

Definitions of Pediatric Pancreatitis and Survey of Present Clinical Practices

*Veronique D. Morinville, †Sohail Z. Husain, ‡Harrison Bai, §Bradley Barth, ||Rabea Alhosh, ¶Peter R. Durie, #Steven D. Freedman, **Ryan Himes, †Mark E. Lowe, ††John Pohl, ‡‡Steven Werlin, §§Michael Wilschanski, ||Aliye Uc, on Behalf of the INSPPIRE Group

ABSTRACT

Objectives: There is limited literature on acute pancreatitis (AP), acute recurrent pancreatitis (ARP), and chronic pancreatitis (CP) in children. The International Study Group of Pediatric Pancreatitis: In Search for a Cure (INSPPIRE) consortium was formed to standardize definitions, develop diagnostic algorithms, investigate disease pathophysiology, and design prospective multicenter studies in pediatric pancreatitis.

Methods: Subcommittees were formed to delineate definitions of pancreatitis, and a survey was conducted to analyze present practice.

Results: AP was defined as requiring 2 of the following: abdominal pain compatible with AP, serum amylase and/or lipase values ≥ 3 times upper limits of normal, and imaging findings of AP. ARP was defined as ≥ 2 distinct episodes of AP with intervening return to baseline. CP was

diagnosed in the presence of typical abdominal pain plus characteristic imaging findings, or exocrine insufficiency plus imaging findings, or endocrine insufficiency plus imaging findings. We found that children with pancreatitis were primarily managed by pediatric gastroenterologists. Unless the etiology was known, initial investigations included serum liver enzymes, triglycerides, calcium, and abdominal ultrasound. Further investigations (usually for ARP and CP) included magnetic resonance or other imaging, sweat chloride, and genetic testing. Respondents' future goals for INSPPIRE included determining natural history of pancreatitis, developing algorithms to evaluate and manage pancreatitis, and validating diagnostic criteria.

Conclusions: INSPPIRE represents the first initiative to create a multicenter approach to systematically characterize pancreatitis in children. Future aims include creation of patient database and biologic sample repository.

Key Words: acute pancreatitis, acute recurrent pancreatitis, chronic pancreatitis, definitions, pediatrics, practice parameters

Received December 29, 2011; accepted February 6, 2012.

From the *Division of Pediatric Gastroenterology and Nutrition, Montreal Children's Hospital, McGill University, Montreal, Canada, the †Department of Pediatrics, Division of Gastroenterology, Hepatology, and Nutrition, Children's Hospital of Pittsburgh, Pittsburgh, PA, the ‡Department of Pediatrics, Yale University School of Medicine, New Haven, CT, the §Department of Pediatrics, University of Texas Southwestern Medical School, Dallas, TX, the ||Department of Pediatrics, University of Iowa Carver College of Medicine, Iowa City, IA, the ¶Department of Pediatrics, Hospital for Sick Children, Toronto, Canada, the #Department of Medicine, Harvard Medical School, Boston, MA, the **Baylor College of Medicine, Houston, TX, the ††University of Utah, Salt Lake City, UT, the ‡‡Medical College of Wisconsin, Milwaukee, WI, and the §§Hadassah University Hospitals, Jerusalem, Israel.

Address correspondence and reprint requests to Dr Aliye Uc, 2865 JPP Pediatrics, University of Iowa, 200 Hawkins Dr, Iowa City, IA 52242 (e-mail: aliye-uc@uiowa.edu).

V.D.M. and S.Z.H. participated equally in the present study.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.jpjn.org).

INSPIRE members 2010–2011: Maisam Abu-Al-Haija, Rabea Alhosh, Harrison Bai, Bradley Barth, Melena Bellin, Pam Brown, Peter Durie, Douglas Fishman, Steven Freedman, Cheryl Garipey, Matthew Giefer, Jeff Goldsmith, Tanja Gonska, Julia Greer, Ryan Himes, Sohail Husain, Mel Hyman, Daina Kalnins, Soma Kumar, James Lopez, Mark Lowe, Alan Mayer, Veronique Morinville, Keith Ooi, John Pohl, Alexandra Quittner, Sarah Jane Schwarzenberg, Aliye Uc, James Varni, Narayanan Venkatasubramini, Michael Wilschanski, Steven Werlin. Definitions subcommittee: Veronique D. Morinville (chair), Ryan Himes, John Pohl, Steven Werlin. Survey subcommittee: Sohail Husain (chair); Harrison X. Bai, Bradley Barth, Michael Wilschanski, Rabea Alhosh.

The authors report no conflicts of interest.

Copyright © 2012 by European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

DOI: 10.1097/MPG.0b013e31824f1516

(*JPGN* 2012;55: 261–265)

Publications from the last few decades describe an increasing incidence of AP in both children and adults (1–3). This may represent a true rise in the incidence of pediatric pancreatitis or other factors such as improved awareness of the condition (4–6). The prevalence of AP in adults ranges between 6 and 45/100,000 person-years in various populations and ages, with lesser rates reported in younger patients (1,2,7). Two studies estimated the incidence of pancreatitis at 3.6 and 13.2 cases per 100,000 children (8,9). The latter number is in the range of the incidence for pancreatitis in adults, confirming that the pancreatitis is not a rare disease in children (10).

There is limited literature regarding acute recurrent pancreatitis (ARP) and chronic pancreatitis (CP) in children. The epidemiology and the natural history of pediatric ARP and CP are not well understood, and there are no evidence-based diagnostic, prognostic, and treatment guidelines for these disorders. Consequently, pediatric specialists often rely on diagnostic, prognostic, and treatment guidelines that have been derived from adults. This is problematic because the etiologies of pancreatitis in children are markedly different from adults, and all of the prognostic algorithms and therapeutic guidelines fail to consider the unique age-related requirements of childhood. For instance, major factors implicated in CP in adults include alcohol use and cigarette smoking, confounders that are rarely found in children (11–15). Because childhood-onset ARP and CP are relatively uncommon, efforts to ascertain retrospective clinical data from single institutions have failed to advance the field of knowledge concerning the incidence, natural history, morbidity, and mortality of these conditions. Furthermore, there have been no multicenter clinical trials in children. To advance our present understanding of ARP and CP, we formed a consortium

named International Study Group of Pediatric Pancreatitis: In Search for a Cure (INSPPIRE). Present members of the consortium include gastroenterologists with an interest in pancreatitis and individuals from related disciplines (please refer to the Sponsorship section).

The first objectives of the consortium were to develop a consensus statement on the definitions of childhood-onset AP, ARP, and CP with the goal of accurately phenotyping children for future studies; and survey pediatric gastroenterologists with an interest in pancreatitis to estimate the prevalence of AP, ARP, and CP and to obtain data on present clinical practice concerning diagnostic evaluation and management. Respondents were also asked to list their top research priorities. The eventual goal was to develop a database of children with ARP and CP and to understand the epidemiology, etiologies, natural history, and outcome in a well-phenotyped cohort of children with ARP and CP.

METHODS

Diagnostic Definitions

A subcommittee (V.D.M. [chair], R.H., J.P., S.W.) was formed in summer 2010. The goals of the subcommittee were to review available literature for consensus definitions of AP, ARP, and CP (16–18), develop a draft document for circulation to other members of the INSPPIRE group during fall 2010, and draft a revised document to achieve final consensus at the INSPPIRE meetings in December 2010 and May 2011. The goal of the subcommittee was to develop the definitions that would accurately

classify children with pancreatitis, and thus create a homogenous population that could be easily phenotyped and included in future prospective studies.

Clinical Survey

A subcommittee (S.H. [chair], B.B., M.W., R.A., H.B.) was formed in summer 2010. The goals of the subcommittee were to develop a survey to determine the demographic features of the respondents, their present practice patterns, and to ascertain data on the number of children with AP, ARP, and CP seen at each institution. Practice patterns were determined by developing clinical vignettes that were designed to reflect many of the diagnostic, etiologic, and therapeutic challenges relating to ARP and CP (see the online-only Appendix for the survey questionnaire, <http://links.lww.com/MPG/A105>). The survey protocol was approved by the University of Texas Southwestern Medical Center institutional review board (STU 092010–223). The Internet-based survey instrument SurveyMonkey (Palo Alto, CA) was used for survey enrollment. Pediatric gastroenterologists within INSPPIRE (21 total) were invited to complete the survey in late 2010.

RESULTS

Diagnostic Definitions

The definitions for pediatric AP, ARP, and CP are outlined in Table 1 (19,20).

TABLE 1. Definitions of pancreatitis in children

Entity	Clinical definition
AP	Requires at least 2 of 3 criteria: 1. Abdominal pain suggestive of, or compatible with AP (ie, abdominal pain of acute onset, especially in the epigastric region) 2. Serum amylase and /or lipase activity at least 3 times greater than the upper limit of normal (IU/L) 3. Imaging findings characteristic of, or compatible with AP (eg, using U/S, CECT, EUS, MRI/MRCP)
Pediatric onset	First episode of AP occurring before the patient's 19th birthday
ARP	Requires at least 2 distinct episodes of AP (each as defined above), along with: • Complete resolution of pain (≥ 1 -month pain-free interval between the diagnoses of AP) OR • Complete normalization of serum pancreatic enzyme levels (amylase and lipase), before the subsequent episode of AP is diagnosed, along with complete resolution of pain symptoms, irrespective of a specific time interval between AP episodes
CP	Requires at least 1 of the following 3: 1. Abdominal pain consistent with pancreatic origin and imaging findings suggestive of chronic pancreatic damage* 2. Evidence of exocrine pancreatic insufficiency [†] and suggestive pancreatic imaging findings* 3. Evidence of endocrine pancreatic insufficiency [‡] and suggestive pancreatic imaging findings* OR • Surgical or pancreatic biopsy specimen demonstrating histopathologic features compatible with CP

AP = acute pancreatitis; ARP = acute recurrent pancreatitis; CECT = contrast-enhanced computerized tomography; CP = chronic pancreatitis; EUS = endoscopic ultrasonography; MRI/MRCP = magnetic resonance imaging/magnetic resonance cholangiopancreatography; U/S = transabdominal ultrasonography.

*Suggestive imaging findings of chronic pancreatitis/chronic pancreatic damage including: ductal changes (irregular contour of the main pancreatic duct or its radicles; intraductal filling defects; calculi, stricture or dilation) and parenchymal changes (generalized or focal enlargement, irregular contour [accentuated lobular architecture], cavities, calcifications, heterogeneous echotexture). Imaging modalities may include CT, MRI/MRCP, ERCP; U/S; EUS (in which at least 5 EUS features [as defined by the Rosemont classification (19)] must be fulfilled).

[†]Exocrine pancreatic insufficiency to be diagnosed via fecal elastase-1 monoclonal assay $< 100 \mu\text{g/g}$ stool (2 separate samples done ≥ 1 month apart); or coefficient of dietary fat absorption $< 90\%$ on a 72-hour fecal fat collection. Neither test should be performed during an acute pancreatitis episode because the results may be temporarily low. Children with classic cystic fibrosis, exhibiting early-onset pancreatic insufficiency without earlier evidence of any meaningful pancreas sufficiency, typically should not be diagnosed as having CP. They do not have chronic abdominal pain and pancreatic imaging findings described in the CP criteria.

[‡]Endocrine pancreatic insufficiency to be diagnosed via 2006 World Health Organization criteria for the diagnosis of diabetes mellitus (fasting glucose $\geq 7.0 \text{ mmol/L}$ (126 mg/dL) or plasma glucose $\geq 11.1 \text{ mmol/L}$ (200 mg/dL) 2 hours after glucose load 1.75 g/kg children (to maximum 75-g glucose load) (20).

AP

Abdominal pain associated with AP may be vague in children and may not radiate to the back. Lipase elevations may be a more sensitive finding in younger children, although either lipase and/or amylase elevation may be observed. Although recommended imaging modalities are similar to those used for adult patients, pediatric experts are more likely to select tests that limit radiation exposure (ie, transabdominal ultrasonography [U/S]) and recognize that certain modalities may be more difficult to perform because of patient size and sedation needs (eg, endoscopic retrograde cholangiopancreatography [ERCP], endoscopic ultrasonography [EUS], or magnetic resonance cholangiopancreatography [MRCP]).

Imaging features compatible with AP include pancreatic edema, pancreatic or peripancreatic necrosis, peripancreatic inflammation, acute fluid collections, pancreatic hemorrhage, pancreatic abscess, and pancreatic pseudocyst (signifying a recent AP episode).

Although imaging is not necessary as part of the diagnostic workup for AP if the other 2 criteria are fulfilled, transabdominal U/S is frequently used to rule out an obstructive etiology (eg, choledochal cyst, traumatic injury, tumor, stones). Imaging is frequently normal in AP because the U/S is the imaging modality of choice in most pediatric cases (5).

ARP

We propose that the term ARP be used instead of recurrent acute pancreatitis (RAP) to avoid confusion with the same abbreviation, RAP, which is commonly used by pediatricians to describe recurrent abdominal pain. An important exclusion would include a child who, following an episode of AP, presented with recurrence of pain and imaging showing a well-formed pseudocyst. The presence of a pseudocyst would suggest a complication arising from the first episode of pancreatitis rather than a new episode.

CP

CP, histopathologically defined in the same manner as in adults, consists of an inflammatory process characterized by irreversible morphologic changes and fibrotic replacement of the pancreatic parenchyma. In CP, fibrosis and ductal obstruction may give rise to radiographically evident calcifications and pancreatic duct irregularities such as strictures and dilations, or histologic evidence of sclerosis/fibrosis, acinar and islet cell loss, inflammatory infiltrates, pancreatic duct abnormalities/scarring, and intraductal calculi (21,22). Because a histopathological diagnosis of pediatric-onset CP is rare due to the risks of performing a pancreatic biopsy, clinical criteria are considered more pragmatic for defining CP (12,19,22,23); however, should a surgical resection specimen or biopsy be available, CP could be diagnosed based on compatible findings.

Importantly, children could present with features diagnostic of CP without having had an earlier diagnosis of AP. Abdominal pain in CP may be variably described by children; therefore, imaging characteristic of chronic pancreatic damage in conjunction with chronic abdominal pain symptoms fulfills diagnostic criteria for CP. Children with classic exocrine pancreatic insufficiency due to cystic fibrosis typically should not be diagnosed as having CP.

Clinical Survey

A 91% response rate was achieved for the internet-based survey, which included 19 of the 21 eligible members (17 attending

gastroenterologists and 2 pediatric gastroenterology trainees). Only 16 members representing the most senior attending gastroenterologists from 16 different institutions were included in the final analysis. The majority were physicians practicing in the United States (75%), who represented all of the geographic regions. Sixty-three percent had been practicing pediatric gastroenterology for >10 years. All of the physicians practiced at either tertiary or quaternary academic centers.

Approximately two-thirds of respondents felt that the number of admissions for AP has increased in the previous 3 years at their respective institutions. Half of the group (56%) estimated that they managed >40 children with AP each year at their institution, and about one fifth (19%) reported that they followed >100 patients per year. Most (69%) managed only 1 to 3 cases of severe AP per year. Considering patients with ARP, the majority of respondents were split between seeing 11 to 20 children per year (31%) or 31 to 40 children per year (38%) (Fig. 1A). The majority of physicians (56%) followed 11 to 20 outpatients with CP at their institution (Fig. 1B).

Pediatric gastroenterologists participated primarily in the care of children with pancreatitis. Respondents were more likely to be involved in the management of children with ARP (89%) and CP (94%), than those presenting with AP (63%).

There was general agreement on most of the practice parameters for AP and ARP. Severe AP was defined as pancreatitis leading to multiorgan dysfunction, pancreatic necrosis, or death. Bowel rest and intravenous fluids were the initial management for AP (81% of mild AP vs 75% of severe AP, whereas 18% instituted total parenteral nutrition). Resolution of abdominal pain was the most important factor in deciding when to begin oral feedings (50% of respondents). Forty-four percent of participants would “often” use enteral tube feedings in the course of AP management. Morphine or related opioid drugs were the medications of choice for pain control in AP (94%). Seventy-five percent provided narcotics for CP-associated pain, with (50%) or without (25%) centrally acting agents, such as gabapentin. Sixty-nine percent of respondents “often” or “always” referred children with CP to a pain clinic or pain specialist.

Most respondents (63%) stated that their routine evaluation of a child presenting with AP of unclear etiology and lacking a family history of pancreatitis included liver enzymes, serum triglycerides, and calcium levels, as well as an abdominal ultrasound (Fig. 2). Sixty-nine percent of the respondents reserved other imaging modalities such as magnetic resonance imaging/MRCP (MRI/MRCP) as well as genetic testing or sweat chloride to children presenting with ARP or CP without a clear etiology or

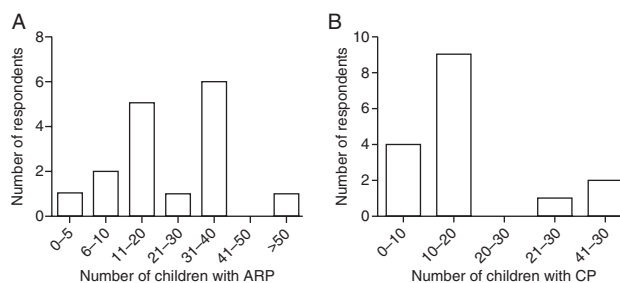


FIGURE 1. International Study Group of Pediatric Pancreatitis: In Search for a Cure survey demographics. Respondents were asked to estimate the number of children they followed at their institution with (A) acute recurrent pancreatitis (ARP), and (B) chronic pancreatitis (CP). Results show the number of children with ARP and CP that are seen by the respondents.

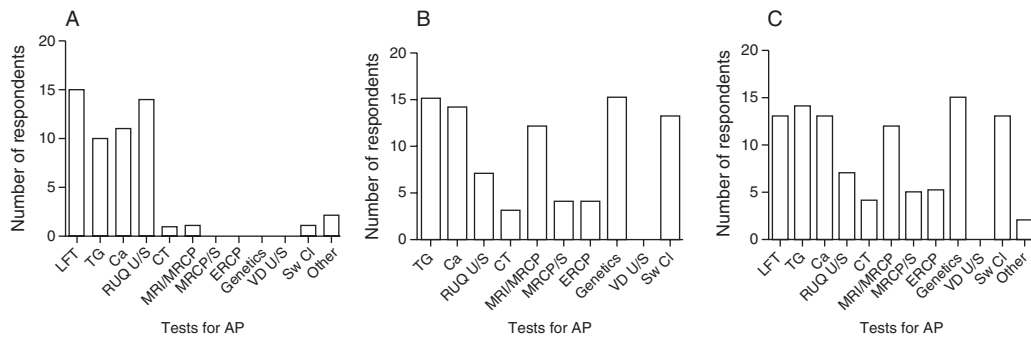


FIGURE 2. INSPPIRE survey diagnostics. Respondents were presented with clinical case scenarios and asked to choose within a list of suggested investigations for (A) single-episode mild AP without known etiology or family history of pancreatitis; (B) acute recurrent pancreatitis (ARP) (2 episodes within 1 year) without known etiology or family history of pancreatitis or pancreatic cancer. Ca = serum calcium; CT = computerized tomography; ERCP = endoscopic retrograde cholangiopancreatography; genetics: gene testing for protease serine-1, serine protease inhibitor Kazal type 1 (SPINK1), cystic fibrosis transmembrane conductance regulator (CFTR) mutations; INSPPIRE = International Study Group of Pediatric Pancreatitis: In Search for a Cure; LFT = liver function tests; MRCP/S = magnetic resonance cholangiopancreatography with secretin; MRI/MRCP = magnetic resonance imaging/magnetic resonance cholangiopancreatography; RUQ U/S = right upper quadrant ultrasound; Sw Cl = sweat chloride; TG = serum triglycerides; VD U/S = vas deferens ultrasound.

family history of pancreatitis or pancreatic cancer. Ninety-four percent of respondents would order genetic testing for protease serine-1 (cationic trypsinogen), serine protease inhibitor Kazal type 1, and cystic fibrosis transmembrane conductance regulator mutations to evaluate for the etiology of ARP or CP, irrespective of the age of presentation. All of the practitioners had access to advanced endoscopic procedures as necessary (eg, ERCP and/or EUS), although most respondents (88%) relied on the expertise of adult gastroenterology colleagues to perform these procedures.

All of the participants measured fecal elastase levels to diagnose or monitor for pancreatic exocrine insufficiency, whereas 44% also performed a 3-day stool collection for fecal fat analysis. A minority of the respondents routinely evaluated exocrine function further via endoscopic pancreatic function testing including secretin stimulation with or without cholecystokinin stimulation, stool chymotrypsin, serum trypsinogen, or serum levels of fat-soluble vitamins.

The 3 main goals the group identified for future investigation were to determine the natural history (clinical course and outcome) of children with acute and CP; to develop algorithms for diagnosing, evaluating, and managing patients with acute or CP; and to establish and validate diagnostic criteria for acute and CP in children. Other important goals included determining the optimal imaging for diagnosis, standardizing the assignment of etiologies, identifying gene mutations in children with “idiopathic” ARP, and predicting clinical outcomes following an acute episode of pancreatitis.

DISCUSSION

In the present study, we highlighted the following observations: pancreatitis (acute, recurrent acute, and chronic) is an emerging problem in pediatrics; there are no established diagnostic criteria and evidence-based therapeutic options for children with pancreatitis; and due to limited numbers of children with pancreatitis at a single center, a multicenter effort is needed to establish a well-phenotyped cohort of children to understand the etiology and natural history of ARP and CP and to design therapeutic trials.

The constitution of INSPPIRE represents the first initiative to create a multicenter approach to systematically characterize pancreatitis in children. Our consortium is geographically diverse and includes nationally and internationally recognized pancreatologists

as well as young and mid-career members who are developing pediatric pancreatology as their focus. The efforts described in this manuscript represent the first attempt of our group to formalize standard definitions of AP, ARP, and CP in children that will be used in future research efforts and to document the present status of practice patterns in pediatric pancreatitis. We also identified the most important questions in pediatric pancreatitis as we continue our efforts to develop a database of children with ARP and CP to understand the epidemiology, etiologies, natural history, and outcome of these diseases.

Our efforts parallel a multicenter effort of adult patients with pancreatitis, the North American Pancreatitis Study 2 (24). Constitution of North American Pancreatitis Study 2 has led to a better understanding of the epidemiology, etiology, and outcomes of pancreatitis in adult patients. We anticipate that INSPPIRE will achieve similar results in pediatric pancreatitis.

This is the first study describing the definitions of AP, ARP, and CP in pediatric patients. We acknowledge that these definitions are based on the sparse pediatric literature and expert opinions mostly derived from adult studies. The use of expert opinion has clear limitations because it is based on personal experience rather than on scientific scrutiny. Because there is such a paucity of literature and lack of presently well-accepted standards, the opinion from a group of experts is the best first step to developing a standardized practice. As we continue our investigations on pediatric pancreatitis, we anticipate that these diagnostic criteria will require refinement.

There were several limitations of our clinical survey. First, we had a small sample size; however, the respondents were all experts and clinicians with a clinical interest in the field of pediatric pancreatitis, and the response rate was excellent (91%). Second, the survey was based on recollection and not actual database reviews; hence, there was the possibility of recall bias. Third, because the data were taken from tertiary and quaternary care centers, we may not have captured the management of children followed at community-based hospitals. The number of patients followed at primary care facilities will probably be small because children with ARP and CP are typically referred to the tertiary care centers for consultation or further testing. Nevertheless, future studies will include children with ARP and CP followed at primary and secondary care facilities; however, in spite of the limitations, the general patterns of care and numbers of cases can be used to guide future work.

The results of this survey offered insights into how pediatric pancreatitis practice differs from adult practice. For example, there was infrequent use of invasive workups (eg, ERCP, EUS) as first-line testing. By contrast, U/S was used in the initial presentation more commonly than computed tomography scanning to limit radiation exposure. MRI/MRCP was frequently performed in cases of pediatric ARP and CP, emphasizing its importance in the investigation of anatomical abnormalities. Based on our study and the present practice, ultrasound and MRCP should be considered to exclude anatomical abnormalities in children with ARP and CP.

Pediatric specialists rarely ordered enteral tube feedings in cases of AP, even though “early” enteral tube feeding is recommended in the management of severe AP in adults (25–28). Pancreatic stimulation tests were also rarely used for the diagnosis of exocrine pancreatic dysfunction in children; INSPPIRE members tended to use fecal elastase measurements instead.

There are limited data on the etiology and diagnostic testing of ARP and CP in children (29,30). Our survey represents the first multicenter effort to describe the practice patterns at institutions that evaluate and treat children with ARP and CP. We have demonstrated that most experts are relatively conservative with the workup of a single episode of AP, but detailed investigation is implemented once a child presents with ARP or CP. Based on our study, we are presently unable to make solid recommendations for the diagnostic testing of ARP and CP, nor are we able to comment on the reliability of diagnostic techniques used for the assessment of exocrine pancreatic function. This will be the focus of future studies.

A larger multicenter sample of properly phenotyped and subsequently genotyped pediatric patients with pancreatitis will help determine appropriate testing and optimal management while limiting unnecessary tests and interventions. Health-related quality of life measurements of this pediatric population may also be beneficial to determine whether medical management is optimal (31).

In summary, the INSPPIRE Consortium is the first multicenter effort to overcome the barriers that have hampered progress in the field of pediatric pancreatology and to develop evidence-based therapies for pediatric patients with ARP and CP. We described the definitions of AP, ARP, and CP. We also reported the demographics and the clinical practice patterns of pediatric pancreatitis and identified the most important questions for prospective studies. Future plans of INSPPIRE include working on the priorities identified by the group through well-designed, multicenter research collaborations, including the development of diagnostic and management algorithms, understanding the etiology, epidemiology, and natural history of ARP and CP in children, and investigating whether functional alterations in cystic fibrosis transmembrane conductance regulator, protease serine-1, serine protease inhibitor Kazal type 1, or other modifier genes contribute to the presence and severity of pediatric pancreatitis. The creation of a database and a biorepository of children with ARP and CP will be a crucial step to answering these questions.

REFERENCES

1. Satoh K, Shimosegawa T, Masamune A, et al. Nationwide epidemiological survey of acute pancreatitis in Japan. *Pancreas* 2011;40:503–7.
2. Yadav D, Lowenfels AB. Trends in the epidemiology of the first attack of acute pancreatitis: a systematic review. *Pancreas* 2006;33:323–30.
3. Joergensen M, Brusgaard K, Cruger DG. Incidence, prevalence, etiology, and prognosis of first-time chronic pancreatitis in young patients: a nationwide cohort study. *Dig Dis Sci* 2010;55:2988–98.
4. Bai HX, Lowe ME, Husain SZ. What have we learned about acute pancreatitis in children? *J Pediatr Gastroenterol Nutr* 2011;52:262–70.
5. Park A, Latif SU, Shah AU, et al. Changing referral trends of acute pancreatitis in children: a 12-year single-center analysis. *J Pediatr Gastroenterol Nutr* 2009;49:316–22.
6. Morinville VD, Barmada MM, Lowe ME. Increasing incidence of acute pancreatitis at an American pediatric tertiary care center: is greater awareness among physicians responsible? *Pancreas* 2010;39:5–8.
7. Shen HN, Lu CL. Incidence, resource use, and outcome of acute pancreatitis with/without intensive care: a nationwide population-based study in Taiwan. *Pancreas* 2011;40:10–5.
8. Keim V, Witt H, Bauer N, et al. The course of genetically determined chronic pancreatitis. *JOP* 2003;4:146–54.
9. Rebours V, Boutron-Ruault MC, Schnee M, et al. The natural history of hereditary pancreatitis: a national series. *Gut* 2009;58:97–103.
10. Corfield AP, Cooper MJ, Williamson RC. Acute pancreatitis: a lethal disease of increasing incidence. *Gut* 1985;26:724–9.
11. Sajith KG, Chacko A, Dutta AK. Recurrent acute pancreatitis: clinical profile and an approach to diagnosis. *Dig Dis Sci* 2010;55:3610–6.
12. DiMaggio MJ, DiMaggio EP. Chronic pancreatitis. *Curr Opin Gastroenterol* 2010;26:490–8.
13. Al-Haddad M, Wallace MB. Diagnostic approach to patients with acute idiopathic and recurrent pancreatitis, what should be done? *World J Gastroenterol* 2008;14:1007–10.
14. Whitcomb DC. Genetic aspects of pancreatitis. *Annu Rev Med* 2010;61:413–24.
15. Etamad B, Whitcomb DC. Chronic pancreatitis: diagnosis, classification, and new genetic developments. *Gastroenterology* 2001;120:682–707.
16. Romagnuolo J, Guda N, Freeman M, et al. Preferred designs, outcomes, and analysis strategies for treatment trials in idiopathic recurrent acute pancreatitis. *Gastrointest Endosc* 2008;68:966–74.
17. Nieselstein RA, Robben SG, Blickman JG. Hepatobiliary and pancreatic imaging in children—techniques and an overview of non-neoplastic disease entities. *Pediatr Radiol* 2011;41:55–75.
18. Trout AT, Elsayes KM, Ellis JH, et al. Imaging of acute pancreatitis: prognostic value of computed tomographic findings. *J Comput Assist Tomogr* 2010;34:485–95.
19. Catalano MF, Sahai A, Levy M, et al. EUS-based criteria for the diagnosis of chronic pancreatitis: the Rosemont classification. *Gastrointest Endosc* 2009;69:1251–61.
20. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* 2003;26(suppl 1):S5–20.
21. Behrman SW, Fowler ES. Pathophysiology of chronic pancreatitis. *Surg Clin North Am* 2007;87:1309–24.
22. Buchler MW, Martignoni ME, Friess H, et al. A proposal for a new clinical classification of chronic pancreatitis. *BMC Gastroenterol* 2009;9:93.
23. Glasbrenner B, Kahl S, Malfertheiner P. Modern diagnostics of chronic pancreatitis. *Eur J Gastroenterol Hepatol* 2002;14:935–41.
24. Whitcomb DC, Yadav D, Adam S, et al. Multicenter approach to recurrent acute and chronic pancreatitis in the United States: the North American Pancreatitis Study 2 (NAPS2). *Pancreatology* 2008;8:520–31.
25. Hegazi R, Raina A, Graham T, et al. Early jejunal feeding initiation and clinical outcomes in patients with severe acute pancreatitis. *J Parenter Enteral Nutr* 2011;35:91–6.
26. Kumar A, Singh N, Prakash S, et al. Early enteral nutrition in severe acute pancreatitis: a prospective randomized controlled trial comparing nasojejunal and nasogastric routes. *J Clin Gastroenterol* 2006;40:431–4.
27. Singh N, Sharma B, Sharma M, et al. Evaluation of early enteral feeding through nasogastric and nasojejunal tube in severe acute pancreatitis: a noninferiority randomized controlled trial. *Pancreas* 2012;41:153–9.
28. Petrov MS, Correia MI, Windsor JA. Nasogastric tube feeding in predicted severe acute pancreatitis. A systematic review of the literature to determine safety and tolerance. *JOP* 2008;9:440–8.
29. Sanchez-Ramirez CA, Larrosa-Haro A, Flores-Martinez S, et al. Acute and recurrent pancreatitis in children: etiological factors. *Acta Paediatr* 2007;96:534–7.
30. Lucidi V, Alghisi F, Dall'Oglio L, et al. The etiology of acute recurrent pancreatitis in children: a challenge for pediatricians. *Pancreas* 2011;40:517–21.
31. Pohl JF, Limbers CA, Kay M, et al. Health-related quality of life in pediatric patients with long-standing pancreatitis. *J Pediatr Gastroenterol Nutr* 2012;54:824–7.