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Authors

Troendle, David M
Fishman, Douglas S
Barth, Bradley A
et al.

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Therapeutic Endoscopic Retrograde Cholangiopancreatography in Pediatric Patients With Acute Recurrent and Chronic Pancreatitis

Data From the INSPPIRE (INternational Study group of Pediatric Pancreatitis: In search for a cuRE) Study

David M. Troendle, MD,* Douglas S. Fishman, MD,† Bradley A. Barth, MD, MPH,* Matthew J. Giefer, MD,‡ Tom K. Lin, MD,§ Quin Y. Liu, MD,|| Maisam Abu-El-Haija, MD,§ Melena D. Bellin, MD,¶ Peter R. Durie, MD,# Steven D. Freedman, MD, MPH,** Cheryl Gariepy, MD,†† Tanja Gonska, MD,# Melvin B. Heyman, MD, MPH,‡‡ Ryan Himes, MD,† Sohail Z. Husain, MD,§§ Soma Kumar, MD,|||| Mark E. Lowe, MD, PhD,§§ Veronique D. Morinville, MD,¶¶ Chee Y. Ooi, MBBS, PhD,### Joseph Palermo, MD,§ John F. Pohl, MD,*** Sarah Jane Schwarzenberg, MD,¶ Steven Werlin, MD,††† Michael Wilschanski, MD,‡‡‡ M. Bridget Zimmerman, PhD,§§§ and Aliye Uc, MD,|||||

Objective: The aim of this study was to characterize utilization and benefit of therapeutic endoscopic retrograde cholangiopancreatography (ERCP) in children with acute recurrent pancreatitis (ARP) or chronic pancreatitis (CP).

Methods: From August 2012 to February 2015, 301 children with ARP or CP were enrolled in the INSPPIRE (INternational Study group of Pediatric Pancreatitis: In search for a cuRE) study. Physicians reported utilization and benefit of therapeutic ERCP at enrollment. Differences were analyzed using appropriate statistical methods.

Results: One hundred seventeen children (38.9%) underwent at least 1 therapeutic ERCP. The procedure was more commonly performed in children with CP compared with those with ARP (65.8% vs 13.5%, $P < 0.0001$). Utility of therapeutic ERCP was reported to be similar between ARP and CP (53% vs 56%, $P = 0.81$) and was found to be helpful for at least 1 indication in both groups (53/99 patients [53.5%]). Predictors for undergoing therapeutic ERCP were presence of obstructive factors in ARP and CP, Hispanic ethnicity, or white race in CP.

Conclusions: Therapeutic ERCP is frequently utilized in children with ARP or CP and may offer benefit in selected cases, specifically if ductal obstruction is present. Longitudinal studies are needed to clarify the efficacy of therapeutic ERCP and to explore subgroups that might have increased benefit from such intervention.

Key Words: bile ducts, bile stent, children, endotherapy, pancreatic ducts, pancreatic stent

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Acute pancreatitis (AP) in children was considered to be uncommon, but its incidence is now recognized to approach that reported in adults.^{1–3} While many children recover without long-term effects, a subset of patients will have further episodes of pancreatitis and/or develop chronic pancreatitis (CP). With advanced noninvasive imaging modalities, endoscopic retrograde cholangiopancreatography (ERCP) is infrequently utilized solely as a

From the *Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX; and †Section of Pediatric Gastroenterology and Nutrition, Baylor College of Medicine, Houston, TX; ‡Department of Pediatrics, Seattle Children's Hospital, Seattle, WA; §Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH; ||Department of Medicine and Pediatrics, Cedars-Sinai Medical Center, Los Angeles, CA; ¶Department of Pediatrics, University of Minnesota, University of Minnesota Masonic Children's Hospital, Minneapolis, MN; #Department of Paediatrics, University of Toronto, and Research Institute, The Hospital for Sick Children, Toronto, Canada; **Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA; ††Department of Pediatrics, The Ohio State University and Nationwide Children's Hospital, Columbus, OH; ‡‡Department of Pediatrics, University of California at San Francisco, San Francisco, CA; §§Department of Pediatrics, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA; ||||Department of Pediatrics, Rady Children's Hospital, San Diego, CA; ¶¶Department of Pediatrics, Montreal Children's Hospital, McGill University, Montreal, Canada; ###Faculty of Medicine, School of Women's and Children's Health, University of New South Wales and Sydney Children's Hospital Randwick, Sydney, Australia; ***Division of Pediatric Gastroenterology, University of Utah, Salt Lake City, UT; †††Department of Pediatrics, Medical College of Wisconsin, Milwaukee, WI; ‡‡‡Department of Pediatric Gastroenterology, Hadassah Hebrew University Hospital, Jerusalem, Israel; and §§§Department of Biostatistics, University of Iowa College of Public Health; and |||||Stead Family Department of Pediatrics, University of Iowa Carver College of Medicine, Iowa City, IA.

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Address correspondence to: Aliye Uc, MD, Stead Family Department of Pediatrics, The University of Iowa Carver College of Medicine, BT1120-C JPP, 200 Hawkins Dr, Iowa City, IA 52242 (e-mail: aliye-uc@uiowa.edu).

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diagnostic modality. However, ERCP is frequently applied as a therapeutic modality to manage patients with sequelae of acute recurrent pancreatitis (ARP) and CP. Endoscopic interventions such as therapeutic ERCP have traditionally been undertaken after failure of noninvasive maneuvers such as eliminating possible instigating environmental factors or when medication trials are ineffective and before more invasive surgical interventions are pursued.

The literature regarding ARP and CP in the pediatric population is sparse, and even fewer data are published on appropriate interventions to ameliorate or prevent recurrences of pancreatitis or consequences of CP.⁴⁻⁷ Given its favorable benefit/risk profile compared with surgical interventions, therapeutic ERCP is still recommended by most experts to be the first reasonable approach to treat select patients, for example, with CP.⁸ Collaborative efforts among adult providers have led to significant advances in understanding etiologies and clinical outcomes from surgical and endoscopic interventions in adult patients with ARP and CP.^{9,10}

The INSPPIRE (International Study group of Pediatric Pancreatitis: In search for a cure) consortium was formed to address gaps in knowledge of pediatric ARP and CP. The present study analyzes baseline information entered on patients in this database to describe the utilization and efficacy of endoscopic intervention on pediatric patients with ARP or CP as reported by the providers responsible for patient enrollment. We identify predictors of therapeutic ERCP utilization and report its utility.

MATERIALS AND METHODS

Study Design and Participants

Demographic and clinical data were collected from 16 institutions using patient/parent and physician questionnaires for children who fulfilled the criteria for ARP or CP and were 19 years or younger at the time of enrollment, as previously described.¹¹ Patient information was entered into the REDCap (Research Electronic Data Capture,¹² Vanderbilt University, Nashville, Tenn) database from September 2012 to July 2015 and represented baseline information of the INSPPIRE cohort. All centers obtained institutional review board approval or the equivalent for their country. These 301 subjects (155 with ARP and 146 with CP) have been reported in different contexts in previous reports.^{13,14}

Definitions

The definitions utilized for ARP and CP have previously been described.¹⁵ In summary, ARP was defined as at least 2 distinct episodes of AP with complete resolution of pain (≥ 1 -month pain-free interval between diagnoses of AP) or complete normalization of pain and serum pancreatic enzymes levels (amylase and lipase) before the subsequent episode of AP was diagnosed. Chronic pancreatitis was diagnosed when pancreatic imaging findings suggestive of CP were identified in the setting of either chronic pancreatic type pain, evidence of exocrine pancreatic insufficiency, or endocrine pancreatic insufficiency. Suggestive imaging findings of CP include: ductal changes (irregular contour of the main pancreatic duct or its radicles; intraductal filling defects; calculi, stricture, or dilation) or parenchymal changes (generalized or focal enlargement, irregular contour [accentuated lobular architecture], cavities, calcifications, heterogeneous echotexture). Imaging modalities may include computed tomography, magnetic resonance imaging, magnetic resonance cholangiopancreatography, ERCP; transabdominal ultrasound; or endoscopic ultrasound

(in which at least 5 endoscopic ultrasound features [as defined by the Rosemont classification¹⁶] must be fulfilled).

Statistical Analysis

Differences were compared using Fisher's exact test or χ^2 test for categorical variables depending on sample size and the Student's *t*-test for continuous variables. All differences were considered significant at a 2-sided $P < 0.05$. Data were analyzed utilizing SAS 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

We analyzed the 301 patients entered into the INSPPIRE database as of July 2015; 155 (51.5%) were diagnosed as having ARP and 146 (48.5%) as having CP. Patient characteristics are presented in Table 1. Therapeutic ERCP was undertaken in 117 (38.9%) of the patients.

Of the 155 children with ARP, 21 (13.5%) underwent therapeutic ERCP. The results of a univariate analysis evaluating predictors for application of therapeutic ERCP in patients with

TABLE 1. Patient Characteristics

| Total | n (%) |
|-----------------------------------|--------------|
| Age at enrollment, mean (SD), y | 11.9 (4.6) |
| Age at first attack, mean (SD), y | 8.7 (4.9) |
| Sex, female | 172 (57) |
| Ethnicity, Hispanic | 63/276 (23) |
| Race, n = 265 | |
| White | 214 (81) |
| Multiracial | 20 (8) |
| Black | 10 (4) |
| Asian | 14 (5) |
| Other | 7 (3) |
| ARP | 155 (52) |
| CP | 146 (48) |
| Exocrine insufficiency | 46/259 (18) |
| Endocrine insufficiency | 13/278 (5) |
| Risk factors | |
| Toxic-metabolic | |
| Medications | 23/195 (12) |
| Ethanol exposure | 7/287 (2) |
| Active smoker | 4/287 (1) |
| Passive smoke exposure | 24/269 (9) |
| Autoimmune | 30/220 (14) |
| Obstructive factors | 97/296 (33) |
| Genetic risk factors | |
| PRSS1 | 65/196 (33) |
| SPINK1 | 35/177 (20) |
| CFTR | 54/193 (28) |
| CTRC | 9/121 (7) |
| Therapies attempted | 194/294 (66) |
| Medical therapies | 145/289 (50) |
| Therapeutic ERCP utilization | 117/301 (39) |
| Surgery (non-TPIAT) | 61/292 (21) |
| TPIAT | 29/291 (10) |

CFTR indicates cystic fibrosis transmembrane conductance regulator; CTRC, chymotrypsin C; PRSS1, protease, serine 1; SPINK1, serine peptidase inhibitor, Kazal type 1; TPIAT, total pancreatectomy and islet autotransplantation.

ARP are included in Table 2. Children suspected to have obstructive factors contributing to their disease process were significantly more likely to undergo therapeutic ERCP.

Of the 146 patients with CP, 96 (65.8%) underwent therapeutic ERCP. Patients with CP were more likely to undergo therapeutic ERCP compared with ARP (65.8% vs 13.5%, $P < 0.0001$). The results of a univariate analysis evaluating predictors for utilization of therapeutic ERCP in patients with CP were included in Table 3. Children who were of Hispanic ethnicity or white race and those who were suspected to have obstructive factors contributing to their disease process were significantly more likely to have therapeutic ERCP. In contrast, patients with alcohol exposure or autoimmune pancreatitis were significantly less likely to have therapeutic ERCP.

Table 4 shows benefit of various endoscopic interventions reported by the physician questionnaires. While therapeutic ERCP, particularly pancreatic interventions such as sphincterotomy, stone removal, and stenting, was utilized more commonly in the CP group, its efficacy was not significantly different comparing patients with ARP and those with CP. Biliary stenting was infrequently performed in both cohorts.

DISCUSSION

In our cohort, therapeutic ERCP was relatively infrequently performed in our patients with ARP, especially compared with patients with CP. When utilized in patients with ARP, therapeutic ERCP was done more frequently in patients with obstructive factors or pancreatic anatomical anomalies. Otherwise, therapeutic ERCP was not utilized as frequently in patients with other contributing variables causing pancreatitis. More than half of the patients with ARP who had a therapeutic ERCP performed were reported to have improvement of symptoms. Our study volume was similar to one of the largest pediatric ERCP studies for pediatric pancreatitis by Agarwal et al,⁶ who described 221 ERCPs in 172 children, of whom 19 had ARP. Of these 19 children, 63% were reported to have improvement of symptoms after therapeutic ERCP, similar to our observed rate of improvement of 56%. Otto et al¹⁷ also evaluated a large series of pediatric ERCP for pancreatitis and found a similar rate of children with anatomical abnormalities (13/106) contributing to recurrent pancreatitis, but their study did not evaluate the effectiveness of ERCP-guided endotherapy for relief of symptoms in children with ARP or CP. Coté et al¹⁸ demonstrated that biliary sphincterotomy alone may be as effective as dual biliary and pancreatic sphincterotomy to prevent AP episodes in adult patients with idiopathic ARP. Unfortunately, the small number of sphincterotomies performed in our ARP cohort did not allow us to perform an analogous analysis, but the reported utility of biliary and pancreatic sphincterotomies in our cohort was similar (60% for biliary vs 50% for pancreatic). From our data, although therapeutic ERCP was used much less frequently in children with ARP compared with CP, its benefit in children with ARP was similar to those with CP. Whether therapeutic ERCP should be utilized at a greater frequency in managing children with ARP remains to be determined, but evidence should best come from longitudinal prospective studies evaluating the outcomes of such intervention.

Similar to the pediatric INSPPIRE consortium, several adult centers in a collaborative effort formed the North American Pancreatitis Study 2 (NAPS2) and first published in 2008 their collective data on ARP and CP in adult patients.⁹ This was soon followed by a focused analysis of the NAPS2 data assessing the pattern of use of therapeutic ERCP and surgical therapies and their perceived effectiveness for only CP as based on completed physician questionnaires.¹⁰ In the present study from the pediatric-based INSPPIRE consortium, a similar analysis was performed

TABLE 2. Predictors of Therapeutic Endoscopy Utilization in Pediatric ARP

| Variables | Underwent Therapeutic ERCP (n = 21), n (%) | No Therapeutic ERCP (n = 134), n (%) | P |
|---|--|--------------------------------------|---------|
| Sex, female | 14 (67) | 74 (55) | 0.325 |
| Ethnicity, Hispanic | (n = 20) 11 (55) | (n = 125) 93 (74) | 0.074 |
| Race | (n = 17) | (n = 121) | 0.414 |
| White | 14 (82) | 98 (81) | — |
| Multiracial | 3 (18) | 9 (7) | — |
| Black | 0 (0) | 5 (4) | — |
| Asian | 0 (0) | 7 (6) | — |
| Other | 0 (0) | 2 (2) | — |
| Age at first acute attack, mean (SD), y | (n = 18) 9.1 (5.1) | (n = 122) 9.0 (5.0) | 0.967 |
| Exocrine insufficiency | 0/16 (0) | 2/111 (2) | 1.0 |
| Endocrine insufficiency | 0/19 (0) | 6/122 (5) | 1.0 |
| Alcoholic | 0/19 (0) | 2/131 (2) | 1.0 |
| Active smoker | 0/20 (0) | 1/130 (1) | 1.0 |
| Passive smoking exposure | 1/19 (5) | 11/121 (9) | 1.0 |
| Autoimmune pancreatitis | 3/13 (23) | 13/99 (13) | 0.394 |
| Other autoimmune diseases | 3/19 (16) | 11/124 (9) | 0.400 |
| Genetic risk factors | | | |
| <i>PRSSI</i> | 0/11 (0) | 15/77 (19) | 0.199 |
| <i>SPINK1</i> | 3/10 (30) | 7/68 (10) | 0.113 |
| <i>CFTR</i> | 3/10 (30) | 27/79 (34) | 1.0 |
| <i>CTRC</i> | 0/6 (0) | 5/42 (12) | 1.0 |
| Obstructive factors | 14/21 (67) | 36/131 (27) | 0.0004* |
| Pancreas divisum | 4/20 (20) | 9/126 (7) | 0.081 |
| Sphincter of Oddi disorders | 3/20 (15) | 2/124 (2) | 0.019* |
| Gallstones | 3/19 (16) | 6/128 (5) | 0.093 |
| Pancreatic duct malunion | 2/20 (10) | 5/126 (4) | 0.245 |
| Duct obstruction | 0/20 (0) | 1/128 (1) | 1.0 |
| Annular pancreas | 0/20 (0) | 3/128 (2) | 1.0 |
| Choledochal cyst | 3/20 (15) | 2/128 (2) | 0.018* |
| Medications | | | |
| Pain medications | 7/13 (54) | 34/102 (33) | 0.217 |
| Medical therapies | 8/19 (42) | 36/130 (28) | 0.198 |
| Pancreatic enzymes | 7/19 (37) | 25/130 (19) | 0.130 |
| Pancreatic enzymes (not for PI) | 7/19 (37) | 24/130 (18) | 0.076 |
| Vitamins/antioxidants | 1/18 (6) | 11/127 (9) | 1.0 |
| Steroids | 0/18 (0) | 0/125 (0) | — |
| Octreotide | 0/19 (0) | 2/128 (2) | 1.0 |

*Statistically significant.

CFTR indicates cystic fibrosis transmembrane conductance regulator; *CTRC*, chymotrypsin C; PI, pancreatic insufficiency; *PRSSI*, protease, serine 1; *SPINK1*, serine peptidase inhibitor, Kazal type 1.

TABLE 3. Predictors of Therapeutic Endoscopy Utilization in Pediatric CP

| Variables | Underwent Therapeutic ERCP (n = 96), n (%) | No Therapeutic ERCP (n = 50), n (%) | P |
|---|--|-------------------------------------|----------|
| Sex, female | 60 (62) | 24 (50) | 0.093 |
| Ethnicity, Hispanic | (n = 85) 19 (22) | (n = 46) 3 (7) | 0.021* |
| Race | (n = 80) | (n = 47) | 0.010* |
| White | 68 (85) | 34 (72) | — |
| Multiracial | 4 (5) | 4 (8) | — |
| Black | 6 (6) | 0 (0) | — |
| Asian | 1 (1) | 6 (13) | — |
| Other | 2 (3) | 3 (7) | — |
| Age at first acute attack, mean (SD), y | (n = 81) 8.3 (4.6) | (n = 38) 8.1 (4.9) | 0.827 |
| Age at first diagnosis CP, mean (SD), y | (n = 72) 9.7 (4.4) | (n = 32) 11.3 (4.6) | 0.106 |
| Exocrine insufficiency | 29/89 (33) | 15/43 (35) | 0.793 |
| Endocrine insufficiency | 6/93 (6) | 1/44 (2) | 0.429 |
| Alcoholic | 1/90 (1) | 4/47 (9) | 0.028* |
| Active smoker | 1/90 (1) | 2/47 (4) | 0.271 |
| Passive smoking exposure | 9/84 (11) | 3/45 (7) | 0.540 |
| Autoimmune pancreatitis | 2/68 (3) | 12/40 (30) | <0.0001* |
| Other autoimmune diseases | 5/92 (5) | 3/46 (7) | 1.0 |
| Genetic risk factors | | | |
| <i>PRSSI</i> | 34/75 (45) | 16/33 (48) | 0.762 |
| <i>SPINK1</i> | 16/69 (23) | 9/30 (30) | 0.473 |
| <i>CFTR</i> | 14/71 (20) | 10/33 (30) | 0.233 |
| <i>CTRC</i> | 4/53 (8) | 0/20 (0) | 0.570 |
| Obstructive factors | 38/95 (38) | 9/49 (18) | 0.009* |
| Pancreas divisum | 16/91 (18) | 6/49 (12) | 0.408 |
| Sphincter of Oddi disorders | 2/91 (2) | 0/48 (0) | 0.545 |
| Gallstones | 5/92 (5) | 1/47 (2) | 0.664 |
| Pancreatic duct malunion | 5/91 (5) | 1/48 (2) | 0.664 |
| Duct obstruction | 4/93 (4) | 0/48 (0) | 0.299 |
| Annular pancreas | 1/93 (1) | 0/48 (0) | 1.0 |
| Choledochal cyst | 2/93 (2) | 0/48 (0) | 0.548 |
| Medications | | | |
| Pain medications | 42/73 (58) | 20/36 (56) | 0.844 |
| Medical therapies | 72/94 (77) | 29/46 (63) | 0.093 |
| Pancreatic enzymes | 55/93 (59) | 22/46 (48) | 0.060 |
| Vitamins/antioxidants | 14/89 (16) | 6/45 (13) | 0.713 |
| Steroids | 3/90 (3) | 5/45 (11) | 0.116 |
| Octreotide | 4/89 (4) | 1/46 (2) | 0.661 |

*Statistically significant.

CFTR indicates cystic fibrosis transmembrane conductance regulator; *CTRC*, chymotrypsin C; *PRSSI*, protease, serine 1; *SPINK1*, serine peptidase inhibitor, Kazal type 1.

yielding specific data for CP, but also included ARP (Tables 2 to 4), but limited to only therapeutic ERCP. Several key comparisons between the current INSPPIRE CP data and those from the NAPS2 cohort are notably important to highlight. Despite notable differences in the mean ages of the patients (12 years in INSPPIRE vs 49 years in NAPS2) and primary identified risk factors (genetics/obstructive factors in INSPPIRE vs alcohol in NAPS2), the utilization of therapeutic ERCP (66% for INSPPIRE vs 61% for NAPS2) and the perceived utility of this therapy (53% for INSPPIRE vs 43% for NAPS2) were remarkably similar for patients with CP in both cohorts.¹⁰ Interestingly, biliary interventions were performed more often in the adult NAPS2 cohort compared with the current pediatric data (biliary sphincterotomy: 42% vs 26%, biliary stenting: 14% vs 8%), possibly reflective of the less frequent occurrence of CP-related biliary strictures encountered in pediatric patients. In contrast, pancreatic interventions such as pancreatic stenting and stone removal were performed more often in the INSPPIRE cohort (44% and 22%, respectively) compared with the NAPS2 cohort (36% and 11%, respectively), possibly reflecting the fact that obstructive pathology within the pancreatic duct was more frequently identified in pediatric cohort as well. These differences in therapeutic ERCP utilization between adult and pediatric cohorts deserve further study, because they may provide clues into differences in underlying mechanisms of disease, disease progression, and which subgroups of patients may be more amenable to specific endoscopic interventions. These differences are also important to consider as endoscopists performing therapeutic ERCP in children attempt to apply the relatively abundant adult literature in this area to pediatric patients in which a paucity of literature currently exists for the purpose of guiding management decisions.

In uncomplicated CP, several adult studies have shown that therapeutic ERCP can be helpful in improving the chronic pain associated with this disease.¹⁹⁻²¹ The technical goals of therapeutic

TABLE 4. Benefit of Endoscopic Interventions in Pediatric ARP and CP

| Intervention | ARP (n = 155), n (%) | CP (n = 146), n (%) | P |
|-------------------------------------|----------------------|---------------------|----------|
| Therapeutic ERCP performed | 21 (14) | 96 (66) | <0.0001* |
| Helpful for at least 1 indication | 9/16 (56) | 44/83 (53) | 0.812 |
| Biliary sphincterotomy performed | 11/151 (7) | 36/136 (26) | <0.0001* |
| Helpful | 6/10 (60) | 12/30 (40) | 0.300 |
| Biliary stenting performed | 2/151 (1) | 11/138 (8) | 0.006* |
| Helpful | 2/2 (100) | 3/10 (30) | — |
| Pancreatic sphincterotomy performed | 4/151 (3) | 68/138 (49) | <0.0001* |
| Helpful | 2/4 (50) | 33/66 (50) | — |
| Pancreatic duct stenting performed | 6/151 (4) | 60/137 (44) | <0.0001* |
| Helpful | 2/5 (40) | 28/57 (49) | — |
| Pancreatic stone removal performed | 1/151 (1) | 30/137 (22) | <0.0001* |
| Helpful | 1/1 (100) | 18/18 (100) | — |

*Statistically significant.

ERCP in CP typically include alleviating pancreatic ductal obstructions due to stones or strictures, stenting of the main pancreatic duct, and treatment of regional complications such as peripancreatic fluid collections and strictures of the intrapancreatic portion of the bile duct. Clinical guidelines by the European Society of Gastrointestinal Endoscopy suggest that therapeutic ERCP should be considered as a first-line treatment for patients with uncomplicated CP.⁸ However, others advocate for reserving this intervention for those with imaging-proven main pancreatic duct obstruction.²² In our study cohort, a majority of children with CP who undergo therapeutic ERCP are suspected to have pancreaticobiliary obstruction. Adult studies have also shown that benign biliary strictures, such as those seen in CP, are very responsive to endoscopic stenting, with response rates between 80% and 90%.^{23–25} As mentioned previously, this intervention was rarely undertaken in our pediatric cohort, and curiously only 3 of the 10 children with CP who had biliary stents placed were reported to benefit from this intervention. We are unable to account for this discrepancy; however, it is possible that the diminutively sized biliary tree of the pediatric-aged patients may preclude some of the effective stenting therapies developed in adults (ie, placement of multiple plastic or fully covered metal biliary stents).

As previously described by the INSPPIRE consortium, genetic mutations in pancreatitis-related genes are frequently identified in pediatric ARP and CP.¹³ Limited retrospective studies have suggested that therapeutic ERCP may be effective at decreasing rates of recurrent pancreatitis and help manage chronic pain for these patients.^{5,7} Although therapeutic ERCP offers an effective alternative to treat the disease sequelae in this subgroup, it does not address the underlying genetic defect. Therefore, care should be taken in equating technical procedural success with improvements in pain and quality of life. The relatively invasive nature of therapeutic ERCP and the potential for adverse events invoke the need for ongoing studies to examine the long-term effects of these procedures in children with ARP and CP. Unfortunately, the retrospective nature of our data collection regarding pain did not allow us to comment on patient or family perceptions as to whether therapeutic ERCP led to any tangible benefits in this regard. However, the majority of physician respondents believed that therapeutic ERCP was helpful for their patients, although this result may be skewed because of bias on behalf of the provider. Clearly, prospective studies are still warranted to determine the effects of therapeutic ERCP on pain and quality of life in children with ARP and CP. Of particular interest is elucidating where in the treatment paradigm therapeutic ERCP should be considered for various subgroups of patients in relation to other potential treatment modalities such as medications, extracorporeal shock-wave lithotripsy, surgical interventions, and total pancreatectomy with auto islet cell transplantation.

This study has several significant limitations that need to be taken into consideration. Subjects were recruited from tertiary care centers, which may introduce referral bias toward children with more severe and disabling forms of ARP and CP. Another limitation is the subjective nature of procedural effectiveness that was utilized. In addition, the timing of the intervention in relation to the assessment of procedural effectiveness was not standardized because all patients were analyzed at enrollment. It is hoped that incorporating annual follow-up questionnaires, as well as more objective measures of effectiveness such as rates of recurrent pancreatitis, pain medication utilization, school days missed, among others, into the longitudinal INSPPIRE database will help overcome these limitations as the consortium continues its study of pediatric ARP and CP in a systematic manner. Nevertheless, the large number of well-phenotyped pediatric patients with ARP

and CP allowed us to assess therapeutic ERCP utilization in these patients and gain insight into its perceived effectiveness according to providers.

In summary, this study is unique in that it is the first multicenter assessment of therapeutic ERCP utilization and perceived benefit in pediatric patients with ARP and CP. We document that therapeutic ERCP is more commonly undertaken in patients with CP compared with ARP and in those identified to have obstructive factors contributing to their disease burden. Further systematic investigation is needed in this area, including prospective comparative studies evaluating therapeutic interventions in ARP and CP incorporating assessment of outcomes including quality of life after these interventions.

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