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CLINICAL AND PRACTICE VARIATIONS IN PEDIATRIC ACUTE RECURRENT OR CHRONIC PANCREATITIS: REPORT FROM THE INSPPIRE STUDY

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Abstract

Objective: To determine whether clinical characteristics and management of pediatric acute recurrent pancreatitis (ARP) and chronic pancreatitis (CP) differ across INSPPIRE (**IN**ternational **S**tudy Group of **P**ediatric **P**ancreatitis: **I**n Search for a Cu**RE**) sites.

Study Design: Data were collected from INSPPIRE and analyzed per US regions and "non-US" sites. Between-group differences were compared by Pearson Chi-Square test. Differences in disease burden were compared by Kruskal-Wallis test.

Results: Of 479 subjects, 121 (25%) were enrolled in West, 151 (32%) Midwest, 45 Northeast (9%), 78 (16%) South and 84 (18%) at non-US sites. Hispanic ethnicity was more common in South ($p<0.0001$); white race in Northeast ($p=0.009$). CP was less common and time from diagnosis of first acute pancreatitis to CP was longer in children at non-US sites ($p=0.0002$ and $p=0.011$ respectively). Genetic mutations were most common among all groups; *PRSS1* variants predominated in Midwest ($p=0.002$). Gallstones were more frequent in South ($p=0.002$). ERCP and CT imaging were more commonly utilized in US compared to non-US ($p<0.0001$), but there were no differences in the use of MRI/MRCP. Disease burden was highest in the West and Midwest, possibly because total pancreatectomy and islet autotransplantation (TPIAT) referral sites were located in these regions. All therapies were less commonly administered in non-US sites ($p<0.0001$).

Conclusion: This is the first study to describe geographical variations in the INSPPIRE cohort, which possibly reflect variations in practice and referral patterns. The underlying reason behind the lower frequency of CP and fewer treatments in non-US sites need to be further explored.

Keywords

pediatric pancreatitis; acute recurrent pancreatitis; chronic pancreatitis; pancreas; pancreatic disease

INTRODUCTION

Pancreatitis is increasingly recognized in childhood (1, 2). Most children with acute pancreatitis (AP) completely recover. Some develop recurrent attacks of acute pancreatitis or acute recurrent pancreatitis (ARP) and some have irreversible changes in their pancreas

consistent with chronic pancreatitis (CP) (3, 4). Risk factors predisposing children to early onset CP and its sequelae are the focus of an ongoing longitudinal National Institute of Health INSPPIRE 2 (**IN**ternational **S**tudy Group of **P**ediatric **P**ancreatitis: **I**n search for a cu**RE**) Cohort Study within Consortium for the Study of Chronic Pancreatitis, Diabetes and Pancreatic Cancer (CPDPC) (5).

Through INSPPIRE, we demonstrated the importance of genetic risk factors, high disease burden and influence of certain mutations, anatomical variants or age of disease onset on disease outcome and behavior in pediatric ARP and CP (1, 2, 6, 7).

Genetic risk factors are most prevalent among children with ARP and CP all around the world, although there are variations in the type of genes or type of variants within the genes (8–14). Three single center studies suggest that frequencies of pancreatitis-associated gene mutations vary even within the US (15–17). It is unknown whether different risk factors and/or institutional practices influence pancreatic disease behavior and outcomes.

In this study, we aimed to identify variations in demographics, risk factors, management and outcomes of pediatric ARP and CP across the different geographical regions within the INSPPIRE cohort. Our findings are consistent with various risk factors and practices among different regions that may potentially affect the disease outcome. As we start to better identify phenotypic and genotypic characteristics of the pediatric cohorts, understand institutional practices and streamline management protocols, we may be able to apply personalized medicine to individual patients and improve outcomes of children with ARP and CP.

MATERIALS AND METHODS

Study design and participants

Clinical information including demographics, past medical history, family and social history, medications, hospitalizations, risk factors, diagnostic work-up, treatment modalities and outcome information were obtained from children with ARP or CP aged ≤ 19 years enrolled at the 20 participating INSPPIRE centers using a protocol described previously (3). ARP was diagnosed based on at least 2 episodes of AP separated by at least 4 weeks between these episodes with resolution of pain (18). CP was diagnosed based on at least one of the following: (i) abdominal pain with imaging findings of chronic pancreatitis; (ii) exocrine pancreatic insufficiency and imaging findings of chronic pancreatitis; (iii) endocrine pancreatic insufficiency and imaging findings of chronic pancreatitis (18).

All information was collected through standardized patient and physician questionnaire forms and entered into REDCap (Research Electronic Data Capture, Vanderbilt University, Nashville Tennessee) at all centers from March 2012 to February 2017. All centers obtained institutional review board approval for this study. or the equivalent for their country prior to enrolling subjects. Consent was obtained from the parents of participants less than 18 years and directly from participants 18 years or older. Children gave assent at the age specified by the local institutional review board.

Regions were determined by United States census region (Northeast, Midwest, South, and West) of the INSPPIRE center at which the patient was enrolled. Briefly, the Northeast region included sites in Pennsylvania and Massachusetts; Midwest sites in Iowa, Indiana, Minnesota, Ohio, Missouri and Wisconsin; South sites in Texas; West sites in California, Utah and Washington states. The other centers in the following cities (Toronto, Montreal, Sydney and Jerusalem) were grouped as “non-US sites”.

Statistical analysis

Summary statistics were presented as mean with standard deviation (SD), median with interquartile range (IQR), or frequency count with percentage. Pearson Chi-Square test was used to compare categorical variables and between group differences, ANOVA was used for age, Log-rank test was used for time from AP to CP development. Kruskal-Wallis test was used to compare differences in the disease burden among regions. A p-value <0.05 was considered statistically significant.

RESULTS

Patient Characteristics

Out of 479 participants; 212 had CP (44%), 267 ARP (56%); 121 (25%) were enrolled from INSPPIRE sites in the West, 151 (32%) Midwest, 45 (9%) Northeast, 78 (16%) South and 84 (18%) “non-US sites”. Demographics of these patients and their distribution across INSPPIRE regions are shown in Table 1. Sex distribution was similar between the groups and mostly female. Hispanic ethnicity predominated in the South ($p < 0.0001$), White race in the Northeast. Children were older at the time of enrollment in the Midwest ($p = 0.038$). CP diagnosis was less common and time from diagnosis of first AP to CP was longer in children in the non-US sites (p=0.0002 and p=0.011, respectively).

Risk Factors

Risk factors were evaluated under four categories, genetic *(CFTR, SPINK1, PRSS1, CTRC)*, obstructive, toxic/metabolic and autoimmune (Table 2). Genetic mutations were the most common risk factors across all regions. *PRSS1* mutations predominated in the Midwest ($p < 0.01$) vs obstructive risk factors being most common in the South ($p = 0.002$). Gallstones were a prominent obstructive risk factor in the South (p=0.001). Functional pancreatic sphincter dysfunction and duct obstruction were also more common in the South (p=0.040 and p=0.015, respectively). Tobacco exposure (active or passive) was described more frequently in the non-US sites and in the South (p= 0.007). There were no differences in autoimmune factors across regions.

Imaging Findings

We next examined the utilization of imaging studies across the pediatric sites and whether findings were consistent with chronic pancreatitis. Table S1 summarizes results of all imaging studies in all participants at the time of enrollment. Endoscopic retrograde cholangiopancreatography (ERCP) and computed tomography scan (CT) imaging were more commonly done in the US (p<0.0001 for both), but there was no difference in magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP)

utilization across regions. There were 349 patients that had at least one MRCP done of the n=479 patients in the study. For these 349 patients, the number of MRCP done for each patient ranged from 1 to 8 MRCP, for a total of 532 MRCP performed. Seventy-one (13%) were done with secretin, 347 (65%) without secretin; in 114 studies secretin use was unknown or not specified (22%). Table S2 shows the use of secretin with Magnetic resonance cholangiopancreatography (MRCP) at all sites. Secretin was more commonly used at Midwest and Northeast sites compared to others. Overall, imaging findings of CP including abnormal main pancreatic duct, side branches, pancreatic duct stones, and pancreatic duct strictures were less common in the non-US sites ($p<0.0001$, $p=0.002$, $p=0.003$ respectively). Fat stranding was also less common in the non-US sites ($p=0.030$), and pancreatic atrophy was less frequent in Northeast ($p=0.028$).

Treatment Modalities

All therapies (medical, endoscopic and surgical) were mostly utilized in the US when compared to the non-US sites ($p < 0.0001$ for all) (Table 3). Medical therapies mostly included pancreatic enzymes for replacement or pain, pain medications (narcotic and non-narcotic), multivitamins/antioxidants. Steroids and octreotide were uncommonly used, and their usage was not different across the sites. Pain medications and vitamins/antioxidants were least reported by patients in the South when compared to others ($p<0.0001$ and $p=0.001$, respectively).

All endoscopic therapies were less commonly done by non-US sites. Specifically, biliary sphincterotomy, pancreatic sphincterotomy and pancreatic duct stent placements were the less commonly performed procedures at non-US sites when compared to regions within the US ($p <0.0001$ for all). Biliary duct stent placement was not a common procedure overall, and pancreatic duct stone removal was uncommon in the Northeast and non-US sites ($p=0.0003$). No cholecystectomy was recorded at non-US sites ($p=0.0003$). Total pancreatectomy and islet autotransplantation (TPIAT) was mainly reported at Midwest sites where two large referral sites (Cincinnati and Minnesota) are located ($p <0.0001$).

Disease Burden

Table 4 summarizes disease burden across INSPPIRE sites including pain, emergency room visits, hospitalizations, and missed school days. The disease burden was highest in the Midwest and West regions with high constant and episodic pain scores, and reported days missed from school due to pancreatitis. Children at the non-US sites reported less pain overall.

DISCUSSION

This is the first study to describe geographical variations in demographics, risk factors, disease burden and management trends of pediatric ARP and CP. Utilizing the INSPPIRE cohort, we identified several differences across regions that may be associated with risk factors and variations in management. The regional variations may have an impact on disease outcome.

The most interesting finding of this study was the lower number of CP at the non-US sites. Imaging findings consistent with irreversible pancreatic damage (i.e., ductal stones, abnormal side branches) (5) were also uncommon in these children. Interestingly, there was no significant difference in risk factors between these children and others. They had relatively less disease burden, less frequent pain, and underwent fewer medical, endoscopic and surgical therapies, probably because CP was less common at these sites compared to US sites. These children may eventually develop CP, perhaps at a slower rate for unknown reasons.

There were some variations in imaging choices between sites. The non-US sites did not utilize ERCP or CT scan as frequently as the US sites. However, the utilization of MRI or MRCP was similar between the cohorts. MRCP has become the imaging modality of choice to evaluate the pancreatic ductal changes commonly seen in pediatric CP (2, 6). It does not expose children to radiation and it is as accurate as ERCP in evaluating moderate or severe parenchymal changes and performs very well in diagnosing early and mild CP, preferably if done with secretin (19, 20). Secretin use was overall low across all sites, except sites in Midwest where two TPIAT sites were located (Cincinnati and Minnesota) and Northeast. It is also possible that the higher frequency of CP reported at US sites could be secondary to overutilization of ERCP and not the high frequency of CP. Another possibility is the differences in interpretation of radiological studies between US and non-US sites. There is no uniform agreement between radiologists on the interpretation of CP findings in children.

All treatment modalities (medical, surgical, endoscopic) were utilized more commonly in the US when compared to the non-US sites. Likewise, pain (constant pain score) and disease burden (i.e. missed school days) were also significantly less in patients enrolled at non-US sites. It is not known whether a less aggressive approach (fewer interventions/surgeries) would contribute to disease burden and natural history of the disease. Fewer procedures and lower disease burden may be related to lower frequency of CP in children at non-US sites. It is not known whether social and cultural differences and parenting behaviors have an impact on pain at different geographical locations.

This study once again confirmed the dominance of genetic risk factors in pediatric ARP and CP, but have not identified whether they contributed to geographical phenotypic variations. Genetic risk factors, namely *CFTR, PRSS1, SPINK1* and *CTRC* mutations were not different across all regions. Genetic testing across INSPPIRE sites was performed at the clinicians' discretion; therefore, a genetic work-up was not always complete for all patients. Genotyping was done only for four pancreatitis-associated genes, *CFTR, PRSS1, SPINK1* and *CTRC*, but not all recently discovered genes, such as *CPA1, CEL, CEL-HYB, CLDN2*, thus a genetic risk factor could have been missed.

There are geographical variations in genetic risk factors of ARP and CP across the world and even within the US. Overall, *SPINK1* variants are most common in Asia (~30–50%), (9, 21) where *PRSS1* and *CFTR* mutations are relatively rare (8, 9). In German and Polish cohorts, there is an even distribution of gene variants in patients with CP: *PRSS1* variants (8–15%); *SPINK1* ~20%; *CFTR* (all variants) ~5–15% (22, 23). An Italian study reported fewer *SPINK1* mutations (7.1%), *PRSS1* mutations (4.5%), and more frequent *CFTR* mutations

(39.6%) (10) in a pediatric cohort with ARP. In the US, the gene variant frequency varies from site to site. Single center studies from Denver, Cincinnati and Milwaukee reported the following gene mutations in pediatric ARP and CP: *CFTR* (30%, 38%, 48%, respectively); *SPINK1* (4%, 25%, 27%, respectively); *PRSS1* (10%, 4%, 24%, respectively) (15–17). In the INSPPIRE cohort, mutations were reported in the following genes of children with ARP: *CFTR* (34%), *SPINK1* (13%), *PRSS1* (17%), *CTRC* (10%). In the CP group, % patients with *CFTR* mutations was 24%; *SPINK1* (25%); *PRSS1* (46%); and *CTRC* (5%) (1) . Variations in genetic patterns across the world are probably related to race and ethnicity. Patients in the US were similar in sex and race with less Hispanic ethnicity in the Cincinnati group compared to others (15–17). In the current study, most children with *PRSS1* mutations were enrolled in the Midwest region, where two TPIAT-performing sites are located (University of Minnesota and CCHMC). Disease burden was highest in the West and Midwest, possibly because TPIAT referral sites (University of Minnesota, CCHMC, UCSF) were located in these regions. We have not collected the original residence of children enrolled into INSPPIRE, therefore it is not known how many children were referred from certain geographical locations.

A higher risk of CP has been shown in children with *PRSS1, CPA1, CEL, SPINK1* and *CTRC G60G* variants; early onset CP has been associated with *PRSS1* or *SPINK1* variants and pancreatic ductal stones with *SPINK1* mutations (1, 2, 6, 14, 22, 24, 25). Genetic risk factors could not explain the lower frequency of CP at sites Non-US sites. Patients' original location was not queried and the study was not powered to identify the impact of individual gene variants. Going forward, a more detailed analysis of geographical locations and individual gene variants could uncover the role of gene variants on disease behavior.

We observed a much higher percentage of children with Hispanic ethnicity enrolled at the Southern sites where obstructive risk factors and specifically, gallstones were more common. It can be postulated that obesity explains higher risk of gallstones in the South, as we reported a higher percentage of obesity in Hispanic children in the INSPPIRE cohort (26). However, Western sites without a higher risk of gallstones also had a high prevalence of Hispanic children and distribution of BMI at centers with a high prevalence of Hispanic children (Children's Hospital of LA, UCSF, UTSW, Baylor) were not different when compared to other centers (26). It is likely that other factors played a role in the higher percentage of gallstones in the South. Untreated obstructive gallstones can cause recurrent attacks of acute pancreatitis; sludge and gallstones can contribute to perpetuating pancreatic inflammation and cause fibrosis via biliary inflammation, bile and/or pancreatic duct obstruction, papillary stenosis or obstruction (27). Further studies are required to determine the mechanisms involved.

In summary, we have found significant regional differences across INSPPIRE sites including variations in ethnicity, frequency of CP, type of genetic mutations, diagnostic and therapeutic practices and disease burden. The reason for differences between regions is not entirely clear, but probably multifactorial involving various genetic risk factors, referral patterns, and practice differences across sites. The healthcare delivery systems between regions may also have played a role in geographical differences. For example, in contrast to the United States, Canada and Australia have a universal, publicly-funded health care systems. A broader study

involving more US and non-US sites across a wider geographical region, including original location of referred patients, thorough genotyping of the cohorts and broader consensus for imaging diagnosis of CP may better define the impact of risk factors and variations of practices on disease outcome.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What is known?

- Genetic risk factors are most common in pediatric acute recurrent pancreatitis (ARP) and chronic pancreatitis (CP).
- Disease burden is more frequent in children with CP compared to ARP.

What is new?

- We observed regional differences in the INSPPIRE cohort: CP was less frequently diagnosed and all therapies were less frequently utilized at non-US sites; *PRSS1* variants predominated in Midwest; disease burden was highest in West and Midwest; obstructive factors, particularly gallstones were more frequent in South.
- Geographical differences in demographics, risk factors, management trends may have an impact on disease outcomes.

Table 1.

Demographic Characteristics of the INSPPIRE Cohort by Region

	West (n=121)	Midwest (n=151)	Northeast (n=45)	South (n=78)	Non-US sites (n=84)	p-value*
Sex (Female)	73 (60%) (n=117)	86 (57%) (n=128)	26 (58%) (n=43)	46 (59%) (n=71)	42 (50%) (n=83)	0.69
Ethnicity (Hispanic)	41 (35%)	17 (13%)	4 (9%)	40 (56%)	4 (5%)	<0.0001
Race	(n=94)	(n=130)	(n=42)	(n=67)	(n=83)	
White	77 (82%)	112 (86%)	40 (95%)	53 (79%)	59 (71%)	0.009#
Multi-racial	9 (10%)	7 (5%)	1 (2%)	5 (7%)	8 (10%)	
African American	3 (3%)	7 (5%)	0 (0%)	4 (6%)	0 (0%)	
Asian	4 (4%)	3 (2%)	0 (0%)	4 (6%)	10 (12%)	
Other	1 (1%)	1 (1%)	1 (2%)	1 (1%)	6 (7%)	
Age at enrollment						
Mean±SD	11.6±4.5	12.7±4.3	11.1±4.6	11.0±4.5	11.9±4.7	0.038
Age at first diagnosis	(n=105)	(n=144)	(n=41)	(n=73)	(n=77)	
Mean±SD	8.6±4.8	9.2±4.5	8.5±4.5	8.1±4.6	9.9±4.9	0.14
Duration of disease, yrs	(n=98)	(n=132)	(n=35)	(n=70)	(n=80)	
Median (IQR)	1.4 (0.6–4.4)	2.6 (1.0–5.2)	2.2 (1.0–4.8)	2.2 (0.9–4.4)	1.5 (0.7–2.7)	0.031
% Diagnosed with CP	59 (49%)	80 (53%)	19 (42%)	35 (45%)	19 (23%)	0.0002
Age at first diagnosis CP	(n=52)	(n=76)	(n=17)	(n=29)	(n=15)	
Mean±SD	9.8±4.3	10.7±4.1	9.0±4.5	9.4±4.4	12.3±3.3	0.11
Time from AP to CP, yrs	(n=100)	(n=135)	(n=40)	(n=69)	(n=80)	
Median (IQR)&	3.0 (0.2–14.3)	2.9 (1.3–7.5)	4.9 (1.7–>13.0)	3.4 (0.7–>8.7)	7.7 (3.7–8.9)	0.011

AP: Acute Pancreatitis; CP: Chronic Pancreatitis

*Categorical variables were compared using Pearson chi-square test; ANOVA for age; Log-rank test for time from AP to CP

#Comparison for race was categorized as White and non-White

&from Kaplan-Meier curve

Table 2.

Risk Factors of ARP and CP by Region

	West (n=121)	Midwest (n=151)	Northeast (n=45)	South (n=78)	Non-US sites (n=84)	p-value*
Genetic mutations	52/76 (68%)	97/122 (80%)	19/31 (61%)	29/62 (47%)	26/42 (62%)	0.0003
PRSS1	19/76 (25%)	52/119 (44%)	9/36 (25%)	11/62 (18%)	9/40 (23%)	0.002
SPINK1	16/72 (22%)	27/111 (24%)	5/30 (17%)	8/58 (14%)	5/36 (14%)	0.41
CFTR	26/72 (36%)	42/113 (37%)	6/32 (19%)	13/60 (22%)	15/54 (28%)	0.10
CTRC	3/43 (7%)	6/89 (7%)	1/11 (9%)	1/39 (3%)	4/28 (14%)	0.48
Obstructive factors	44/121 (36%)	39/150 (26%)	9/45 (20%)	33/77 (43%)	14/80 (18%)	0.001
Pancreas divisum	14/116 (12%)	16/143 (11%)	3/44 (7%)	9/76 (12%)	6/80 (8%)	0.75
Functional pancreatic sphincter dysfunction	1/118 (1%)	1/139 (1%)	1/45 (2%)	5/72 (7%)	3/79 (4%)	0.040
Gallstones	5/119 (4%)	3/146 (2%)	0/45 (0%)	10/74 (14%)	3/79 (4%)	0.002
Pancreaticobiliary malunion	7/118 (6%)	1/144 (1%)	1/45 (2%)	3/74 (4%)	3/80 (4%)	0.19
Traumatic PD stricture	0/118 (0%)	1/146 (1%)	0/44 (0%)	0/75 (0%)	1/80 (1%)	0.84
Duodenal diverticulum	0/119 (0%)	0/144 (0%)	0/45 (0%)	0/76 (0%)	1/80 (1%)	0.43
Duct obstruction	2/119 (2%)	0/146 (0%)	0/45 (0%)	5/76 (7%)	2/80 (3%)	0.015
Annular pancreas	1/120 (1%)	0/145 (0%)	0/45 (0%)	1/76 (1%)	1/80 (1%)	0.79
Biliary cyst	5/120 (4%)	2/147 (1%)	0/45 (0%)	2/76 (3%)	1/80 (1%)	0.39
Toxic/Metabolic factors	18/116 (16%)	35/142 (25%)	7/35 (20%)	24/77 (31%)	24/72 (33%)	0.035
Alcohol	0/121 (0%)	1/148 (1%)	1/44 (2%)	3/78 (4%)	2/84 (2%)	0.15
Tobacco (Active or Passive)	3/116 (3%)	9/142 (6%)	4/43 (9%)	11/75 (15%)	12/79 (15%)	0.007
Hypertriglyceridemia	6/105 (6%)	7/133 (5%)	1/35 (3%)	4/66 (6%)	5/66 (8%)	0.91
Chronic Renal Failure	1/115 (1%)	2/140 (1%)	0/35 (0%)	2/76 (3%)	0/70 (0%)	0.62
Medications	10/112 (9%)	19/143 (13%)	3/35 (9%)	8/74 (11%)	7/65 (11%)	0.83
Autoimmune factors	7/92 (8%)	15/115 (13%)	8/32 (25%)	7/56 (13%)	8/74 (11%)	0.14
Autoimmune pancreatitis	2/93 (2%)	3/113 (3%)	2/35 (6%)	1/52 (2%)	3/74 (4%)	0.84
Other autoimmune diseases	5/118 (4%)	12/136 (9%)	6/39 (15%)	6/75 (8%)	6/79 (8%)	0.25

*Categorical variables were compared using Pearson chi-square test

ARP: Acute Recurrent Pancreatitis; CP: Chronic Pancreatitis; PD: pancreatic duct;

CFTR: cystic fibrosis transmembrane conductance regulator; PRSS1: cationic trypsinogen; CTRC: chymotrypsin C;

SPINK1: serine protease inhibitor Kazal-type 1

Denominators represent data available for each group

Table 3.

Treatment Modalities in Children with ARP and CP by Region

	West (n=121)	Midwest (n=151)	Northeast (n=45)	South (n=78)	Non-US sites (n=84)	p-value*
Medical Therapies	72/118 (61%)	80/141 (56%)	17/45 (37%)	29/77 (38%)	18/84 (21%)	<0.0001
Pain medications	56/111 (50%)	71/128 (55%)	16/42 (38%)	18/70 (26%)	26/80 (33%)	<0.0001
Celiac nerve block	1/119 (1%)	5/145 (3%)	0/43 (0%)	0/77 (0%)	0/83 (0%)	0.064
Pancreatic enzymes	62/118 (53%)	64/140 (46%)	11/45 (24%)	25/77 (32%)	12/84 (14%)	<0.0001
Vitamins/antioxidants	51/115 (46%)	62/126 (49%)	23/42 (55%)	17/71 (24%)	28/82 (33%)	0.001
Steroids	3/111 (3%)	3/133 (2%)	0/44 (1%)	0/75 (0%)	3/82 (4%)	0.42
Octreotide	3/115 (3%)	5/135 (4%)	0/45 (0%)	1/77 (1%)	1/84 (1%)	0.52
Endoscopic Therapies	72/119 (61%)	62/145 (43%)	7/42 (17%)	42/77 (55%)	7/83 (8%)	<0.0001
Biliary sphincterotomy	26/116 (22%)	29/141 (21%)	1/40 (3%)	15/77 (19%)	1/83 (1%)	<0.0001
Pancreatic sphincterotomy	41/116 (36%)	41/141 (29%)	3/39 (8%)	24/76 (32%)	3/83 (4%)	<0.0001
Pancreatic duct stent	29/115 (25%)	43/142 (30%)	6/42 (14%)	18/77 (23%)	3/83 (4%)	<0.0001
Biliary duct stent	2/117 (2%)	13/141 (9%)	0/41 (0%)	3/77 (4%)	0/83 (0%)	0.002
Pancreatic duct stone removal	16/118 (14%)	18/141 (13%)	0/40 (0%)	17/76 (22%)	2/83 (2%)	0.0003
Surgical Therapies	32/120 (27%)	53/145 (37%)	11/43 (26%)	12/77 (16%)	3/83 (4%)	<0.0001
Cholecystectomy	20/120 (17%)	29/145 (20%)	4/43 (9%)	8/77 (10%)	0/82 (0%)	0.0003
Cyst/pseudo-cyst operation	7/119 (6%)	3/145 (2%)	1/43 (2%)	2/77 (3%)	3/83 4%)	0.52
Lateral pancreaticojejunostomy	8/119 (7%)	4/145 (3%)	3/43 (7%)	2/77 (3%)	0/83 (0%)	0.076
Partial pancreatectomy	3/119 (3%)	1/145 (1%)	0/43 (0%)	0/77 (0%)	0/83 (0%)	0.19
TPIAT	5/119 (4%)	38/144 (26%)	3/43 (7%)	1/77 (1%)	1/83 (1%)	<0.0001

*Categorical variables were compared using Pearson chi-square test

ARP: Acute Recurrent Pancreatitis; CP: Chronic Pancreatitis; TPIAT: Total pancreatectomy/islet autotransplantation

Denominators represent data available for each group

Table 4.

Disease Burden in Children with ARP and CP by Region

	West (n=121)	Midwest (n=151)	Northeast (n=45)	South (n=78)	Non-US sites (n=84)	p-value*
Pattern of abdominal pain	(n=112)	(n=128)	(n=40)	(n=70)	(n=82)	
- No abdominal pain	5 (5%)	13 (10%)	4 (10%)	14 (20%)	14 (17%)	0.004
- Usually pain free; episodes of mild-moderate pain	17 (15%)	16 (13%)	6 (15%)	8 (11%)	16 (20%)	(Non-US
- Constant mild-moderate pain	6 (5%)	8 (6%)	0 (0%)	4 (6%)	4 (5%)	sites has less
- Usually pain free; episodes of severe pain	33 (29%)	45 (35%)	19 (48%)	21 (30%)	30 (37%)	pain)
- Constant mild-moderate pain; episodes of severe pain	41 (37%)	37 (29%)	9 (23%)	19 (27%)	13 (16%)	
- Constant severe pain	10 (9%)	9 (7%)	2 (5%)	4 (6%)	4 (5%)	
Constant Pain score	(n=108)	(n=113)	(n=39)	(n=70)	(n=79)	
Median (IQR)	0 (0–40)	0 (0–19)	0 (0–0)	0 (0–0)	0 (0–0)	<0.0001
Episodic Pain score	(n=106)	(n=103)	(n=38)	(n=66)	(n=79)	
Median (IQR)	70 (43–84)	68 (14–87)	63 (37–84)	31 (0–74)	57 (0–82)	0.008
Number of ER visits-lifelong** (average/year)	(n=51)	(n=75)	(n=25)	(n=44)	(n=45)	
Median (IQR)	1.4 (0.4–4.2)	1.4 (0.4–2.8)	1.0 (0.6–2.4)	1.1 (0.0–2.0)	1.2 (0.4–2.1)	0.45
Number of ER visits-past year	(n=106)	(n=114)	(n=38)	(n=68)	(n=79)	
Median (IQR)	2 (1–3)	2 (1–3)	1.5 (0–2)	1 (0–2)	2 (0–3)	0.10
Number of hospitalizations- lifelong** (average/year)	(n=56)	(n=76)	(n=25)	(n=44)	(n=46)	
Median (IQR)	1.7 (0.5–3.7)	1.3 (0.5–2.6)	1.0 (0.6–2.0)	1.1 (0–1.9)	0.9 (0–1.9)	0.15
Number of hospitalizations -past year	(n=107)	(n=113)	(n=40)	(n=69)	(n=79)	
Median (IQR)	1 (1–3)	2 (0–3)	1 (0–2)	1 (0–2)	1 (0–2)	0.32
Days missed school past month (school aged children)	(n=87)	(n=105)	(n=27)	(n=59)	(n=67)	
Median (IQR)	3 (0–10)	3 (0–8)	2 (0–5)	0 (0–4)	1 (0–6)	0.015

*Kruskal-Wallis test was used to compare among the regions

**Among those with at least 1 year duration of disease

ARP: Acute Recurrent Pancreatitis; CP: Chronic Pancreatitis; ER: Emergency Room