Published in final edited form as:

J Pediatr. 2015 April ; 166(4): 890–896.e1. doi:10.1016/j.jpeds.2014.11.019.

PEDIATRIC CHRONIC PANCREATITIS IS ASSOCIATED WITH GENETIC RISK FACTORS AND SUBSTANTIAL DISEASE BURDEN

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Abstract

Objective—To determine the clinical presentation, diagnostic variables, risk factors and disease burden in children with chronic pancreatitis.

Study design—We performed a cross-sectional study of data from INSPPIRE (**In**ternational **S**tudy Group of **P**ediatric **P**ancreatitis: **I**n search for a cu**RE**), a registry of children with acute recurrent pancreatitis and chronic pancreatitis. Between-group differences were compared using Wilcoxon rank-sum test.

Results—Among 170 subjects in the registry, 76 (45%) had chronic pancreatitis; 57% were female, 80% were Caucasian, median age at diagnosis was 9.9 years. Pancreatitis-predisposing genetic mutations were identified in 51 (67%) and obstructive risk factors in 25 (33%). Toxic/metabolic and autoimmune factors were uncommon. Imaging demonstrated ductal abnormalities and pancreatic atrophy more commonly than calcifications. Fifty-nine (77%) reported abdominal pain within the past year; pain was reported as constant and receiving narcotics in 28%. Children with chronic pancreatitis reported a median of 3 emergency room visits and 2 hospitalizations in the last year. Forty-seven subjects (70%) missed one day of school in the past month due to chronic pancreatitis; 26 (34%) missed 3 or more days. Children reporting constant pain were more likely to miss school (p=0.002), visit emergency room (p=0.01) and experience hospitalizations (p=0.03) compared with children with episodic pain. Thirty-three children (43%) underwent therapeutic ERCP; one or more pancreatic surgeries were performed in 30 (39%).

Conclusions—Chronic pancreatitis occurs at a young age with distinct clinical features. Genetic and obstructive risk factors are common, and disease burden is substantial.

Keywords

abdominal pain; quality of life; pediatric gastroenterology; genetics

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Chronic pancreatitis is not commonly diagnosed in children. No pediatric-specific epidemiology is available, but studies in Olmsted County, Minnesota and the Netherlands found an incidence rate of 0.5/100,000 in ages 0-34 years (1) and under 20 years.(2) The incidence of chronic pancreatitis increases with age; adults have an incidence 4-9 times higher than younger individuals. (1,2)

In adults, chronic pancreatitis is associated with severe debilitating pain, loss of work, and multiple hospitalizations. Unrelenting pain and recurrent exacerbations may lead to malnutrition, social deprivation, and depression. Surgery is frequently used to relieve pain. (3-6) To date, no systematic studies report the epidemiology, etiology or outcome of this disorder in children. A few single center-studies suggest that children with chronic pancreatitis often have genetic risk factors and that chronic pancreatitis causes severe pain and disability in the pediatric age group. (7-10) However, these pediatric studies are limited in that the cohorts are small, the studies are retrospective, and the work-up is not always complete. Most of the existing information on diagnostic modalities and treatment options is derived from adult studies.

Progress in understanding the epidemiology, etiology, treatments and outcomes of chronic pancreatitis in adults has been made through large multi-centered studies such as the North American Pancreatitis Study 2 (NAPS-2), that collected data on >1000 patients with acute recurrent pancreatitis (ARP) and chronic pancreatitis. (11) The predominant etiology of chronic pancreatitis in adults is environmental toxins, including alcohol and tobacco. (2,12,13) These factors are likely to be less important in children. Data collected from well-phenotyped children is crucial to better understand the epidemiology, etiologies, pathogenesis, natural history and outcome of chronic pancreatitis. With this improved knowledge, it may be possible to design diagnostic and therapeutic pathways for chronic pancreatitis in children.

The **In**ternational **S**tudy Group of **P**ediatric **P**ancreatitis: **I**n search for a cu**RE** (INSPPIRE) consortium formed to fill in the gaps in information on ARP and chronic pancreatitis in children. (14) In this report, we describe the demographic, clinical and imaging findings of children with chronic pancreatitis from a large cohort of well-phenotyped children. Our analysis of children with chronic pancreatitis in the INSPPIRE registry demonstrates that chronic pancreatitis in the pediatric age group is overwhelmingly associated with genetic causes and that it creates a significant disease burden for children and families.

METHODS

Demographic and clinical information on children with ARP or chronic pancreatitis with onset of illness ≤19 years of age at fourteen centers in four countries were entered into the INSPPIRE registry. The development and management of the INSPPIRE consortium has been described elsewhere. In brief, this multi-center, multi-national consortium carefully gathers data on the presentation, risk factors, diagnosis, and management of children with ARP and chronic pancreatitis (14). For the current work, we performed a multinational cross-sectional study of data from children who, at enrollment, met the definition of chronic pancreatitis. Data were collected between September 1, 2012 and August 31, 2013 and represented baseline data of the INSPPIRE chronic pancreatitis cohort. The consensus definition of chronic pancreatitis in children required one of the following: (1) abdominal pain consistent with pancreatic origin and imaging findings suggestive of chronic pancreatic damage; (2) evidence of exocrine pancreatic insufficiency and imaging findings suggestive of pancreatic damage; (3) evidence of endocrine pancreatic insufficiency and imaging findings suggestive of pancreatic damage; or (4) a surgical or pancreatic biopsy demonstrating histopathology features compatible with chronic pancreatitis. (15)

Data collected through standardized questionnaires included demographics, past medical history, family history, phenotypic features, risk factors, diagnostic evaluation, medications, hospitalization data, treatments and therapeutic interventions, outcome information and quality of life including specifics about pain. Questions included severity and intensity of the pain using the visual analog scale, patterns of pain (constant versus episodic), frequency, severity and duration of pain episodes, visits to emergency department and hospitalizations for pain. (14) Both patient and physician questionnaires were completed to minimize reporting bias. Physicians utilized interactions with the patient and review of the medical record (test results, hospitalizations, imaging results and reports) to complete their

questionnaires. Results were recorded in REDCap™ (Research Electronic Data Capture, Vanderbilt University) System database (16) to allow secure electronic capture of the data.

All centers had permission from their Institutional Review Boards, or the equivalent for their country, to proceed. All Boards met the criteria of the Declaration of Helsinki. (17) Consent was obtained from the parents of subjects <18 years of age and from subjects themselves if ≥18; children gave assent at the age specified by the local Institutional Review Board, or the equivalent for the country.

Summary statistics are presented as median (25^{th}, 75^{th} percentile). Between-group differences were compared using non-parametric Wilcoxon rank-sum tests for continuous variables. Statistical analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, NC). A p-value ≤0.05 was considered statistically significant.

RESULTS

Of the 194 subjects in the INSPIRRE Consortium database at the time of this study, 170 subjects had sufficient data in their questionnaires for analysis. Of this 170, 76 (45%) were diagnosed with chronic pancreatitis (Table I).

There was a slight preponderance of females (57%) and 80% of the subjects with chronic pancreatitis were Caucasian. Nearly all subjects (n=75, 96%) had a prior history of one or more episodes of acute pancreatitis, defined by at least two of the following: abdominal pain, elevated amylase or lipase ≥3x the upper limit of normal, or imaging findings of acute pancreatitis. The most commonly identified risk factors for chronic pancreatitis were pancreatitis-predisposing genetic mutations, with one or more mutations present in 51 subjects (67%) (Table II). In 12 cases, genetic testing was negative, and in 13 cases (17%) genetic testing was not done or the results were not known. The most common chronic pancreatitis-associated mutation was in the PRSS1 gene (n=33/61 tested), with the most frequent PRSS1 mutations being R122H (n=19) and N29I (n=4).

Additional subjects were identified with genetic mutations in SPINK1 (n=14/53), CFTR (n=11/59), and CTRC (n=2/40). Of the 11 children with CFTR mutations, 7 had one or more mutations associated with CF, 3 had mutations that may be associated with CF-related disorders, and 1 had a mutation of unknown significance. Sweat test was performed in 8/11; only 1 subject had a positive sweat chloride. Nine patients were known to carry mutations in more than one of the genes predisposing to chronic pancreatitis (SPINK1 + CFTR in 5, SPINK1 +CTRC in 2, PRSS1 + CFTR in 1, and PRSS1 + SPINK1 in 1).

Obstructive risk factors were identified in 25 (33%), with the most common obstructive risk being pancreas divisum in 15 subjects. Autoimmune and toxic/metabolic risk factors were rare (one patient each with hyperlipidemia, medication, propionic acidemia). Although alcohol was identified as a potential risk factor for pancreatitis by medical caregivers in 1 case, 4 adolescent subjects reported a past or current history of alcohol consumption. Sixteen subjects (21%) had more than one risk factor identified; in particular, of the 15 subjects with pancreas divisum, 8 also had a genetic risk factor (2 PRSS1, 3 SPINK1, 1 CFTR, 1 CFTR-

SPINK1, 1 SPINK1-CTRC). Of the remaining 7 subjects with pancreas divisum, 5 had no or incomplete genetic testing.

Eight subjects in the consortium (11%) had no risk factors identified although 5 of the 8 did not have genetic testing or the results were unknown at time of study entry, so genetic risks cannot be excluded in these individuals.

Presentation and diagnostic features of chronic pancreatitis

Subjects were diagnosed with chronic pancreatitis at a median age of 9.9 years (IQ range 6.1, 14.0) including one subject with changes of chronic pancreatitis before age 2 years. In subjects with chronic pancreatitis, the first episode of acute pancreatitis was diagnosed at a median age of 6.8 years (IQ range 4.5, 12.1), with 7 subjects diagnosed with their first pancreatitis episode at less than 2 years of age. There was a median interval of 0.7 years (IQ range 0.1, 2.8) between the first diagnosed attack of pancreatitis and the diagnosis of chronic pancreatitis. As PRSS1-associated chronic pancreatitis may be severe, (18) we analyzed this group of subjects separately to determine if they had a different age of presentation than other children. When subjects with PRSS1 mutations were analyzed separately from those who did not have PRSS1 mutations, the age at presentation for pancreatitis was not significantly different from those with other forms of chronic pancreatitis.

The most common clinical symptoms raising concern for chronic pancreatitis by the treating physician were ARP and/or persistent pain (n=63 and 54, respectively; Table III). Modalities used to establish the diagnosis including clinical features (i.e. abdominal pain and prolonged elevation of lipase>30 days) and initial imaging evidence of chronic pancreatitis are summarized in Table IV (available at www.jpeds.com). Pancreatic calcifications were present in only 9 (12%) on initial imaging, even though ductal dilatation (61%), irregularity (47%), and stricture (21%), and pancreatic atrophy (21%) were more common. Most subjects had undergone at least one abdominal MRI scan (n=68, 90%) with or without MRCP. CT scan was less commonly performed and only 21% of subjects had an endoscopic ultrasound to evaluate for chronic pancreatitis. Diagnosis was made using ERCP alone or with other imaging modalities in 47%. It is unknown how often ERCP was performed solely for diagnosis.

Disease burden in children with chronic pancreatitis

Seventy-two children or their parents (95%) completed the patient questionnaire regarding pain symptoms; 59 subjects with chronic pancreatitis reported abdominal pain within the past year and 13 subjects did not. The subjects reporting abdominal pain due to pancreatitis within the past year had a shorter duration of disease (median 1.9 years vs. 6.4 years, p=0.008) and were more likely to have genetic risk factors for disease (75% vs. 38% p=0.01).

In those with episodic pain, severe pain was more common (n=21) than mild to moderate pain (n=10). Subjects with constant abdominal pain reported mild to moderate pain without episodic pain (n=2), or mild to moderate pain with additional episodes of severe pain (n=22), or constant severe pain (n=4) (Table V).

Twenty-seven children (36%) were taking narcotic analgesics at the time of entry into the database, and an additional 4 reported regular use of tramadol or codeine. Among the narcotic-treated children, the frequency of narcotic use was daily in 12 patients, a few times per week for 5, a few times per month for 4, less than once a month for 4, and unknown for 2 patients.

Fifty-seven parent/children provided information regarding frequency of emergency department encounters and hospitalizations. Only 1 of these 57 subjects reported no hospitalizations and no emergency department visits. On average, subjects reported a median of 3.0 (IQ range 1, 5) emergency department visits and 2 (IQ range 1, 3) hospitalizations in the last year. Seventy-percent (33/47 responders) indicated one or more missed day of school in the past month due to chronic pancreatitis and 26 patients (34%) had missed 3 or more days of school in the most recent month.

The subjects with constant pain did not differ in age at onset of disease or duration of pancreatitis, compared with those with episodic pain and pain-free intervals. However, the subjects with a constant pain pattern missed significantly more days of school (median 8.0 days vs. 1.5 days with episodic pain, p=0.005), experienced significantly more hospitalizations in the past year (3.0 vs. 1.0, p=0.01), and had significantly more emergency department visits in the past year (3.0 vs. 1.0, p=0.01). The number of lifelong hospitalizations and ED visits did not differ in children with constant vs. episodic pain patterns.

Treatment for chronic pancreatitis

Treatments directed at chronic pancreatitis are displayed in Table VI (available at www.jpeds.com). The majority of subjects (75%) had tried pancreatic enzymes, of these, 28% felt they were helpful for pain and 14% felt the pancreatic enzymes reduced recurrence of acute pancreatitis. ERCP was performed 55 subjects (72%), with intervention in 33. In the group with intervention, 22 felt they had improvement in pain as a result of the intervention. One or more pancreatic surgeries were performed in 30 (39%) of children, including lateral pancreaticojejunostomy in 11 (14%), partial resection in 1 (1%), and total pancreatectomy with islet autotransplantion (TPIAT) in 21 (28%). Surgery was perceived as helpful in 8 (73%) patients undergoing lateral pancreaticojejunostomy, in one patient undergoing partial resection, and in 20 (95%) patients undergoing TPIAT.

DISCUSSION

Herein we describe the demographic, clinical and imaging findings of children with chronic pancreatitis from a multicenter, multinational study. A combination of genetic, environmental and metabolic risk factors contribute to the development of acute recurrent and chronic pancreatitis in adults.(18,19) In our study, the majority of children with chronic pancreatitis (67%) had identifiable genetic risk factors associated with pancreatitis. Over half of the children with genetic risk factors had a mutation in the PRSS1 gene. The second largest group of risk factors for chronic pancreatitis was congenital obstructive conditions (33%) (most commonly pancreas divisum). Our study results expand on those of several small, single center retrospective studies, which reported association with genetic risk

factors in Korean (47% PRSS1 or SPINK1 (7)), Italian (39.6%, CFTR, SPINK1 and/or PRSS1 (8)), Polish (33.6%, PRSS1 and SPINK1 (9)) and US children (79% CFTR, PRSS1, and/or SPINK1 (10)) with ARP or chronic pancreatitis. Very few of our study subjects had environmental risk factors as the cause or as contributors to their chronic pancreatitis. These findings contrast with those of the North American Pancreas Study-2 (NAPS2), which found alcohol as the sole cause or major contributor to chronic pancreatitis in 44.5% of the 539 adults with chronic pancreatitis and smokers over-represented in idiopathic pancreatitis. (6)

We may, in fact, be underestimating the impact of gene mutations as risk factors for chronic pancreatitis, because we do not have analysis of the most commonly tested genes associated with chronic pancreatitis (PRSS1, CFTR, SPINK1) for every child in the database. Children with a positive test for a single genetic risk factor or who were found to have pancreas divisum did not always undergo complete genetic testing. Studies in adults and children have found that many individuals with pancreatitis have genetic abnormalities in more than one gene (10,20) and our data support genetic testing of children with chronic pancreatitis in an effort to establish a complete understanding of the genetic factors associated with chronic pancreatitis. Development of testing for more recently reported genetic associations with chronic pancreatitis, for example, mutations in trypsinogen-degrading enzyme chymotrypsin C (CTRC), calcium-sensing receptor (CASR), and carboxypeptidase A1 (CPA1),(19, 21) may increase the number of children with identified genetic risk factors for chronic pancreatitis.

It is still debated whether pancreas divisum plays a direct role in the development of ARP/chronic pancreatitis. Pancreas divisum is more commonly found in persons with ARP/chronic pancreatitis (22) and specifically in those with pancreatitis-associated gene mutations (23, 24, 25). In one study, pancreas divisum was found in 7% subjects without pancreatic disease, but 15-45% of patients with pancreatitis and gene mutations, raising the question whether pancreas divisum by itself is sufficient to cause pancreatitis (26). In our study, pancreas divisum was present in ~20% of children with chronic pancreatitis and ~50% of whom had a genetic risk factor. Overall, our results are in agreement with pancreas divisum being associated with genetic mutations, therefore possibly a cofactor in the development of chronic pancreatitis. Although the frequency of pancreas divisum is relatively high in our study, we do not have a control group to compare the frequency of pancreas divisum to children without chronic pancreatitis.

In our consortium, children with chronic pancreatitis were young at the time of their first attack of pancreatitis–less than 7 years old on average. This is consistent with a study of a large number of patients with PRSS1-associated pancreatitis, where the median age of the first symptoms of hereditary pancreatitis was 10 years. (26) Because our data collection has limited longitudinal information, we cannot determine how quickly ARP progressed to chronic pancreatitis in our cohort, but we can comment that many children were affected early in childhood, often before puberty. This emphasizes the importance for pediatric providers to the possible diagnosis of pancreatitis in young children presenting with symptoms of recurrent abdominal pain.

In our study, the most commonly found radiographic signs of chronic pancreatitis in children were ductal abnormalities and pancreatic atrophy. In contrast to adults with chronic pancreatitis, (6) pancreatic calcifications were not a typical finding of childhood chronic pancreatitis. Our cohort underwent several imaging modalities performed for diagnostic/therapeutic purposes and will most likely need many more imaging studies done over the years. To avoid excess ionizing radiation, we suggest that clinicians avoid CT and ERCP for diagnosis alone and attempt to utilize MRI/MRCP and ultrasound (US). ERCP can be reserved for interventions such as stone removal or stricture management, as is recommended for adults. (27)

We demonstrated substantial disease burden in pediatric chronic pancreatitis, with extreme disruption of normal childhood and education. Children with chronic pancreatitis suffered from chronic and severe abdominal pain, and had frequent emergency department visits, hospitalizations and school absences. Only a few pediatric studies examine the impact of chronic pancreatitis on health-related quality of life. (28,29) A single-center study of 38 children with ARP and chronic pancreatitis reported that school functioning was the most affected dimension of health-related quality of life (29). The loss of time in school in our study is comparable with the substantial loss of work days or days of school in adults with chronic pancreatitis: (3) 71% of adults with constant pain missing ≥ 5 days of work or school per month. Children are also comparable with adults in the burden of repeated hospitalizations. (3) The significant burden of pain in children with chronic pancreatitis undoubtedly contributes to the significantly impaired health-related quality of life across all dimensions, as well as higher fatigue, in children with chronic pancreatitis. (29)

Our data reflect the current lack of a standardized approach to the diagnosis and treatment of chronic pancreatitis in children. The clear definition of pediatric chronic pancreatitis used in the INSPIRRE study was only proposed in 2012 (15) and has not been tested prospectively. Our data show that risk factors for chronic pancreatitis can be found in the majority of children with chronic pancreatitis, and some children will have more than one factor involved, consistent with the evolving picture of chronic pancreatitis being the result of multiple causes. (18) However, we currently lack a clear recommendation for evaluation of children with chronic pancreatitis, and insurance companies are reluctant to reimburse for many of the diagnostic tests. Similarly, in terms of therapy for chronic pancreatitis, the children in the consortium have undergone multiple medical and procedural treatments, none of which have been subjected to randomized trials in children–and few subjected to clinical trials in adults. The absence of rigorous data to guide treatment of children with chronic pancreatitis is a significant limitation of the current literature and an important focus of INSPPIRE for the future.

This study has several limitations. Enrollment occurred as subjects presented in pediatric tertiary care centers, possibly biasing our data collection to include children with more severe chronic pancreatitis. A large number of children (28%) in our consortium had TPIAT, the result of a single center with a well-established program (University of Minnesota). These children might be expected to have more serious disease and more complications than other children with chronic pancreatitis. Because each subject's evaluation was completed as per the treating physician's choice at the time of diagnosis with the goal to follow

prospectively, complete data sets were available on many but not all subjects in the consortium. Complete testing of genetic mutations associated with chronic pancreatitis was not performed on every child in our registry, and genetic testing was not performed at the same laboratory for every subject. In particular, CFTR mutational analysis results depend on whether a limited number of mutations are assessed or complete gene sequencing is performed. Questionnaires asked for information regarding effectiveness of therapy that may be subject to recall bias. Our data may underestimate environmental factors, because children may not be candid about their tobacco or alcohol use, even with their parents out of the exam room. Parents may not have been candid about second-hand smoke exposure, particularly given the low frequency of this in our data. (30) Collection of prospective, standardized data on children longitudinally, including predisposing genes and environmental risks from early in the course of ARP through the development of chronic pancreatitis would allow the full impact of genetic/environmental factors to be clear. For example, as the association of smoking with the development of chronic pancreatitis in adults has become clear, (6) it is important to investigate the risk to children exposed to second-hand smoke.

In summary, in contrast to adults with chronic pancreatitis, the environmental factors, such as alcohol use, are rare in children. The majority of children with chronic pancreatitis have either genetic risk factors, obstructive lesions, or both. Affected children experience substantial abdominal pain, frequent emergency department visits, hospitalizations and loss of time in school, similar to adults with chronic pancreatitis. Research focused on medical and surgical strategies to treat chronic pancreatitis and effective pain management programs are crucial to improve the quality of life for children with chronic pancreatitis.

ACKNOWLEDGMENTS

We would like to thank Debra Pfab, Ethan Valentine, Katherine Lilli, Brian Finley, Donna Smith, Katherine Keenan, Vikki Scaini, Nick Peterson, Christina Gorges, Shannon Riggs, Elizabeth Garnett, Tiffanie Hales, Thea Pugatch, Roxanne Strachan, Vanessa Bonett, Lily Nahidi, Cynthia Tsai, and Kara Cooper for enrolling patients into the study, entering data into the database, for IRB, REDCap and administrative support.

Supported by the Institute for Clinical and Translational Science through the National Institutes of Health (DK096327 [to A.U.] and UL1 TR000442). This publication's contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH. M.H. is the Editor of *Journal Pediatric Gastroenterology and Nutrition*. J.P. serves on the Editorial Board of *Practical Gastroenterology* and the speaker's bureau for Medical Education Resources, Inc. A.U. is a receives honoraria for serving as a consultant for Abbvie, Inc, for exocrine pancreatic function testing.

ABBREVIATIONS

ARP	acute recurrent pancreatitis
CFTR	cystic fibrosis transmembrane conductance regulator
CTRC	trypsinogen-degrading enzyme chymotrypsin C
ERCP	endoscopic retrograde pancreatography
INSPPIRE	**In**ternational **S**tudy Group of **P**ediatric **P**ancreatitis: **I**n search for a cu**RE**
IQ	interquartile range

MRI	magnetic resonance imaging
MRCP	magnetic resonance cholangiopancreatogram
PRSS1	protease, serine 1
SPINK1	serine protease inhibitor Kazal-type 1
TPIAT	total pancreatectomy with islet autotransplantion

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Table 1

Demographic characteristics of CP cohort

Characteristic	
Gender (Female, n (%))	43 (57%)
Age (years, median, 25th and 75th percentile)	13.0 (10.5, 17.0)
Ethnicity (n, (%))	
Non-Hispanic	61 (80%)
Hispanic	12 (16%)
Unknown	3 (4%)
Race (%)	
Caucasian	61 (80%)
Black/ African-American	4 (5%)
Native American	3 (4%)
Asian	2 (3%)
More than one race	2 (3%)
Other, or unknown	4 (5%)

CP, chronic pancreatitis

Table 2

Factors contributing to the etiology CP

	n (%) *
CP pts with history of ≥1 episode acute pancreatitis	73 (96%)
Risk factors for pancreatitis	
Genetic	51 (67%)
PRSS1	33 (43%)
SPINK1	14 (19%)
CFTR	11 (14%)
CTRC	2 (3%)
Autoimmune	3 (4%)
Obstructive	25 (33%)
Pancreas divisum	15 (20%)
Sphincter of Oddi dysfunction	1 (1%)
Gallstones	3 (4%)
Pancreatic duct mal-union	2 (3%)
Pancreatic duct obstruction	1 (1%)
Other	5 (7%)
Toxic/metabolic	8 (11%)
Alcohol (MD determined)	1 (1%)
Passive smoking (exposure)	3 (4%)
Hyperlipidemia	1 (1%)
Medication	1 (1%)
Metabolic disease	1 (1%)
Other	1 (1%)
None cited	8 (11%)

* The total exceeds 100% as some children have more than one factor. CP, chronic pancreatitis.

Table 3

Presentation of disease

	Median (25th and 75th percentile)
Age at first attack acute pancreatitis (y)	6.8 (4.5, 12.1)
Age at diagnosis of CP (y)	9.9 (6.1, 14.0)
Duration of diagnosed CP (y)	2.2 (1.5, 5.4)
Symptoms raising suspicion for CP	**n (%)**
Recurrent acute pancreatitis	63 (83%)
Pain	54 (74%)
Steatorrhea	8 (10%)
Diabetes	1 (1%)

CP, chronic pancreatitis; y, years

Table 4

Diagnostic modalities for diagnosis of CP

	n (%) *
Modalities used to establish diagnosis	
Clinical suspicion (i.e. abdominal pain, + prolonged elevation of lipase >30 days)	15 (20%)
ERCP	36 (47%)
CT scan	13 (17%)
MRCP and/or MRI	43 (57%)
EUS	8 (11%)
Abdominal ultrasound	18 (24%)
Surgery	1 (1%)
Histology	2 (3%)
First imaging evidence of CP	
Calcifications	9 (12%)
Pancreatic ductal stricture	16 (21%)
Pancreatic ductal dilation	46 (61%)
Pancreatic ductal irregularity	36 (47%)
Pseudocysts	6 (8%)
Pancreatic atrophy	16 (21%)
Other	6 (8%)

* Total is greater than 100% as children may have more than one feature of CP on imaging and more than one imaging method used to make the diagnosis. CP, chronic pancreatitis; ERCP, endoscopic retrograde cholangiopancreatography; CT, computed tomography; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; EUS, endoscopic ultrasonography.

Table 5

Burden of CP in children

Disease burden (number of respondents)	
Pattern of abdominal pain (59)	**n (%)**
Usually pain free, with episodes of mild to moderate pain	10 (17%)
Usually pain free, with episodes of severe pain	21 (36%)
Constant mild to moderate pain	2 (3%)
Constant mild to moderate pain, plus episodes of severe pain	22 (37%)
Constant severe pain	4 (7%)
Mean pain scores (scale 0-100)	**median (25th and 75th percentile)**
Constant pain (15)	55 (30, 78)
Episodic pain (50)	80 (62, 94)
Number of	**median (25th and 75th percentile)**
ER visits lifelong (48)	5 (3, 14)
ER visits last year (47)	3 (1, 5)
Hospitalizations lifelong (52)	5.5 (2.5, 14.5)
Hospitalizations last year (48)	2 (1, 3)
Days of school missed past 1 month (47)	3 (0, 8)
* **Pancreatic insufficiency (55)**	**n (%)**
Exocrine insufficient	19 (34%)
Endocrine insufficient&	1 (1%)

* Excludes post-total pancreatectomy;

& 1 patient with diabetes prior to total pancreatectomy.

Table 6

Treatments employed for children with CP

Treatment modalities	n (%) tried
Medications (n=63)	
Pancreatic enzymes (for pain or recurrent pancreatitis)*	7 (75%)
Anti-oxidants/ vitamins	14 (22%)
Steroids for autoimmune pancreatitis	3 (5%)
Octreotide	2 (3%)
Procedures (n=76)	
Any ERCP	55 (72%)
Pancreatic sphincterotomy	45 (59%)
Biliary sphincterotomy	21 (28%)
Pancreatic stent	35 (46%)
Biliary stent	4 (5%)
Stone removal	19 (25%)
Celiac plexus block	3 (4%)
Surgery (n=76)	
Cholecystectomy	15 (20%)
Lateral pancreaticojejonstomy	11 (14%)
Partial pancreatectomy	1 (1%)
Total pancreatectomy + islet autotransplant	21 (28%)

*An additional 5 patients were on pancreatic enzyme therapy to treat exocrine insufficiency or for nutritional management, not to treat pain or reduce frequency of acute pancreatitis. CP, chronic pancreatitis