Updates in Pediatric Pancreatology: Proceedings of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition *Frontiers in Pediatric Pancreatology* Symposium

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ABSTRACT

The Pancreas Committee of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition aims to promote awareness of pediatric pancreatic diseases, support clinical and basic science research in the field, educate pediatric gastroenterologists, and advocate on behalf of pediatric patients with pancreatic disorders. At the 2017 Annual North American Society for Pediatric Gastroenterology, Hepatology and Nutrition meeting, the Pancreas Committee held a full day symposium on pediatric pancreatic diseases, entitled, ''*Frontiers in Pediatric Pancreatology*.'' The symposium served as a timely and novel academic meeting that brought together individuals with a vested interest in the care of children with pancreatic disorders. The objective of this day-long course was to update practicing gastroenterologists on the latest advances in research, management algorithms, endoscopic therapies, radiographic resources, surgical approaches, and novel drug therapies targeted to pediatric pancreatitis. Presentations were divided into 4 modules: diagnosis, risk factors, and natural history of pancreatitis; pancreatic imaging and exocrine function; management of pancreatitis; and new frontiers in pediatric pancreatitis research. The course fostered a unique ecosystem for interdisciplinary collaboration, in addition to promoting discussion and stimulating new research hypotheses regarding pediatric pancreatic disorders. Oral presentations by experts in various fields of pancreatology led to thought-provoking discussion; in addition, a meet-the-professor luncheon stimulated critical evaluation of current research in pediatric pancreatic diseases, highlighting knowledge gaps and future research endeavors. The current report summarizes the major learning points from this novel symposium focusing on the growing demographic of pediatric pancreatic diseases.

Key Words: childhood pancreatic disorders, chronic pancreatitis, exocrine insufficiency, medication-associated pancreatitis

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Pancreatitis is the most common pancreatic disease of childhood with an increasing incidence estimated at 13 cases in 100,000 children per year (1–3). There continues to be a dearth of pediatric literature, and most pediatric gastroenterologists typically rely on diagnostic, prognostic, and treatment guidelines published in adult pancreatitis. In recent years, however, there has been a newfound interest in pediatric pancreatic diseases, and a growing cohort of pediatric gastroenterologists have become engaged in collectively studying and treating acute and chronic pancreatitis (CP). The past decade has seen advances not only in diagnostic and therapeutic modalities but also radiographic, endoscopic, and basic science research related to pediatric pancreatic disorders. On November 1, 2017 the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN)

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Pancreas Committee held a single day symposium during its Annual Meeting, entitled, ''*Frontiers in Pediatric Pancreatology*,'' which included 234 attendees, of whom 20% identified themselves as trainees. The focus of the full day symposium was to report the most current advances in pediatric pancreatic disease to a target audience of pediatric gastroenterologists, gastroenterology trainees, clinical and basic sciences researchers, and specialized affiliated health care providers. The goal was to highlight current research, both clinical and basic science, which could be used to aid in the treatment of children with pancreatic disease, to demonstrate gaps in knowledge, to foster discussion and collaboration, and to stimulate a new generation of pediatric gastroenterologists to enter the field of pediatric pancreatology. The Symposium reflected years of preparation by the NASPGHAN Pancreas Committee, including the initial formation of a scientific organizing committee to brainstorm on pancreas-related topics that would be of interest to a broad audience, and subsequent limitations as to number and type of presentations, to address the needs and maintain interests of both clinicians and basic researchers. Topics were then divided up into modules to present data that had thematic overlaps and allow discussion amongst the involved speakers at the conclusion of each. The final symposium agenda was divided into 4 modules. The current manuscript presents the available proceedings from each of the sessions.

MODULE 1: DIAGNOSIS, RISK FACTORS, AND NATURAL HISTORY OF PANCREATITIS IN CHILDREN

Why Do Some Drugs Cause Pancreatitis?—Sohail Z. Husain, MD

Drugs are associated with acute pancreatitis (AP) in upwards of a fifth of all cases in children (4). Drug exposure can either be a sole etiology for the pancreatitis or, in about a third of cases, it can predispose patients with other concomitant risk factors to the development of pancreatitis. Determining causation beyond mere association is often challenging and requires knowledge of the pattern of pancreatitis previously reported with the drug exposure (5). Questions that need to be asked include the temporal sequence, or latency period, between first exposure (or sometimes dose escalation) and pancreatitis onset, whether there was relief after stopping the drug, and, in select cases, whether there was recurrence of pancreatitis after a repeat challenge (6). It is important to recognize the drugs that are definitely associated with pancreatitis. They include several antiepileptics, particularly valproic acid, some medications for inflammatory bowel disease, such as the thiopurines and mesalamine, and the chemotherapeutic drug asparaginase. The mechanisms underlying drug-induced pancreatitis are not well understood. Some drugs, for example, valproic acid, appear to dampen the ability of the pancreas to regenerate, whereas others, for example, asparaginase, trigger nutrient deprivation responses in the pancreas. Emerging insight into these mechanisms, and their pharmacogenomic determinants, is likely to help with screening patients for the likelihood of developing pancreatitis with drug exposure. The information could also guide rescue therapies for pancreatitis in conditions in which the drug is an integral part of the therapeutic regimen; a prime example is asparaginase, which is a crucial treatment for acute lymphoblastic leukemia. In the meantime, for most other drugs, the drug exposure should be immediately discontinued upon identification of a probable role in the development of pancreatitis. It has been reported that some drugs can be rechallenged without recurrence of pancreatitis (7); however, more research and further investigation into this area and specific drugs is needed. Such decision making will require a more comprehensive analysis of patient outcomes and database accrual of patient information into a framework similar to the existing drug-induced liver injury network.

The Role of Endoscopy in Children With Pancreatitis—Quin Y. Liu, MD

Endoscopic methods to evaluate and treat childhood pancreatitis include endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography (ERCP). EUS affords the ability to noninvasively visualize the pancreas up close, to evaluate for features of chronic inflammation, and importantly to obtain tissue by fine-needle aspiration or fine-needle core biopsy. Although studies have not been conducted in children, positive EUS findings for CP changes have shown to have a high correlation of 96.2% with histological fibrosis scores for chronic changes to the pancreas (8). EUS-guided drainage is also the modality of choice for the treatment of pancreatic fluid collections such as pseudocysts and walled-off necrosis. As a result of the growing use of EUS and the wider availability of cross-sectional imaging modalities, the use of ERCP for the diagnosis of pancreatic disease is diminishing. ERCP continues to play a dominant therapeutic role in the management of ductal complications of pancreatitis, including pancreatic duct strictures and pancreatic duct stones. Data from the INSPPIRE (International Study Group of Pediatric Pancreatitis: In Search for a Cure) consortium have shown that children with CP have a higher likelihood of undergoing therapeutic ERCP compared with children with acute recurrent pancreatitis (ARP). Also, children have a good response to therapeutic ERCP for pancreatic duct stone clearance and also stenting for pancreatic duct stricture with decrease incidences of AP attacks (9,10). The efficacy of ERCP for idiopathic ARP, on the contrary, is less clear (11). The utilization of EUS and ERCP will continue to expand in pediatric pancreas diseases as more pediatric gastroenterologists are being trained in these endoscopic modalities. It will be important to study key questions about the role of endoscopy in pediatric pancreatitis, such as the optimal timing of endoscopic management and whether patients with certain subsets of patients, for example, with distinct etiologies, have a more favorable response to endotherapy.

MODULE 2—PANCREATIC IMAGING AND EXOCRINE FUNCTION IN CHILDREN

Imaging Methods to Assess the Pancreas in Children: Emphasis on Emerging Technologies—Andrew T. Trout, MD

Ultrasound (US), computerized tomography (CT), and magnetic resonance imaging (MRI) are the mainstay for imaging pediatric pancreatic diseases. When selecting a modality for routine imaging of pancreatic disease, pediatric gastroenterologists should be aware of the strengths and weaknesses of each of these modalities. Briefly, US benefits from portability and lower cost but provides a limited field of view. CT and MRI provide better characterization of the pancreas and surrounding tissues, with MRI excelling at duct and parenchymal characterization and CT having advantages for detection of pancreatic calcifications and for rapid assessment of an unstable patient.

Newer imaging techniques are allowing physicians to move beyond the basic assessment of pancreatic morphology and viability, to a more in-depth characterization of both parenchymal and ductal health, as well as exocrine function. Such techniques are currently exploratory, but they hold great promise as potential biomarkers in clinical studies, particularly in the pediatric population in which noninvasive techniques are highly preferred.

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Examples of emerging techniques include: tissue stiffness, which reflects inflammation and fibrosis and can now be measured noninvasively by both US and MRI (12). MRI also allows increased parenchymal characterization through signal mapping (T1, T2, and diffusion) (13) and can be leveraged to noninvasively assess exocrine function in response to secretin administration. Historically, qualitative assessments of pancreatic secretory function have been the norm but a more quantitative assessment of secretory function is being developed, along with normal ranges for both adults and children (14). With the recent Food and Drug Administration approval of microbubble contrast agents, contrast-enhanced US is also now available in the United States, allowing an additional means to image perfusion of the pancreas and peripancreatic tissues.

Diagnosis and Treatment of Exocrine Pancreatic Insufficiency in 2017—Mark E. Lowe, MD

The pancreas has dual exocrine and endocrine functions. Pancreatic acinar cells secrete large amounts of digestive enzymes that digest starch, protein, and fats. The failure to produce enough enzymes for nutrient processing is termed exocrine pancreatic insufficiency (EPI). Starches require amylase to convert them into products that can be absorbed in the intestine. Pancreatic proteases digest native proteins, and oligopeptides that are initially hydrolyzed by gastric pepsin. Lipases act on dietary fats, mostly triglycerides, to release the acyl chains from the glycerol backbone. Enterocytes take up the resultant fatty acids. Although carbohydrate or protein maldigestion can produce symptoms, fat maldigestion is the cause of steatorrhea, the primary symptom of EPI. The presence of EPI can be measured by what are termed direct or indirect tests of pancreatic function. No test measures both the secretory and digestive capacity of pancreatic enzymes. Fecal elastase-1 has become the preferred indirect test for pancreatic function. It is only useful for detecting severe EPI. The treatment of EPI is with pancreatic enzyme replacement therapy (PERT). In dosing PERT, the effect of low pH on pancreatic lipase activity and timing of the enzymes with the release of dietary fat from the stomach are important considerations. Most dietary fat leaves the stomach 30 to 60 minutes after eating. Increasing the dose of PERT is not always the answer in patients with gastrointestinal symptoms and other causes for the symptoms should be considered. A new in-line cartridge with immobilized lipase can efficiently digest fats in real time as formula is being infused for tube-fed patients (15). On the horizon are recombinant preparations of digestive enzymes. Diagnosing EPI and the optimal timing of enzyme administration to benefit digestion remain challenges in the care of patients with EPI.

Endoscopic Pancreatic Function Testing—Maisam Abu-El-Haija, MD

Direct testing of pancreas exocrine function may be warranted in cases in which the diagnosis of EPI is uncertain. The main method of direct PFT is to sample pancreatic fluid secretions upon hormonal secretagogue stimulation with cholecystokinin (CCK), secretin, or in combination. CCK and secretin stimulate pancreatic acinar cell enzyme secretion and ductal secretion of fluid and bicarbonate, respectively. The history of direct pancreatic function testing dates back to the early 1950s when Dreiling and colleagues (16–18) described a double lumen tube method to diagnose EPI. The test required 60 minutes and used individual catheters to aspirate gastric and duodenal fluid. From the duodenal fluid, the bicarbonate concentration and fluid volume were measured. In adults, bicarbonate concentrations of 80 mEq/L or less are diagnostic of EPI. Since the test is time consuming, requires fluoroscopy, and is unpleasant for the patient, it is not readily available at most centers. As a result, there has been increasing interest in the use of endoscopic pancreatic function testing (ePFT) to collect duodenal fluid. The ePFT also uses CCK or secretin to stimulate pancreatic secretions (19,20). Duodenal fluid is sampled over 15 to 60 minutes via a catheter inserted with its end visually positioned next to the ampulla of Vater. Most people will monitor the peak enzyme activity and bicarbonate concentration. Endoscopic pancreatic function testing eliminates the need for radiation exposure and in adults has been shown to be less costly, compared to the double-lumen method (21).

One of the largest studies on the utility of ePFT in children (22), involving more than 500 pediatric patients, showed that testing is feasible and can aid in the investigation of EPI in children. The investigators showed that enzyme activities mature with age in a growing child; hence, caution must be used when interpreting ''isolated enzyme deficiency'' especially in a child younger than 2 years of age. A short version of ePFT over 15-minute period has been described in children (22). Additional data, however, need to be gathered in this developing field. In order to improve the quality of evidence supporting utilization of ePFTs in EPI diagnosis, there needs to be further work on reliability of results, the ideal secretagogue(s), the best type of fluid measurements and their normative values across different ages, and standardization of collection protocols in the pediatric population.

MODULE 3—MANAGEMENT OF PANCREATITIS IN CHILDREN

Management of Acute Pancreatitis in Adults: Lessons Applicable to Pediatric Care—Timothy B. Gardner, MD

Over the course of the last decade, there has been an increasing incidence of pediatric AP and an increasing prevalence of biliary disease related to the underlying obesity epidemic. This has led to an increase in the number of pediatric patients with AP, as well in the number of patients with complications attributable to AP such as pancreatic fluid collections and necrosis.

In adults, we have learned that aggressive initial fluid resuscitation (20 mL/kg of body weight) of lactated Ringer's solution appears to improve outcomes in AP. The trials which demonstrate the benefit of lactated Ringer's to date, however, have been small and the primary outcomes (usually improvement in the systemic inflammatory response syndrome) often do not mirror important clinical outcomes (23). In addition, the recognition of under-resuscitation as a risk factor for worsening outcomes in AP, has led to a general belief in aggressive, intravenous fluid resuscitation as a cornerstone of management in the first 24 hours (24). As such, there has been a seismic change in not only the type of fluid used in AP (lactated Ringer's) but also in the amount of volume used for initial resuscitation.

Antibiotics that are at times used as a preventive strategy in patients with severe AP are in actuality not effective in preventing necrosis or death, and this has been shown definitively in both cohort and randomized controlled trials (25,26).

It is critical that patients be fed enterally as soon as possible, and oral feeding does not lead to more complications than does tube feeding. In adults, randomized controlled data support the use of early oral feedings—within at least 48 hours—and if tube feeding is necessary, nasogastric rather than nasojejunal feedings are acceptable (27). Even if oral/tube feedings are not tolerated and parenteral nutrition is needed, ''trickle'' oral/tube feedings should be used to prevent intestinal bacterial translocation and cause infected necrosis.

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Finally, the recognition of the different kinds of pancreatic fluid collections that may develop at different time-lines in AP—including pseudocysts and walled off pancreatic necrosis–allows for treatment recommendations that are more appropriate to the etiology. Increasingly, endoscopic management of complex fluid collections has become the standard of care for management.

In summary, recent advances in care based on adult data include the following: the use of aggressive fluid resuscitation at admission with lactated Ringer's solution; the use of antibiotics only in documented infection, but not as prophylaxis in the setting of pancreatic necrosis; aggressively starting enteral nutrition with 24 hours of admission if feasible; the possibility of initiating enteral nutrition orally; and recognizing the different types of pancreatic fluid collections and their distinct treatment strategies (16,17).

Pain Self-management Interventions for Children With Chronic Pancreatitis—Tonya M. Palermo, PhD

Abdominal pain is present in the majority (87%) of pediatric patients with ARP or CP (28,29). Children with pain are subjected to a high number of medical investigations, surgical interventions, and opioid prescriptions. As pain becomes more frequent and severe, it reduces health-related quality of life (QOL) across multiple domains of physical, psychological, and social functioning (29,30). Pain also impacts healthcare utilization and is associated with a high economic and societal burden (28,31). Nonpharmacological interventions for children with CP are urgently needed. A biopsychosocial understanding of pain and disability can guide assessment and treatment. Intervening during childhood presents a unique opportunity to teach effective pain self-management that may decrease emergency room visits and hospital admissions, reduce opioid use, and subsequently prevent or lessen the enormous impact of adult chronic pain and its associated disability. In other chronic painful conditions including gastrointestinal disorders, psychological interventions, particularly self-management interventions, have been effective for reducing pain and pain impact (eg, disability and depressive symptoms) in pediatric and adult populations (31). Despite their relevance, to date, self-management interventions have not been evaluated in children with CP. One solution for addressing barriers for access to psychological self-management pain interventions is to use internet interventions and mobile health apps to deliver treatment. Internet and mobile interventions are showing effectiveness for managing chronic pain in other pediatric populations and may be extended to children with CP (32).

The Role of Surgery in Pediatric Pancreatitis in 2017—Jaimie D. Nathan, MD

Indications for surgical intervention in ARP and CP in children may include biliary or duodenal obstruction, symptomatic pseudocysts that are not amenable to endoscopic approaches, and rarely, acute necrotizing pancreatitis requiring debridement. The most common indication for surgery in pancreatitis is, however, in the management of chronic pain and debilitation, often in the setting of chronic opioid use. Importantly, a subset of children with CP and ARP suffer from debilitating abdominal pain and severely impaired QOL. Surgical interventions are indicated in this cohort of children if they have failed to respond to medical or endoscopic management approaches. Of note, increased symptom duration (>3 years) before operation can result in poorer surgical outcomes, including lack of pain relief or improvement QOL. For this reason, a timely and comprehensive multidisciplinary evaluation is warranted early during the course of disease. In children deemed to be surgical candidates, decisions to go for conventional surgical approaches, such as pancreatic resections and drainage procedures, depend on the pancreatic ductal anatomy and gland morphology (33). Decompression of a dilated pancreatic duct can be achieved by the Puestow or the Frey procedure; however, the Puestow is falling out of favor due to high intermediate and long-term failure rates with recurrence of pain and debilitation. In patients with an inflammatory mass in the head of the pancreas, duodenum-preserving pancreatic head resections, such as the Beger, Berne, or Frey, are typically considered, as they are parenchyma-sparing, compared to the Whipple pancreaticoduodenectomy, thereby resulting in lower rates of exocrine insufficiency and diabetes over the long term. In patients with small duct disease (defined by a nondilated pancreatic duct) and without a dominant inflammatory head mass, total pancreatectomy with islet autotransplantation (TPIAT) is a preferred option. In addition, TPIAT is indicated in patients who have failed previous conventional operations and suffer from recurrence of pain and poor QOL. In the pediatric population, TPIAT results in pain relief and liberation from opioids in approximately 85% to 90% of patients. Although longer-term glycemic outcomes are awaited (34), children undergoing TPIAT have insulin independence rates that exceed those in adults. In children with genetic risk factors for pancreatitis, it is generally felt that TPIAT will provide superior outcomes to resections and drainage operations, with sustained relief and a lower long-term adenocarcinoma risk. The multicenter National Institutes of Health (NIH)-funded study Advancing Treatment for Pancreatitis: A Prospective Observational Study of TPIAT (POST) aims to define patient and disease characteristics associated with favorable pain, health-related QOL, and glycemic outcomes, as well as optimal timing of TPIAT and cost-effectiveness (35). In addition, studies to maximize islet engraftment, function and survival and to develop alternative implantation sites to the liver are new frontiers for improving glycemic outcomes after TPIAT.

MODULE 4—NEW FRONTIERS IN PEDIATRIC PANCREATIC RESEARCH

Cellular and Animal Models in Pediatric Pancreatitis—John F. Eisses, MD

Despite the sizeable morbidity and mortality of pancreatitis, treatments are still largely supportive. Most experimental therapeutic strategies have focused on ways to control the florid inflammation that occurs following the initiation of pancreatic injury. The challenge is that by the time most patients present with pancreatitis, marked pancreatic injury has already occurred and multiple inflammatory pathways have been activated. Several cellular and animal models for pancreatitis have been developed especially due to the inaccessible nature of human pancreatic tissue; however, they typically focus on isolated aspects of the pathogenic response. These models can facilitate a better understanding of the pathophysiologic mechanisms driving pancreatic injury, and the recovery mechanisms allowing pancreatic regeneration (36,37). In addition to animal models, several pancreatic cell lines have been established for research purposes and have become a springboard to understand more complex interactions, through coculture techniques. An exciting development is the ability to make organoids from patient samples (38). Pancreatic organoids are clusters of cells that can be coaxed into forming the semblance of pancreatic tissue. They can be used to test drug toxicity and the therapeutic response to medications for pancreatic disorders (39,40). It is important to recognize that the cellular and animal models of pancreatic disease have notable similarities and differences with the clinical entities they are intended to model (41).

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Novel Targets in the Management of Pancreatitis—Vikesh K. Singh, MD

As mentioned earlier, the pathophysiology of AP is complex and poorly understood, and most of our understanding of these pathophysiologic pathways is based on animal models which fail to fully mimic the human disease (41). As a result, no single target for drug development has emerged, and care of the patient with AP remains supportive. Although many drugs have been evaluated for the treatment of AP, no drug has been found to be effective thus far (42). The limitations of these studies, from a clinical standpoint, include small sample sizes, inclusion of patients with variable times between the onset of symptoms and presentation, predicted severe AP scores having poor positive predictive values for actual severe AP, lack of adjustment for co-interventions that impact outcomes (eg, fluid therapy), and most importantly, a lack of clear endpoints that incorporate clinical and patient-reported outcomes. The fact that most therapies have been general, rather than etiology specific, has also limited usefulness. A few notable exceptions, however, exist. Targets of drug development programs currently include the complement cascade and calcium signaling within acinar cells. Clinically speaking, there has been significant progress in the primary prevention of post-ERCP pancreatitis with the use of rectal indomethacin and fluid therapy. Progress in the secondary prevention of pancreatitis is also being evaluated, with the recent development of an antisense apoCIII inhibitor for patients with hypertriglyceridemic pancreatitis and the use of the cystic fibrosis transmembrane conductance regulator (CFTR) modulators, such as, ivacaftor in patients with cystic fibrosis (43), with studies ongoing on their usefulness in others with CFTR abnormalities/dysfunction.

Power of Consortia and Collaborations in Studying Pediatric Pancreatitis—Aliye Uc, MD

AP affects roughly 1 in 10,000 children, and while 15% to 35% develop recurrent episodes; a small subset acquires CP (possibly <1 in 100,000) (3,44). Although rare, pediatric pancreatitis is costly and significantly affects the lives of families (28,45). There has been an increase in the number of children diagnosed with pancreatitis within the last decade, likely because of an increased awareness of the disease. Recent literature in the field mostly describes risk factors and sequela; only a few have focused on treatment and outcomes. Diagnostic and treatment guidelines are now being developed, but they rely mostly on expert opinion or adult literature (46). Likewise, there are at the moment only a handful of NIH research funds currently awarded to projects studying pediatric pancreatitis.

The field of pediatric pancreatology desperately needs evidence-based research of the highest quality with double-blinded, randomized controlled clinical trials and validated outcomes. Because pediatric pancreatitis is relatively rare, large numbers of patients for such studies can only be acquired through a multicenter collaboration. INSPPIRE was the first ever NIH-funded multicenter pediatric study to better characterize ARP and CP (47). The plan is to expand its role to performing randomized controlled trials, with the goal to develop better therapeutic alternatives for children. Finally, a similar collaboration could be developed to better understand children who develop even a single episode of AP. In summary, pediatric pancreatology has greatly evolved within the last decade. However, there is still a long road ahead before novel therapies can be offered. Continued commitment from funding organizations is paramount for the advancement of this growing field.

Summary of Lunch Breakout Sessions Focusing on Identifying Directions for Future Research in Pediatric Pancreatology—Veronique D. Morinville, MD

Symposium participants were subdivided into tables of 10 to 12 during the lunch break, with a moderator assigned to each group to facilitate discussion and assemble key topics for future research in pediatric pancreatology. The discussions focused on improved understanding of the epidemiology, disease burden, and incidence of pancreatitis in children and factors related to its increased incidence in recent decades; age-specific differences in laboratory tests (amylase, lipase) and how they might affect diagnostic criteria; better understanding of mechanisms leading to drug-induced pancreatitis and an interest in developing a database to help better classify medication associations; increased understanding of the role of genetics (specifically CFTR) in pancreatitis and identifying other novel genetic risk factors; better evidence for the management of AP (fluids, pain, imaging; standardized order sets); Improved diagnostic methods for CP (criteria necessary; imaging); improved standardization of testing for EPI (eg, ePFT);management of CP, with a focus on nutritional therapy in both exocrine- and endocrine-insufficient populations, endoscopic/surgical therapies, and pain management; and methods of increasing collaborations between centers and among NASPGHAN and its sister societies, to further these efforts. In order to promote further discussion and foster future research and research collaborations among audience members, the suggestions were collated and verbally summarized for the overall group at the conclusion of the symposium.

CONCLUDING REMARKS

The single topic symposium, *Frontiers in Pediatric Pancreatology*, was the first full-day educational symposium on pediatric pancreatic disease organized by NASPGHAN and the first such symposium within North America. The purpose of the current Proceedings Report was to highlight the academic presentations made therein. Although the objective of the symposium was to update the general pediatric gastroenterology provider about pediatric pancreatic disease, numerous other themes and needs emerged. There are still many gaps in the knowledge base and management approaches for pediatric AP. Recently, NASPGHAN published management recommendations for pediatric AP (48). Also recently, a joint NASPGHAN/European Society for Paediatric Gastroenterology Hepatology and Nutrition (European sister society) working group developed recommendations in regards to the nutritional management in AP, ARP, and CP (49). This was, however, based predominantly on expert opinion and the adult literature. There is great potential for growth in this field, particularly because there is currently a dearth of research in many facets of pediatric pancreatology. For example, the ability to predict severe AP continues to be a challenge in pediatrics, as does defining clinically meaningful endpoints that will help direct future research. Optimal timing for endoscopic therapy in both ARP and CP continues to be debated, as do ideal measures of EPI. Interest in ePFT has been increasing in recent years. Standardization of ePFT will, however, require that as a field we firstly compare variations in protocols among the various centers currently performing ePFT. From this data gathering, we will secondly need to identify 1 or a few protocols to test in a multicenter fashion for diagnostic accuracy in assessing EPI. The reporting of such data should be according to STARD guidelines (50). Once an optimal protocol is devised, the final step will be to establish normal and disease standards. The optimal timing of surgical or endoscopic therapies is still unclear, and long-term

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outcome data are lacking. Despite our progress to date, we are still in the early phases of identifying the optimal approaches to therapy and long-term management. As we continue to advance our knowledge of pediatric pancreatic disease, we must remember that the financial, emotional, and societal burden of CP in children cannot be underestimated.

In spite of the challenges that remain, progress continues at an increasing pace. Advances in radiographic imaging are allowing pediatric gastroenterologists to offer less invasive diagnostic modalities, while concomitantly reducing nonionizing radiation exposure. Targeted drug therapies, particularly in cystic fibrosis and hypertriglyceridemia, have allowed us to further understand the pathophysiology of pancreatic function. Through advances in genomic studies and with organoids and in vitro models of pancreatic disease, it is hoped that increased understanding of etiologies and mechanisms will help in the development of new therapeutic targets. This single topic symposium brought together topic experts and trainees in pediatric pancreatic disease and served as a platform from which future collaborations, research hypotheses, and innovative thinking will launch. It is our hope that the *Frontiers in Pediatric Pancreatology Symposium* will serve as a starting point for the growth of a promising, untapped field in pediatric pancreatology.

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