

Direct Costs of Acute Recurrent and Chronic Pancreatitis in Children in the INSPPIRE Registry

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See “Acute Recurrent Pancreatitis in Children: A Study From the Pediatric Health Information System” by Olyae et al on page 450 and “Recurrent Pancreatitis in Children—More Data Still Needed” by Bennett on page 362.

ABSTRACT

Objective: To estimate selected direct medical care costs of children with chronic pancreatitis (CP) and acute recurrent pancreatitis (ARP).

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What Is Known

- Acute recurrent and chronic pancreatitis are uncommon in children.
- Children with these conditions have a substantial burden of disease, with many hospitalizations, procedures, and pain.

What Is New

- Children with acute recurrent and chronic pancreatitis have high health care costs, resulting in a total conservative estimate of US costs of \$60 to \$70 million per year.
- Highest estimated costs are for hospitalization, surgical and radiographic procedures, and medications.
- Strategies to reduce hospitalization would reduce health care costs for acute recurrent and chronic pancreatitis.

Methods: We performed a cross-sectional study of data from International Study Group of Pediatric Pancreatitis: In Search for a Cure (INSPPIRE), a multinational registry of children with ARP or CP. We determined health care utilization and estimated costs of hospitalizations, surgical and endoscopic procedures, and medications in our study population. Health care utilization data were obtained from all subjects enrolled in the study, and costs were calculated using national United States costs.

Results: We included 224 subjects (median age 12.7 years), 42% of whom had CP. Mean number of hospitalizations, including for surgery and endoscopic retrograde cholangiopancreatography, was 2.3 per person per year, costing an estimated average \$38,755 per person per year. Including outpatient medications, estimated total mean cost was \$40,589 per person per year. Subjects using surgical procedures or endoscopic retrograde cholangiopancreatography incurred mean annual costs of \$42,951 per person and \$12,035 per person, respectively. Estimated annual costs of pancreatic enzyme replacement therapy, diabetic medications, and pain medications were \$4114, \$1761, and \$614 per person, respectively. In an exploratory analysis, patients with the following characteristics appear to accrue higher costs than those without them: more frequent ARP attacks per year, reported constant or episodic pain, family history of pancreatic cancer, and use of pain medication. **Conclusions:** ARP and CP are uncommon childhood conditions. The severe burden of disease associated with these conditions and their chronicity results in high health care utilization and costs. Interventions that reduce the

need for hospitalization could lower costs for these children and their families.

Key Words: economic, health care costs, hospitalization, pain, quality of life

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In recent years, the number of children with acute pancreatitis (AP) has increased to approximately 1 in 10,000, an incidence less than but approaching to that reported in adults (~1–5:10,000), depending on the population described (1–7). Most children with AP have a single episode that resolves without complications, but a subset develops acute recurrent pancreatitis (ARP) or chronic pancreatitis (CP) (8). This group experiences recurrent episodes of pancreatitis with increased risk of complications. No epidemiological studies have focused on children, but overall ARP is reported in 15% to 35% of children following AP (1,2,4,9) and as 0.5 or less than 0.5 per 100,000 in adult studies with younger populations (<34 years (10) and <25 years (11)). Despite modest incidence rates, ARP and CP are associated with significant disease burden. Children with these diseases experience frequent abdominal pain, emergency room visits, and hospitalizations, and they undergo numerous endoscopic and surgical procedures (12,13).

In adults, the high burden of disease associated with CP leads to a disproportionately high cost of medical care (14). The sources of these costs include hospitalization, complications of CP (including endocrine and exocrine insufficiency), and pain management. Adult patients with AP also incur substantial costs, estimated at \$2 billion yearly in the United States (US) (15). A study reported an increased incidence of AP, length of stay, and higher charges in children hospitalized for AP (16). The direct medical costs of pancreatitis of children with ARP and CP have not been analyzed, but are expected to be high.

In this study, we examined selected direct medical costs of ARP and CP in children enrolled in the International Study Group of Pediatric Pancreatitis: In search for a Cure (INSPPIRE) registry at baseline. These direct costs include those of hospitalizations, procedures, and medications. These costs further define the burden of ARP and CP in children.

METHODS

Study Population

The design and implementation of the INSPPIRE registry has been described previously (17). In brief, the consortium collects data on the demographics, presentation, risk factors, diagnosis, and management of children with ARP or CP. For the present work, we included health care utilization data from subjects with ARP or CP enrolled at baseline at all sites, including 2 Canadian, 1 Israeli, 1 Australian, and 12 US Centers, because we considered utilization of treatments to be similar across countries. We applied only US national health care cost data, so that the costs would be uniform and comparable. This method is frequently used when determining care costs across international clinical trials (18). The consensus definition of ARP and CP in children has been published previously (8). We used data from subjects enrolled between August 2012 and March 2014.

Patient and physician questionnaires used in the INSPPIRE database have been described (17). Patient questionnaires queried emergency department visits, hospitalizations, and medication used for pain. Physicians used interactions with the patient and review of the medical record (test results, hospitalizations, imaging results, and reports) to complete the questionnaires. Results were recorded in REDCap (Research Electronic Data Capture, Vanderbilt University) System database (19) to allow secure electronic capture of the data.

All of the centers had permission from their institutional review boards or the equivalent for their country to proceed.

Consent was obtained from the parents of subjects younger than 18 years and from subjects themselves if 18 years and more than 18 years; children gave assent at the age specified by the local institutional review board.

Health Care Utilization

We estimated utilization and mean costs of total hospitalizations due to ARP or CP, including for operations or endoscopic procedures (endoscopic retrograde cholangiopancreatography (ERCP)); ARP- or CP-associated operations; and ARP- or CP-associated ERCP procedures reported for each patient at enrollment in INSPPIRE. In addition, we also estimated the cost of ARP- or CP-associated medications (pancreatic enzymes, diabetes medications, corticosteroids, and pain medications) in our study population.

Data on frequency of ARP- or CP-associated hospitalization and medication use were obtained from the INSPPIRE patient questionnaire, whereas data on the number of surgical and ERCP procedures performed were obtained from the physician questionnaire. Patient recall for hospitalizations is stronger than less-dramatic health care use such as physician visits and may be more accurate than physicians' recall if patients are hospitalized at more than 1 health care system (20,21). Disease onset was defined as either the date of diagnosis of pancreatitis or date of first hospitalization due to pancreatitis, whichever occurred first. If the date of diagnosis or of first hospitalization was unavailable, the date of first onset of symptoms was used as the time when the disease began. Because data on medication dosage, frequency, and duration were rarely reported, we assumed that patients were given the recommended indication-specific dose for each reported medication for a total of 1 year.

Because there are no large volume data on ERCP in children, we based our calculations on adult literature (22). We assumed that all surgical procedures required hospitalization, and, to be conservative, that 56.5% of ERCP procedures were performed in inpatient setting, with the remaining performed in outpatient setting (22). We also assumed that operations or ERCP procedures performed in an inpatient setting included a physician fee for the procedure performed in addition to hospitalization cost. We assumed ERCP procedures performed in an outpatient setting included a facility fee and a physician fee for the ERCP procedure.

We assumed that the patient-reported number of ARP- and CP-associated hospitalizations included hospitalizations for surgical or ERCP procedures. If a patient's total number of surgical or ERCP procedures exceeded the patient-reported number of ARP- and CP-associated hospitalizations, the number of surgical or ERCP procedures was then used to estimate a patient's total number of hospitalizations.

Costs

We used a "bottom-up" approach to estimate the mean cost of pancreatitis in children by adding together the various elements that make up the diagnosis and treatment. This commonly used approach multiplies the unit cost of a particular diagnosis and treatment by the mean amount of utilization for diagnosis and treatment to obtain the mean total cost estimate (23). We estimated 2013 US mean costs (not charges) of ARP- or CP-associated hospitalizations, including operations or therapeutic/diagnostic ERCP procedures, overall, and stratified these data by patient clinical characteristics to identify potential areas of high costs in INSPPIRE (Fig. 1). Charges were converted to costs using the Medicare cost-to-charge ratio. We used mean costs despite the fact that costs may be skewed. This was done because health care systems prefer calculation of mean costs to plan their expenses (24). Study outcomes were expressed as the cost of surgical and ERCP procedures or ARP- or CP-associated medications per

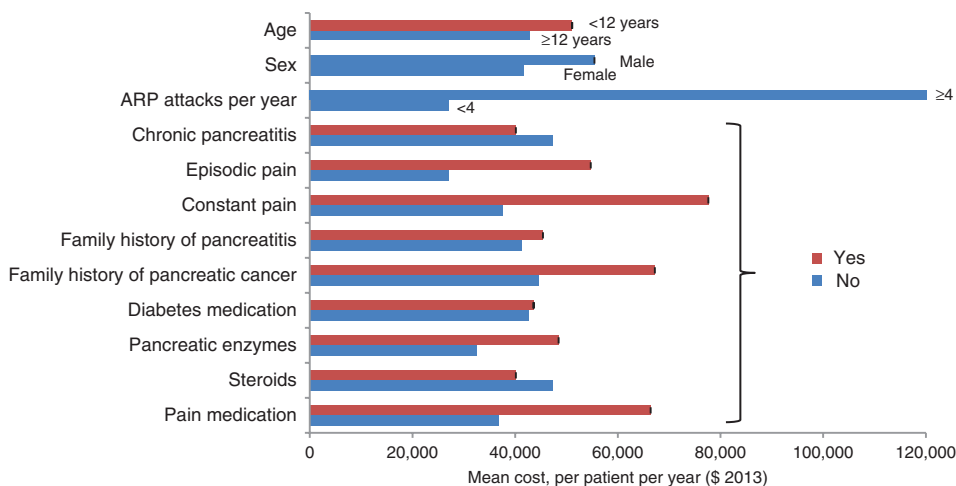


FIGURE 1. Total health care costs of the INSPPIRE cohort. Costs of hospitalization, including for surgical or ERCP procedures, and medication in INSPPIRE patient population at baseline, stratified by patient clinical characteristics (n = 219). ERCP = endoscopic retrograde cholangiopancreatography; INSPPIRE = International Study Group of Pediatric Pancreatitis: In Search for a Cure.

person per year among those who underwent the procedure or were on the medications. We also expressed the same costs per person per year over all the subjects analyzed. This analysis provided an estimate of costs for both high users of medical resources and the larger population of children with ARP or CP.

Costs of ARP- or CP-associated hospitalizations were obtained from the Healthcare Cost and Utilization Project-Kids’

Inpatient Database 2012 (25) using *International Classification of Diseases-9* codes 577.0 and 577.1 (Table 1). Costs of ARP- or CP-associated surgical and ERCP procedures requiring hospitalization were also obtained from Healthcare Cost and Utilization Project-Kids’ Inpatient Database 2012 (25) using the relevant *International Classification of Diseases-9* codes, or from the literature (26). Physician fees for the surgical or ERCP procedure

TABLE 1. Cost estimates for hospitalization, procedures, or medications related to pancreatitis in INSPPIRE at baseline (n = 219), in 2013 US dollars

Hospitalization or procedure	Cost per unit (\$)	No. hospitalizations or procedures		Reference
		n	%	
ARP/CP hospitalizations	14,913	1200		(18)
Surgical therapies		86		(18)
Cholecystectomy	13,047	35	40.6	(18)
Celiac nerve block	10,330	3	3.5	(18)
Cyst/pseudocyst operation (with drainage)	21,736	7	8.1	(18)
Puestow procedure	68,820	12	5.5	(18)
Partial removal of pancreas	37,887	1	0.5	(18)
Complete removal of pancreas with islet autotransplantation	195,590 [†]	28	14.0	(18,19)
ERCP procedures*		198		
Biliary sphincterotomy	9567	38	19.2	(18,20,21)
Pancreatic sphincterotomy	9567	63	31.8	(18,20,21)
Bile duct stenting	11,862	11	5.6	(18,20,21)
Pancreatic duct stenting	10,500	58	29.3	(18,20,21)
Pancreatic duct stone removal	8037	28	14.1	(18,20,21)
Medication type (n, %)	Cost per patient per year (\$) [‡]	Cost per patient per year overall (\$) [§]		
Pancreatic enzymes (74, 33.9%)	4114	1306		
Diabetes medication (17, 7.6%)	1761	201		
Steroids (5, 2.3%)	91	2		
Pain medication (87, 39.9%)	614	219		

ARP = acute recurrent pancreatitis; CP = chronic pancreatitis; ERCP = endoscopic retrograde cholangiopancreatography; HCUP KID = Healthcare Cost and Utilization Project Kids’ Inpatient Database; INSPPIRE = International Study Group of Pediatric Pancreatitis: In Search for a Cure.

* Costs for ERCP were calculated assuming that 56.5% of total ERCPs were performed in hospital, and the remaining in an outpatient setting (17); inpatient ERCP included hospitalization costs (HCUP-KID) (18) and physician fee for procedure (20); outpatient ERCP included facility fee of \$1501 (21).

[†] Estimated cost of complete removal of pancreas is \$90,239 (20); estimated cost of islet autotransplantation is \$105,051 (19).

[‡] Among those taking specified medication.

[§] Among all INSPPIRE patients.

were obtained from Medicare Physician Fee Schedule 2013 (27) using the current procedural terminology codes. Facility fees were obtained from the Medicare Ambulatory Surgical Center Fee Schedule 2013 (28). Medication costs were the average wholesale price using RED BOOK Online 2013 (29) and discounted at 17% for contract pricing. All of the costs were adjusted to 2013 dollars using the Consumer Price Index for medical care services (30).

Exploratory Analysis of Difference in Costs

We calculated the mean frequency and mean cost of hospitalization per person per year for selected patient characteristics. We chose not to perform statistical analysis of risk factors because of small sample size and variation in the source of the different utilization variables in our survey questions. Patient characteristics that could potentially affect hospitalization costs included socio-demographic factors (age and sex), frequency of ARP attacks, presence of CP, presence of pain (episodic or constant), family history of CP or ARP, family history of pancreatic cancer, and use of certain medications, including diabetes medication, pancreatic enzymes, and pain medication.

RESULTS

Cohort

We analyzed data of the 224 INSPPIRE subjects enrolled at the time of study. Median age of our study population was 12.7 years (mean = 12.2 years, range 1.8–23.7 years). Among these patients, 218 (97%) were reported as ever having ARP. Of 180 responders, 76 (42%) reported to be having CP. Eleven subjects were indeterminate (clarity of ARP vs CP was not established). Median disease duration was 3.0 years (mean = 4.1 years, range = 0–19.7 years), and most patients (~97%) had been hospitalized at least once because of ARP or CP during their duration of disease (Table 2).

Total Costs

The mean number of annual hospitalizations including for surgical and ERCP procedures in the INSPPIRE patient population was 2.3 per person, costing an estimated average of \$38,755 per person per year. Including medications (pancreatic enzyme, diabetes medication, steroids, and pain medication), the estimated mean cost across our study population was \$40,589 per person per year.

Costs of Surgical Therapy

Among 219 subjects on whom data on surgical therapies were available, 60 (28%) patients had 86 surgical therapies across their duration of disease (Tables 1 and 2). The most common operations were cholecystectomy and total pancreatectomy with islet autotransplantation (TPIAT) (Table 1).

Estimated mean costs of surgical procedures was \$42,951 per person per year among those who had any surgical procedure and \$12,099 per person per year overall in our study population (Fig. 2A, pale blue bars). Across disease duration, patients who underwent TPIAT had the highest surgical cost per person per year (\$45,769). Patients who underwent cyst/pseudocyst operation, cholecystectomy, or Puestow procedure (pancreaticojejunostomy) had surgery costs ranging from \$10,431 to \$31,043. Patients who underwent partial removal of the pancreas or had a celiac nerve block had the lowest surgical cost per person per year (<\$2500). Across our study population, TPIAT also had the highest cost per person per year (\$6017). The remaining subjects had total mean costs per operation type ranging from \$12 to \$4434 per person per year overall.

Costs of ERCP

Among 219 subjects on whom data on surgical therapies were available, 95 (43%) patients had 198 ERCP procedures across their duration of disease (Tables 1 and 2). Ninety-six percent of ERCP were done for therapeutic purposes. The most common

TABLE 2. Population and clinical characteristics of pediatric patient population in INSPPIRE at baseline

Characteristic	Overall (n = 224)			
	n	Median	Mean	Range or %*
Age, y		12.7	12.2	1.8–23.7
Male/female	88/136			44
Disease duration, y		3.0	4.1	0.03–19.7
Ever had additional ARP attacks	218			97
No. ARP attacks per person per year, hospitalization for ARP		2.0	3.9	0.06–84.2
Initial hospitalization for ARP	211			97
No. additional hospitalizations for ARP		3.0	5.0	0–30
No. hospitalization for ARP per person per year		1.4	2.4	0–28
Had surgical therapy	60			27
Had ERCP	95			43
Potential predictors of hospitalization costs				
Had chronic pancreatitis	76			42
Experienced episodic pain	143			88
Experienced constant pain	43			27
Family history of ARP/CP	80			44
Family history of pancreatic cancer	24			14
Diabetes medication	15			7
Pancreatic enzymes	71			36
Pain medication	80			41

ARP = acute recurrent pancreatitis; CP = chronic pancreatitis; ERCP = endoscopic retrograde cholangiopancreatography.

* Percentages are out of total number of responders for each question, which may be fewer than the total n = 224.

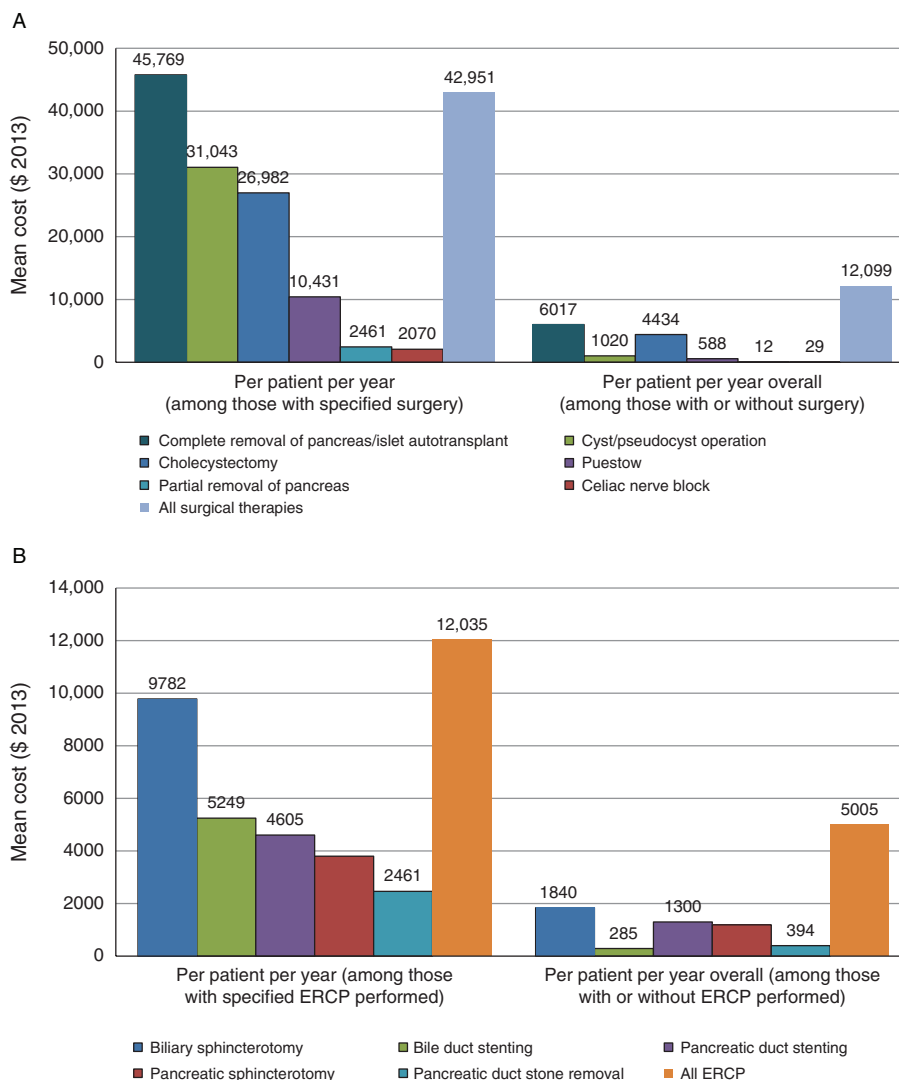


FIGURE 2. Costs of surgical and endoscopic interventions in the INSPPIRE cohort. A, Mean costs of surgical therapies in INSPPIRE at baseline, stratified by type of surgery (n = 219). B, Mean costs of ERCP in INSPPIRE at baseline, stratified by type of ERCP (n = 219). ERCP = endoscopic retrograde cholangiopancreatography; INSPPIRE = International Study Group of Pediatric Pancreatitis: In Search for a Cure.

ERCP procedures performed were pancreatic sphincterotomy and pancreatic duct stenting (Table 1). We were unable to delineate whether sphincterotomy or stenting or stone removal was done separately or concurrently during the same session.

Estimated mean cost of ERCP procedures was \$12,035 per person per year among those who had any procedure, and \$5005 per person per year for all patients (Fig. 2B, orange bars). Across disease duration, patients who underwent biliary sphincterotomy had the highest ERCP cost per person per year (\$9782). Patients who underwent ERCP procedures for other reasons had ERCP costs ranging from \$2461 to \$5249. Across our study population, biliary sphincterotomy, pancreatic duct stenting, and pancreatic sphincterotomy had ERCP cost ranging from \$1185 to \$1840 per person per year overall, whereas bile duct stenting and duct stone removal cost <\$400 per person per year overall.

Costs of Medication

In our study population, between 30% and 40% of patients were on pancreatic enzyme or pain medications, and <10% took

steroids or diabetes medication (Table 1). Those taking pancreatic enzymes had the highest estimated medication cost per person per year (\$4114), followed by those on diabetes medication (\$1761), then those on pain medication (\$614), and lastly those on corticosteroids (\$91).

Exploratory Analysis of Potential High-Cost Areas

We estimated per person per year costs of ARP- or CP-associated hospitalizations, as well as medications, stratified by patients' clinical characteristics to provide better understanding of total costs (Fig. 1). Patients with the following characteristics accrued higher costs (at least 50% more) than those without them including more frequent ARP or CP attacks per year (≥ 4 attacks), reported constant or episodic pain, positive family history of pancreatic cancer, and use of pain medication. Other demographic or clinical characteristics also did not appear to be associated with higher costs.

DISCUSSION

ARP and CP represent uncommon conditions in children, but they are accompanied by large disease burdens, including pain, emergency room visits, and recurrent hospitalizations (12,13). These medical complications are costly as we estimated an average annual cost of \$40,589 per child for ARP or CP in our population. Assuming an incidence of 0.5 of 100,000 per year for CP (10,11), and a US population of 313.9 million, >1500 children will present with CP in the US in the next year (similar data are not available for ARP). By extrapolating these costs from the INSPPIRE registry, pediatric CP alone may result in an estimated \$64 million cost to the US health care system per year. This estimate is similar to the previously reported \$52 million per year hospitalization costs in the US for pediatric acute pancreatitis (15). It is important to note that, pediatric acute pancreatitis is usually a single event, although children with CP will continue to accrue higher lifetime costs as a result of repeated hospitalizations, procedures, and ongoing need for medical or surgical therapy.

In our study, children who had surgical and endoscopic procedures had the highest estimated health care costs, with surgical procedures costing \$42,951 per person per year and ERCP costing \$12,035 per person per year. Our results are similar to but expand on those of Pant et al (13) who reported a higher disease burden and hospital costs using Nationwide Kids' Inpatient Database (median \$24,000 for CP vs \$16,000 for non-CP admissions) in children with CP.

Children who had TPIAT had the highest health care costs in our study population. Although TPIAT is a costly procedure, it may result in lower lifetime costs in CP and ARP by reducing pain and improving the quality of life (31–33). A study of TPIAT for adults with minimal change chronic pancreatitis demonstrated decreased mean annual admissions, endoscopy, imaging, and narcotic use 1 year after TPIAT (33). Furthermore, early surgery for CP in adults may reduce the risk of pancreatic insufficiency and the need for further intervention (34). This study did not factor in the costs for TPIAT, but calculated the costs for hospitalizations and complications of CP and emphasized cost savings if these were reduced. The ongoing early surgery versus optimal current step-up practice for chronic pancreatitis (ESCAPE) study, a randomized controlled, parallel, superiority multicenter study of early pancreatic surgery versus surgery after exhausting medical and endoscopic interventions, may help answer these questions, at least for adults (35).

As in other studies of health care costs of pancreatitis, pain is likely a major driver of many of the high costs of caring for these children. Pain is frequently the immediate cause of admission, surgical intervention, and endoscopic intervention for children with ARP or CP. In the North American Pancreatitis Study-2 cohort, >90% of 414 patients with CP had been admitted to the hospital for pain at least once (36). In North American Pancreatitis Study-2, patients with constant pain had 10 or more than 10 hospitalizations for pain during their lifetime, compared with 2 or less than for those with intermittent pain. Also in that study, 45% of adults with constant pain used "pain medication" regularly, compared with 22.3% of those with intermittent pain. Burden of pain in children with CP is not well studied. In a previous study, more than 80% of children with CP reported some form of pain within the previous year (12). Therefore, we expect that pain control in the ARP or CP population may result in significant reduction of economic costs. Head-to-head trials of interventions to reduce pain in children (both endoscopic and surgical) and trials to examine optimal timing of surgical procedures (similar to ESCAPE) would allow more effective and, thus, less costly care of children with these conditions.

Our study has several limitations. Because health care utilization data in our study population was acquired retrospectively,

some therapies and hospitalizations may be omitted. Study physicians at each site reviewed subject charts to extract as much data as possible, but data on some episodes may not have been available. Self-reported data on medication use in our survey often lacked information on dose and treatment duration, thus necessitating some dose standardizing assumptions on our part when estimating medication costs. We were unable to separate whether sphincterotomy or stenting or stone removal were done separately or concurrently at one session. Similarly, we were only able to address the selected direct costs of ARP or CP. We were unable to include other imaging costs (magnetic resonance cholangiopancreatography, magnetic resonance imaging, computed tomography, and endoscopic ultrasound), because the INSPPIRE registry did not include the full extent of imaging studies used in each subject at the time of data analysis. The INSPPIRE population may not be representative of the care of all children with ARP or CP because it consists of referral centers, with 1 center performing the majority of the TPIAT operations. Furthermore, we did not account for cost differentials that are likely present between sites. Prospective data collection with larger number of patients accounting for all costs would be more representative of the actual cost of ARP and CP in children.

In addition to the direct costs of ARP or CP in children, we expect that the indirect economic costs would likely be high. Parents lose substantial time at work caring for children during exacerbations, both those requiring hospitalization and those that do not. Medical costs and travel expenses to tertiary medical centers may not be reimbursed by health insurance and would add to cost. Among adults with CP, the ability to work declines as the disease progresses (37,38). It is possible that parental work also declines as their child's pancreatitis progresses (39). Social and psychological costs are even harder to quantify, but may be substantial and lifelong. Structured interviews of adults with CP have described significant impact on their physical, psychological, and social functioning (40). In adults with nonalcoholic pancreatitis, depression is common (41). Most concerning is the evidence of the negative effects of pain duration on cognitive performance in CP (42). Taken together, the life-long economic impact of ARP or CP in children may be far greater than reflected in the direct costs of medical care described by our data.

CONCLUSIONS

ARP and CP are uncommon in the pediatric age group, but because of high disease burden, they are associated with high health care costs. Studies that improve our knowledge of these disorders and enhance our outpatient pain management strategies may reduce the need for hospitalizations, lower health care costs, and improve quality of life of these children and their families.

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