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Pancreatic Enzyme Use Reduces Pancreatitis Frequency in Children with Acute Recurrent or Chronic Pancreatitis: A report from INSPPIRE

A. Jay Freeman[1,*], **Kenneth Ng**[2,*], **Fuchenchu Wang**[3], **Maisam A. Abu-El-Haija**[4], **Ankur Chugh**[5], **Gretchen A. Cress**[6], **Douglas S. Fishman**[7], **Cheryl E. Gariepy**[1], **Matthew J. Giefer**[8], **Praveen Goday**[1], **Tanja Y. Gonska**[9], **Amit S. Grover**[10], **Douglas Lindblad**[11], **Quin Y. Liu**[12], **Asim Maqbool**[13], **Jacob A. Mark**[14], **Brian A. McFerron**[15], **Megha S. Mehta**[16], **Veronique D. Morinville**[17], **Robert A. Noel**[18], **Chee Y. Ooi**[19], **Emily R. Perito**[20], **Sarah Jane Schwarzenberg**[21], **Zachary M. Sellers**[22], **Michael Wilschanski**[23], **Yuhua Zheng**[24], **Ying Yuan**[3], **Dana K. Andersen**[25], **Mark E. Lowe**[26], **Aliye Uc**[6] **Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC)**

[1]Nationwide Children's Hospital, The Ohio State University College of Medicine, Columbus, OH

[2]Johns Hopkins Children's Center, Johns Hopkins University School of Medicine, Baltimore, MD

[3]The University of Texas, MD Anderson Cancer Center, Houston, TX

[4]Cincinnati Children's Hospital Medical Center, College of Medicine, University of Cincinnati, Cincinnati, OH

[5]Children's Wisconsin, Medical College of Wisconsin, Milwaukee, WI

[6]University of Iowa, Stead Family Children's Hospital, Iowa City, IA

[7]Baylor College of Medicine and Texas Children's Hospital, Houston, TX

[8]Ochsner Hospital for Children, New Orleans, LA

[9]Hospital for Sick Children, Toronto, ON, Canada

[10]Boston Children's Hospital and Harvard Medical School, Boston, MA

[11]Children's Hospital of Pittsburgh, University of Pittsburgh Medical Center, Pittsburgh, PA

[12]Cedars-Sinai Medical Center, Los Angeles, CA

[13]Children's Hospital of Philadelphia, Philadelphia, PA

[14]University of Colorado School of Medicine, Children's Hospital Colorado, Aurora, CO

[15]Riley Hospital for Children, Indiana University School of Medicine, Indianapolis, IN

[16]University of Texas Southwestern Medical School, Dallas, TX

Corresponding Author and Guarenter of the Article: A. Jay Freeman, MD, MSc, Alvin.freeman@nationwidechildrens.org.

*Denotes co-first authors

Author Contributions:

All authors listed meet the 4 criteria for authorship proposed by the ICMJE.

[17]Montreal Children's Hospital, McGill University, Montreal, QC, Canada

[18]Baylor College of Medicine, San Antonio, TX

[19]University of New South Wales, Sydney Children's Hospital Randwick, Sydney, NSW, Australia

[20]University of California San Francisco, San Francisco, CA

[21]University of Minnesota Masonic Children's Hospital, Minneapolis, MN

[22]Stanford University, Palo Alto, CA

[23]Hadassah Hebrew University Hospital, Jerusalem, Israel

[24]Children's Hospital Los Angeles, Los Angeles, CA

[25]Division of Digestive Diseases and Nutrition, National Institute of Diabetes and Digestive and Kidney Disease, National Instituites of Health

[26]Washington University School of Medicine, St. Louis, MO

Abstract

Background: Among children who suffer from acute recurrent pancreatitis (ARP) or chronic pancreatitis (CP), acute pancreatitis (AP) episodes are painful, often require hospitalization, and contribute to disease complications and progression. Despite this recognition, there are currently no interventions to prevent AP episodes. In this retrospective cohort study, we assessed the impact of pancreatic enzyme therapy (PERT) use on clinical outcomes among children with pancreatic sufficient ARP or CP.

Methods: Children with pancreatic sufficient ARP or CP in the INSPPIRE-2 cohort were included. Clinical outcomes were compared for those receiving versus not receiving PERT, as well as frequency of AP before and after PERT. Logistic regression was used to study the association between development of AP episodes after starting PERT and response predictors.

Results: Among 356 pancreatic sufficient participants, 270 (76%) had ARP and 60 (17%) received PERT. Among those on PERT, 42% did not have a subsequent AP episode, during a mean 2.1 years of follow-up. Children with a *SPINK1* mutation (p=0.005) and those with ARP (compared to CP, p=0.008) were less likely to have an AP episode after starting PERT. After initiation of PERT, the mean AP annual incidence rate decreased from 3.14 down to 0.71 ($p<0.001$).

Conclusion: In a retrospective analysis, use of PERT was associated with a reduction in the incidence rate of AP among children with pancreatic sufficient ARP or CP. These results support the need for a clinical trial to evaluate the efficacy of PERT to improve clinical outcomes among children with ARP or CP.

Keywords

acute pancreatitis; pancreatic enzymes; PERT; pediatrics; chronic pancreatitis

INTRODUCTION

Pediatric pancreatitis is associated with high medical, surgical, financial, and social burden(1). While adult risk factors for pancreatitis consist primarily of lifestyle choices such as smoking and alcohol exposure (2), the etiologies associated with pediatric ARP and CP most commonly involve genetic factors (3). Despite our understanding related to the burden of disease and its underlying causes, a lack of preventative therapy means the incidences of acute recurrent pancreatitis (ARP) and chronic pancreatitis (CP), as defined by the INternational Study Group of Pediatric Pancreatitis: In Search for a CuRE (INSPPIRE) (4) have increased over the last decade (5)

In children with ARP or CP, acute pancreatitis (AP) flares are a main source of disease burden – causing pain, hospitalization, and missed school and work(1) – and likely contribute to disease progression(6). Among children with AP, the progression from ARP to CP can occur rapidly with a median interval from the initial AP attack to CP of 4 years (7, 8). Furthermore, similar to adults with CP, approximately one-third of children with CP progress to exocrine pancreatic insufficiency (EPI)(9, 10), many within six years of their initial AP episode(7). Despite the high disease burden associated with pediatric pancreatitis, and the rapid progression from AP to CP, we have no proven treatments that can halt or delay the disease progression.

Multiple interventions have targeted pain in CP (11, 12), with pancreatic enzymes therapy (PERT) being among the most studied interventions(13). The rationale for PERT use in ARP or CP is to create negative feedback inhibition. Cholecystokinin releasing factor (CCK-RF) is stimulated by nutrients in the intestine, leading to cholecystokinin (CCK) activation and pancreatic stimulation(14). Exogenous PERT is thought to inactivate CCK-RF and thereby lower CCK secretion and pancreatic exocrine activity, theoretically decreasing a pain stimulus (15). Despite the theoretical mechanism, a meta-analysis of five studies that compared PERT versus placebo in adults with CP found no efficacy for PERT in alleviating abdominal pain(16). However, there have been no prior studies looking at negative feedback inhibition nor the potential role of PERT reducing subsequent episodes of AP or impacting progression from ARP to CP in children.

Although evidence supporting the efficacy of PERT is lacking, the use of PERT among children with pancreatic sufficient ARP or CP is not uncommon, occurring in nearly 20% of these patients(10). In this analysis, we assessed the impact of PERT on clinical outcomes among children with pancreatic sufficient ARP or CP in the INSPPIRE-2 dataset. The primary aim of the study was to determine if PERT use decreased the incidence rate of AP among children with ARP or CP.

METHODS

The methods and protocols for INSPPIRE have been thoroughly described previously(17, 18). The INSPPIRE-2 cohort includes patients from 22 tertiary care centers in four countries, funded by the Consortium for the Study of Chronic Pancreatitis, Diabetes and Pancreatic Cancer (CPDPC)(19). Standard INSPPIRE definitions for AP, ARP and CP

were previously described(4). Progression from ARP to CP, or development of EPI and/or diabetes, is based on the clinical judgement of each treating physician but there is no mandated approach to screening for these clinical outcomes. All centers have obtained local institutional review board approval 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. All data was entered into the CPDPC's central data management center. Children with ARP or CP enrolled in the INSPPIRE-2 registry from July 1st, 2017, through May 13th, 2022, were included for analysis. Participants were analyzed as ARP or CP based on characterization at end of the study period.

For this analysis, pancreatic sufficiency was based on clinical documentation. Patients with fecal elastase levels consistent with exocrine insufficiency (<200μg/g stool) prior to initiating pancreatic enzymes, or within 6 months of initiating pancreatic enzymes, were excluded. The indication for starting PERT in pancreatic sufficient subjects was not available. Frequency of AP episodes and clinical outcomes related to disease burden were collected as previously reported (10). Briefly, patient and physician questionnaires assessed the following: i) abdominal pain associated with pancreatitis within the past year; ii) severity and pattern of the abdominal pain; iii) number of pain-related emergency room (ER) visits and hospitalizations; iv) pain interference in several life domains; v) days of school missed; and vi) medications specifically used for pain. Subjects rated pain severity using a 0–10 numeric scale with accompanying Wong-Baker Faces scale(20). The impact of pain on the six domains was queried utilizing a 5-point Likert scale(21). Surgical history as it pertains to this cohort includes only operations (e.g. cholecystectomy) and does not include ERCP.

STATISTICAL ANALYSES

Descriptive statistics were used to summarize participant demographics, risk factors and clinical outcomes, including mean, standard deviation (SD) and interquartile range (IQR) for continuous variables, and frequencies for categorical variables. Our first analysis focused on comparing the group with ARP or CP on PERT to those not on PERT within INSPPIRE to determine whether the groups differed in any significant way. The second analysis compared ARP subjects on PERT against CP subjects on PERT. Lastly, we compared the AP incidence rate between ARP subjects who developed additional AP episodes after starting PERT, as well as evaluating the clinical characteristics of those subjects without additional AP episodes after starting PERT. Fisher's exact test was used to compare categories variables between groups and assess the association between categorical variables. Wilcoxon rank-sum test was used to compare continuous variables between groups. Logistic regression was used to study the association between development of additional AP episodes after starting PERT and predictor variables. For the multivariate analysis, we screened the candidate covariates using univariate logistic regression at the significance level of 0.05, and then applied stepwise model selection procedure with the significance level of 0.05 to build the multivariate inferential model. As disease category (ARP or CP) was of particular interest, it was directly included in the multivariate model without performing variable selection. A p-value of < 0.05 was denoted as statistically significant. The statistical analysis was carried out using R version 4.1.0 (http://www.R-project.org).

RESULTS

There were 356 pancreatic sufficient children within the INSPPIRE-2 cohort (N=812) available for inclusion. Among those participants, 270 (75.8%) had ARP and 86 (24.2%) had CP. Sixty (16.9%) received PERT and 296 (83.1%) did not receive PERT. All patient with CP were diagnosed based on the combination of imaging findings,end organ sequelea and pain patterns per INSPPIRE criteria(4, 18). Demographics, categorized by enzyme use, are shown in Table 1 with no significant differences between the groups noted.

Among all participants, those with a *PRSS1* (*cationic trypsinogen*) mutation were more likely to have received PERT (p=0.008) (Table 2). Previous surgical history, other common genetic risk factors for pancreatitis and pancreas divisum were not associated with PERT use. Of note, among participants with CP, those with obstructive factors (defined as ductal stricture or presence of stones) were less likely to receive PERT (p=0.038), but this association was not seen among those with ARP or in the total cohort (Table 2). Pain, number of ER visits, number of hospitalizations and number of days of school missed were not associated with the initiation of PERT (Supplemental Table 1). There was only one patient that developed diabetes during the study period.

Among those participants who received PERT, 32 (53%) had ARP and 28 (47%) had CP. There were no demographic differences among those with ARP compared to those with CP. The demographics of those children on PERT is shown in Supplemental Table 2.

Among those who started PERT during the study period, 25 (42%, 19 ARP, 6 CP) did not have an additional episode of AP after starting PERT during a mean follow up of 2.1 years (IQR = (1.03, 2.75)); 35 (58%, 13 ARP, 22 CP) children who were on PERT had at least one additional episode of AP over a similar amount of follow up time (mean 3.05 years, IQR = (1.45, 4.27), p=0.156). As shown in Supplemental figure 1, the mean number of AP episodes before PERT was significantly higher (3.78 episodes for those with ARP and 3.79 episodes for those with CP) compared to after the intiation of PERT(0.91 episodes for those with ARP and 2.32 episodes for those with CP), highlighting the overall decrease in AP episodes after the initiation of PERT. Amongst children on PERT, those with no additional AP episodes did not have a mean difference in interval from first AP episode to PERT initiation compared to those that had one or more additional AP episodes after starting PERT (2.66 years vs 2.36 years, p=0.653) or number of AP episodes prior to starting PERT (3.56 vs 3.94, p=0.945). Children with *a SPINK1* (*Serine protease inhibitor Kazal-type 1*) mutation were less likely to have any additional AP episode after initiation of PERT (p=0.008), while no significant difference was observed among those with a positive pancreatic surgical history (p=1), PRSS1 mutation (0.111), *CFTR* (*cystic fibrosis transmembrane conductance regulator*) mutation (p=0.734), *CTRC* (*chymotrypsin-C)* mutation (p=0.289), obstructive factors (p=0.527) or pancreas divisum (p=0.281) (Table 3).

Children reporting either constant pain (p=0.037) or episodic pain (p=0.034) prior to initiating PERT were statistically more likely to have a subsequent AP episode after initiating PERT. Other pain variables, including intense episodic pain (p=0.073), pain impacting activity (p=0.067) and pain impacting socialization (p=0.067) all trended towards

being associated with increased risk for subsequent AP episodes but did not reach statistical significance (Table 4).

After univariate analysis (Table 3), two covariates remained significant predictors of developing subsequent AP episodes while on PERT: subject's cohort status (ARP or CP) and the presence of a *SPINK1* mutation (Table 5). CP patients were 9.47 times more likely to have subsequent AP episodes compared to ARP patients on PERT (p=0.008). Patients with a *SPINK1* mutation were less likely to experience additional episodes of AP after starting PERT while holding other covariates constant (OR=0.53, p=0.005). Given the significance of the *SPINK1* findings, we looked further to see if there was anything else different about this subgroup. We found that only 7% of Hispanic or Latino subjects were *SPINK1* positive compared to 36% of the rest of the cohort (p<0.001). Among the 57 subjects with a *SPINK1* mutation in our cohort, 19 (33%) had one additional mutation (2 with *PRSS1* mutation, 16 with a *CFTR* mutation and 3 with a *CTRC* mutation).

Among children who took PERT during the study period, the annualized incidence rate of AP decreased significantly. Prior to starting PERT, the mean annual incidence rate for of AP episodes was 3.14 (IQR = (1.11, 4.13)) which decreased significantly to 0.71 (IQR = (0, 1.22). As shown in Figure 1, in the full study cohort of children with ARP or CP, the mean annual incidence rate of AP episodes decreased by 2.44 episodes per year (p <0.001) after the initiation of PERT. Evaluating just those children with CP, the mean number of AP episodes decreased by 2.18 episodes per year (p=0.001), while among children with ARP, this decrease was more pronounced at 2.66 episodes per year (p<0.001). Of note, during the study time frame, there were 89 study partcipants with EPI on PERT. Among this subgroup, annual incidence rate was 3.06 episodes per year prior to PERT with a significant decrease to 0.46 episodes per year afterwards (p <0.001).

DISCUSSION

To our knowledge this is the first study to evaluate the clinical impact of PERT use on children with pancreatic sufficient ARP and CP. As an analysis of the INSPPIRE-2 cohort, our study uses the largest available study population of children with ARP or CP. In our cohort, children with both ARP and CP had a significantly lower rate of AP episodes after starting PERT than before. This study has clinical implications as the use of PERT is currently not recommended in consensus guidelines for the management of pediatric ARP and CP unless EPI is present(22), based largely on adult literature showing a lack of efficacy for pancreatic enzymes to treat pain(23). However, within our cohort, comprised of children cared for at tertiary centers with dedicated pediatric pancreatologists, nearly 17% of children with pancreatic sufficient ARP and CP were treated with PERT, highlighting the need to better understand the potential impact of this intervention on clinical outcomes. This is likely due to the theoretical benefit of negative feedback inhibition where pancreatic enzymes may lead to decreased CCK secretion(15), as well as a desire to maximize growth and nutrition among children, as well as its favorable safety profile.

Off-label use of PERT to treat ARP and CP in adults is frequently observed among those patients experiencing more severe disease evident by increased pain symptoms(16). Our

data, however, showed no association between measures of disease burden and use of PERT. Specifically, there was no association observed between pain scales and decision to initiate PERT, nor was any association observed between frequency of ER visits, hospitalizations or days of school missed. This data highlights that while pain is the primary marker of disease burden among adults, other clinical outcomes may be better suited to assess disease burden among children. The only variable that was positively associated with PERT use was the presence of a *PRSS1* mutation. This may be due to previous findings from INSPPIRE showing that patients with a *PRSS1* mutation were more likely to progress rapidly from ARP to CP(7) or provider perception that the physiologic impact of the gain of function mutation resulting in increased conversion of trypsinogen to trypsin may be more susceptible to negative feedback inhibition. Additionally, non-enteric coated enzymes are the preferred PERT for pain management in adults(16), yet only two subjects in our cohort were prescribed a non-enteric coated pancreatic enzyme formulation suggesting pain management was not the primary factor in initiating PERT.

Among the 60 patients on PERT, there were no observed differences when categorized by ARP or CP. Instead of observing a disproportionate number of children with CP on PERT, we observed that 47% of patients on PERT had CP, mirroring the proportion of subjects with CP within the INSPPIRE-2 cohort(10). This once again highlights that a lack of meaningful medical intervention and concerns related to disease progression, rather than disease burden, may be driving the decision to initiate PERT in this population.

A key observation from this study is that 42% of participants started on PERT experienced no additional AP episodes during the follow up period. Importantly, follow up time, age at first AP episode and number of AP episodes were not different between subjects who did have additional AP episodes after starting PERT vs subjects who did not, favoring against temporal or indication bias. Presence of ARP or *SPINK1* positivity were associated with a lack of subsequent AP episodes after PERT were started. The association with ARP suggests that PERT may be more efficacious for preventing AP earlier in the disease course, before progression to CP. The connection between *SPINK1* and PERT response is less clear and further analysis showed no additional association with other key variables (such as additional genetic mutations) or clinical outcomes. *SPINK1* mutations are felt to alter protease/antiprotease balance due to decreased inactivation of intrapancreatic trypsin. *PRSS1, CTRC* and *CFTR* mutations are believed to increase the risk of pancreatitis via mechanisms that result in increased conversion of trypsinogen to trypsin, while the role of the *SPINK1* protein is more protective after trypsinogen is activated to trypsin (24). As such, one possible explanation is that PERT may lead to upregulation of *SPINK1*-independent protective pathway leading to decreased autoactivation of trypsinogen and/or increased degradation of trypsin. Both of these observations require validation in future studies and deserve additional consideration to determine the mechanism of response.

Very relevant to clinical care, those patients reporting either constant or episodic pain prior to starting PERT were more likely to have subsequent AP episodes after PERT was started. Other pain symptoms such pain impacting socialization or physical activity were not significantly associated with development of future AP episodes after PERT was started. This is further evidence that PERT is not an effective pain intervention for ARP or CP, as

has been reported in adult studies (13). More importantly, given that those with ARP were less likely to have a subsequent AP episode, and the presence of pain is more likely to result in further AP episodes, this data again suggests that intervention early in the disease progression may be more efficacious.

The most important finding from this study is the decreased incidence rate of AP episodes after the initiation of pancreatic enzymes. Participants in our cohort experienced a highly significant decreased rate of AP episode after starting PERT, which was slightly more pronounced among those with ARP than with CP. Given the mean age at first AP episode in our cohort was approximately 9.5 years of age, the lifelong implications could be immense and further underscores that earlier intervention is likely needed to impart long-term clinical impact. Repeated bouts of AP are believed to result in cumulative damage leading to chronic pancreatitis(25, 26). Therefore, any intervention leading to decreased frequency of AP episodes may slow, or even prevent, disease progression to CP and it sequalae including diabetes, EPI and chronic pain. While we also saw a significant difference in the incidence rate of AP among those with EPI, it is difficult to know if this is because of the impact of PERT or due to acinar cell injury that no longer has the ability to elicit an AP event. Furthermore, given the number of variables between the two groups, a direct comparison of the incidence rates between those with EPI compared to those that were PS on PERT was not possible.

As a retrospective, observational study, the study has limitations. Notably, pancreatic sufficiency was defined clinically; not every patient had a fecal elastase or other objective measure of pancreatic function. All data in the INSPPIRE-2 reflects provider preference and as such, data such as genetic testing and diabetes screening is not uniformly obtained. Additionally, progression from ARP to CP is based on real-life clinical follow-up and therefore it is possible that progression to CP may have occurred in a small subset of patients categorized as ARP over the two-to-three year study period. Furthermore, dosage, frequency, compliance rates and indication for PERT were provider specific and not available, so the possibility of dose-response could not be investigated. Although different formulations of PERT were reported, the small n-value for some formulations prohibited the ability to perform an active comparator analysis or other more rigorous study designs. Finally, the retrospective review of INSPPIRE-2 required a pre-post study design that is inherently a less rigorous methodology as compared to randomized controlled trials, but is a well-recognized approach to determine temporal association between exposure and outcome and to inform future studies. Despite these limitations, our data shows a clear signal of clinical improvement among those children with pancreatic sufficient ARP and CP who were started on PERT. The limitations of this study result in a relatively weak level of evidence that should not change clinical management but rather inform future studies. Given the lack of any approved intervention, the safety profile of PERT, along with the significant lifetime disease burden for these children, it is necessary to study the potential of PERT to improve clinical outcomes among children with ARP and CP in a prospective, multi-center, randomized, placebo-controlled interventional trial that will inform future clinical care.

CONCLUSION

In a retrospective analysis, use of PERT by children with pancreatic sufficient ARP or CP was associated with decreased annual incidence of AP. In a subset of patients, no additional AP episodes were experienced after initiating enzymes, which was more common among those with ARP. This work suggests a clinical trial is warranted to prospectively determine the impact of PERT on pancreatic sufficient ARP and CP in children, focusing on intervention early in the disease course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of Interest:

A.J.F. is a consultant for Takeda and Alcresta, receives research funding from the Cystic Fibrosis Foundation and Anagram Therapeutics, and is a board member for CAPER. T.G. received a research grant from Vertex Pharmaceuticals, and she is a consultant for Cystic Fibrosis Foundation (CFF). A.U. is a consultant for CFF and Abbvie. M.E.L. is a consultant for CFF and UpToDate. S.J.S. is a consultant for UpToDate, Nestle, Abbvie, and the Cystic Fibrosis Foundation, and she has a grant from Gilead. V.D.M. is an Associate Editor for JPGN Reports. M.A.H. is the President of CAPER, The remaining authors report no conflicts of interest.

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What is known:

- Children with acute recurrent or chronic pancreatitis suffer significant morbidity
- Currently there are no therapies to prevent episodes of pancreatitis in children

What is new here:

- In a retrospective cohort, children started on PERT experience fewer episodes of acute pancreatitis
- Over 40% of children started on PERT experience no additional pancreatitis episodes over the next two years
- A clinical trial is required to determine the efficacy of PERT to prevent episodes of pancreatitis in children

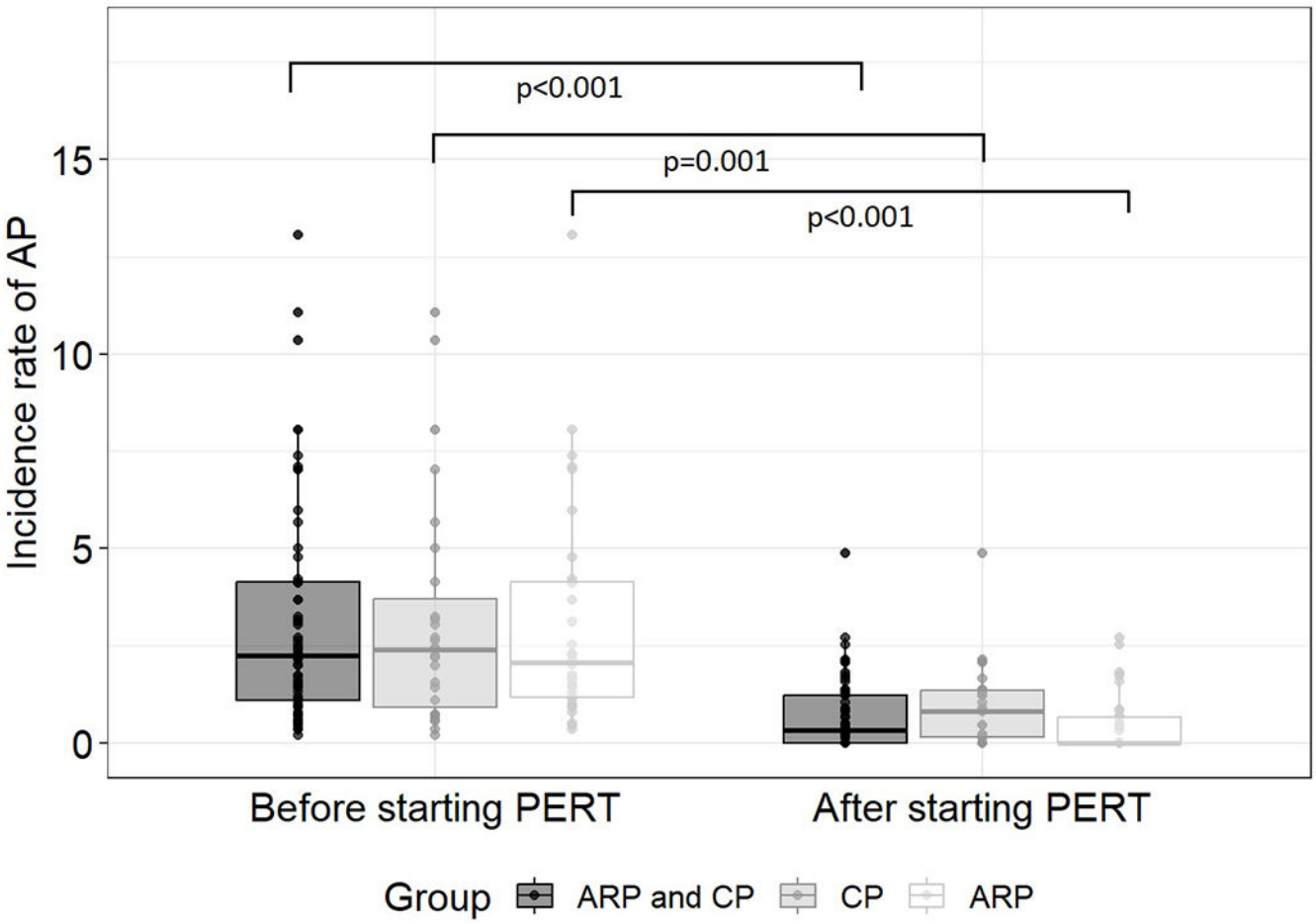

Figure 1:
Box and whiskers plot showing significant decrease in annual incidence rate of AP before and after initiation of pancreatic enzymes among children with ARP and CP

Table 1:

Demographics of the INSPPIRE-2 cohort with clinically defined pancreatic sufficiency.

	No Enzymes (N=296)	On Enzymes (N=60)	P-value
Gender			
Number of Response	296	60	0.204
F	150 (50.7 %)	36 (60.0 %)	
M	146 (49.3 %)	24 (40.0 %)	
Age at 1st AP			
Number of Response	296	60	0.497 *
0-5 years	53 (17.9 %)	16 (26.7 %)	
6-12 years	163 (55.1 %)	27 (45.0 %)	
13+ years	80 (27.0 %)	17 (28.3 %)	
Mean (SD)	9.66 (4.14)	9.20 (4.49)	
Median (Q1-Q3)	10.00 (6.00-13.00)	10.00 (5.00-13.00)	
Race			
Number of Response	296	60	0.637
Black or African American	17 (5.7 %)	2 (3.3 %)	
Other	66 (22.3 %)	11 (18.3 %)	
White	213 (72.0 %)	47 (78.3 %)	
Ethnicity			
Number of Response	294	60	0.873
Hispanic or Latino	79 (26.9 %)	15 (25.0 %)	
Not Hispanic or Latino	215 (73.1 %)	45 (75.0 %)	
BMI (%)			
Number of Response	290	59	0.864
Mean (SD)	69.33 (180.73)	63.44 (32.01)	
Median (Q1-Q3)	61.77 (25.25-94.46)	77.00 (29.70-89.06)	

* The p-value of Age at 1st AP was derived by considering age at 1st AP as a continuous variable.

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Table 2:

Clinical factors associated with the use of pancreatic enzymes

	ARP			CP			All Subjects		
	No Enzymes (N=238)	On Enzymes (N=32)	P-value	No Enzymes (N=58)	On Enzymes (N=28)	P-value	No Enzymes (N=296)	On Enzymes (N=60)	P-value
Surgical History									
Number of Response	235	32	0.133	57	28	0.181	292	60	0.545
Yes	23 (9.8%)	6 (18.8%)		17 (29.8%)	4 (14.3%)		40 (13.7%)	10 (16.7%)	
No	212 (90.2%)	26 (81.2%)		40 (70.2%)	24 (85.7%)		252 (86.3%)	50 (83.3%)	
PRSS1									
Number of Response	153	21	0.254	44	24	0.282	197	45	**0.008**
Positive	15 (9.8%)	4 (19.0%)		12 (27.3%)	10 (41.7%)		27 (13.7%)	14 (31.1%)	
Negative	138 (90.2%)	17 (81.0%)		32 (72.7%)	14 (58.3%)		170 (86.3%)	31 (68.9%)	
CFTR									
Number of Response	156	19	>0.99	39	22	0.131	195	41	0.589
Positive	56 (35.9%)	7 (36.8%)		7 (17.9%)	8 (36.4%)		63 (32.3%)	15 (36.6%)	
Negative	100 (64.1%)	12 (63.2%)		32 (82.1%)	14 (63.6%)		132 (67.7%)	26 (63.4%)	
CTRC									
Number of Response	131	17	>0.99	34	22	0.642	165	39	0.734
Positive	9 (6.9%)	1 (5.9%)		2 (5.9%)	2 (9.1%)		11 (6.7%)	3 (7.7%)	
Negative	122 (93.1%)	16 (94.1%)		32 (94.1%)	20 (90.9%)		154 (93.3%)	36 (92.3%)	
SPINK1									
Number of Response	151	24	>0.99	41	24	0.397	192	48	0.706
Positive	33 (21.9%)	5 (20.8%)		14 (34.1%)	5 (20.8%)		47 (24.5%)	10 (20.8%)	
Negative	118 (78.1%)	19 (79.2%)		27 (65.9%)	19 (79.2%)		145 (75.5%)	38 (79.2%)	
Obstructive Factors									
Number of Response	232	32	0.81	58	28	**0.038**	290	60	0.624
Yes	44 (19.0%)	5 (15.6%)		31 (53.4%)	8 (28.6%)		75 (25.9%)	13 (21.7%)	
No	188 (81.0%)	27 (84.4%)		27 (46.6%)	20 (71.4%)		215 (74.1%)	47 (78.3%)	
Pancreas Divisum									
Number of Response	231	32	0.137	58	28	0.589	289	60	0.24

	ARP			CP			All Subjects		
	No Enzymes (N=238)	On Enzymes (N=32)	P-value	No Enzymes (N=58)	On Enzymes (N=28)	P-value	No Enzymes (N=296)	On Enzymes (N=60)	P-value
Yes	13 (5.6%)	4 (12.5%)		14 (24.1%)	5 (17.9%)		27 (9.3%)	9 (15.0%)	
No	218 (94.4%)	28 (87.5%)		44 (75.9%)	23 (82.1%)		262 (90.7%)	51 (85.0%)	

Table 3:

Summary of Univariate Analysis (AP-PERT represents those patients started on PERT without subsequent pancreatitis episode(s), AP-PERT-AP represents those patients who had additional episode(s) of pancreatitis after starting PERT)

	AP-PERT (N=25)	AP-PERT-AP (N=35)	P-value
PRSS1			
Number of Response	18	27	0.111
Positive	3 (16.7%)	11 (40.7%)	
Negative	15 (83.3%)	16 (59.3%)	
CFTR			
Number of Response	13	28	0.734
Positive	4 (30.8%)	11 (39.3%)	
Negative	9 (69.2%)	17 (60.7%)	
CTRC			
Number of Response	14	25	0.289
Positive	2 (14.3%)	1 (4.0%)	
Negative	12 (85.7%)	24 (96.0%)	
SPINK1			
Number of Response	19	29	**0.008**
Positive	8 (42.1%)	2 (6.9%)	
Negative	11 (57.9%)	27 (93.1%)	
Obstructive Factors			
Number of Response	25	35	0.527
Yes	4 (16.0%)	9 (25.7%)	
No	21 (84.0%)	26 (74.3%)	
Pancreas Divisum			
Number of Response	25	35	0.281
Yes	2 (8.0%)	7 (20.0%)	
No	23 (92.0%)	28 (80.0%)	

Table 4:

Association between pain symptoms before starting pancreatic enzymes and subsequent episodes of acute pancreatitis after starting pancreatic enzymes (AP-PERT represents those patients started on PERT withou subsequent pancreatitis episode(s), AP-PERT-AP represents those patients who had additional episode(s) of pancreatitis after starting PERT)

	AP-PERT (N=25)	AP-PERT-AP (N=35)	P-value
Abdominal Pain Frequency			
Number of Response	22	30	0.392
Less than once a month	15 (68.2 %)	16 (53.3 %)	
At least once a month	7 (31.8 %)	14 (46.7 %)	
Temporal nature - Constant			
Number of Response	23	30	**0.037**
Yes	3 (13.0 %)	12 (40.0 %)	
No	20 (87.0 %)	18 (60.0 %)	
Temporal nature - Episodic			
Number of Response	22	29	**0.034**
Yes	16 (72.7 %)	28 (96.6 %)	
No	6 (27.3 %)	1 (3.4 %)	
Intensity - Constant			
Number of Response	25	35	0.077
No or little pain (<=2)	7 (28.0 %)	3 (8.6 %)	
More pain (>2)	18 (72.0 %)	32 (91.4 %)	
Intensity - Episodic			
Number of Response	25	35	0.073
No or little pain (<=2)	5 (20.0 %)	1 (2.9 %)	
More pain (>2)	20 (80.0 %)	34 (97.1 %)	
Pain Impact - Enjoyment			
Number of Response	25	35	0.296
Not at all or a little	14 (56.0 %)	14 (40.0 %)	
Somewhat or quite a bit	11 (44.0 %)	21 (60.0 %)	
Pain Impact - Concentration			
Number of Response	25	35	0.116
Not at all or a little	15 (60.0 %)	13 (37.1 %)	
Somewhat or quite a bit	10 (40.0 %)	22 (62.9 %)	
Pain Impact - Activities			
Number of Response	25	35	0.067
Not at all or a little	15 (60.0 %)	12 (34.3 %)	
Somewhat or quite a bit	10 (40.0 %)	23 (65.7 %)	
Pain Impact - Recreation			
Number of Response	25	35	0.115
Not at all or a little	16 (64.0 %)	14 (40.0 %)	

	AP-PERT (N=25)	AP-PERT-AP (N=35)	P-value
Somewhat or quite a bit	9 (36.0 %)	21 (60.0 %)	
Pain Impact - School			
Number of Response	25	35	0.116
Not at all or a little	15 (60.0 %)	13 (37.1 %)	
Somewhat or quite a bit	10 (40.0 %)	22 (62.9 %)	
Pain Impact - Socialization			
Number of Response	25	35	0.067
Never or rarely	15 (60.0 %)	12 (34.3 %)	
Somewhat or often	10 (40.0 %)	23 (65.7 %)	
Pain impact score			
Number of Response	24	31	0.233
Mean (SD)	1.34 (1.67)	1.82 (1.48)	
Median (Q1-Q3)	0.00 (0.00-3.13)	2.00 (0.00-3.09)	
Number of ER Visits Past 12 Months			
Number of Response	18	22	0.378
Mean (SD)	2.56 (2.59)	3.45 (3.17)	
Median (Q1-Q3)	2.00 (1.00-3.00)	3.00 (1.00-4.00)	
Number of Hospitalizations Past 12 Months			
Number of Response	18	19	0.498
Mean (SD)	2.33 (2.50)	2.63 (2.14)	
Median (Q1-Q3)	2.00 (1.00-3.00)	2.00 (1.00-4.00)	
Number of days of School Missed Last month			
Number of Response	14	21	0.852
Mean (SD)	2.50 (3.23)	2.67 (4.22)	
Median (Q1-Q3)	0.00 (0.00-6.00)	0.00 (0.00-5.00)	

Table 5:

Odds ratios from multivariant analysis.

	Odds Ratio	(95% CI)	p-value
Cohort - CP	9.474	(1.796, 49.976)	**0.008**
SPINK1 - Positive	0.053	(0.007, 0.422)	**0.006**