To The Editors:

We sincerely thank the peer reviewers for their time and thoughtful comments in consideration of our review manuscript: Treatment of Primary Sclerosing Cholangitis in Children. We have addressed their comments and critiques, and upgraded and improved the text accordingly. We feel the updated manuscript is more clear and comprehensive. Please see below for responses to each individual comment. (Editor comments below in bold).

Reviewer #1

Ylinen E et al. in Acta Paediatr 2017 has reported an association between HLA B*08, DRB1*03 and DRB1*13 and autoimmune liver and biliary diseases in children. This finding should be reported and commented.

We added this important association to the manuscript as follows:

"Most children with PSC have IBD(1, 2). The two disorders share pathophysiologic mechanisms along the "gut-liver axis"(3). Hypothesized pathogenic mechanisms for PSC include an inappropriate and dysregulated immune response in genetically susceptible individuals (4-6). Ylinen et al. noted an association with HLA B*08, DRB1*03 and DRB1*13 human leukocyte antigen (HLA) haplotypes due to the substantial association with autoimmune liver and biliary diseases(REF 1)."

REF 1: Ylinen E, Salmela L, Perasaari J, Jaatinen T, Tenca A, Vapalahti O, et al. Human leucocyte antigens B*08, DRB1*03 and DRB1*13 are significantly associated with autoimmune liver and biliary diseases in Finnish children. Acta Paediatr. 2017;106(2):322-6.

Tenca et al. in J Pediatr Gastroenterol Nutr. has described a possible association between having a pet (i.e., a cat) and the development of autoimmune liver disease (PSC, PSC-AIH AND AIH) in children. This finding should be reported and commented.

Please see the revised section regarding environmental risk factors below:

Additionally other mechanisms include defects in the normal mechanisms that protect the liver from the toxicity of bile acids (7-9), a pathogenic distortion in the fecal microbiome leading to the accumulation of toxic bile acid species and a subsequent inappropriate inflammatory response (10-14), migration of gut-activated mucosal lymphocytes to the liver (15), disruption of the intestinal epithelial barrier due to inflammation (16-18), and an inappropriate inflammatory response to bacterial products and toxic bile acids delivered to the liver through the inflamed gut via the portal vein (19-21). Like in IBD, environmental exposures play a major role in the complex etiopathogenesis of PSC as well. Living with a pet, especially a cat, has been associated with increased incidence of autoimmune liver disease in children, for instance(REF 2).

REF 2: Tenca A, Farkkila M, Jalanko H, Vapalahti K, Arola J, Jaakkola T, et al. Environmental Risk Factors of Pediatric-Onset Primary Sclerosing Cholangitis and Autoimmune Hepatitis. J Pediatr Gastroenterol Nutr. 2016;62(3):437-42.

Tenca A et al. in United European Gastroenterol J 2016 has reported the largest retrospective series in Europe of children with PSC systematically followed-up with ERC with brush cytology and flow-cytometry. This finding should be reported and commented…The use of ERCP with brush cytology as screening method for biliary dysplasia has been reported recently by Boyd S et al in Endoscopy 2016.

We expanded upon our discussion of cholangiocarcinoma with the addition of these important findings as below:

ERCP is the key tool for diagnosis of CCA. Of adult PSC patients with DS, 26% ultimately developed CCA (22). CCA is far rarer in children than in adults with PSC. No cases of CCA occurred in children with PSC over 20 years of follow-up with ERCP in one cohort (REF 3).

CCA developed in fewer than 1% of children in a large series, who were all over age 15 with large duct involvement (2). CCA should still be considered in a PSC patient with a DS regardless of age.

REF 3: Boyd S, Tenca A, Jokelainen K, Mustonen H, Krogerus L, Arola J, et al. Screening primary sclerosing cholangitis and biliary dysplasia with endoscopic retrograde cholangiography and brush cytology: risk factors for biliary neoplasia. Endoscopy. 2016;48(5):432-9.

Reviewer #2

In the part of liver transplantation, authors took MELD score to evaluate the severity of pediatric liver diseases, but in fact, for pediatric patients, PELD (Pediatric end-stage liver disease) score is the more scientific and common indictor.

MELD score is applied to children over the age of 12 years. Since the median age of diagnosis of PSC in children is 12 years , and the median age of transplant is 16 years, the adult MELD score is ultimately more appropriate for this population.

There was an opinion that any remaining recipient biliary duct tissue was at risk for the subsequent development of fibrotic changes though not present in the time of liver transplantation, so it is advisable to choose Roux-en-Y choledochojejunostomy to reconstruct the pathway for bile excretion rather than duct-to-duct biliary anastomosis. However, in the manuscript, authors used just one sentence to put forward that those two methods showed similar effects, please discuss more.

We have expanded on the section regarding roux-en-Y. Please see below.

Roux-en-Y choledochojejunostomy and duct-to-duct biliary anastomosis are both considered

surgical options for biliary reconstruction. Tradition long suggested removing the entire common bile duct was helpful with some stating a Roux-en-Y is the "method of choice" (REF 4). Recent data, however, has identified similar graft and patient survival with each anastomosis type. Potential advantages of a duct-duct anastomosis include ease of intervention with biliary strictures using ERCP and shorter operative times. Downsides of duct-duct anastomosis would include the risk of residual biliary tissue if concern for cholangiocarcinoma persists. Single center data suggests lower rates of post-LTx cholangitis and late onset non-anastomotic strictures (REF 5). A recent meta-analysis supported many of these findings with the only significant difference occurring with higher rates of ascending cholangitis in those who received a Roux-en-Y (REF 6). While no official recommendations can be made, this remains a topic of discussion for surgeons and patients and should be determined based on surgical expertise and availability of advanced endoscopy.

REF 4: Welsh FK and Wigmore SJ. Roux-en-Y Choledochojejunostomy is the method of choice for biliary reconstruction in liver transplantation for primary sclerosing cholangitis. Transplantation. 2004 Feb 27;77(4):602-4.

REF 5: Sutton, ME et al. Duct-to-duct reconstruction in liver transplantation for primary sclerosing cholangitis is associated with fewer biliary complications in comparison with hepaticojejunostomy. Liver Transpl. 2014 Apr;20(4):457-63

REF 6: Pandaboyana S et al. Meta-analysis of Duct-to-duct versus Roux-en-Y biliary reconstruction following liver transplantation for primary sclerosing cholangitis. Transpl Int. 2015 Apr;28(4):485-91

A large part of pediatric PSC patients has concomitant autoimmune hepatitis (AIH), which is so-called AIH-PSC overlap syndromes. According to the reference (Hepatology. 2017;66(2):518-527), the percentage was 33%. So how to deal with this part of pediatric patients?

We more specifically addressed some of the challenges in managing AIH in the setting of PSC, but ultimately refer the readers to other sources as the PSC in AIH carries the same prognosis

and follows a similar clinical course to PSC without AIH. We clarified and expanded upon these points in the text as follows:

Autoimmune hepatitis with PSC

At least 33% of children with PSC meet diagnostic criteria for AIH. There is no formal definition for AIH that occurs with PSC, no standardized way to review histopathology for AIH in the setting of PSC however, and no agreement on terminology (overlap syndrome, juvenile sclerosing cholangitis, autoimmune sclerosing cholangitis, PSC with features of autoimmune hepatitis, PSC and autoimmune hepatitis). A standard diagnostic scoring tool and common definition of AIH in PSC remains a needed addition to the field. Ultimately the clinical outcomes of AIH in the setting of PSC is the same as in AIH alone. A prospective study of steroid and azathioprine immunosuppression for AIH and AIH with PSC showed near universal response rates of lobular inflammation, and no liver transplants after 10 years of follow-up in patients with AIH alone. Patients with AIH and PSC however had either stable or progressive ductular disease, even with remission of the lobular AIH inflammatory component. The survival with native liver observed in the AIH with PSC patients was similar to the survival of patients with PSC alone. A large retrospective series confirmed similar outcomes of PSC patients with or without AIH "overlap."

PSC patients with persistently elevated aminotransferases, particularly over 4-5 time the upper limit of normal, should be worked up for a potentially-treatable component of lobular inflammation from autoimmune hepatitis. Antinuclear, smooth muscle and liver kidney microsomal antibodies, as well as total IgG level and a liver biopsy should be obtained in such patient. We recommend immunosuppression with standard agents (typically prednisone and azathioprine) and following published guidelines and protocols (REF 7). Clinicians should be aware that due to enzyme elevations from ductular disease, normal biochemistry may not be an achievable target however. Clinicians should treat to histologic remission rather than biochemical remission, and histology should be obtained prior to escalation of immunosuppression to ensure that there is actually a treatable, lobular inflammatory component(REF 8).

REF 7: Manns MP, Czaja AJ, Gorham JD, Krawitt EL, Mieli-Vergani G, Vergani D, et al. Diagnosis and management of autoimmune hepatitis. Hepatology. 2010;51(6):2193-213.

REF 8: Jaramillo, C., Valentino, P.L. & Deneau, M. Curr Hepatology Rep (2017) 16: 198. https://doi.org/10.1007/s11901-017-0353-y

How about the development of metabolic disorders such as hepatic osteodystrophy and fat-soluble vitamin deficiency in pediatric PSC patients? Does PSC influence the children's growth? How to deal with them?

While important, specific nutritional complications in cirrhotic patients with PSC are common to patients with cirrhosis and end-stage liver disease from any cause, and fall outside the scope of this manuscript.

Are antihistamines, cholestyramine and other medicines also used in the pediatric PSC patients to control pruritus? If so, please add them.

We expanded upon the discussion regarding antihistamines and other medications. Please see below.

"Formal treatment guidelines for medical therapy of pruritus in adult PSC have recommended antibiotics such as rifampin, opioid antagonists including naloxone, selective serotonin reuptake inhibitors such as sertraline, bile acid sequestrants such as cholestyramine and antihistamines such as diphenhydramine and hydroxyzine. While antihistamines and cholestyramine may be used they are infrequently prescribed in children. The strength of evidence for many of these therapies is lacking (24). "

References should be updated according to the comments above.

We added the additional references, as noted above.

Thank you again for taking the time to review the manuscript. Please let us know if you have any further questions or concerns.

Best Regards,

Mark Deneau, MD MS