

Primary Sclerosing Cholangitis: The Pediatric Perspective

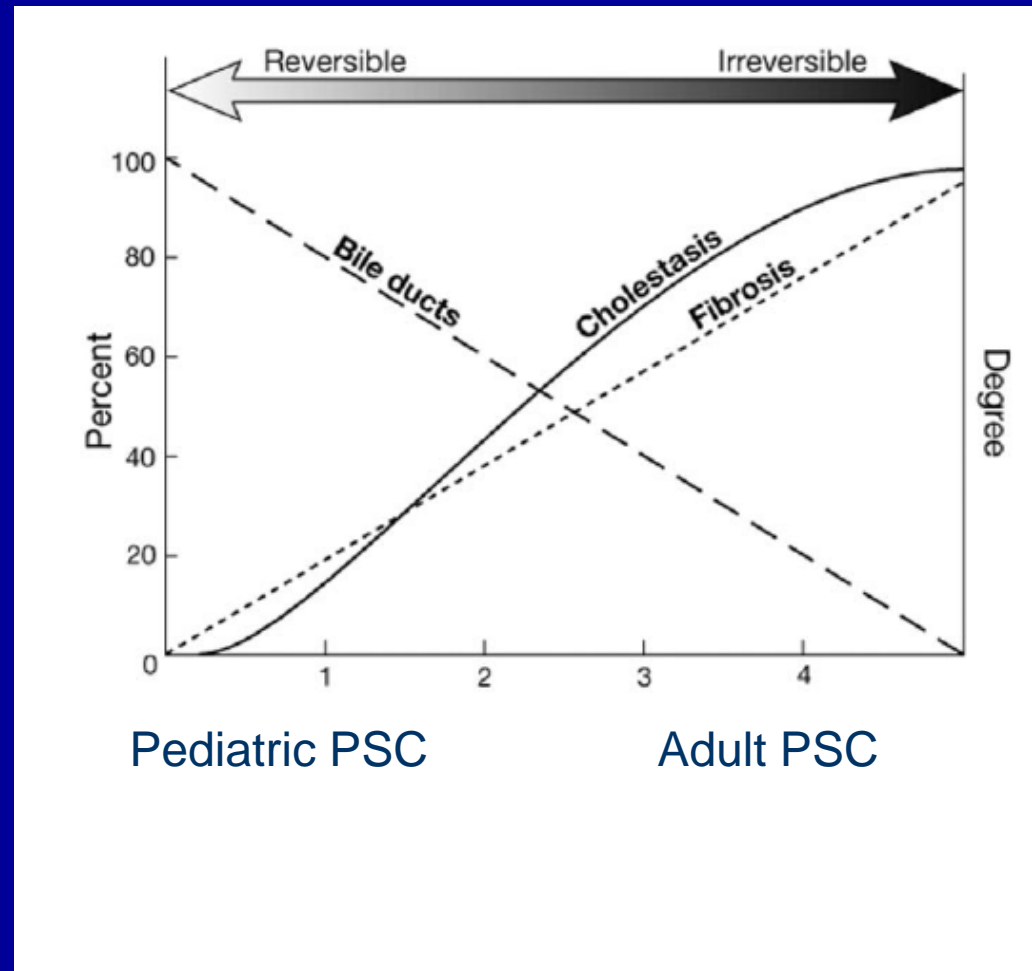
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Objectives

- **Understand differences between adult and pediatric Primary Sclerosing Cholangitis (PSC)**
- **Highlight the available pediatric PSC data**
- **Provide a snapshot of children with PSC at The Children's Hospital**
- **Highlight the current research efforts at The Children's Hospital in pediatric PSC**

Adult and Pediatric PSC: Continuum or different diseases?



Epidemiology of Pediatric PSC

Adults:

- Incidence: 1/ 100,000
- Prevalence: 8-14/100,000

Pediatrics

- No published pediatric data
- Likely considerably less

Pediatric PSC: Clinical Features

- **Symptoms:**

- Fatigue, pruritus, jaundice, abdominal pain, fevers, weight loss

- **Labs**

- Higher AST/ALT than adults
- Alkaline phosphatase: normal or increased
 - Elevated bone isoenzymes induced by growth.
- ↑ GGT levels: more reliable
- May be less cholestatic than adults
- Auto antibodies:
 - +ANA (50%) and +pANCA (80%)
 - In adults, assumed to be non-specific

Pediatric PSC: Clinical Course

- Dominant Strictures: rare
- Recurrent Cholangitis: rare
- Cholangiocarcinoma: extremely rare
- **Metabolic Bone Disease**
 - **Related to duration of PSC and IBD**
 - **Particular concern in pediatrics when amassing bone strength**
- Health Related Quality of Life: decreased

Pediatric PSC: The Limited Data

Author	N	% Male	Mean Age (Years)	% with IBD	% with AIH features
Debray	19	53	7.1	37	11
Wilschanski	32	72	11.2	53	28
Gregorio	27	44	11.8	44	100
Feldstein	52	65	13.8 ± 4.2	81	27
Floreani	3	0	15.3	33	100
Miloh	47	62	11 ± 4.9	59	25

IBD in pediatric PSC : less common vs. ascertainment bias

Autoimmune Hepatitis/PSC Overlap Syndrome

- Higher AST/ALT, ↑ total IgG, + specific auto-antibodies.
 - ANA, anti-smooth muscle, anti-liver kidney microsomal antibody
- Liver biopsy required for diagnosis
- Affected adults
 - 1.4-8%
 - Younger than others with only PSC
 - Less likely to have IBD
- **Pediatrics:**
 - **25-28% of patients**
 - **Benefit from immunosuppression**
 - **Prognosis in children compared to adults may be different**

Small Duct PSC

- Involved biliary ducts too small for ERCP identification
- Liver biopsy required for diagnosis
- Less aggressive than large duct PSC
- Smaller cholangiocarcinoma risk than large duct PSC.

- **Adults:**
 - 5-15% have isolated small duct disease

- **Pediatrics:**
 - 36% have isolated small duct disease

The Children's Hospital of Denver Liver Center

- **29 patients with PSC**
 - 18 (62%) male
 - 13 (45%) Ulcerative Colitis
 - 7 (24%) with AIH/PSC Overlap Syndrome
 - 5 post-transplant
 - 1 awaiting transplant
 - 2 died

Actuarial Survival in Pediatric PSC

Mayo Clinic: 52 patients

•Liver Transplant: 11

• 6.6 ± 3.6
years after
diagnosis

•3 Recurrent PSC

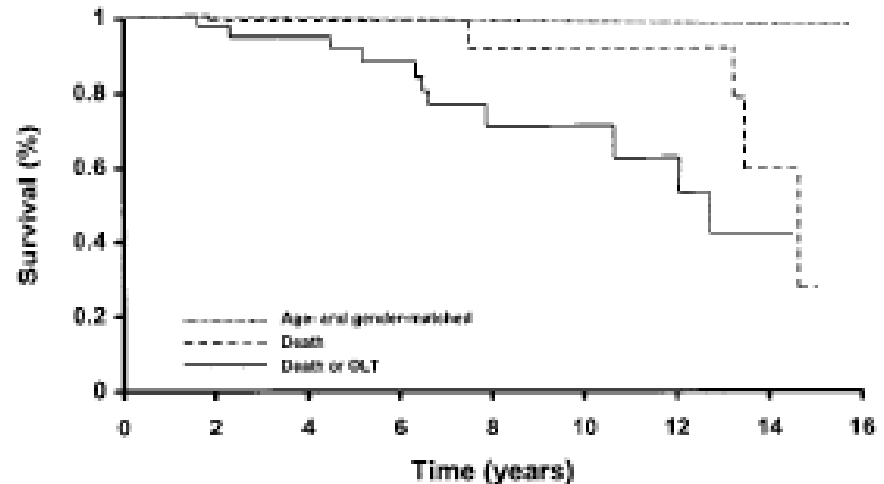


Fig. 1. Actual survival of children with PSC and the expected survival for a cohort of a U.S. Caucasian population matched by age and sex and the same amount of observation time. There were 5 deaths (including 4 posttransplantation) in the PSC group and 0.28 expected deaths in the matched population group. Using death as an end point, survival in children with PSC was significantly shorter than in the matched population group ($P < .001$). Similarly, using liver transplant or death, whichever occurred first as an end point, survival free of liver transplantation was significantly shorter in the PSC than in the matched population group ($P < .001$). (Dotted line), age and gender matched; (dashed line), death; (solid line), death or orthotopic liver transplantation.

Transplant Free Survival In Pediatric PSC

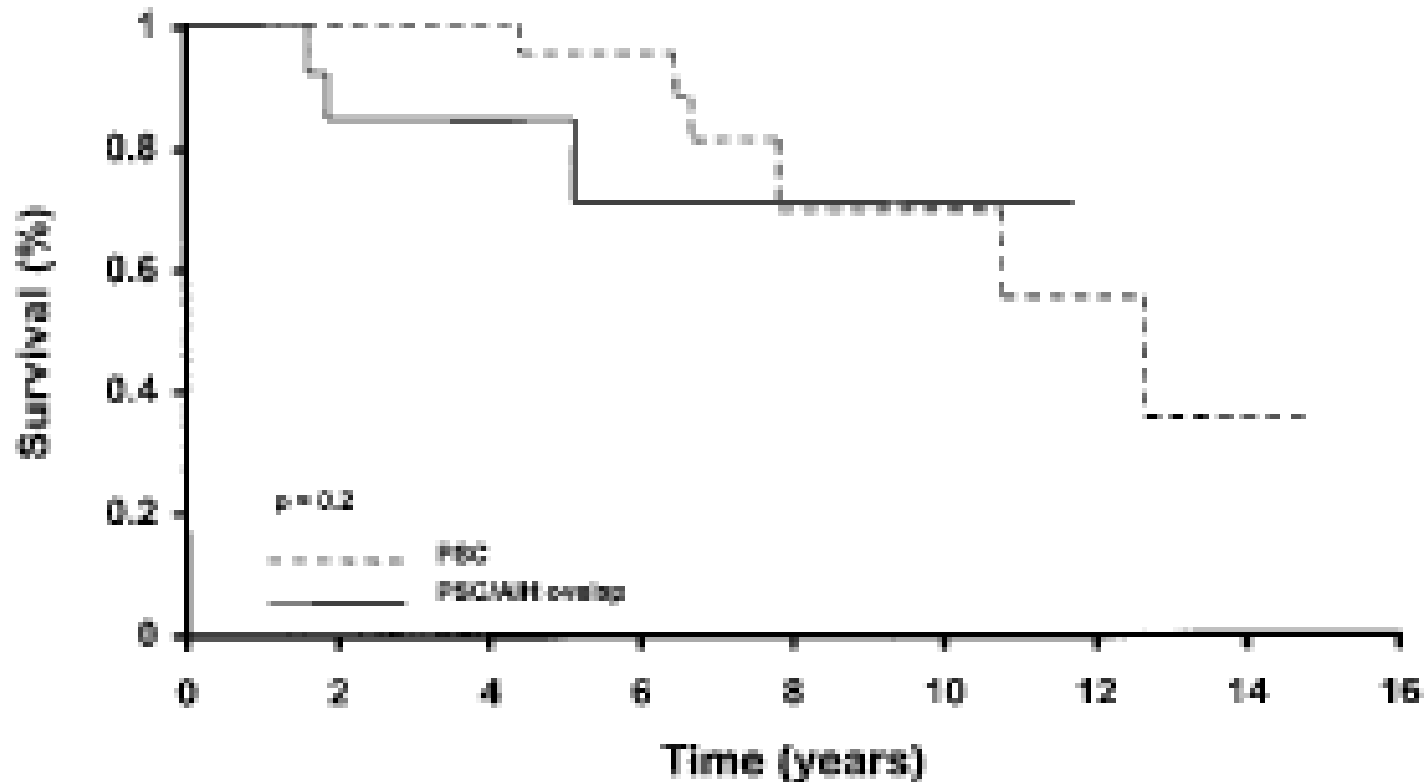


Fig. 3. Actual survival free of liver transplantation in children with PSC alone (dashed line) and those with PSC/AIH overlap (solid line). $P = .2$.

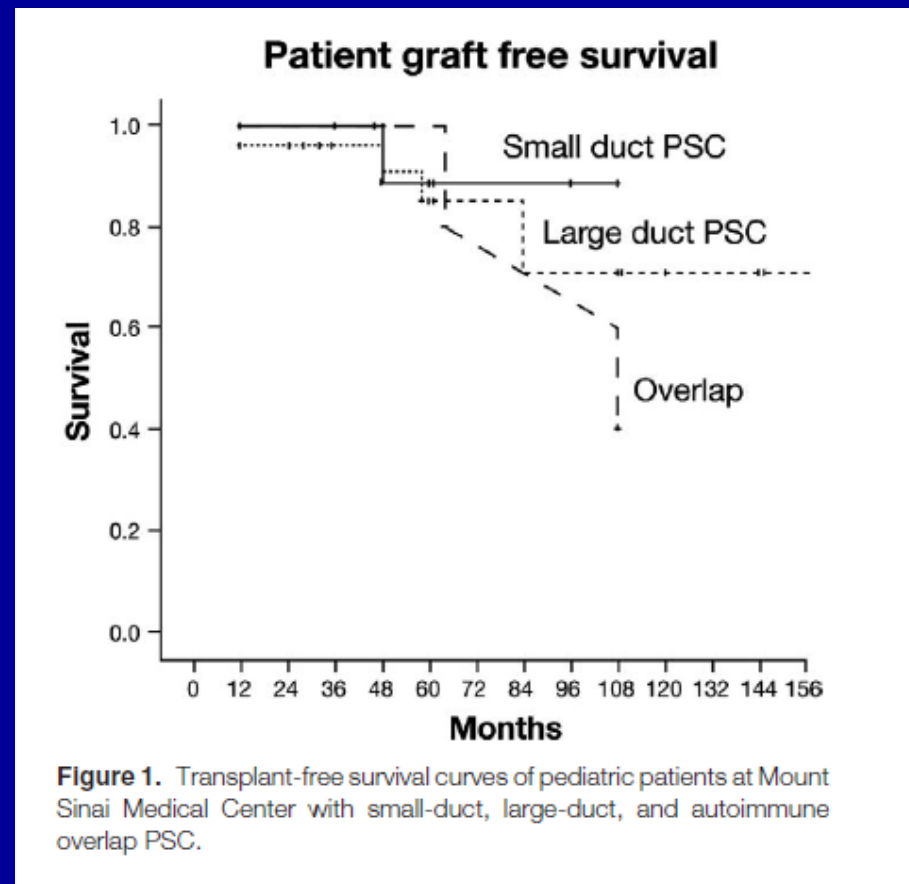
Transplant Free Survival in Pediatric PSC

Mt. Sinai: 47 patients

Liver Transplant: 9
-3 overlap syndrome

-2 isolated small duct disease

-10 year post-transplant survival: 89%



Ursodeoxycholic Acid: Friend or Foe

Adults

- Large trials unable to show significant effect on disease outcome
- High-dose study showed an adverse effect on hard endpoint ¹
- **Many centers recommend discontinuing UDCA in PSC patients**

Pediatrics

- Widespread use and well-tolerated
- Children experience more prompt and striking biochemical improvement than in adults
- Caution in generalizing adult data to pediatrics
- Reluctance of pediatric hepatologists to discontinue UDCA based on adult data

Should UDCA therapy be stopped in pediatric PSC patients to avoid possible long-term adverse outcomes at the risk of losing a possible beneficial effect on early disease progression?

UDCA for Pediatric PSC: A Pilot Withdrawal/Reinstitution Trial

STOPSC Pediatric Consortium

Principal Investigators: Dennis Black and Benjamin Shneider

Pediatric PSC: Liver Transplantation

SPLIT (Studies in Pediatric Liver Transplant)

- ~30 centers US centers, 1995-2008
- Transplants for PSC: 79 of 2297 participants (2.6%)
 - 71% whole, 15% LRD, 10% segmental grafts
 - 67% Caucasian vs. 56% non- PSC, $p=0.02$
 - PELD at transplant 1.6 vs 12 non-PSC, $p < 0.0001$
 - Months on wait list: 10.2 vs 4.6 non-PSC, $p<0.0001$
 - No difference in wait list mortality

SPLIT: Pediatric PSC

- **Inflammatory Bowel Disease**
 - Pre-transplant: UC 46%, Crohn's in 3.3%
 - Post-transplant: 10%
- **Overall post-transplant mortality: 9%**
 - 1 yr patient survival 98.7% vs 91.1% non-PSC, p=0.03
 - 5 year survival not different (86.6%)
- **Overall post-transplant graft loss: 15%**
 - No difference in 1 or 5 year graft survival compared to non PSC
- **Recurrent PSC: 9.8%**
 - Mean 18.7 ± 13.8 months post OLT

Conclusions

- **Children are not little adults !!!**
- **In pediatric PSC, the disease itself, the treatment and prognosis may be different than adults**
- **We have more questions than answers**