STOPSC Update

Dennis Black, MD

STOPSC

- Studies of Primary Sclerosing Cholangitis (STOPSC) is a collaborative effort among 13 centers (10 pediatric and 10 adult programs) in the United States and Canada whose primary objective is to collect and analyze information required to understand the etiology, pathogenesis, and treatment of primary sclerosing cholangitis (PSC).

- STOPSC is funded by The Morgan Foundation whose goal is to sponsor and facilitate both basic and clinical research to discover new treatments and ultimately a cure for primary sclerosing cholangitis. The STOPSC Genetic Repository is partially funded by PSC Partners Seeking a Cure.

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STOPSC
Studies of Primary Sclerosing Cholangitis

Study Objectives

- To identify risk factors, including genetic and environmental factors, for development of PSC and understand the mechanisms involved in the pathogenesis of PSC.

- To identify the role of genetic factors in the predilection for disease, disease severity and response to treatment (HLA haplotypes, cftr, mdr3, nod2, as well as inflammatory mediator gene polymorphisms, liver disease modifier genes).

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Study Objectives

- To help develop diagnostic tests/approaches that can diagnose the disease in its early stages, as well as surrogate markers for the severity, progression and response to treatment of the disease.
- To evaluate and compare the efficacy and safety of various treatments of PSC.
- To collect information that will help characterize the disease and clarify the relationship between childhood and adult forms of PSC.

Study Objectives

- To study the natural history and clinical course of the disease in children and adults.
- To better understand the relationship of PSC with associated diseases, such as autoimmune hepatitis and inflammatory bowel disease.
- To identify risk factors and biomarkers for the development of cholangiocarcinoma.

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Study Objectives

- To develop and test models which predict patient outcomes (cirrhosis, portal hypertension, cholangiocarcinoma, death, transplantation, etc.).
- To characterize and follow trends in therapies of PSC.
- Develop a cohort of well characterized subjects for future clinical trials.

STOPSC Participating Centers

ADULT PROGRAMS

- Mount Sinai Medical Center
- Beth Israel Deaconess Medical Center
- Virginia Commonwealth University
- Mayo Clinic
- Tufts University
- University of California, San Francisco
- University of Colorado, Denver
- Toronto Western Hospital
- University of California, Davis
- University of Pittsburgh

PEDIATRIC PROGRAMS

- LeBonheur Children's Medical Center
- Mount Sinai Medical Center
- Cincinnati Children's Hospital
- Children's Hospital Boston
- Mayo Clinic
- University of California, San Francisco
- Children's Hospital of Denver
- Children's Memorial Hospital, Chicago
- Hospital for Sick Children, Toronto
- Children's Hospital of Pittsburgh

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STOPSC Studies of Primary Sclerosing Cholangitis

STOPSC Progress 2007

- Establishment of infrastructure
  - Governance/committees
  - Recruitment of centers, including PI's and coordinators
  - Development of eligibility criteria, exclusion criteria and data forms
  - Database construction and data entry algorithms
  - Central radiology and imaging data forms
  - Liver pathology data forms
  - Center IRB approvals
  - Center LOA negotiations
  - Coordinator training and center certification
- Subject recruitment started

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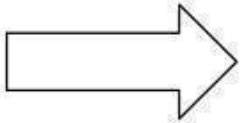
Scheduled Assessments

Baseline Assessments
Time of Diagnosis

Follow-up Assessments
Yearly Assessments

Enrollment
Demographics
Eligibility Criteria

Forms to be Completed
Diagnostic Studies
Clinical Status
Interventions/Therapies
Laboratory Assessments
Social Information
Family Medical History



Forms to be Completed
Diagnostic Studies
Clinical Status
Interventions/Therapies
Laboratory Assessments
Social Information
Family Medical History

Non-Scheduled (Event Based) Assessments

Non-scheduled assessments are required when a specific event occurs

Liver Biopsy
Radiology
Liver Transplant
Cholangiocarcinoma
Exit
Death

Genetic Repository

- STOPSC Genetic Repository Committee
  - Chris Bowlus
    - UC, Davis
  - Peter Durie
    - Hospital for Sick Children, Toronto
  - Steve Freedman
    - Harvard
  - Kostas Lazaridis
    - Mayo
  - Ravinder Anand
    - EMMES

Genetic Repository

- All STOPSC subjects are being consented for genetic repository
- Options being considered
  - Morgan Foundation/NIDDK private/public partnership to provide free access to NIDDK DNA repository
  - Contract with Mayo Clinic Labs
  - Free use of Canadian Cystic Fibrosis Repository for one year and pay shipping costs only (courtesy of Dr. Peter Durie)
  - Wait for funding of NIDDK U01 grant (early 2009)

Eligibility Criteria

Eligibility Criteria

Participants must be evaluated for eligibility within 5 years of diagnosis of one of the following disease classifications to be eligible for STOPSC.

- **ADULT (≥ 18 years)**
  - Large Duct PSC
  - Small Duct PSC
  - PSC/AIH Overlap
- **PEDIATRIC (< 18 years)**
  - PSC
  - PSC/AIH Overlap
  - AIH only

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Inclusion Criteria
Large Duct PSC – Adults

1. Increased serum alkaline phosphatase as a marker for cholestasis

2. ERCP, PTC or MRCP evidence of intrahepatic and/or extrahepatic bile duct irregularities consistent with PSC

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Inclusion Criteria
Small Duct PSC – Adults

1. Increased serum alkaline phosphatase as a marker for cholestasis

2. No ERCP, PTC or MRCP evidence of intrahepatic and/or extrahepatic bile duct irregularities consistent with PSC

3. Either Inflammatory Bowel Disease OR Liver biopsy consistent with chronic biliary injury

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Inclusion Criteria

PSC/AIH Overlap – Adults

1. Meets criteria for large duct or small duct PSC

2. Liver histology with features of both PSC and AIH

Inclusion Criteria
PSC – Pediatric

Two of three required for diagnosis:

1. Serum alkaline phosphatase or GGT increased more than 50% above the upper limit of normal for age
2. ERCP, PTC or MRCP findings of intrahepatic and/or extrahepatic bile duct irregularities consistent with PSC
3. Liver biopsy abnormalities consistent with chronic biliary injury

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Inclusion Criteria

PSC/AIH Overlap – Pediatric

1. Meets criteria for diagnosis of PSC

2. Liver histology with features of both PSC and AIH

Inclusion Criteria
AIH – Pediatric

1. Meets definite or probable criteria definition of the International Autoimmune Hepatitis Working group (see *Journal of Hepatology* 31: 929, 1999)

2. No diagnosis of PSC

Patients Diagnosed with PSC between 2001-2006

Expected retrospective participant enrollment based on a five year period across all centers:

Adult:	**1,070**
Pediatric:	**170**
Total:	**1,240**

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Estimate of Patients Diagnosed with PSC Annually Across Participating Centers

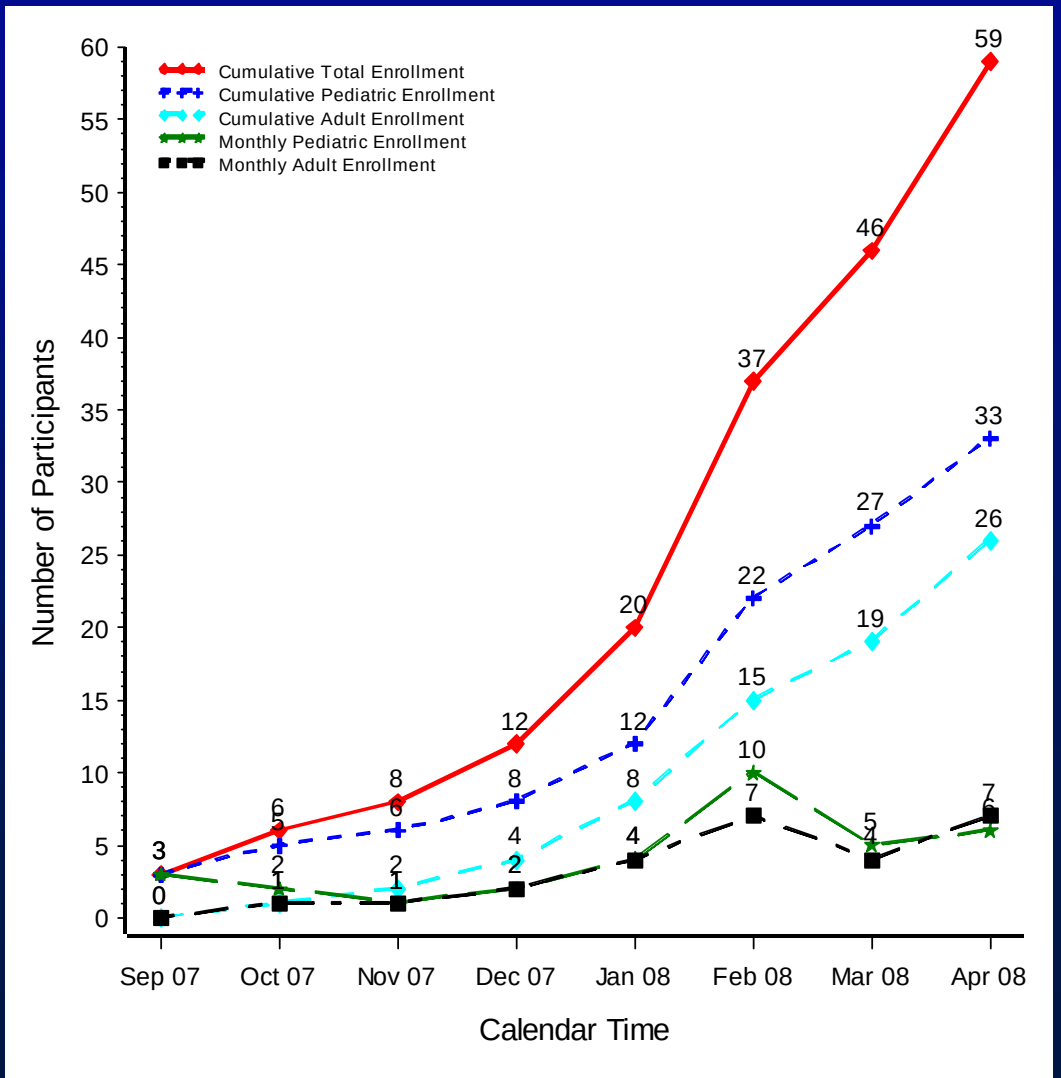
Expected annual participant enrollment across all centers:

Adult:	**225**
Pediatric:	**40**
Total:	**265**

Data Summary
April, 2008

Dennis Black
Ravinder Anand
Wendy Yin

Participants Enrolled By Calendar Time



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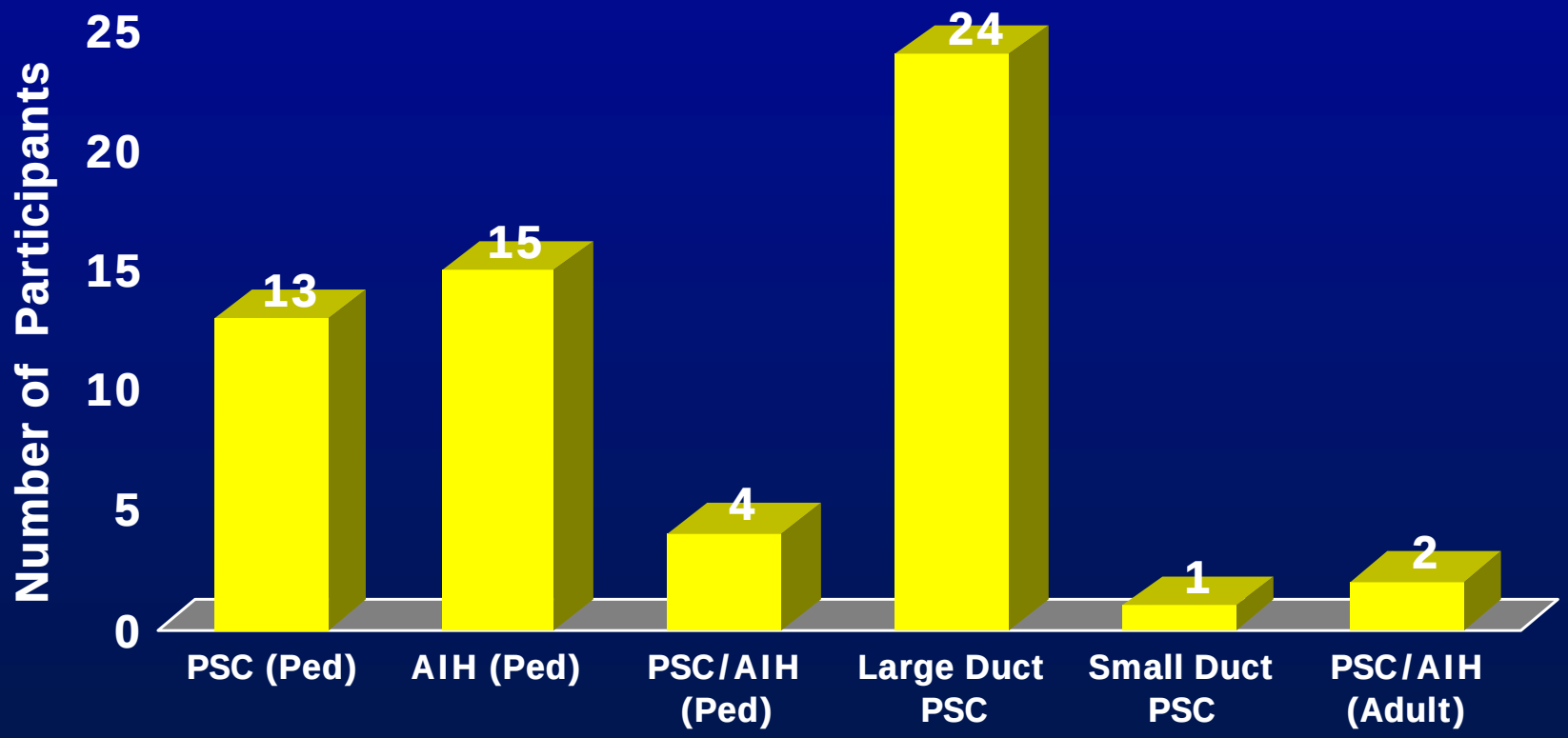
Participants Enrolled By Disease Classification



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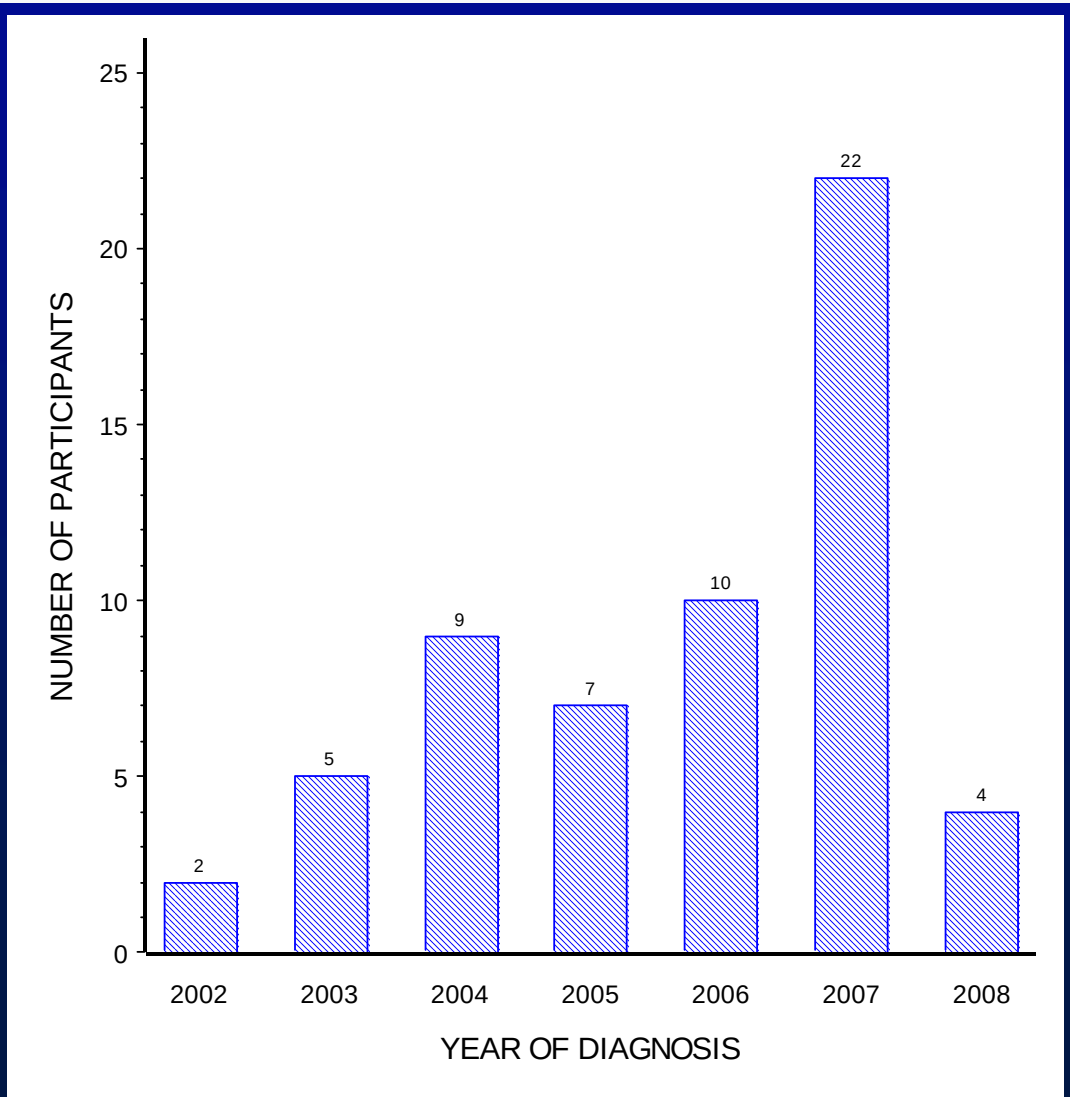
Participants Enrolled By Year of Diagnosis



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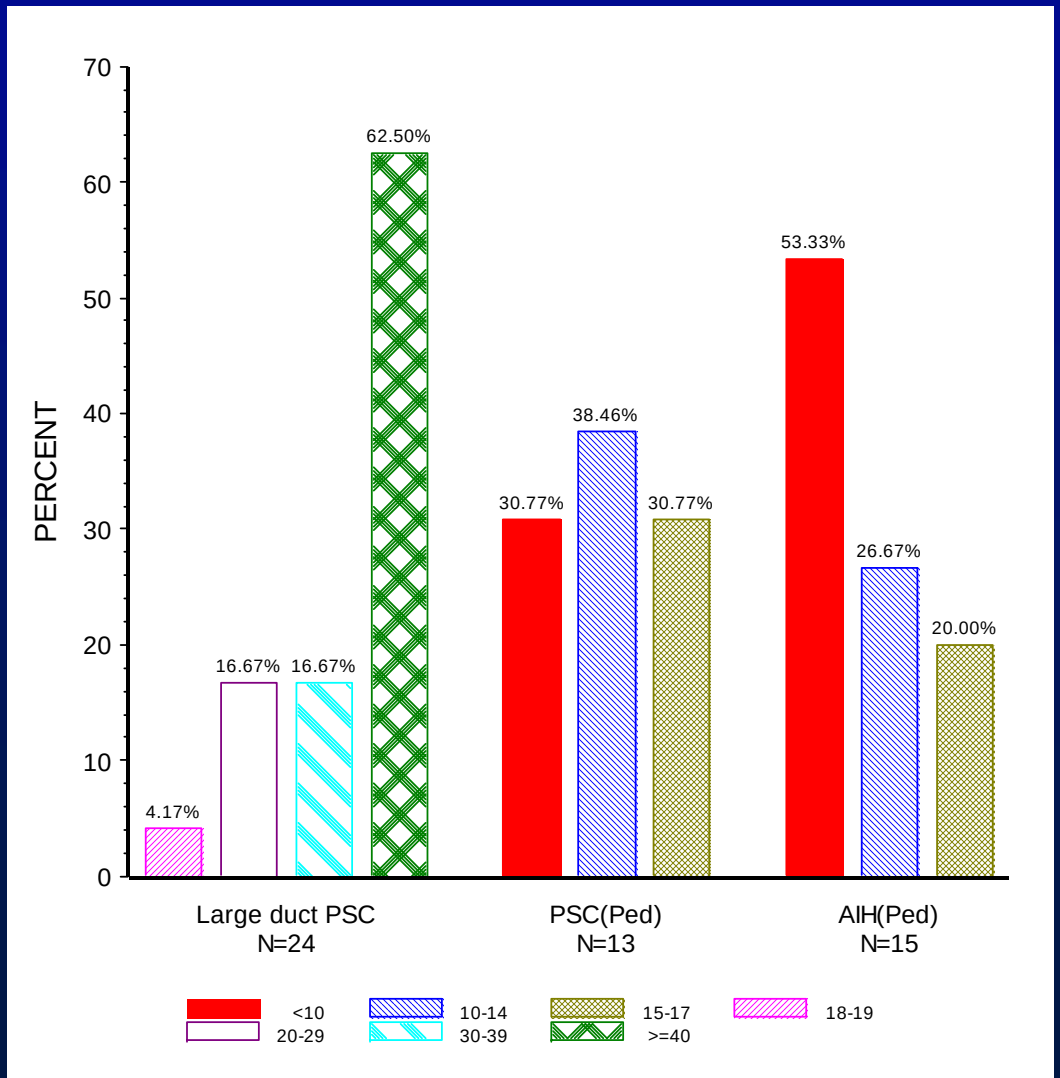
Studies of Primary Sclerosing Cholangitis

Participants Enrolled By Age at Diagnosis and Disease Classification



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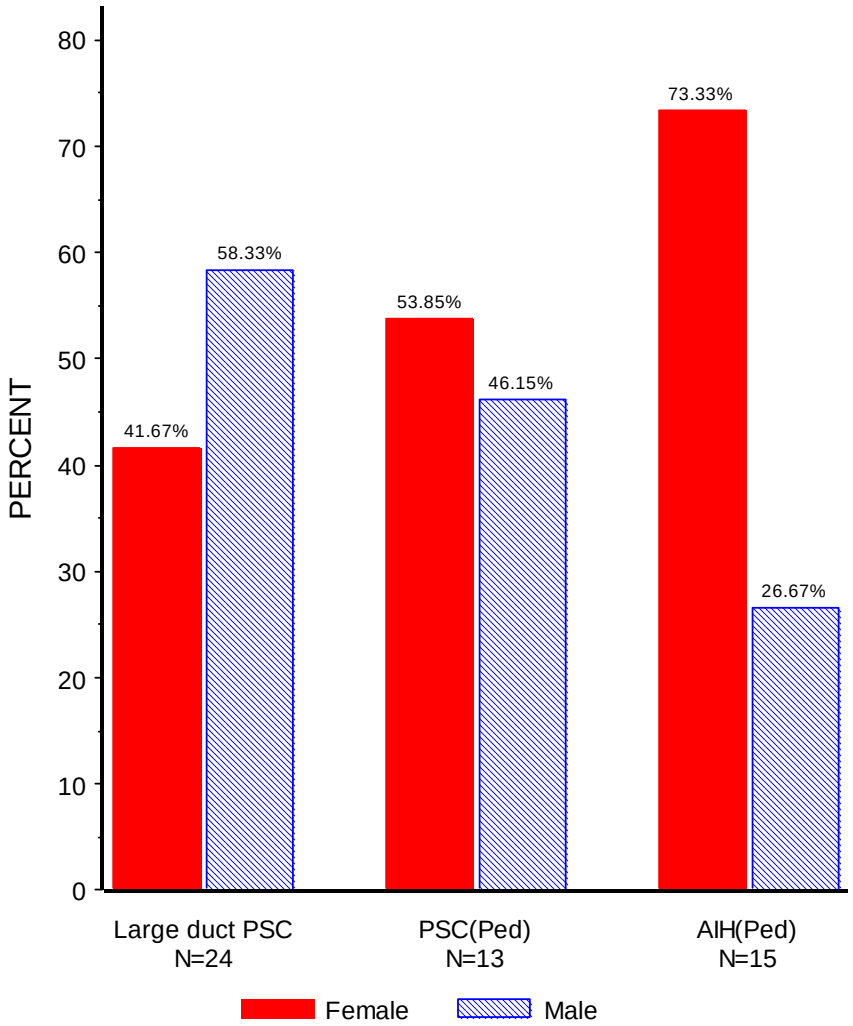
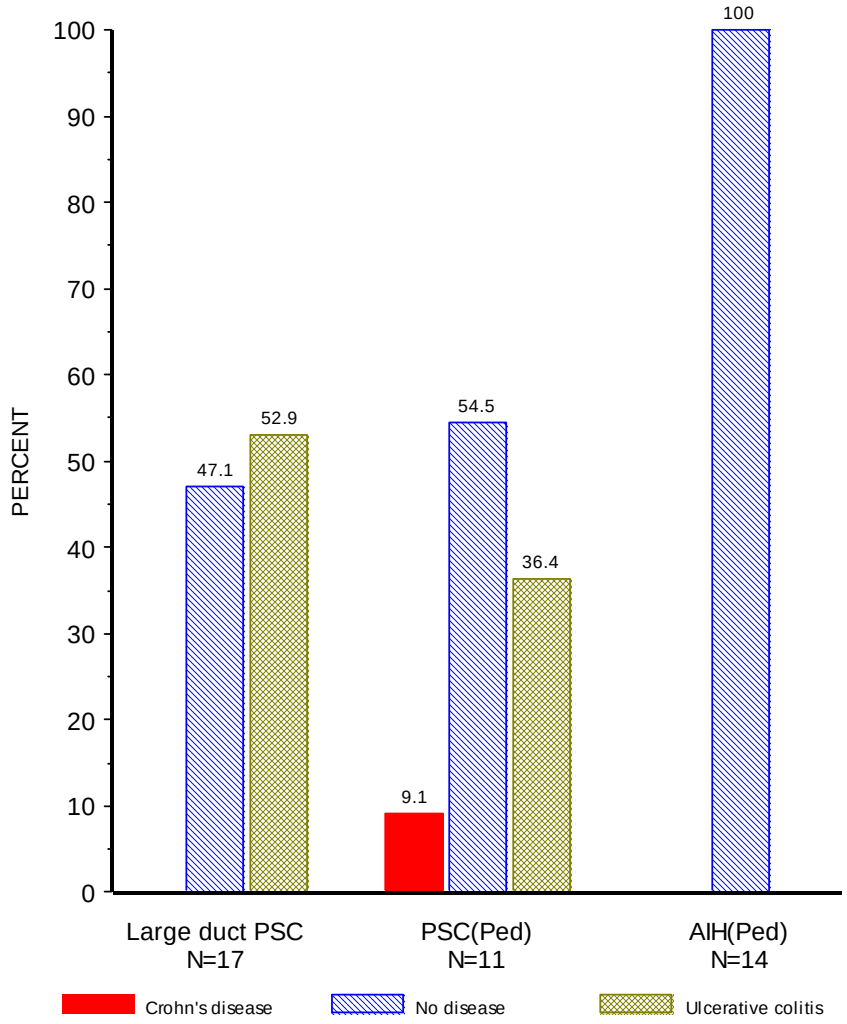
Studies of Primary Sclerosing Cholangitis

Participants Enrolled
By Gender and Disease Classification



Other Diseases At Diagnosis By Disease Classification



PSC Diagnosis Criteria For PSC or PSC/AIH Overlap Participants
Participants Age <18 At Diagnosis

Elevated Alk. Phos. Or Elevated GGT	Imaging Study	Biopsy	PSC		PSC/AIH	
			N	%	N	%
Total			**13**	**100.0**	**4**	**100.0**
No	Abnormal	Abnormal	1	7.7	0	0.0
Yes	Normal	Abnormal	1	7.7	0	0.0
Yes	Abnormal	Normal	2	15.4	0	0.0
Yes	Abnormal	Abnormal	5	38.5	2	50.0
Yes	Abnormal	Not Eval.	3	23.1	0	0.0
Yes	Not Eval.	Abnormal	1	7.7	2	50.0

General Physical Exam By Disease Classification
Participants Age <18 At Diagnosis

	PSC (Peds)		AIH (Peds)	
	N	Mean±SE	N	Mean±SE
Height (cm)	10	132.6±8.6	14	135.6±9.5
Height Z Score	10	-0.8±0.4	14	0.2±0.3
Weight (kg)	10	36.0±5.8	14	39.8±5.7
Weight Z Score	10	-0.3±0.5	14	0.6±0.3
BMI Z Score	10	0.4±0.4	13	0.5±0.4

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Symptoms At Diagnosis By Disease Classification

	Large Duct PSC		PSC (Ped)		AIH (Ped)	
	N	%	N	%	N	%
Total Patients	**17**	**100.0**	**11**	**100.0**	**14**	**100.0**
Pruritus (Yes)	3	17.6	0	0.0	0	0.0
Chronic Fatigue						
Missing	1	5.9	1	9.1	0	0.0
Yes	4	23.5	1	9.1	1	7.1
Abdominal Pain (Yes)	5	29.4	8	72.7	4	28.6
Diarrhea (Yes)	5	29.4	3	27.3	1	7.1
Blood in Stool (Yes)	4	23.5	4	36.4	0	0.0
Fever / Chills (Yes)	0	0.0	2	18.2	2	14.3
Anorexia (Yes)	1	5.9	1	9.1	1	7.1
Vomiting Blood (Yes)	0	0.0	1	9.1	0	0.0

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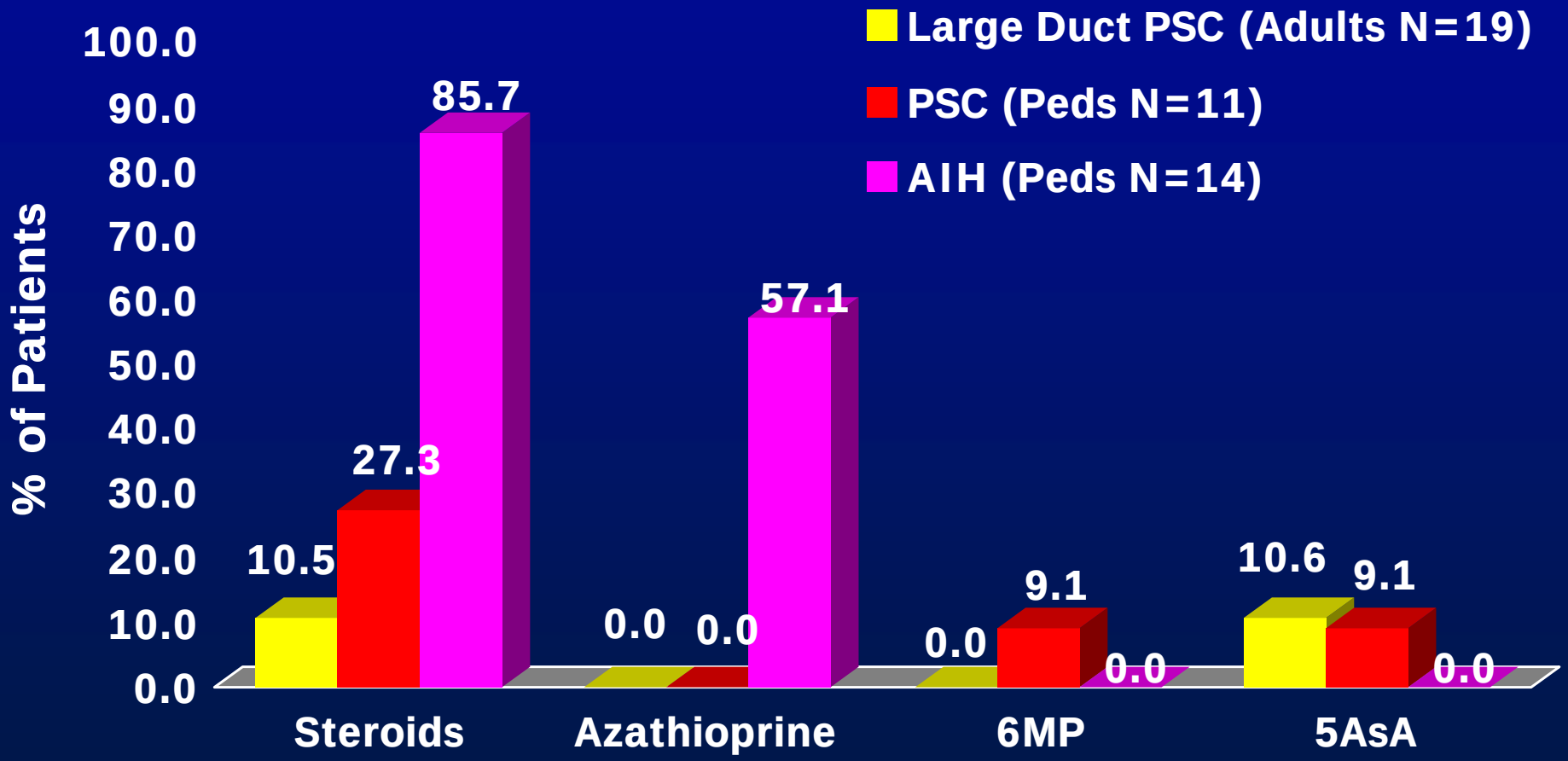
Medications Used at Diagnosis



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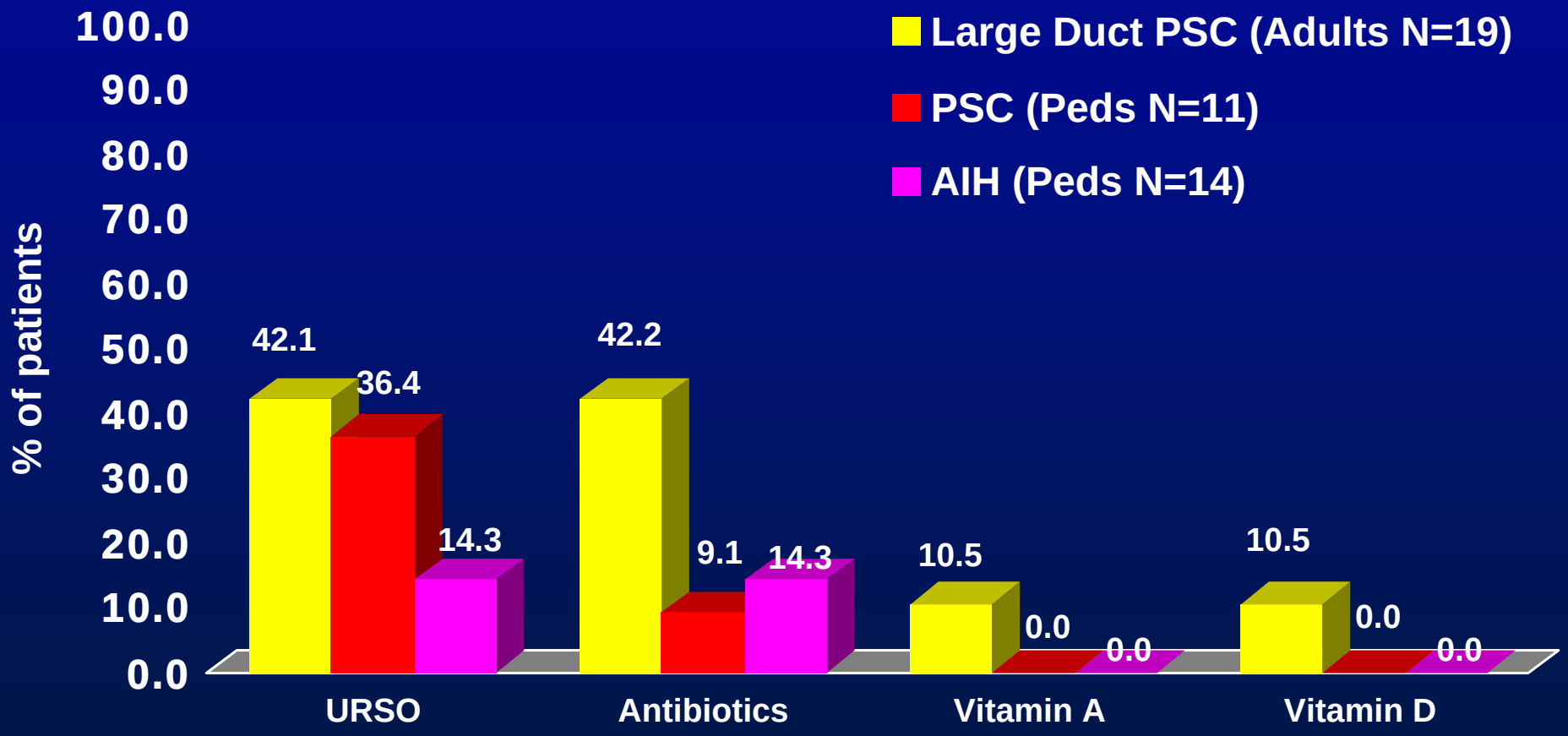
Medications Used at Diagnosis



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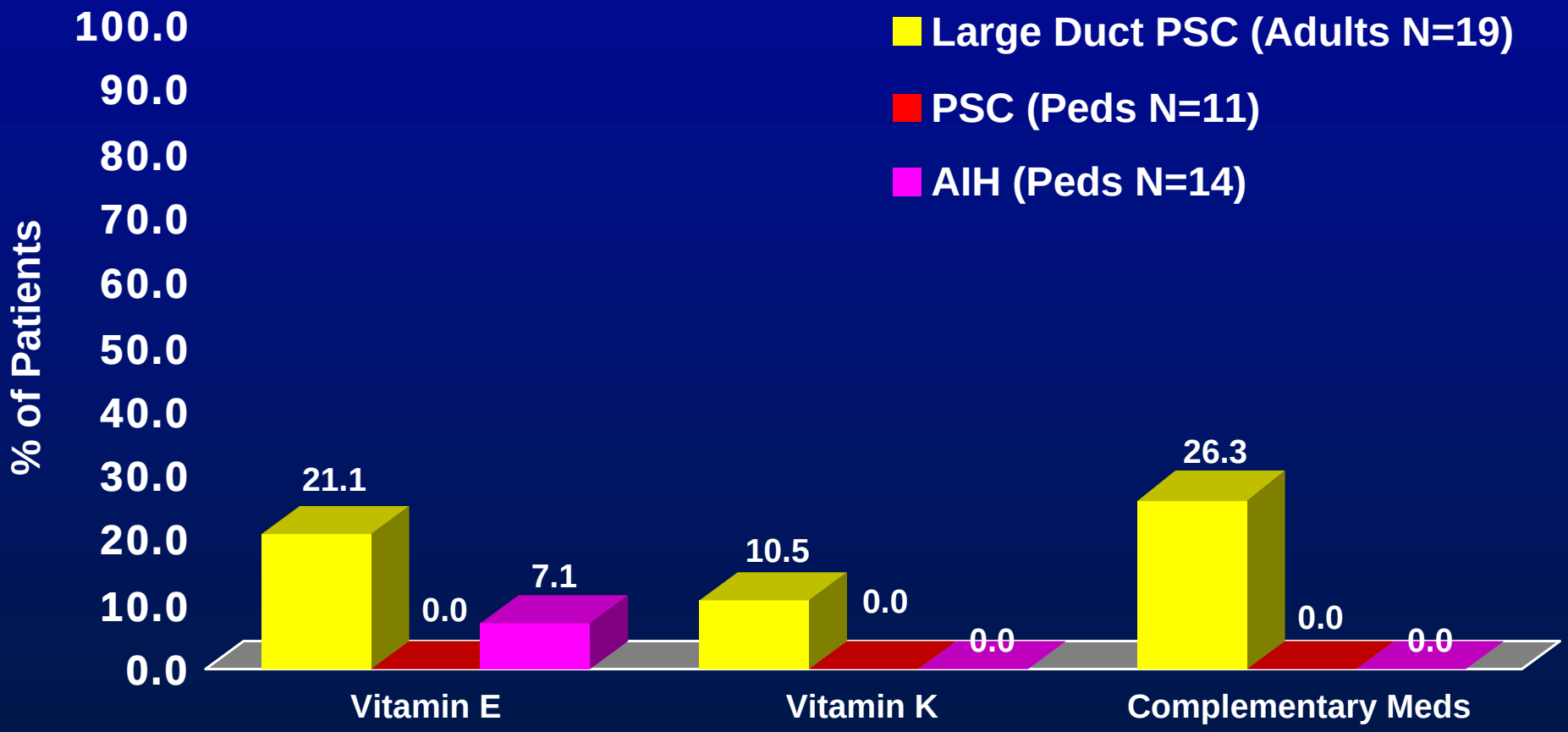
Medications Used at Diagnosis



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Medication Dosage at Diagnosis

	Large Duct PSC (Adults)		PSC (Peds)		AIH (Peds)	
	N	Mean±SE	N	Mean±SE	N	Mean±SE
Corticosteroids (mg/day)	2	10.0 ±0.0	3	14.0±8.3	11	36.4±2.0
Urso (mg/day)	8	806.3±167.6	4	812.5±87.5	2	570.0±30.0

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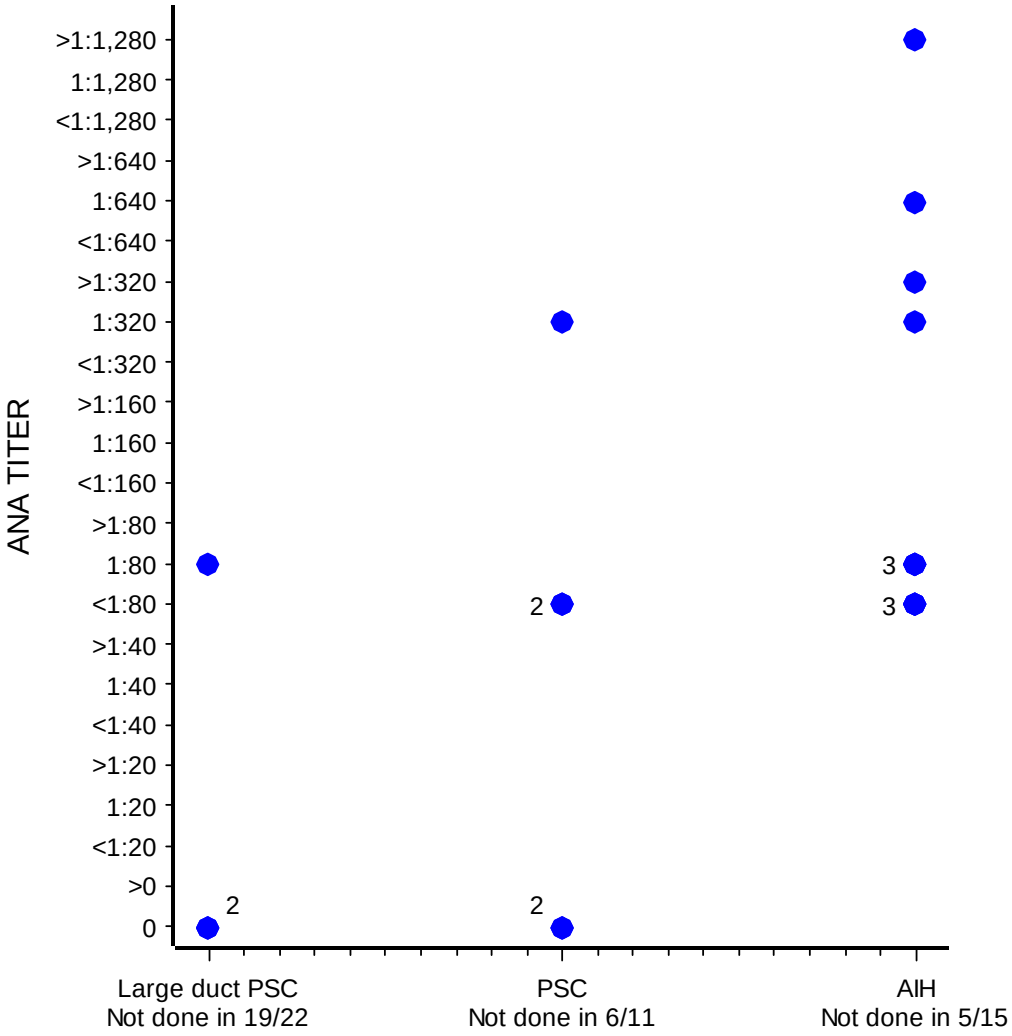
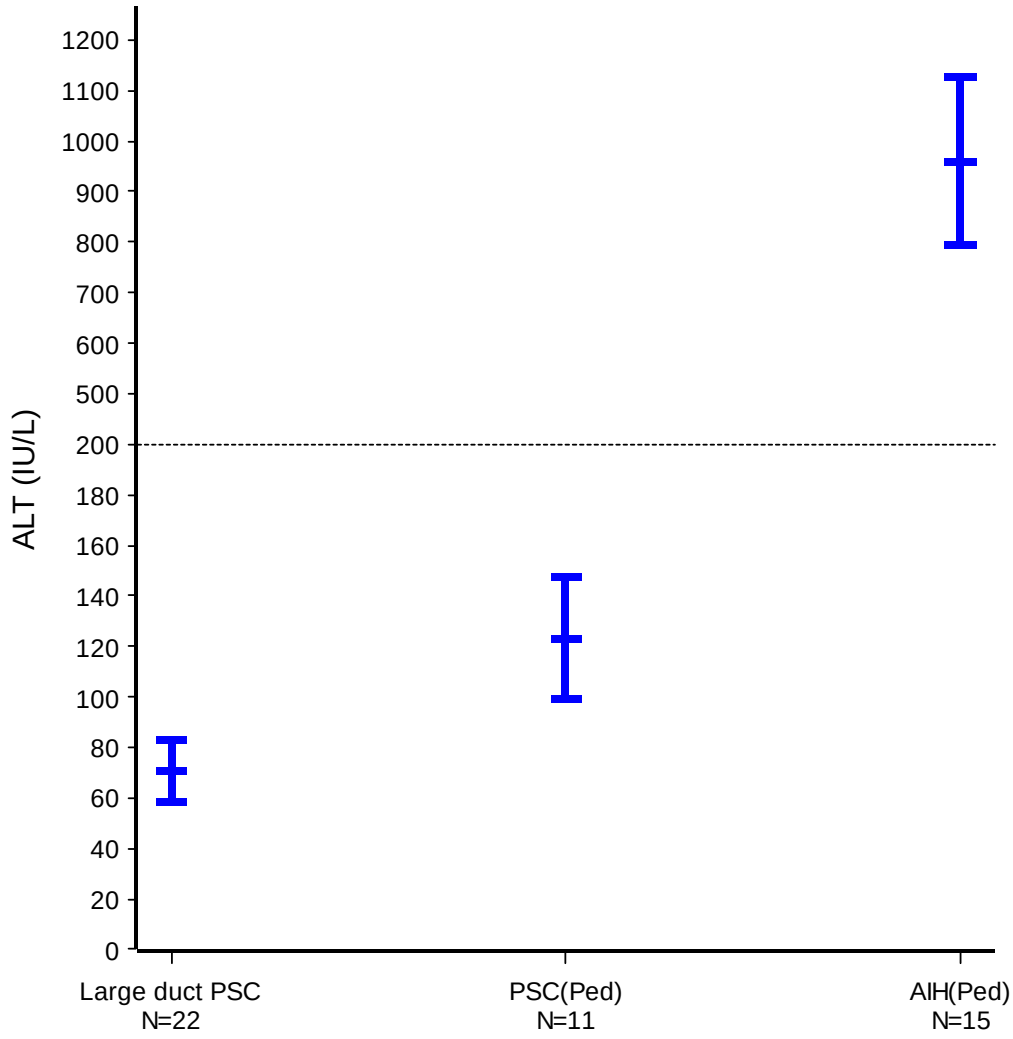
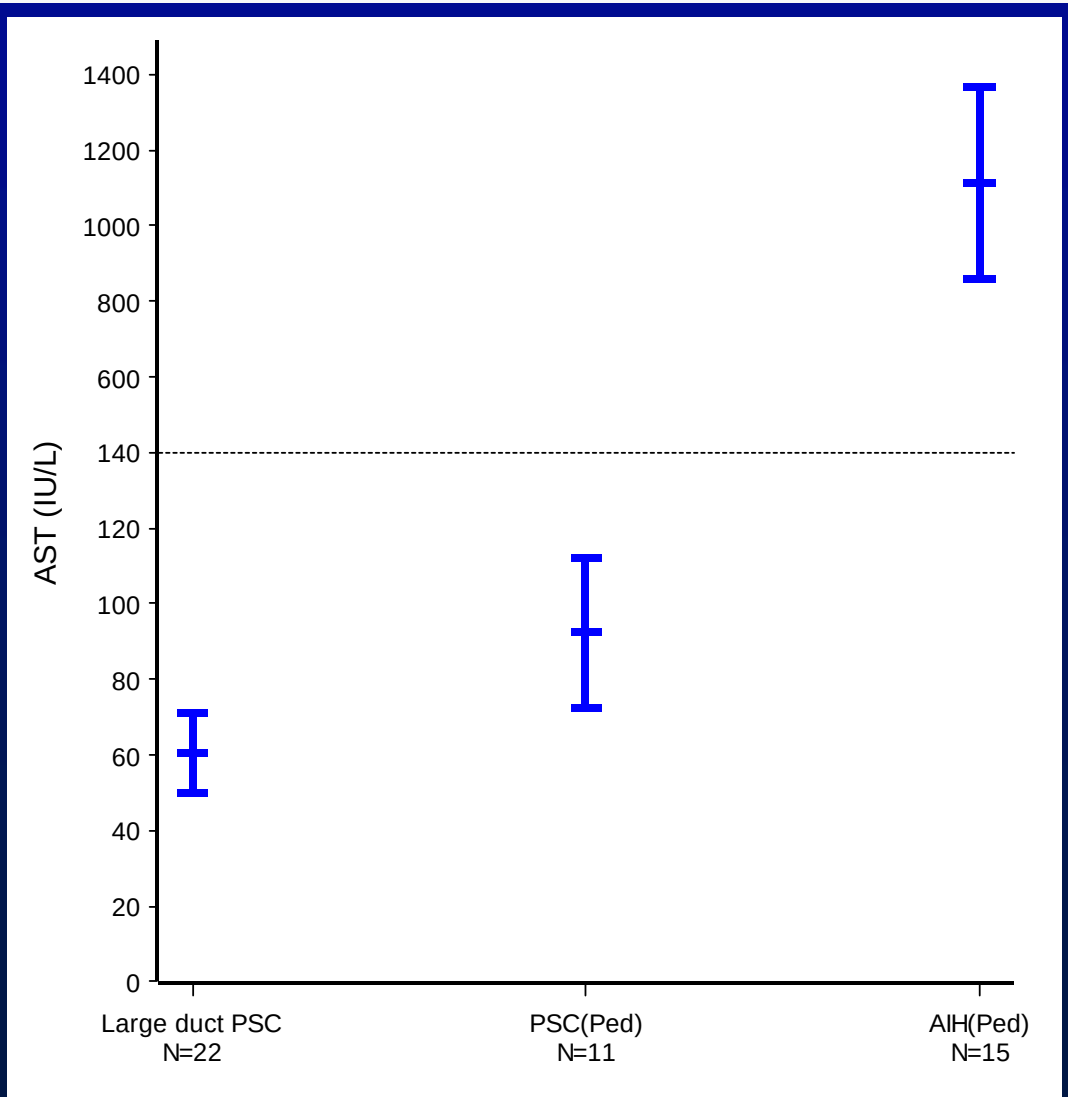
ANA Titer
By Disease Classification



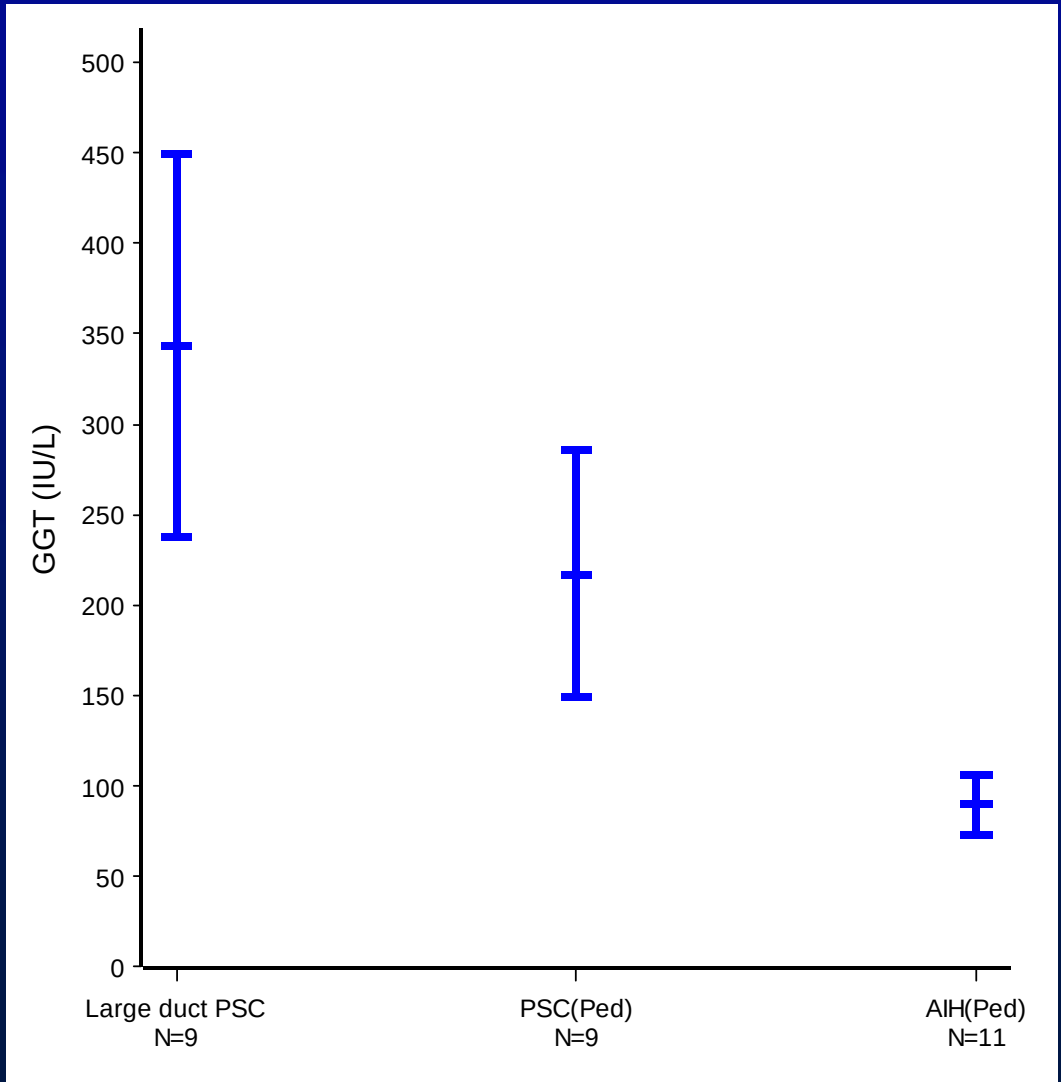
ALT (IU/L)
By Disease Classification
Mean ± SE



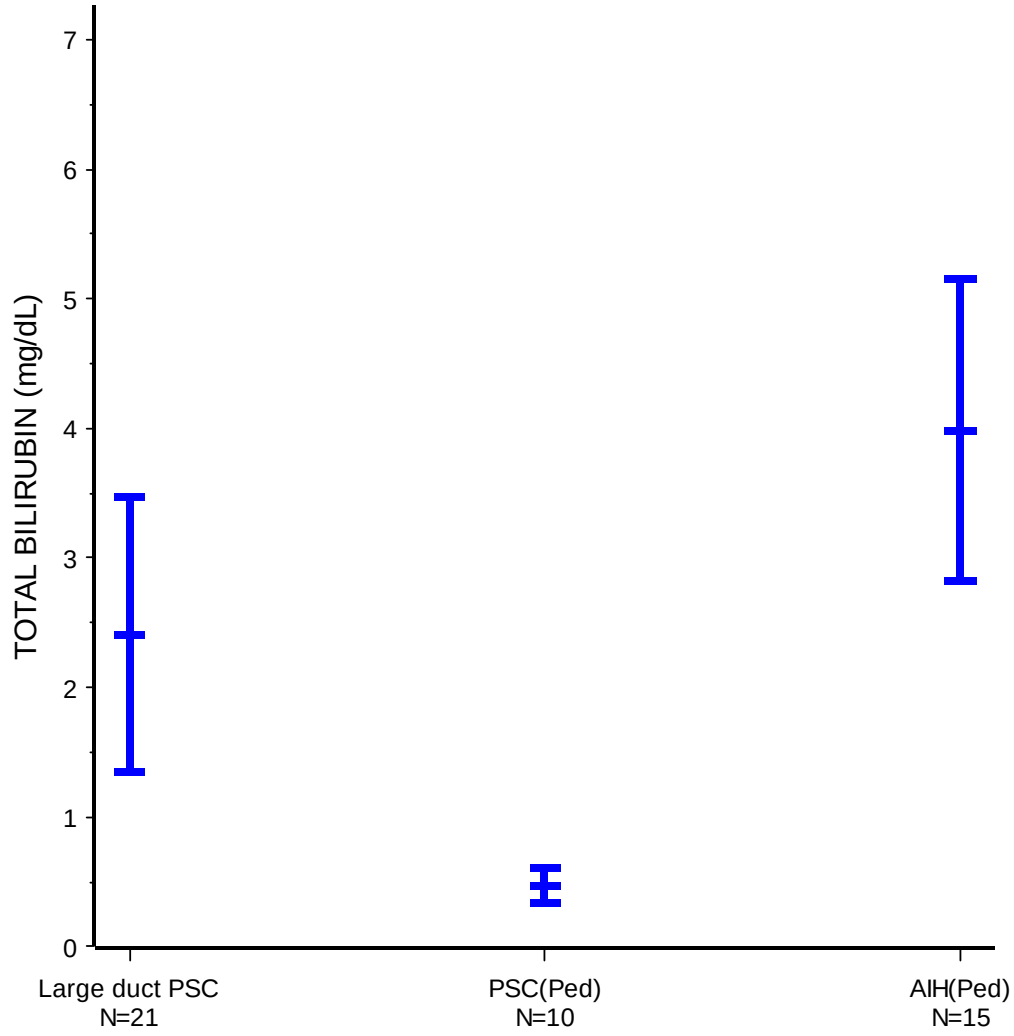
AST (IU/L)
By Disease Classification
Mean ± SE



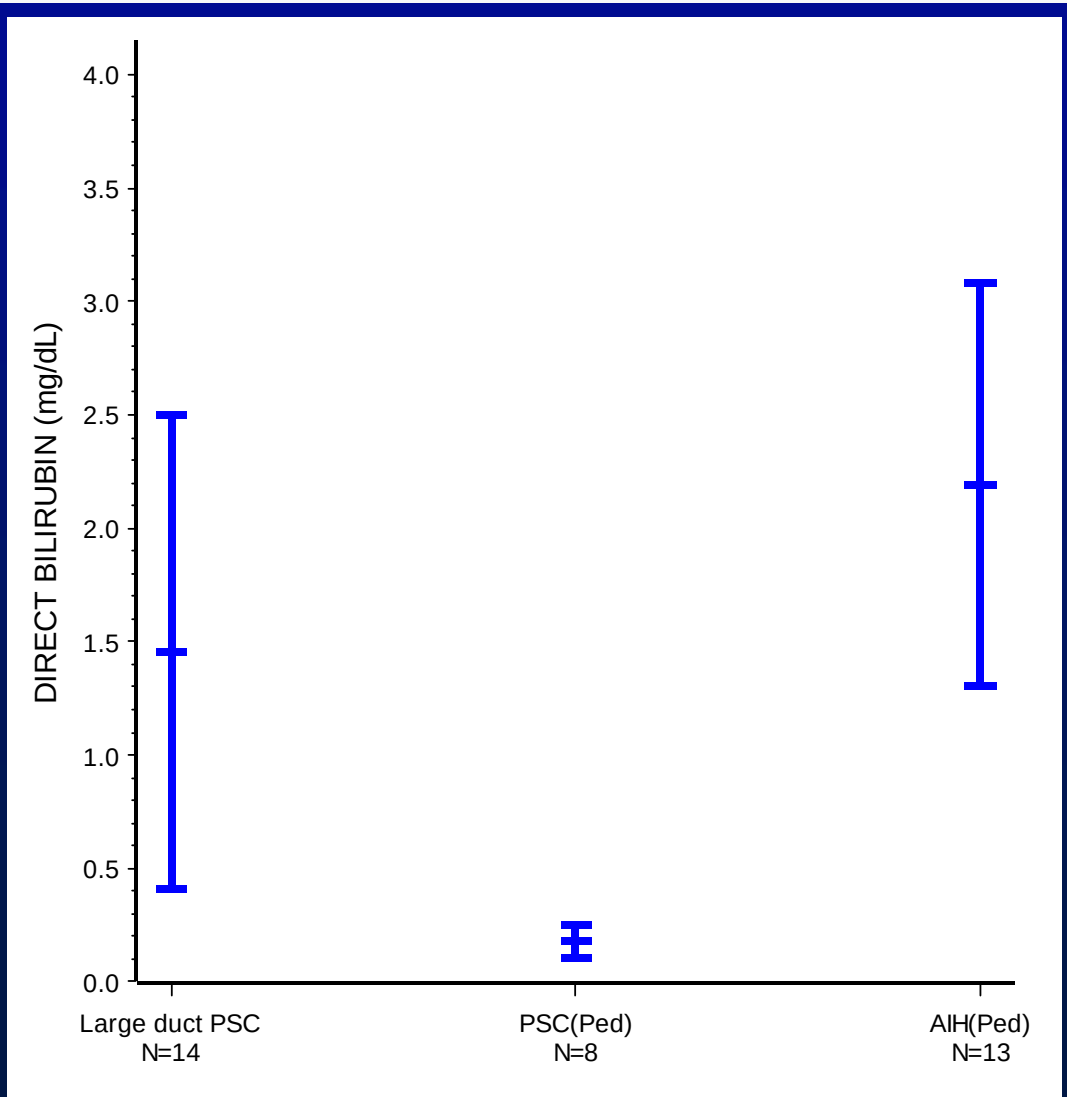
GGT (IU/L)
By Disease Classification
Mean ± SE



Total Bilirubin (mg/dL) By Disease Classification Mean ± SE



Direct Bilirubin (mg/dL) By Disease Classification Mean ± SE



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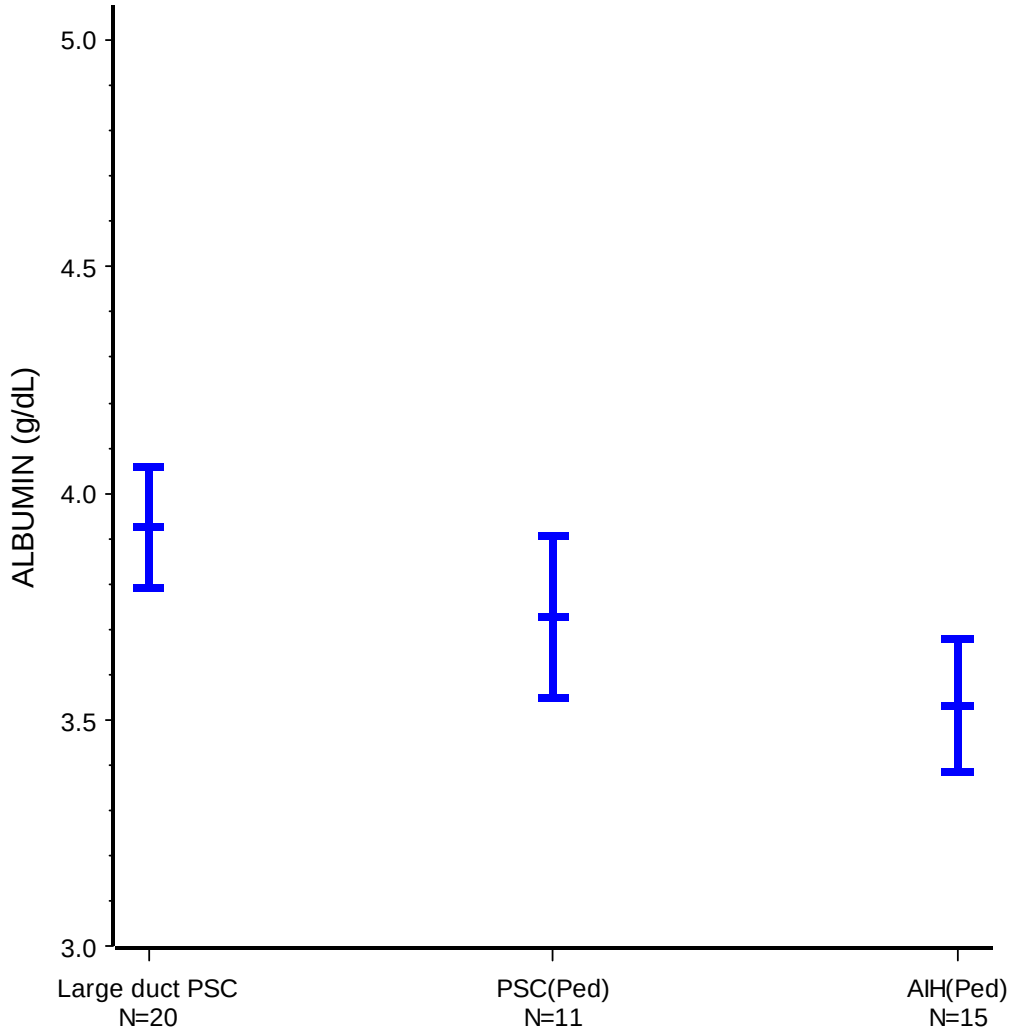
Albumin (g/dL)
By Disease Classification
Mean ± SE



Ancillary Studies

- "A Genome-Wide Association Study of PSC in North America: The STOPSC Cohort" Chris Bowlus and the STOPSC Genetics Committee
- "Non-Invasive Test of Liver Function (Cholate Shunt) to Track Disease Progression" Greg Everson, U of Colorado
- "Effect of High-Dose Vitamin D on Cholestasis" Joe Odin, Mt. Sinai
- "Undiagnosed Biliary Tract Pathology: A Prospective Evaluation by MRCP" Gideon Hirschfield, Toronto

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Ancillary Studies

- "Systematic Evaluation of Elevated IgG4 in Determining PSC Prognosis" Gideon Hirschfield, Toronto
- "Multi-Center Analysis of the Significance of Autoimmune Histologic Features in Children with PSC" Ben Shneider, U of Pittsburgh
- "mRNA Profile of Malignant and Benign Strictures in PSC Patients" Seng-Ian Gan, Tufts

NIDDK Multi-Center Clinical Study Cooperative Agreement (U01) PAR-08-058

- Investigator-initiated, multi-center clinical studies
- Two-part process that includes an implementation planning (U34) grant that may be waived.
- Will fund longitudinal study
- Five years of support
- In order not to delay the initiation of the multi-center clinical study (U01), the peer review and award of grant will be completed within four months of the receipt (Oct 5) of the application when possible.

Development of Disease Biomarkers (PA-06-147)

- Provide resources to validate candidate biomarkers for well-defined human diseases of liver, kidney, urological tract, digestive and hematologic systems, and endocrine and metabolic disorders, diabetes and its complications, and obesity, for which there are no or very few biomarkers, or for which standard biomarkers are currently prohibitively invasive or expensive.
- Specific mention of PSC and AIH
- R01 mechanism (R21 PA expired)
- May have multiple PI's

Pilot and Feasibility Clinical Research Studies in Digestive Diseases and Nutrition (PA-06-301)

- Encourage pilot and feasibility clinical and epidemiological research studies of new therapies or means of prevention of digestive and liver diseases and nutritional disorders associated with digestive and liver diseases.
- R21 mechanism, no preliminary data required
- May request a project period of 2 years with a combined budget for direct costs of up $275,000 for the 2-year period

Pilot and Feasibility Clinical Research Studies in Digestive Diseases and Nutrition (PA-06-301)

- One focus of this funding opportunity is on diseases that ordinarily have little research support because they are uncommon or rare, or difficult to manage, or are not the focus of pharmacological therapy
- Specific mention of AIH and PSC in childhood, as well as use of multicenter consortia

2008 - 2009 Goals

- Activation of all participating centers
- Continued recruitment of participants
- Institute abbreviated data collection to enter subjects diagnosed more than 5 years ago
- System of recruitment of subjects outside of participating centers
- Functioning repository ASAP
- Complete site training for liver pathologists
- Submission of NIH grant applications

2008 - 2009 Goals

- Explore funding for genetic studies and collaboration with other groups to power genome-wide association studies with case controls
- Submit abstract for AASLD annual meeting (Data closure: May 9, 2008; Abstract deadline: June 5, 2008)
- Publications Committee to develop the annual report template (Data closure: December 31, 2008)

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Studies of Primary Sclerosing Cholangitis

Biliary Tree Findings In Participants with Abnormal Biliary Tree By Disease Classification

	Large Duct PSC		PSC (Ped)	
	N	%	N	%
Total	**20**	**100.0**	**5**	**100.0**
Stricture (Yes)	16	80.0	2	40.0
Beading				
Missing	0	0.0	1	20.0
Yes	10	50.0	1	20.0
Stone (Yes)	2	10.0	0	0.0
Sludge (Yes)	1	5.0	0	0.0
Mass (Yes)	0	0.0	0	0.0

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