatocytes but rather to medium- and large-sized bile ducts (>100 μm in diameter) which are not captured in a typical percutaneous liver biopsy. The smaller bile ducts (<100 μm) are affected by the resultant obstruction and gradually disappear ("ductopenia"). The characteristic pathologic features of PSC are concentric

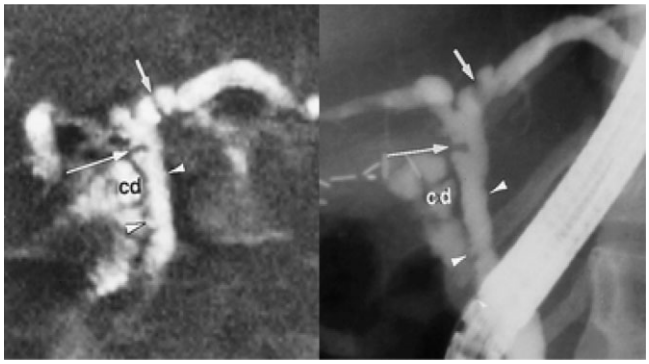

Fig. 3. Magnetic resonance (left panel) compared to endoscopic retrograde cholangiography (right panel) in a patient with extra- and intrahepatic PSC. Reprinted from: Fulcher AS, Turner MA, Franklin KJ, Shiffman M, Sterling RK, Luketic VA, Sanyal AJ. Primary sclerosing cholangitis: Evaluation with MR cholangiography—a case control study. Radiology 200-;215:71-80,[49] with permission from the Radiological Society of North America.

periductal fibrosis ("onion-skinning") that progresses to a narrowing and then obliteration of the small bile ducts leaving a bile duct scar (Fig. 4).[52-54] The bile duct epithelium may exhibit degeneration and atrophy. Chronic cholestasis leads to bile stasis, pseudoxanthomatous changes, Mallory bodies, and copper accumulation, most typically in the periportal region. These changes are not pathognomic of PSC and can occur with chronic extrahepatic bile duct obstruction from any cause.[55] The differential diagnosis should include primary biliary cirrhosis (PBC), biliary atresia, autoimmune hepatitis and graft-versus-host disease.[56]

Systems for grading and staging PSC have not been rigorously tested for reliability. Stage 1 disease is marked by bile duct injury and portal inflammation with minimal fibrosis; Stage 2 by expansion of portal tracts, periportal fibrosis and further inflammation; Stage 3 by fibrous septa, bridging fibrosis, and progressive ductopenia; Stage 4 by cirrhosis.[53] Systems that separate grade (activity) from stage (fibrosis) have not been developed and better systems for use in clinical trials are needed.

The primary injury in PSC is to the major bile ducts, which are rarely available except at the time of autopsy or liver transplantation. The bile ducts are thickened and sclerotic and demonstrate alternating areas of strictures and dilatation.[57] Dysplasia and malignant transformation may be found in advanced cases.

Sessions Three and Four. Pathogenesis

Dr. Nicholas LaRusso (Mayo Clinic Foundation, Rochester, MN) provided an overview of cholangiocyte pathobiology. PSC is a cholangiopathy, belonging to a spectrum of diseases characterized by injury to and obliteration of cholangiocytes.[58] Cholangiocytes are epithelial cells and have several physiologic functions, the best characterized being transport of water, ions, and solutes into bile.[59] Cholangiocytes represent only 3% to 5% of cells in the liver, but produce 40% of the volume of bile. Cholangiocytes probably also function as sensors and modulators of bile flow and can reabsorb bile salts and other components. Cholangiocytes are heterogeneous; those from small bile ducts have different morphology, gene expression and response to injury than those from larger bile ducts. Cholangiocytes proliferate in response to injury and can assume an activated phenotype with *de novo* expression of receptors, cytokines and chemokines. Cholangiocytes interact with other cells in the liver including macrophages and immunocytes as well as with matrix proteins, microbes and xenobiotics.

The cholangiopathies include genetic conditions (Alagille syndrome, cystic fibrosis, fibropolycytic diseases), immune-mediated disorders (PSC, PBC, autoimmune cholangitis, allograft rejection, graft-versus-host disease), infections (cholangitis due to bacteria, fungi, parasites or viruses), drug-induced injury (floxuridine), ischemic damage (hepatic artery thrombosis), malignancies (cholangiocarcinoma) and diseases of unknown etiology (biliary atresia, sarcoidosis, idiopathic vanishing bile duct syndromes).[58] These diseases are associated with bile duct injury which can lead to loss of bile ducts, bile stasis, and secondary hepatocellular injury.

Recent advances in techniques in isolation and study of cholangiocytes have allowed for better understanding of their biology. Cholangiocytes have multiple receptors, transporters, ion channels, and exchangers.[59] Strikingly, cholangiocytes have asingle primary cilium, a long tubular

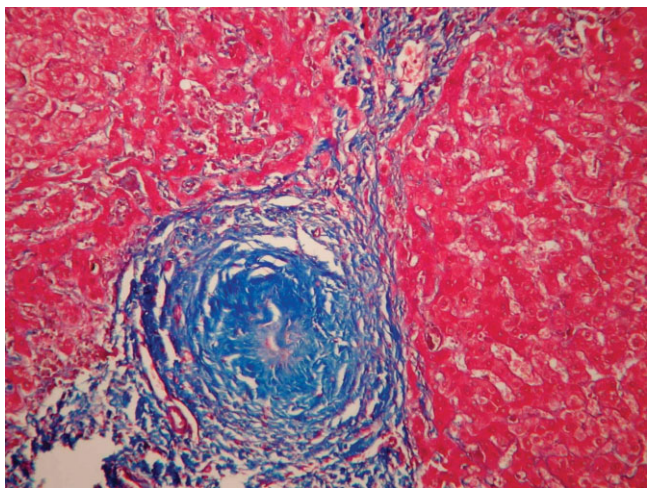

Fig. 4. Histology of PSC showing a typical bile duct scar with resultant ductopenia in PSC. Masson trichrome stain, original magnification ×100. Provided with permission by Dr. Swann Thung.

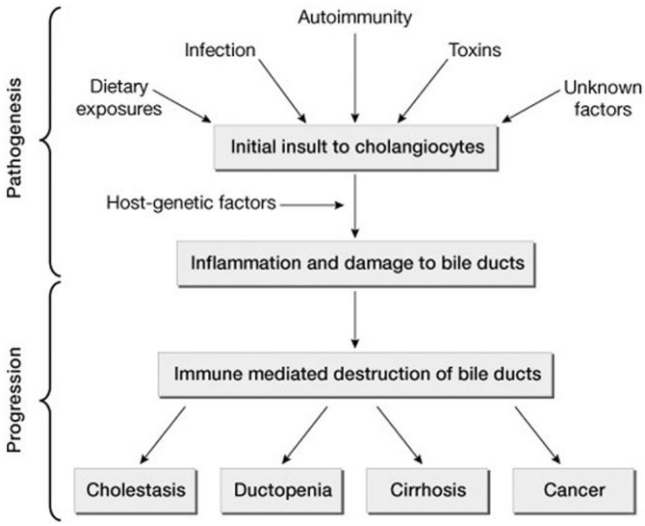

Fig. 5. Proposed pathogenesis and cause of progression in PSC. Modified and reprinted from: Lazaridis KN, Strazzabosco M, LaRusso NF. Cholangiopathies: Disorders of biliary epithelia. Gastroenterology 2004; 127:1565-1577,[58] with permission from the American Gastroenterological Association.

organelle that arises from the centrosome and extends into the duct lumen. Cilia act as mechanical, chemical, and osmotic sensors, and disorders in their structure and function may underlie the pathology of polycystic liver disease and cystic fibrosis.

Cholangiocytes also interact with immune cells and produce as well as respond to cytokines, growth factors and signaling molecules, which are no doubt important in the pathogenesis of immune-related cholangiopathies. The cellular crosstalk between the immune system, macrophages, hepatic stellate cells, and cholangiocytes includes production of and/or response to cytokines, growth factors, endothelin-1, and nitric oxide. The reactive cholangiocyte is likely to play an important role in liver damage and repair (Fig. 5).

Dr. Peter Donaldson (University of Newcastle-Upon-Tyne, UK) discussed the genetics of PSC. The genetic predisposition to PSC is shown by the 100-fold increased risk of this disease among siblings.[60,61] Inheritance of PSC, however, does not follow classical Mendelian genetics, but appears to be complex; one or more genes act alone or in concert to increase or decrease risk.[60,62] Difficulties in genetic studies of PSC are its rarity and delayed expression, factors that preclude traditional linkage analysis.

The major genetic associations described in PSC are with specific alleles of the human MHC, a large region of chromosome 6p21.3, which includes 252 expressed genes, 56 of which are polymorphic. To date, 10 of these 56 have been evaluated in PSC including the human leukocyte antigen (HLA) class I *A*, *B*, and *Cw* genes; the HLA class II *DRB*, *DQA*, *DQB*, and *DPB* genes; and two genes from the MHC class III region, *MICA* and *TNFA*.[60,62,63] Six different MHC haplotypes have been associated with PSC (Table 5), 3 with an increased and 3 with a reduced risk of disease. Some haplotypes appear to carry several risk alleles (*B8-TNFA*2-MICA*008-DRB1*0301* haplotype), while others carry only one (*MICA*002*). To date, no common shared risk allele or peptide sequence has been identified.

The biological bases for the genetic associations between the MHC and PSC are not well understood. HLA class I and II molecules are important in T cell immunity, whereas, the MHC class III MIC-α molecule is important in innate immunity, particularly in the regulation of natural killer (NK) cells.[63]

Further understanding of the role of MHC genes in susceptibility and resistance await better knowledge of specific autoantigen(s) and/or infectious agents in PSC. Importantly, MHC genes alone are unlikely to account for all of the genetic risk in PSC. Non-MHC risk genes of interest include *CARD4*, *CARD15*, as well as *BSEP*, *MDR3*, and *CFTR*.[60,64-66]

Dr. John M. Vierling (Baylor College of Medicine, Houston, TX) described the current status of animal models of PSC. The rarity of PSC and the difficulties in assessing cholangiocyte injury in humans stress the need for a reliable animal model to study pathogenesis and evaluate potential therapies. Unfortunately, no current animal model fully recapitulates the clinical and pathological features of PSC.[67,68]

Cholangiocyte injury and bile duct loss can be induced by several toxins, and pathologic features resembling sclerosing cholangitis can be induced by infusions of formalin, 2,4,5-trinitrobenzene sulfonic acid, alpha-naphthylisothiocyanate, or steroidal sapongenins into the biliary tree of rodents. While immune signals are activated by these toxic injuries, the conditions do not mimic the human disease. A specific murine model of graft-versus-host disease develops features of PSC but with involvement of smaller rather than larger bile ducts.[69]

Infection of immunodeficient mice with *Cryptosporidium* and of rodents and cats with *Helicobacter* species

Table 5. Haplotypes Associated With PSC Disease Risk

Haplotype	Odds Ratio
Increased Risk	
B8-DRB1*0301	2.69
DRB1*1301	3.80
DRB1*1501	1.52
Decreased Risk	
DRB1*0401	0.26
DRB1*0701	0.15
MICA*002	0.12

produce secondary forms of sclerosing cholangitis, which can be used to study pathogen and immune-mediated cholangiocyte injury. A potentially valuable model of PSC was produced in genetically susceptible rats with small bowel bacterial overgrowth after portal infusion with bacterial peptidoglycanpolysaccharides, ligands for innate immune receptors on Kupffer cells.[70] These animals develop histologic and cholangiographic features of PSC. Submucosal colonic injections of the bacterial cell wall product, muramyl dipeptide, results in colitis, peribiliary inflammation, and fibrosis, which resembles PSC. Finally, a proinflammatory, chemotactic peptide secreted by *Escherichia coli* is cleared from portal venous blood by hepatocytes and secreted into bile, where it acts as a chemoattractant for both neutrophils and macrophages, causing peribiliary inflammation and injury.[71] Thus, several animal models exist that exhibit immunological and genetic susceptibility similar to PSC, but none fully recapitulates the human disease.

Dr. Michael Trauner (Medical University, Graz, Austria) discussed the potential role of hepatobiliary transporters in PSC. Normal bile secretion is dependent on and regulated by a large number of hepatic and biliary transporters, defects in which can lead to severe liver disease.[72] The *Mdr2* gene, the murine analog of human *MDR3*/*ABCB4*, encodes a canalicular phospholipid flippase responsible for transport of phospholipids into bile. Humans with *MDR3* mutations develop progressive familial intrahepatic cholestasis, type 3 (PFIC-3) a severe form of chronic cholestasis.[72] In mice, knockout of the *Mdr2* gene results in a spontaneous sclerosing cholangitis with serum biochemical as well as histologic features resembling human PSC.[73,74] Preliminary data indicate that these mice also develop autoantibodies including pANCA. The bile duct injury may be due to defective biliary phospholipid secretion which results in production of "toxic bile," causing cholangiocyte injury.[74] The *Mdr2* knockout mice do not develop IBD or cholangiocarcinoma but can develop hepatocellular carcinoma.

The possibility that mutations in the *MDR3* gene in humans are linked to PSC has been investigated in two recent studies (a total of 80 patients), neither of which found an increase in *MDR3* haplotype distribution.[75,76] However, the hypothesis that injury in PSC is due to defective bile acid or lipid secretion with formation of toxic bile is attractive and deserves further study. Indeed, patients with cystic fibrosis with mutations in their chloride transmembrane conductance regulator gene (CFTR) can develop ductopenia with focal biliary cirrhosis as a result of inspissated bile which injures cholangiocytes. The role of CFTR mutations in PSC is controversial, some studies demonstrating an association[66,77] and others not.[78,79] Other candidate transporters that could play a role in PSC include the canalicular bile salt export pump (BSEP), the cholesterol transporter (ABCG5/G8), and the glutathione transporter (conjugate export pump MRP2).[75,76,80] Chronic inflammation and injury may lead to downregulation of cholangiocyte transporters,[81,82] which may be mediated by proinflammatory cytokines or mediators. These regulatory processes may help to protect hepatocytes from accumulation of toxic biliary constituents.[83-86]

Table 6. Prevalence of Autoantibodies in PSC

Antibody	Reported Prevalence[2]
Atypical perinuclear antineutrophil cytoplasmic antibody (pANCA)	33%-87%
Antinuclear antibody (ANA)	7%-77%
Anti-smooth muscle antibody (SMA)	13%-20%
Antiendothelial cell antibody	35%
Anticardiolipin antibody	4%-66%
Antithyroperoxidase antibody (anti-TPO)	7%-16%
Antithyroglobulin antibody (anti-TG)	4%
Rheumatoid factor (RF)	15%

The *Mdr2* knockout mouse model has recently been used to assess therapies of PSC.[87] Promising results were obtained with use of the side-chain shortened bile acid norUDCA, a C23 homolog of ursodeoxycholic acid (UDCA). NorUDCA, unlike UDCA, undergoes little hepatic conjugation and is reabsorbed by cholangiocytes from bile. Such biliary-hepatocyte shunting circumvents the intestine and may result in improved targeting of the hydrophilic bile acid to injured bile duct epithelium. In the *Mdr2* knockout mouse, norUDCA, but not UDCA, ameliorated the histological changes of sclerosing cholangitis and improved serum liver enzymes. Thus, hepatobiliary transporter defects can cause bile duct injury, and targeting of transporter changes and bile toxicity may afford valuable approaches to therapy of PSC.

Dr. Roger W. Chapman (Oxford University Medical School, Oxford, UK) discussed the evidence that autoimmunity plays a role in PSC. Autoimmunity is defined as immune reactivity against self-molecules that is sufficient to cause cell and tissue injury. Evidence that PSC is an autoimmune disorder include the presence of hyperglobulinemia, multiple autoantibodies, activated immunocytes[88,89] and the association with specific "autoimmune" MHC haplotypes.[60] PSC also is associated with other possible autoimmune conditions such as IBD and, to a lesser extent, autoimmune hepatitis and thyroiditis.

PSC is associated with multiple autoantibodies (Table 6), but most closely with pANCA.[90] Although common in PSC, pANCA is not specific, nor do its levels predict prognosis or response to therapy. While pANCA is rare in

PBC and extra-hepatic obstruction, identical reactivity can be found in up to 42% of patients with autoimmune hepatitis, 34% with ulcerative colitis, and 4% with Crohn's disease. Preliminary results using proteomics suggest that the auto-antigen of pANCA is the nuclear envelop protein, myeloid-specific tubulin-beta isotype 5.[91]

The autoantibodies in PSC including pANCA do not appear to play a pathological role. Nevertheless, the biliary epithelial cell appears to be the target of immune-mediated injury and dense infiltrations with activated T cells and high local concentrations of pro-inflammatory cytokines with increased expression of HLA on bile ducts are common.[92] Thus, PSC appears to be immune-mediated, but direct evidence that it is an autoimmune disease is lacking.

Dr. Daniel Podolsky (Harvard Medical School, Boston, MA) discussed the pathogenesis of IBD as it relates to PSC. Recent findings point to the role of the innate immune response in the pathogenesis of ulcerative colitis and Crohn's disease,[93] and similar studies are now being extended to PSC.

Unlike adaptive immunity, innate immunity is rapid and immediate (rather than delayed), hardwired (not requiring priming), dependent upon pattern molecule recognition (rather than specific antigens), and mediated by macrophages, NK cells and other antigen-presenting cells (rather than B and T cells). Innate immune responses are often triggered by engagement of toll-like receptors (TLRs), a system of transmembrane receptors, the best known of which are TLR4 (the receptor for lipopolysaccharide), TLR3 (dsRNA), TLR5 (flagellin), TLR7/8 (ssRNA), and TLR9 (CpG DNA). The signaling pathways are complex and interactive and many activate nuclear factor kappa B (NFκB) resulting in production of multiple downstream inflammatory mediators. TLRs are highly expressed in gastrointestinal tract epithelial cells including cholangiocytes.[94,95] Activation of the TLRs can modulate transepithelial resistance and decrease epithelial barrier function which may be important in the etiology of PSC.

Genome-wide scans for susceptibility to IBD have identified mutations in the gene *NOD2* (or *CARD15*) in a proportion of familial cases. NOD1 and NOD2 are key intracellular receptors which activate innate immune responses.[96] Thus, a unifying hypothesis is that IBD is caused by abnormalities in the innate immune response which results in heightened immune reactivity to intestinal bacteria. Similarly, activation of TLRs and engagement of the innate immune response has recently been demonstrated in PSC, PBC, and other biliary diseases,[97-100] suggesting that alterations in TLR pathways and NODs may play a role in these diseases as well.

Dr. David H. Adams (University of Birmingham Medical School, Birmingham, UK) discussed the role of T cell activation in PSC. Recent findings suggest that the underlying injury in PSC associated with IBD is due to inappropriate recruitment of mucosal lymphocytes to extra-intestinal tissue.[101,102] Effector cells activated by gut inflammation exhibit increased adhesion to endothelia in other organs mediated by nonspecific adhesion molecules.[103] In PSC, there is aberrant hepatic expression of the gut addressin MADCAM-1 and the gut-specific chemokine CCL25, which are normally restricted to the gut where they regulate recruitment of mucosal lymphocytes.[92,104-106] In PSC, the liver is infiltrated with activated mucosal T cells.[107] These T cells are long-lived memory cells capable of being activated to secrete pro-inflammatory cytokines.[105] The activated T cells can bind to biliary epithelial cells via specific adhesion pathways.[108] Because memory cells, unlike effector cells, are long lived, this mechanism can explain the clinical findings of discrepancies between periods of activity of IBD and that of PSC.[101] However, until the signals responsible for the induction of gut-specific homing receptors in the liver in PSC are determined, it is uncertain whether these processes are primary instigators of the biliary disease or secondary players that amplify liver damage.

Session Five: Therapy of PSC

Dr. Marshall Kaplan (Tufts-New England Medical Center, Boston, MA) provided an overview of medical management of PSC. No therapy has yet been proven to prolong survival or improve outcome of PSC.[41,42,109] Clinical trials of new treatments for PSC are challenging because of its rarity, the lack of understanding of its pathogenesis, the difficulty in identifying the disease early, and the lack of surrogate endpoints for defining benefit. Most therapies that are used are directed at the complications rather than the underlying cause of PSC.

Ursodeoxycholic acid (UDCA), the hydrophilic bile acid, is conventionally recommended for patients with PSC. UDCA therapy can lead to improvements in serum bilirubin, alkaline phosphatase, and ALT, but has not been shown to slow the course of illness or prolong survival. Furthermore, the data on the effects of UDCA on symptoms and quality of life are controversial.[109] In a large, prospective, randomized controlled trial from the United States, UDCA therapy (12-15 mg/kg daily) was associated with improvements in serum liver enzyme abnormalities, but had no effect on liver histology or liver transplant-free survival.[110] Subsequently, small pilot trials suggested that higher doses of UDCA (25-30 mg/kg/day) might be more effective than standard doses.[111,112] A recent report of a randomized controlled trial in 198 pa-

tients from Europe, however, demonstrated no effect of higher UDCA doses on symptoms, serum biochemical abnormalities, quality of life, or transplant-free survival.[113] Death or liver transplantation occurred in 7% of UDCA-treated compared to 11% of placebo-treated patients ($P = .37$). A similar but larger trial of high-dose UDCA therapy in PSC is currently underway in the United States.[114]

In patients with an autoimmune cholangitis, use of corticosteroids has been associated with a high rate of clinical response, in symptoms as well as in serum bilirubin and ALT levels.[115] Whether corticosteroids alter the natural history of this form of PSC has not been established. Certainly, corticosteroids are not beneficial in typical PSC and have considerable risks in this population (osteoporosis, increased susceptibility to infections). Other agents that failed to show efficacy in PSC in controlled trials include methotrexate, colchicine, D-penicillamine, pentoxifyliline, and tacrolimus.[109,116] The use of standard doses of UDCA, although widely recommended, has scant evidence for either short-term or long-term benefit and is unlikely to have an effect on the underlying pathogenesis of PSC. Clearly, new therapies are needed.

Dr. Benjamin Shneider (Mount Sinai School of Medicine, New York, NY) discussed management of PSC in children. There have been no prospective, randomized controlled trials of therapy of PSC in children, and recommendations are based on studies in adults and anecdotal findings from cases series in children.[11,18-22] UDCA (15-30 mg/kg/day) leads to improvements in liver test abnormalities, particularly in children with early disease. Children with autoimmune cholangitis usually have a marked clinical response to corticosteroids with or without azathioprine. Ultimately, however, these agents may not control the disease, and features of chronic cholestasis arise. Because of the known adverse effects of corticosteroids on linear growth and bone mineral density, these agents should be closely monitored and the lowest dose that maintains biochemical remission used. Trials of other approaches to therapy are greatly needed in children, but are unlikely to be initiated without a nationwide or an international initiative.

Dr. Adolph Stiehl (University of Heidelberg, Heidelberg, Germany) provided an overview of the complications of PSC. Nonspecific complications include fatigue, pruritus, metabolic bone disease, steatorrhea, and fat-soluble vitamin deficiencies.[5,11,109] The fatigue of PSC is similar to that of other liver diseases, is rarely disabling and is sometimes, but not reliably, improved with UDCA treatment. In contrast, pruritus in PSC can be severe and interfere with activities of everyday life. Pruritus rarely responds to typical antipruritic medications such as antihistamines, but may respond to resin-binding agents such as cholestyramine. In controlled trials, UDCA has not been associated with improvements in pruritus.[110,113] Rifampin has been used to treat pruritus in patients with liver disease, but its mechanism of action is unclear.[117,118] The bone density and vitamin deficiency complications of PSC should be monitored and treated appropriately. Supplementation with calcium and fat-soluble vitamins is appropriate, particularly in patients with advanced disease.[109]

Specific complications of PSC include bacterial cholangitis, biliary strictures, biliary duct stones and cholangiocarcinoma as well as complications of IBD. Bacterial cholangitis is common in patients with PSC particularly after biliary interventions and may accelerate the progression of the liver injury. Prophylaxis with antibiotics has not been proven to be of benefit, but patients with recurrent cholangitis should be advised to seek medical attention rapidly and start antibiotics at the first sign of biliary infection.[109]

Patients with PSC and IBD are at increased risk of colon cancer. Preliminary reports suggest that UDCA therapy decreases the risk of colon cancer,[119,120] perhaps by changing the intestinal milieu by decreasing concentrations of hydrophobic bile acids in favor of UDCA.[121] Cross-sectional studies indicate a lower rate of colonic epithelial dysplasia among patients receiving UDCA.[120] However, UDCA therapy has not been associated with a lower rate of colon or other cancers in patients with PBC,[122,123] and this effect in PSC awaits further prospective assessment.

Dr. Anthony Kalloo (Johns Hopkins School of Medicine, Baltimore, MD) discussed endoscopic therapy of PSC. Between 10% and 15% of patients with PSC will experience high-grade obstruction from a discrete area of narrowing within the extra-hepatic biliary tree (dominant stricture).[1,2,41] These strictures can cause sudden worsening of jaundice and cholangitis. In the past, dominant strictures were managed surgically. With advanced endoscopic techniques, they can be managed using ERCP with balloon or coaxial dilatation.[124-130] Clinical response can be achieved in 80% of patients without cirrhosis. Endoprostheses can be placed across strictures, but stent occlusion and cholangitis are frequent, and prospective studies failed to show their benefit.[131-135]

Endoscopic dilation of dominant strictures is currently widely practiced despite the lack of prospective randomized controlled trials demonstrating its benefit.[136,137] Retrospective analyses using the Mayo Risk Score to model outcome, however, have suggested that endoscopic dilatation of dominant strictures does improve survival.[130]

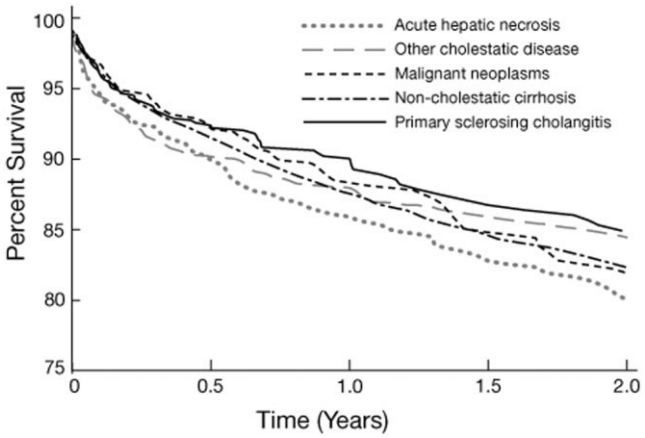

Fig. 6. Patient survival after liver transplantation for PSC with comparisons to acute hepatic necrosis, other cholestatic liver diseases, malignancies, and cirrhosis not due to cholestatic diseases. Adjusted for recipient age, gender, race, body mass index, MELD score at the time of transplant, medical condition, dialysis, diabetes, life support, surgery, and portal vein thrombosis, donor age, gender, race, cause of death, donation after cardiac death of donor, partial/split liver, and cold ischemia time. Analysis of the Scientific Registry of Transplant Recipients carried out by Nathan Goodrich, MS. Supported by contract number 231-00-0116 from the Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services.

Therapeutic endoscopy has risks, and complications occur in 10% of patients, the most common being pancreatitis, acute cholangitis, biliary tract perforation and hemorrhage.[138] These complications usually respond to conservative management. Thus, interventional endoscopic therapy may improve outcome in patients with dominant strictures due to PSC, but should only be done by endoscopists with extensive experience in management of biliary strictures.

Dr. Keith Lindor (Mayo Clinic Foundation, Rochester, MN) discussed future innovative approaches to therapy of PSC. To date, available animal models and *in vitro* studies have suggested autoimmunity, cytokines, infections, and bile acid transporter or ion channel abnormalities as underlying causes of PSC.[5,41,114,139] Accordingly, immunosuppressive agents, anticytokines, antibiotics, and modulators of ion channels or bile acid transporters have been tried in small pilot trials, largely without evidence of success. The agents found to have little effect include corticosteroids, budesonide,[140] tacrolimus,[141] methotrexate,[116,142,143] mycophenolate mofetil,[144] pentoxyfylline,[145] silymarin,[146] and etanercept.[147] Trials of antibiotics such as metronidazole[148] and minocycline have been promising but inconclusive. A small study of docosahexaenoic acid which improves CFTR function is currently underway. Antifibrotic agents such as pirfenidone which inhibit fibrogenesis have also been tested without obvious benefit.[149] Most promising for the near future are inhibitors of TNF action, antifibrotic agents, and inhibitors of formation of toxic bile.[87]

Session Six. Liver Transplantation for PSC

Dr. Robert Merion (University of Michigan, Ann Arbor, MI) reviewed the current status of liver transplantation for PSC. Liver transplantation is the only therapy that can reverse or correct end-stage liver disease from PSC.[150-152] In the United States, approximately 250 liver transplants are done yearly in adults for PSC, representing 5% of all liver transplants (Scientific Registry of Transplant Recipients, 2005). Males account for 70% of candidates, and the median age is 50 years. In relation to other diagnoses, candidates with PSC are more likely to be younger, male, and African American.

The MELD system is currently used for liver organ allocation in the United States, regardless of cause of end-stage liver disease.[31,150-153] At any time, 800 to 900 adult patients with PSC are on the national waiting list, representing 5% to 6% of candidates.In 2004, there were only 10 deaths per 100 patient-years among PSC transplant candidates compared to 17 per 100 among non-PSC candidates. PSC candidates had the lowest death rate of any diagnostic subgroup.

Survival after transplantation is also excellent for candidates with PSC, being 90% at 1 and 84% at 2 years, rates that are higher than any other patient subgroup (Fig. 6).[154-156] Retransplantation rates are higher for patients with PSC than other diagnoses (9.6% vs. 4.9% within 2 years).

The survival benefit of liver transplantation can be calculated by the ratio of death rates on the waiting list compared to that after liver transplantation adjusting for other factors that affect survival.[154] For PSC, the adjusted mortality rate ratio for transplantation is 0.31, which is 69% lower compared to remaining on the waiting list. These features demonstrate the very real benefit of liver transplantation for PSC.

Dr. Estella Alonso (Children's Memorial Hospital, Chicago, IL) addressed the special issues surrounding liver transplantation for children with PSC. PSC is an uncommon indication for liver transplantation in children,[19,20] being the cause for only 73 of 2219 (3.5%) children listed in the Studies of Pediatric Liver Transplantation (SPLIT) registry between 1995 and 2004.[157] Compared to children with other diagnoses, children with PSC were more likely to be male (64% vs. 47%: $P = .004$), Caucasian and older in age (median = 12.7 vs. 1.4 years), and were less likely to be hospitalized. Probably as a consequence, waiting time for transplant was longer for children listed for PSC than other diagnoses. Nevertheless, survival on the waiting list was excellent, with only one

death being recorded. At the time of transplant, children with PSC tended to have milder disease than children with other diagnoses both in terms of clinical status and Pediatric End-Stage Liver Disease (PELD) scores. In addition, posttransplant survival in children with PSC was excellent, with 1-year survival of 98% compared to 87.5% for all other diagnoses ($P = .04$).

Drs. David Adams and James Neuberger (University of Birmingham Medical School, Birmingham, UK) reviewed the issue of PSC recurrence and late complications after transplantation. Transplantation for PSC generally involves resection of the extra-hepatic biliary tree and use of a Roux-en-Y loop.[150] Recurrence of PSC in the transplanted graft bile ducts has been reported, but its frequency, natural history, and optimal management are not well defined. The diagnosis of recurrent PSC is a challenge, in that many features can be mimicked by liver injury caused by ischemia, infection, chronic rejection, biliary obstruction, and medications.[158-161] The reported frequency of recurrent PSC ranged from 1% to 33%, the variation related in part to differences in diagnostic criteria, duration of follow up, and rigor with which the diagnosis is sought.[150,162-166] Factors associated with recurrence were steroid-resistant rejection, OKT3 use, preservation injury, ABO incompatibility, cytomegalovirus infection, lack of history of colectomy, male sex, and donor-recipient gender mismatch, but not specific calcineurin inhibitor use or frequency of rejection.[162-167]

A critical issue is whether recurrence of PSC adversely affects outcome. Instances of graft failure due to recurrent PSC are rare and often confounded by the presence of other forms of liver injury. Overall, the long-term outcome of liver transplantation for PSC has been excellent, with 10-year survival in Europe being as high as 79% (www.eltr.org). Also important in long-term follow up of transplantation for PSC is the accompanying IBD and complications of colon cancer. Overall, the cumulative rate of *de novo* appearance of colitis after liver transplantation has been 6% at 1 and 20% at 5 years.[168] Among persons with preexisting IBD, flares occur in approximately 39%. Instances of cholangiocarcinoma due to recurrent PSC have been published.[169] More important has been colon cancer, which is common, particularly in patients with preexisting ulcerative colitis.[167,170] The cumulative risk for colon cancer is 14% at 5 years and 17% at 10 years. Routine surveillance colonoscopy is recommended, and UDCA is commonly used as means of decreasing the risk of colon cancer, although neither practice has been proven to be effective in this situation.

Session Seven. Cholangiocarcinoma

Dr. Hashem El-Serag (Baylor College of Medicine, Houston, TX) described the epidemiology of cholangiocarcinoma. Cholangiocarcinoma is typically separated into intra- and extra-hepatic forms and categorized separately from gall bladder cancer. Unfortunately, many cancer registries do not separate these forms, and categorization of hilar tumors (Klatskin tumors) as intra- versus extra-hepatic is inconsistent. Data from the U.S. Surveillance, Epidemiology and End Results (SEER) database indicate that the incidence of intrahepatic cholangiocarcinoma (including Klatskin tumors) has risen from 0.32 in 1975-1979 to 0.66 per 100,000 population between 1975 and 2002, while rates of extra-hepatic cholangiocarcinoma have decreased.[171-173] It is not clear whether these are true increases or whether the increases are due to better diagnosis and changes in classification. Nevertheless, similar patterns have been reported from England and Japan.

The incidence of cholangiocarcinoma increases with age with highest rates in the 8th and 9th decade of life. The identifiable risk factors include PSC, IBD, chronic liver disease, cirrhosis, alcohol use, smoking and diabetes.[174,175] Interestingly, in these databases no more than 10% of cholangiocarcinoma are attributed to PSC. Among cohorts of patients with PSC, the risk of developing cholangiocarcinoma ranges from 0.6% to 1.5% per year, leading to a 20% lifetime risk.[176,177] Risk factors are not well defined. This cancer is not associated as closely with cirrhosis as is hepatocellular carcinoma. The risk also appears to be independent of the duration of PSC or IBD. In some studies, UDCA therapy has been associated with a decreased risk of cholangiocarcinoma,[120,178] but not in others.[113,150]

Dr. Naga Chalasani (Indiana University School of Medicine, Indianapolis, IN) discussed the clinical features, diagnosis and natural history of cholangiocarcinoma associated with PSC. Cholangiocarcinoma has several typical presentations.[150,177] Most typically patients with long-standing PSC present with abdominal pain and worsening jaundice, marked elevations in alkaline phosphatase and CA 19-9 levels, and strictures of the extrahepatic biliary tree which upon brushings or biopsy show cholangiocarcinoma. However, cholangiocarcinoma can also present without symptoms, with extra-hepatic manifestations (thrombophlebitis), or as an incidental finding during surveillance or at the time of liver transplantation.

Regardless of presentation, the outcome of cholangiocarcinoma is poor, with survival rare beyond 1 year. If any therapy is to be curative, early diagnosis should be important.[179] However, in prospective studies, the risk was similar at different stages of disease. Among serum tumor

markers for cholangiocarcinoma, the most promising is CA 19-9.[179-181] High CA 19-9 levels (>129 U/L) have a high specificity, but low sensitivity, particularly for small cancers. Addition of testing for carcinoembryonic antigen and serial testing for tumor markers may improve accuracy,[181] but the reliability for early detection has not been defined and the increase in sensitivity is likely to come with an increase in false positive reactions.

Brush cytology and pinch biopsies have been used for surveillance of cholangiocarcinoma in patients with PSC.[182] However, ERCP is not without risk and the added benefit of cytology and biopsy are unproven. Prospective studies using brushing for cytology and biopsies with combinations of specialized tests (such as analysis of p53, K-ras mutations, fluorescent *in situ* hybridization for chromosomal abnormalities) have not materially increased the sensitivity of such screening. Specialized imaging using MR and positron emission tomography scanning have not been systematically studied and tend to have poor sensitivity and specificity. Thus, there is scant evidence that current approaches to surveillance for cholangiocarcinoma are effective in prolonging patient survival.[179]

Dr. Greg Gores (Mayo Clinic Foundation, Rochester, MN) discussed the pathogenesis of cholangiocarcinoma. Cholangiocarcinoma arising during the course of PSC represents a classic example of the role of chronic inflammation in carcinogenesis.[176,179] Studies of cholangiocytes from PSC patients showed that chronic inflammation stimulates expression of nitric oxide synthase which can contribute to carcinogenesis by inducing DNA injury, inhibiting DNA repair, causing increased expression of developmental cell receptors, silencing of tumor suppressor genes, and inhibiting apoptosis.[183-188] Aneuploidy is a common feature of cholangiocarcinoma and may play a role in carcinogenesis in PSC. Aneuploidy detected in cholangiocytes from biliary brushings may appear before the development of cholangiocarcinoma. Furthermore, trisomy-7 may be an early marker possibly due to effects of epidermal growth factor on chromosome 7 in cholangiocarcinoma cells. Understanding the mechanisms of carcinogenesis in PSC may point to specific targets for noncytolytic chemotherapy.

Dr. Massimo Malagó (University of Essen, Germany) provided an overview of the role of surgery and liver transplantation for cholangiocarcinoma. Cholangiocarcinoma is often detected late, when it is no longer resectable or has already spread to other organs.[176,179] Medical management with stenting, radiation therapy, or conventional chemotherapy is largely ineffective, with 1-year survival being rare. Surgical resection of cholangiocarcinoma is also rarely successful; reported 5-year survival rates range from 9% to 28%, although somewhat higher with extrahepatic tumors.[189-191] In view of these results, liver transplantation has been tried, for both resectable and unresectable tumors.[192] In 3 large, single-center series, which included a total of 60 patients, survival was 22% to 77% at 1 year and 0% to 39% at 3 years.[193-196] Because of poor outcomes, many centers will no longer perform liver transplantation for patients with cholangiocarcinoma and will terminate surgery if a patient is found to have an incidental cancer during exploration. On the other hand, innovative approaches using a combination of neoadjuvant chemotherapy, irradiation and transplantation hold some promise.[197-200] Use of these approaches should be limited to centers engaged in prospective studies of defined chemotherapeutic and surgical regimens.

Summary Recommendations for Future Research

Research on PSC would be aided by standardization of nomenclature and diagnostic criteria including definitions of endpoints for clinical trials. Currently, there is little agreement on diagnostic criteria for subgroups of PSC, and terms used to describe PSC are not well defined. Similarly, there are no widely agreed upon staging and grading systems for PSC, based upon clinical features, histology or cholangiographic changes and, consequently, no standard endpoints for clinical trials other than liver transplantation and/or death. Surrogate endpoints would be much more appropriate for evaluation of therapies aimed at the etiology of PSC or directed at early stages of disease. Better definitions would also allow for comparison of results of studies from different areas of the world and would allow for phenotype-genotype comparisons in genetic studies.

Epidemiologic studies of PSC are needed to better define the prevalence and incidence of this disease particularly in special cohorts of patients, such as minority individuals, persons with IBD and persons from areas of the world where PSC is uncommon. These studies should use common criteria for diagnosis and common means for screening or identifying cases. True variation in geographical and racial frequency of PSC may provide insights into its pathogenesis. Risk factors in populations deserving further study include smoking, socioeconomic class, clinical and genetic features of associated IBD, modifying genes, familial associations, and environmental exposures.

Natural history studies of PSC currently paint a picture of a variable course of disease with an average survival of 12 to 17 years. Further, more rigorous studies are needed to help define the full spectrum of disease, factors that contribute to progression, and means of grading and staging disease severity. A cohort study or registry of a large

number of patients with PSC drawn from various referral centers would be helpful in better defining natural history and providing patients for clinical trials. Such cohort studies should include children and appropriate numbers of minority individuals. A special focus should be on autoimmune cholangitis.

The pathogenesis of PSC remains unclear but promising inroads have been made in elucidating genetic and immunologic mechanisms. The basic cell biology of the biliary epithelial cell deserves more attention particularly the response of cholangiocytes to inflammatory signals and injury. An animal model of PSC that adequately reflected the disease course and outcome would be of great benefit, not only in helping to define pathogenesis, but also in developing approaches to prevention and treatment. In this regard, the *Mdr2* knock-out mouse and murine models generated by altering the immune system deserve further study. Ultimately, hypotheses and pathways elucidated in animal models need to be investigated in humans with PSC. A natural history cohort study that provided well characterized serum, tissue and DNA samples would be an invaluable resource for investigation of innovative concepts regarding pathogenesis.

Genetic factors are important in PSC, and further investigation of MHC genes as well as bile transporter and biliary epithelial function genes are justified. Cohort studies would help to provide clinical material and should include arrangements for obtaining informed consent for genetic studies, privacy protection and resources for storing adequate amounts of carefully isolated DNA samples from patients who are fully characterized clinically. Studies of the genetics of IBD should be expanded to include analyses of patients who also have PSC.

Cholangiocarcinoma is the most dreaded outcome of PSC and there are currently no reliable noninvasive markers for early identification nor effective means of treatment or prevention. Cohort studies on PSC should be designed to help identify risk factors for this complication, and stored serum and tissue used to search for and validate biomarkers. New means of imaging the biliary tree and discriminating the nonmalignant effects of PSC from early cholangiocarcinoma deserve evaluation. Finally, new approaches to therapy and prevention should be pursued, particularly ones using noncytolytic modifiers of cell-signaling molecules, growth factors or tumor suppressor genes.

Currently with the exception of endoscopic dilation of dominant strictures, there are no treatments that have proven benefit in PSC. New therapeutic approaches are needed, and standard treatments deserve objective reevaluation for efficacy. Several types of clinical trials are appropriate. Simple, randomized controlled trials of symptomatic therapy of PSC might focus upon clinical endpoints such as symptoms and quality of life. Small, short-term, clinical trials are also appropriate to evaluate innovative therapies using endpoints based on clinical, biochemical, serological, imaging, and possibly histological findings. Examples of agents that might be studied in such trials include bile acid therapies, novel immunosuppressive agents, TNF inhibitors, potent antioxidants, probiotics, and antifibrotic agents. Also important are endoscopic approaches to therapy. Agents found to be promising in small trials should be rapidly evaluated in more rigorous randomized, controlled trials in which larger numbers of patients are enrolled and treated for 2 to 5 years with the major endpoint outcomes being hepatic decompensation, liver transplantation and/or death. These clinical trials would be greatly aided by definition and standardization of terminology and concurrent assessment of surrogate endpoints.

Liver transplantation has provided an effective although expensive and challenging means of treatment for end-stage liver disease due to PSC. Continued monitoring of the frequency, complications and outcome of liver transplantation for PSC will be provided by national databases. Prospective studies of optimal surgical procedures, peritransplant management, and long-term therapy for patients (including children) undergoing transplantation for PSC are important to optimize outcomes and prevent complications. A more rigorous definition of recurrent PSC after transplantation, assessment of its clinical significance of recurrence, analysis of risk factors and development of approaches for prevention and treatment would benefit patients undergoing liver transplantation for this indication.

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