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PEDIATRIC ACUTE RECURRENT AND CHRONIC PANCREATITIS: LESSONS FROM INSPPIRE

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Abstract

Importance—Pediatric acute recurrent pancreatitis (ARP) and chronic pancreatitis (CP) are poorly understood.

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Objective—To characterize and identify risk factors associated with ARP and CP in childhood.

Design—A multinational cross-sectional study of children with ARP or CP at the time of enrollment to INSPPIRE (International Study Group of Pediatric Pancreatitis: In Search for a CuRE) study.

Setting—Participant institutions of the INSPPIRE Consortium.

Participants—From September 2012 to February 2015, 155 children with ARP and 146 with CP (≤ 19 years of age) were enrolled. Their demographic and clinical information were entered into the REDCap database at fifteen centers.

Interventions—None.

Main Outcomes and Measures—A cross-sectional study of the cohort was performed to assess demographics, risk factors, abdominal pain and disease burden. Differences were analyzed using two-sample t-test or Wilcoxon-rank sum test for the continuous variables, and Pearson Chi-square or Fisher's exact test for categorical variables. Disease burden variables (pain variables, hospital/ER visits, missed school days) were compared using Wilcoxon rank-sum test.

Results—The majority of children with CP reported prior recurrent episodes of acute pancreatitis. Gender distribution was similar between the groups. ARP was more common in Hispanics, CP in non-Hispanics. Forty-eight percent of patients with ARP versus 73% of patients with CP had at least one gene mutation in pancreatitis-related genes (p=0.0002). Children with *PRSS1* or *SPINK1* mutations were more likely to present with CP compared with ARP (p<0.0001 and p<0.05 respectively). Obstructive (~30% of patients) and toxic/metabolic risk factors (~20% of patients) did not differ between children with ARP or CP. Pancreatitis-related abdominal pain was a major complaint in 81% of children with ARP or CP within the last year. The disease burden was higher in CP compared with ARP (more ER visits, hospitalizations, missed school days, medical, endoscopic and surgical interventions).

Conclusions and Relevance—Genetic mutations are common in both ARP and CP. Ethnicity and mutations in *PRSS1* or *SPINK1* genes may influence the development of CP. The high disease burden in pediatric CP underlines the importance of identifying predisposing factors for progression of ARP to CP in children.

Acute recurrent pancreatitis (ARP) and chronic pancreatitis (CP) are poorly understood conditions of childhood. [1] Single-center studies estimate that 9–35% of children with acute pancreatitis (AP) suffer from recurrent episodes[2–5] and the incidence of CP is ~0.5 per 100,000 persons per year in young adults.[6,7]

Factors that predispose children to recurrent attacks of AP and progression from ARP to CP are unknown. Although alcohol and smoking have long been recognized as major risk factors for ARP and CP in adults [8], they are uncommon in the pediatric age group. Recent single-center studies have identified several genetic risk factors in children with ARP or CP [4,5,9–14], including mutations in *cystic fibrosis transmembrane conductance regulator (CFTR), cationic trypsinogen (PRSS1), pancreatic secretory trypsin inhibitor (SPINK1), chymotrypsin C (CTRC)* and *carboxypeptidase 1 (CPA1)* genes. Other risk factors include obstructive, traumatic, infectious and metabolic causes.[15,16]

Most of our current knowledge on ARP and CP comes from studies in adults. Since the etiologies of these diseases differ greatly between children and adults, applying the knowledge on the natural history and management of these diseases from adults to children may be inappropriate. The international, multi-center INSPPIRE (International Study Group of Pediatric Pancreatitis: In Search for a CuRE) consortium was created to address this issue by collecting data on the largest group of pediatric patients with ARP or CP to date.[10,17] We have recently reported that genetic and obstructive factors are common in children with CP and the associated disease burden is substantial.[10]

In this study, we analyzed the demographic and clinical characteristics of children with ARP and CP with the goal to identify the risk factors and disease burden.

Methods and Statistics

Study design and participants

Demographic and clinical data were collected in patient/parent and physician questionnaires on children who fulfilled the criteria for ARP or CP from 15 institutions and were ≤19 years of age at the time of enrollment [10,17] ARP was defined as 2 episodes of AP along with resolution of pain (≥ 1 month between episodes) OR normalization of pancreatic enzymes and resolution of pain in between episodes irrespective of time interval. [1] Diagnosis of CP required at least one of the following: abdominal pain plus imaging findings suggestive of chronic pancreatic damage OR exocrine pancreatic insufficiency and imaging findings OR endocrine pancreatic insufficiency and imaging findings. [1] Information was entered into the REDCap™ (Research Electronic Data Capture, Vanderbilt University) database from September 2012 to February 2015, and represented baseline information of the INSPPIRE cohort. All centers obtained Institutional Review Board approval or the equivalent for their country. Seventy-six of the CP subjects were reported in a previous study. [10] We included patients with cystic fibrosis (CF) if they were pancreatic sufficient and having recurrent attacks of acute pancreatitis.

Statistical analysis

Summary statistics were presented as mean with standard deviation (SD), median with interquartile range (IQR), or frequency count with percentage. Subject characteristics, risk and clinical variables were compared between ARP and CP using two-sample t-test or Wilcoxon-rank sum test for the continuous variables, Pearson Chi-square or Fisher's exact test for categorical variables. The results from these statistical tests were reported as difference of means or medians and odds ratio, respectively, with corresponding 95% confidence interval and p-value. A p-value <0.05 was considered statistically significant.

Results

Subject characteristics

Of the 301 patients in the INSPPIRE database, 155 patients met the criteria for ARP and 146 for CP. Demographics of these patients (Table 1) and their distribution across INSPPIRE centers are shown (eTable1). Gender distribution was similar between the groups (57%

female); the majority was white (67% ARP, 76% CP). Children with CP tended to be older at the time of first diagnosis of pancreatitis compared with ARP (10.2±4.5 y/o for CP vs. 9.1±5.0 y/o for ARP; p=0.06). Of the 146 children with CP, 123 (84%) had documented prior episodes of ARP. The date of first AP attack and date of CP diagnosis used to calculate time for progressing from ARP to CP were available in 76 of 123 subjects; the median time was 1 year (interquartile range 1.5 months-2.7 years; range 0–14.3 years).

Family history of AP was similar between the groups, but patients with CP were more likely to have a positive family history of CP (36% in CP vs. 16% in ARP, p <0.0002). CP was less common in Hispanic ethnicity (eTable2).

Risk factors

Risk factors were divided into four categories, genetic *(CFTR, SPINK1, PRSS1, CTRC),* obstructive, toxic/metabolic and autoimmune. At least one risk factor was identified in 111 patients with ARP (72%) and 125 patients with CP (86%). The most common risk factors for development of ARP or CP were genetic and obstructive (Table 2).

Forty-nine of the 102 patients with ARP (48%) and 86 of 118 patients with CP (73%) were positive for at least one gene mutation (p=0.0002). Of the 53 patients with ARP in whom no mutations were identified, 18 were screened for 2 or fewer gene mutations. Of the 32 patients with CP who had no identified mutations, 6 were tested for less than 3 gene mutations.

CFTR was the most common mutation identified in ARP (34%), *PRSS1* in CP (46%). Six children in ARP group had CF as determined with 2 *CFTR* disease causing mutations and/or abnormal sweat chloride; and 2 children in CP group had CF. Children with *PRSS1* or *SPINK1* mutations were more likely to present with CP compared to ARP (p<0.0001 and p=0.039 respectively).

Some children had more than one genetic risk factor. If ≥3 genes were tested, 8/84 patients with ARP (9.5%) and 17/112 patients with CP (15%) had more than one genetic risk factor. *CFTR* and *SPINK1* combination was most common (found in 5 children with ARP and 9 with CP).

Obstructive risk factors were found in 33% of patients with ARP or CP; toxic/metabolic factors were found in 21% (Table 2). Pancreas divisum (PD) was present in 9% of children with ARP and 16% of CP. PD was less frequent with *PRSS1* mutations (eTable3). Obstructive and autoimmune risk factors were not significantly different between children with ARP and CP. Toxic/metabolic factors (26% in ARP vs. 16% in CP, p<0.05) and specifically medications (i.e. azathioprine and 6-mercaptopurine, 18% in ARP vs. 5% in CP, p=0.005) were more common in ARP. Alcohol (1%) and cigarette smoking (4%) were uncommon in pediatric ARP or CP. Sixteen children with ARP and fourteen children with CP were diagnosed with autoimmune pancreatitis (AIP). Only one child with CP had elevated IgG4, consistent with Type I AIP.

Children with ARP or CP often had multiple risk factors. At least one risk factor was identified in 111 (72%) of 155 patients with ARP, and 47/155 (30%) had multiple risk

factors from different categories present. In the remaining 44 patients, only 8 were evaluated for all 4 genes and other risk factors. Of the 146 patients with CP, at least 1 risk factor was identified in 125 (86%) and 40 (27%) had multiple risk factors present. In the remaining 28 patients, only 4 tested negative for all 4 genetic as well as other risk factors.

Burden of disease

Pancreatitis-related abdominal pain was a major complaint in 81% of children with ARP or CP within the last year. The pain was mostly episodic in both groups (Table 3). Although constant and episodic pain scores were slightly higher in CP, the differences were not significant. The numbers of ER visits and hospitalizations were higher in patients with CP compared with ARP ($p<0.01$), but no differences were found between groups for ER visits and hospitalizations within the past year (Table 3).

Table 4 summarizes all imaging studies performed on children with ARP or CP. Overall, imaging studies were more frequently ordered for CP compared to ARP; magnetic retrograde cholangiopancreatography (MRCP) was the most commonly employed imaging modality; some children with CP had up to 9 endoscopic retrograde cholangiopancreatography (ERCP) since their diagnosis. As expected, children with ARP had findings consistent with AP (pancreas enlargement, focal AP, inflammatory changes) compared to children with CP who had evidence of persistent pancreatic injury (atrophy, calcifications, ductal irregularities/obstruction/dilatation/stones, abnormal side branches).

Children with CP were more likely to receive medical, endoscopic and surgical therapies compared with ARP (Table 5). Medical therapy primarily consisted of pain medications and pancreatic enzymes. Acetaminophen and ibuprofen were the leading pain medications for ARP while patients with CP utilized acetaminophen and hydrocodone for pain. Therapeutic ERCP was performed in only 14% of children with ARP compared with 67% of CP. The most common type of surgery for pediatric ARP was cholecystectomy: 8 were done for pain, three for recurrent acute pancreatitis and one for both pain and recurrent pancreatitis. Pain did not resolve after cholecystectomy (0/9 patients); recurrent pancreatitis resolved in 2 of 4 patients. Lateral pancreaticojejunostomy, partial total pancreatectomy, total pancreatectomy/islet cell autotransplantation and celiac plexus block were exclusively performed in CP.

Discussion

This international, multicenter study is the largest characterized cohort of children with ARP and CP, and it is the first observational study comparing a large number of children with ARP to children with CP. The majority of children with CP described a prior history of ARP and tended to be older at the time of diagnosis compared to those children with ARP, suggesting that ARP and CP are a disease continuum. A large proportion of children with ARP or CP had multiple risk factors, suggesting the multifactorial nature of these conditions. The clustering of *PRSS1* or *SPINK1* mutations in children with CP raises the possibility that these gene mutations are important risk factors for progression from ARP to CP in the pediatric population. The disease burden was higher in CP compared with ARP, suggesting the importance of identifying early interventions to prevent or delay progression from ARP to CP.

Among the risk factors analyzed, an underlying genetic predisposition was most commonly found in our patients, almost 50% in ARP and approaching 75% in CP. Our findings agree with previous reports showing genetic mutations as common risk factors in children with ARP or CP.[9,12,14,18,19] We may be underestimating the impact of gene mutations as risk factors for ARP or CP, since we do not have analysis of the most commonly tested genes (*PRSS1, CFTR, SPINK1, CTRC*) for every subject in the database, because gene testing for INSPPIRE patients was at the provider's discretion. Some of the newly discovered pancreatitis susceptibility genes also were not tested, as they were not commercially available (*CPA1, CLDN2, CEL, CEL-HYB).*[11,20–22]

The natural history of pediatric pancreatitis has not been systematically investigated in children. Most of the data in adults that support progression of ARP to CP come from hereditary pancreatitis populations.[27,28] Indeed, pancreatitis follows a severe course in patients with *PRSS1* mutations (particularly R122H and N29I) with first attacks by approximately 10 years of age and progression to CP within the subsequent decade. Our findings support the hypothesis that *PRSS1* is involved in progression from ARP to CP in children as well.

The role of *SPINK1* mutations as a cause of pancreatitis is debated because these mutations can be found in 1–3% of the general population. We report a higher percentage of *SPINK1* mutations in the INSPPIRE cohort (13% ARP; 25 % CP). Similarly, *SPINK1* N34S mutations have been found in ~25% of children with ARP or CP, a higher percentage compared with the general population [12,19,29]. In addition, people with *SPINK1* mutations are more prone to ARP or CP if mutations in other pancreatitis-relevant genes are also present (i.e. *PRSS1, CFTR, CTRC*), with up to 900-fold increased risk by having both *CFTR* and *SPINK1* mutations [30–32]. In our cohort, *CFTR* and *SPINK1* were commonly associated. Taken together, *SPINK1* mutations (alone or in combination with other risk factors) may be playing a role in pediatric ARP/CP development.

We found pancreas divisum (PD) in 9–16% of children with ARP and CP, similar to the frequency found in autopsy studies (5–10%) [33]. PD was associated with decreased frequency in children with *PRSS1* mutations. The majority of studies reporting association of PD with ARP or CP, similar to this study, are based on symptomatic patients who had imaging studies done for the evaluation of pancreatitis. The involvement of PD in the pathogenesis of ARP or CP needs to be further studied.

We found that a large subset of children with ARP or CP had more than one identifiable risk factor including patients with more than one risk factor in a single category (genetic factors), and patients with a combination of factors across categories. Our observations are consistent with previous studies suggesting that the pathogenesis of ARP or CP is multifactorial.

We observed that the majority of children with ARP and CP were white and CP was less common in patients with Hispanic ethnicity. This is likely due to genetic mutations found in Caucasians and not referral bias in our study. In a recent analysis of two large national databases that included over 1.5 million hospitalized US children, CP was also found more

commonly in whites [34]. The possible reduced risk noted in our pediatric Hispanic population may be explained by the lower prevalence of *PRSS1* and *SPINK1* mutations in this group.

Most of the children in our study reported pancreatitis-related pain within the previous year; in one-third pain was chronic. The disease burden was higher in the CP group compared with ARP (more ER visits and hospitalizations; more missed school days; and more medical, endoscopic and surgical therapies). Pancreatitis causes a serious burden on the healthcare system with AP being the number one gastrointestinal cause for admission in adults.[35] With increasing incidence of AP in childhood [36,37], we expect that the disease burden in our cohort is substantial.

We were surprised by the large number of children with AIP in our cohort. The diagnosis of AIP in the medical literature is limited to few case reports. [38] As previously reported, the majority of children with AIP in our study had Type II. Our future goal is to develop diagnostic and therapeutic criteria for pediatric AIP. These guidelines will be aimed to better phenotype children in our database, as well as to bring a unifying definition to this disease.

Our study has several limitations. The prevalence of genetic predisposing factors was underestimated because not every subject underwent genetic testing and when they did, it was not always complete. Newly identified pancreatitis-associated genes could not be identified in our population, as tests are not commercially available. Moving forward, we plan to test INSPPIRE patients for all pancreatitis-relevant genes. While we acknowledge a potential referral bias from large referral centers in our study, we would like to point out that a center that performed most islet cell transplants (University of Minnesota) contributed ~10% to our cohort (eTable 1). The analysis of children with ARP or CP was done at the time of enrollment; therefore assessment of risk factors could not be done over time as children progressed from ARP to CP. Nevertheless, the large number of well-phenotyped patients with ARP or CP allowed us to compare the characteristics of these children. Our study is underpowered to study the role of cholecystectomy on relieving recurrent disease. Prospective data collection is more likely to shed light on this question. Through a prospective registry of longitudinal clinical data, INSPPIRE aims to determine the natural course of pediatric ARP and CP and identify risk factors for the progression to CP.

Conclusions

Pancreatitis-associated gene mutations are the most common risk factors in children with ARP or CP, and multiple risk factors are usually coexistent. The socioeconomic burden of disease is significant given the presence of pain, health care visits and number of diagnostic tests performed. Further work will focus on analyzing the impact of genetic and other risk factors on the natural history of pediatric pancreatitis and its sequelae and developing a standardized approach to the evaluation of children with ARP or CP.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographics

	ARP (n=155)	CP (n=146)	Mean Difference (CP-ARP) or Odds Ratio CP (with 95% CI)
Gender (Female)	88 (57%)	84 (57%)	OR: 1.03 (0.65, 1.63)
Age at enrollment	11.3±4.8	12.6±4.2	1.3 (0.3, 2.3)
Age at diagnosis	9.1±5.0	10.2±4.5	1.1 (−0.1, 2.3)
Ethnicity	(n=145)	(n=131)	
Hispanic	41 (28%)	22 (17%)	OR: 0.51 (0.29, 0.92)
Race	(n=138)	(n=138)	
White	112 (81%)	102 (80%)	OR(vs. non-white): 0.94 (0.51,1.74)
Multi-racial	12 (9%)	8 (6%)	
African American	5 (4%)	5 (4%)	
Asian	7 (5%)	7 (6%)	
Other	2 (1%)	5 (4%)	
BMI percentile	65.1±33.6	60.3±30.6	−4.8 (−12.2, 2.5)

Values are represented as Frequency (%) or Mean ± SD. Statistically significant differences are shown in bold. The differences in numbers between rows reflect available data for these parameters.

Table 2

Risk Factors for ARP in comparison to CP

	ARP (N=155) N (%)	CP (N=146) N (%)	Odds Ratio CP (95% CI)
Genetic	49/102 (48)	86/118 (73)	2.91 (1.66, 5.10)
CFTR	30/89 (34)	24/104 (23)	0.59 (0.31, 1.11)
PRSS1	15/88 (17)	50/108 (46)	4.20 (2.14, 8.22)
SPINK1	10/78 (13)	25/99 (25)	2.30 (1.03, 5.13)
CTRC	5/48 (10)	4/73 (5)	0.50 (0.09, 2.47)
Obstructive	50/152 (33)	47/144 (33)	0.99 (0.61, 1.61)
Pancreas Divisum	13/146 (9)	22/140 (16)	1.91 (0.92, 3.95)
Gallstones	9/147 (6)	6/139 (4)	0.69 (0.24, 2.00)
Pancreaticobiliary Malunion	7/146 (5)	6/139 (4)	0.90 (0.29, 2.73)
Biliary Cyst	5/148 (3)	2/141 (1)	0.41 (0.04, 2.57)
Sphincter of Oddi Dysfunction	5/144 (3)	2/139 (1)	0.41 (0.04, 2.54)
Annular Pancreas	3/148 (2)	1/141 (1)	0.35 (0.01, 4.37)
Autoimmune	16/112 (14)	14/108 (13)	0.89 (0.41, 1.93)
Toxic/Metabolic	39/152 (26)	22/137 (16)	0.55 (0.31, 0.99)
Medications	19/108 (18)	4/87 (5)	0.23 (0.07, 0.69)
Passive Smoking Exposure	12/140 (9)	12/129 (9)	1.09 (0.47, 2.53)
Hypertriglyceridemia	9/104 (9)	2/78 (3)	0.28 (0.03, 1.41)
Chronic Kidney Disease	3/111 (3)	1/91 (1)	0.40 (0.01, 5.10)
Alcohol	2/150 (1)	5/137 (4)	2.80 (0.45, 29.80)
Active Smoking	1/150 (1)	3/137 (2)	3.34 (0.26, 176.27)

Statistically significant differences are shown in bold. The differences in numbers between rows reflect available data for these parameters.

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Table 3

Burden of ARP or CP in Children

	ARP (n=155)	CP (n=146)	Median Difference (CP-ARP) with 95% CI
Pattern of abdominal pain	(n=142)	(n=127)	
- No abdominal pain	18 (13%)	17 (13%)	
- Usually pain free; episodes of mild-moderate pain	21 (15%)	19 (15%)	
- Constant mild-moderate pain	7 (5%)	4 (3%)	OR constant+ severe pain: 1.50 (0.89, 2.51)
- Usually pain free; episodes of severe pain	57 (40%)	39 (31%)	
- Constant mild-moderate pain + episodes of severe pain	31 (22%)	40 (32%)	
- Constant severe pain	8 (6%)	6 (6%)	
Constant Pain score	(n=134)	(n=116)	
Median (IQR)	0 (0–0)	0 (0–15)	OR any constant pain 1.38 (0.76, 2.50)
Range	0–100	0–99	
With any level of constant pain	27 (20%)	30 (26%)	
Episodic Pain score	(n=128)	(n=113)	
Median (IQR)	61 (0–82.5)	70 (37–89)	9.0 (−0.5, 18.5)
Range	0–100	0–100	
With any level of episodic pain	92 (72%)	89 (79%)	
Number of ER visits -- lifelong	(n=129)	(n=114)	
Median (IQR)	2 (1–4)	4.5 (1–10)	2.5 (1.4, 3.6)
Range	0–30	0–300	
Number of ER visits – past year	(n=130)	(n=108)	
Median (IQR)	1.5 (1–2)	2 (0–3)	0.5 (−0.2, 1.2)
Range	0–12	0–20	
Number of hospitalizations -- lifelong	(n=133)	(n=117)	
Median (IQR)	2 (1–4)	4 (1–8)	2.0 (1.0, 3.0)
Range	0–30	0–300	
Number of hospitalizations – past year	(n=132)	(n=111)	0 (−0.7, 0.7)

	ARP (n=155)	CP (n=146)	Median Difference (CP-ARP) with 95% CI
Median (IQR)	1 (1–2)	1 (0–3)	
Range	0–9	0–23	
Days missed school past month	(n=117)	(n=103)	
Median (IQR)	0 (0–5)	2 (0–6)	2 (0.2, 3.8)
Range	0–31	0–40	

Table 4

Imaging Findings in pediatric ARP or CP*

	ARP (n=155)	CP (n=146)	Odds Ratio CP (95% CI)
Imaging studies performed			
ERCP	25 (16%)	97 (66%)	10.29 (5.95, 17.82)
Number ERCP (range)	(1–7)	(1–9)	
1	20	66	
2	3	18	
3	0	6	
≥4	2	7	
CT scan	65 (42%)	88 (60%)	2.10 (1.33, 3.33)
MRI only	40 (26%)	52 (36%)	1.59 (0.97, 2.61)
MRCP	90 (58%)	111 (76%)	2.29 (1.39, 3.76)
EUS	4 (3%)	27 (18%)	8.56 (2.92, 25.15)
Findings (CT/MRI)			
Focal acute pancreatitis	19/96 (20%)	18/123 (15%)	0.65 (0.34, 1.41)
Inflammatory changes	41/98 (42%)	48/124 (39%)	0.88 (0.51, 1.51)
Gland enlargement	35/98 (36%)	19/124 (15%)	0.33 (0.17, 0.62)
Pancreatic atrophy	6/101 (6%)	47/123 (38%)	9.79 (3.97, 24.12)
Calcifications	0/99 (0%)	17/123 (14%)	32.70 (1.94, 551.00)**
Duct irregularities	11/102 (11%)	67/122 (55%)	10.08 (4.90, 20.71)
Pancreatic duct dilatation	9/101 (9%)	74/122 (61%)	15.76 (7.26, 34.20)
Lesions in the pancreas	1/103 (1%)	7/127 (6%)	5.95 (0.74, 270.74)
Gallstones/Sludge	5/100 (5%)	9/124 (7%)	1.49 (0.48, 4.59)
Intrahepatic biliary dilatation	8/98 (8%)	15/124 (12%)	1.58 (0.63, 3.82)
Evidence for liver disease	7/101 (7%)	8/122 (7%)	0.94 (0.33, 2.69)
Findings (CT/MRI/ MRCP/ ERCP)			
Pancreatic duct obstruction (stricture)	3/110 (3%)	39/135 (29%)	14.49 (4.34, 48.41)
CBD stricture (Intrapancreatic portion)	4/125 (3%)	7/142 (5%)	1.57 (0.45, 5.49)
Dilated CBD	13/126 (10%)	35/143 (24%)	2.82 (1.41, 5.61)

	ARP (n=155)	CP (n=146)	Odds Ratio CP (95% CI)
CBD Stone	7/126 (6%)	11/143 (8%)	1.42 (0.53, 3.77)
Findings (CT/MRI/ EUS)			
Peripancreatic inflammation/fat stranding	31/97 (32%)	47/121 (39%)	1.35 (0.77, 2.37)
Findings (CT/MRI/MRCP/ ERCP /EUS)			
Cysts/Pseudocysts	9/129 (7%)	28/142 (20%)	3.27 (1.48, 7.24)
Findings (MRCP/ERCP)			
Main pancreatic duct - Abnormal	16/92 (17%)	97/130 (75%)	13.96 (7.16, 27.24)
Abnormal side branches	4/92 (4%)	56/123 (46%)	18.39 (6.35, 53.23)
Intraductal filling defects or Calculi	1/92 (1%)	36/126 (29%)	36.40 (4.89, 271.19)
Pancreas Divisum	11/92 (12%)	19/126(15%)	1.31 (0.59, 2.90)

* Imaging findings include results from all studies combined

** When there are zero cells, OR was computed based on the logit estimate that used a correction of 0.5 in every cell

Table 5

Treatments for pediatric ARP and CP

	ARP (n=155)	CP (n=146)	Odds Ratio CP (95% CI)
Medications			
Pain medications	41/115 (36%)	62/109 (57%)	2.38 (1.39, 4.08)
Medical therapies	44/149 (30%)	101/140 (72%)	6.18 (3.71, 10.29)
Pancreatic enzymes	32/149 (21%)	82/139 (59%)	5.26 (3.14, 8.82)
Vitamins/anti-oxidants	12/145 (8%)	20/134 (15%)	1.94 (0.91, 4.15)
Steroids	0/143 (0%)	8/135 (6%)	19.13 (1.09, 334.81)**
Octreotide	2/147 (1%)	5/135 (4%)	2.79 (0.45, 29.65)
Procedures			
Any ERCP	21/152 (14%)	96/142 (68%)	13.02 (7.29, 23.34)
Biliary sphincterotomy	11/151 (7%)	36/136 (26%)	4.58 (2.23, 9.44)
Pancreatic duct stent	6/151 (4%)	60/137 (44%)	18.83 (7.78, 45.56)
Biliary stent	2/151 (1%)	11/138 (8%)	6.45 (1.40, 29.65)
Pancreatic duct stone removal	1/151 (1%)	30/137 (22%)	42.06 (5.65, 313.17)
Surgeries			
Surgical therapies	18/149 (12%)	53/143 (37%)	4.29 (2.36, 7.80)
Cholecystectomy	15/148 (10%)	28/143 (20%)	2.16 (1.10, 4.24)
Celiac plexus block	0/149 (0%)	4/142 (3%)	9.71 (0.52, 182.09)**
Cyst/pseudo-cyst operation	3/149 (2%)	5/142 (4%)	1.78 (0.42, 7.57)
Lateral pancreaticojejunostomy	0/149 (0%)	13/142 (9%)	31.17 (1.83, 529.49)**
Partial pancreatectomy	0/149 (0%)	2/142 (1%)	5.32 (0.25, 111.79)**
Total pancreatectomy/islet autotransplant	0/148 (0%)	29/143 (20%)	76.52 (4.63, 1265.67)**

Statistically significant differences are shown in bold. The differences in numbers between rows reflect available data for these parameters.

** When there are zero cells, OR was computed based on the logit estimate that used a correction of 0.5 in every cell