Title
Design and Implementation of INSPPIRE

Journal
Journal of Pediatric Gastroenterology and Nutrition, 59(3)

ISSN
0277-2116

Authors
Morinville, Veronique D
Lowe, Mark E
Ahuja, Monika
et al.

Publication Date
2014-09-01

DOI
10.1097/mpg.0000000000000417

Peer reviewed

Published in final edited form as:
J Pediatr Gastroenterol Nutr. 2014 September ; 59(3): 360–364. doi:10.1097/MPG.0000000000000417.

DESIGN AND IMPLEMENTATION OF INSPPIRE (INTERNATIONAL STUDY GROUP OF PEDIATRIC PANCREATITIS: IN SEARCH FOR A CURE)

Veronique D. Morinville[1,*], **Mark E. Lowe**[2,*], **Monika Ahuja**[3], **Bradley Barth**[4], **Melena D. Bellin**[5], **Heather Davis**[3], **Peter R. Durie**[6], **Brian Finley**[3], **Douglas S. Fishman**[7], **Steven D. Freedman**[8], **Cheryl E. Gariepy**[9], **Matthew J. Giefer**[10], **Tanja Gonska**[6], **Melvin B. Heyman**[11], **Ryan Himes**[7], **Sohail Husain**[2], **Soma Kumar**[9], **Chee Y. Ooi**[12], **John F. Pohl**[13], **Sarah Jane Schwarzenberg**[5], **David Troendle**[4], **Steven L. Werlin**[14], **Michael Wilschanski**, **Elizabeth Yen**[11], and **Aliye Uc**[3]

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

[2]Children's Hospital of Pittsburgh, Pittsburgh, PA

[3]University of Iowa Children's Hospital (UICH), Iowa City, IA

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

[5]University of Minnesota, Amplatz Children's Hospital, Minneapolis, Minnesota

[6]Hospital for Sick Children and University of Toronto, Toronto, ON, Canada

[7]Baylor College of Medicine, Houston, TX

[8]Beth Israel Deaconess Medical Center, Boston, MA

[9]Nationwide Children's Hospital (NCH), Columbus, OH

[10]Seattle Children's Hospital, Seattle, WA

[11]University of California at San Francisco, San Francisco, CA

[12]University of New South Wales and Sydney Children's Hospital Randwick, Sydney, Australia

[13]University of Utah, Salt Lake City, UT

[14]Medical College of Wisconsin, Milwaukee, WI

Abstract

Corresponding author: Aliye Uc, M.D., 2865 JPP Pediatrics, The University of Iowa, 200 Hawkins Drive, Iowa City, IA 52242; Tel: (319) 384-6032; Fax:(319) 353-8967; aliye-uc@uiowa.edu.
*contributed equally

SUPPLEMENTAL DIGITAL CONTENT

- Text material describing Patient and Physician Questionnaires Content for database.
- Tables S1–5 listing particular elements of Patient and Physicians Questionnaires Content for database.
- Figures S1A (describing the INSPPIRE Organizational structure) and S1B (timeline of database development and patient enrollment).

Objectives—Acute recurrent pancreatitis (ARP) and chronic pancreatitis (CP) are rare and poorly understood diseases in children. Better understanding of these disorders can only be accomplished via a multi-center, structured, data collection approach.

Methods—The INSPPIRE Consortium (INternational Study Group of Pediatric Pancreatitis: In search for a cuRE) was created to investigate the epidemiology, etiologies, pathogenesis, natural history and outcomes of pediatric ARP and CP. Patient and physician questionnaires were developed to capture information on demographics, past medical history, family and social history, medications, hospitalizations, risk factors, diagnostic evaluation, treatments and outcome information. Information collected in paper questionnaires was then transferred into REDCap™ (Research Electronic Data Capture), tabulated and analyzed.

Results—The administrative structure of the INSPPIRE Consortium was established and National Institutes of Health funding was obtained. Fourteen sites (10 in United States, 2 in Canada, and 2 overseas) participated. Questionnaires were amended and updated as necessary, followed by changes made into the REDCap™ database. Between September 1, 2012 and August 31, 2013, 194 children were enrolled into the study; 54 % were female; 82% were non-Hispanic, 72% were Caucasian.

Conclusions—The INSPPIRE consortium demonstrates the feasibility of building a multi-center patient registry to study the rare pediatric diseases, ARP and CP. Analyses of collected data will provide a greater understanding of pediatric pancreatitis and create opportunities for therapeutic interventional studies that would not otherwise be possible without a multi-center approach.

Keywords

children; database; questionnaire; acute recurrent pancreatitis; chronic pancreatitis; registry

INTRODUCTION

Acute pancreatitis (AP) was once considered an uncommon disease of childhood. This concept changed with publication of single-center experiences in the United States, Mexico and Australia describing increased rates of pancreatitis in children within the last few decades (1–6). In fact, two studies estimated the incidence of pancreatitis at 3.6 and 13.2 cases per 100,000 children (3, 6), which approaches incidences reported for AP in adults (7).

Most children with pancreatitis have a single, mild, acute episode that resolves without complications. However, a subset of children with AP develops recurrent episodes of acute pancreatitis (acute recurrent pancreatitis, ARP) and some progress to chronic pancreatitis (CP). Patients may endure multiple hospital admissions for the treatment of acute episodes or suffer from debilitating pain in the case of CP. During hospitalization, patients may require intensive care unit admissions, multiple imaging studies, laboratory tests, procedures and surgeries. Peri-pancreatic fluid collections, pain requiring prolonged narcotic use, exocrine and/or endocrine pancreatic insufficiency, nutritional deficiencies, and depression may complicate the disease course. All interventions and complications result in significant economic costs for the families and society. However, the proportion and characteristics of children who develop ARP and/or CP after an episode of AP are not well-described because

pediatric ARP and CP are uncommon and only retrospective studies from single institutions have been reported (8–12).

Within the past decade, great progress has been made in the understanding of pancreatitis in general. The NAPS-2 (North American Pancreatitis Study 2) initiative, consisting of data collected on >1000 adult patients with ARP and CP and from a comparison group of unaffected controls, has provided important information on the epidemiology, etiology, treatments, outcomes and natural history in adults (13). No similar detailed data have been collected for affected children. Without an understanding of the epidemiology, etiologies, pathogenesis, natural history and outcome *in children*, it is impossible to design therapeutic alternatives and ultimately prevention for these diseases. Hence, a prospective multi-center approach is necessary to address the fundamental gaps in the knowledge of pediatric ARP and CP.

To meet the need for the careful collection of data as well as a registry of well-phenotyped pediatric pancreatitis patients for clinical studies, the Pancreatic Interest Group was formed in 2009, and became the INSPPIRE (**In**ternational **S**tudy Group of **P**ediatric **P**ancreatitis: **I**n search for a cu**RE**) group one year later. The initial composition of INSPPIRE included 30 members in 18 institutions, mostly consisting of pediatric gastroenterologists, but also included members of relevant affiliated fields such as endocrinology and pathology. As a group, INSPPIRE held several face-to-face meetings to identify areas of incomplete knowledge and to discuss formation of a consortium to gather information about children with pancreatitis. Consequently, two subcommittees were charged with standardizing the definitions of pediatric AP, ARP and CP and with surveying INSPPIRE members to determine the number of patients followed at each institution to assess current practice parameters and to identify the most important clinical questions in pediatric pancreatitis (14).

After gathering information and discussing our options, the INSPPIRE participants decided that the development of therapeutic strategies to prevent recurrent episodes of AP and progression to CP was the most important goal for our group. To move toward this objective, we recognized the need to gather information about the etiology, epidemiology, therapy and natural history of pancreatitis as a critical first step. In response, the group decided to focus on the development of an electronic database to catalog a well-phenotyped population of children with ARP or CP, and to organize our group structure more formally. Herein, we describe our efforts to create a collaborative international network of pediatric centers to study pediatric pancreatitis, to develop pediatric-specific questionnaires on ARP and CP, and to develop and implement an electronic database for data repository and analysis.

MATERIALS AND METHODS

(A) Development of administrative structure of INSPPIRE

Beginning in 2010, INSPPIRE members periodically met to discuss the development of an administrative structure for the consortium. Expertise was sought from members and founders of other multi-center research consortia. The initial discussions identified important

steps for the planned INSPPIRE consortium, including selecting a principal investigator (PI) for the consortium and as well as members to comprise the steering and executive committees, tasking subcommittees with specific functions, and developing a timeline for meeting milestones. Finally, we developed a strategy to obtain grant funding for project support. An administrative structure was developed based on these criteria.

(B) Inclusion/Exclusion Criteria

Inclusion and exclusion criteria were determined based on previously-published INSPPIRE definitions for pediatric-onset (initial presentation before a patient's 19th birthday) AP, ARP and CP (14).

(C) Development of Questionnaires for Database

Baseline rules were established to ensure comprehensive standardized patient entries. These rules were as follows: (i) Inclusion and exclusion criteria would be strictly respected to ensure the uniformity of the study population; (ii) all data would be collected in a de-identified fashion; (iii) information would be collected about demographics, past medical history, family history, phenotypic features, risk factors, diagnostic evaluation, medications, hospitalization data, treatments and therapeutic interventions, outcome information and quality of life including specifics about pain; (iv) both a patient and physician questionnaire would be applied to minimize reporting bias; (v) patients would be enrolled during a hospitalization or clinic visit, but well-known patients could also be enrolled by mail; (vi) subjects would complete questionnaires based on memory and personal notes whereas physicians would complete questionnaires based on interactions with the patient and review of the medical record (test results, hospitalizations, imaging results and reports); (vii) responses would be entered on paper forms which would eventually be entered electronically or directly into the electronic database. Answers would primarily involve selecting checkboxes for "Yes", "No", or "Uncertain" or entering one-word replies or lists as necessary (for example, lists of medications). Physician questionnaires would allow entering of more detailed information as needed (for example, detailed imaging results).

To develop the pediatric pancreatitis questionnaire, a Questionnaire Subcommittee was first created. North American Pancreatitis Study (NAPS2) and Cystic Fibrosis Gene Modifier Registry Questionnaires were reviewed and used as resources. Drafts were prepared and opened to comments and discussion from the entire group. The final versions of the questionnaires were edited by the principal investigator and approved by all members before implementation **(For the description of patient and physician questionnaires, please refer to** Supplemental Digital Content and Tables S1–5).

(D) Development of a database for entry of information and data analysis

The central premise for database development was to ensure accurate and consistent collection and recording of information to facilitate examination of epidemiology, etiologies, diagnostic approaches, complications, outcomes and surgical therapies in children with ARP and CP. To accomplish our goals, we identified 5 essential properties for the database. First, we required a centralized team and system to insure smooth operation of the electronic database. The REDCap™ (Research Electronic Data Capture, Vanderbilt

University) System, a secure, web-based application specifically designed to support data capture for research, was selected to create the electronic database for use across multiple sites in different countries (15). Second, we needed a reliable electronic platform for uploading data from the questionnaires. Third, we wanted secure local access to the database for all INSPPIRE consortium members that allowed accurate information entry. Fourth, we required a data quality control team to verify the quality and the completeness of the data, to identify discrepancies in entered data and to eliminate duplicate patient entry. Lastly, the database needed to allow sharing de-identified data across the study sites.

RESULTS

A. Building the INSPPIRE Consortium

Our goal was to better understand the disease etiologies, epidemiology, diagnostic modalities and treatment outcomes and to provide a cohort of well-phenotyped patients for future studies of pathogenesis and novel therapies for these diseases. We approached the Program Officials at National Institutes of Health (NIH) and sought advice for an appropriate funding mechanism to continue to support our efforts and build a multi-center data registry and sample repository for pediatric pancreatitis. We identified the R21 grant mechanism, an exploratory/developmental research grant whose aim is to provide support for early and conceptual stages of project development, as an appropriate funding source for INSPPIRE. We successfully competed for funding effective July 1, 2012 (PI: Aliye Uc, UICH). Fourteen other sites (10 in USA, 2 in Canada, 2 overseas) and a total of eighteen collaborators participated in the study.

Institutional Review Board applications were first approved at the coordinating site (UICH, June 2012). By November 1, 2012, all of the sites were approved by their local IRB. Subcontracting of the satellite sites started following IRB approval and was completed by February 28, 2013.

The organizational structure of INSPPIRE is summarized in Supplemental Digital Content (Figure S1A: INSPPIRE Organizational Structure). Thus far, the INSPPIRE Consortium subcommittees have worked on Questionnaire and Database development, Presentations and Publications Policy, Ancillary Studies Policy and Website development (a website being critical to publicize the group’s presence, mission, and research projects and to provide educational information on pediatric pancreatitis for the benefit of patients, families, and physicians alike).

A 24-month initial study timeline was elaborated, within which elements of questionnaire development and database installation were detailed (See results (C) and (D)) (Refer to Supplemental Digital Content, Figure S1B: INSPPIRE Consortium Timeline). The communication between consortium members was maintained via e-mail messages, a wiki page, newsletters, regular teleconferences, and face-to-face meetings at annual meetings of several societies.

B. Patient enrollment

Patient enrollment began at all sites as soon as IRB approval was obtained, but before the subcontracting was completed by the coordinating site (UICH). Patients (new or established) were enrolled during an admission, outpatient visit or by direct contact. This early enrollment greatly benefitted study numbers. When the subcontracting was finally completed eight months into the study, all sites could enter their patients into the REDCap™ database, and enrollment numbers quickly reached 150 study subjects. By the end of September 2013, a total of 194 participants had been entered into the database. Distribution of patients per site is displayed in Figure 1. Patient demographics are presented in Table 1.

During the early phase of the study, all patients and physicians or research coordinators completed the paper questionnaire. After REDCap™ was implemented, the patients and physicians were given the choice of entering their information on paper questionnaires or directly into REDCap™.

C. Physician and Patient Questionnaires: Modifications

An important goal of our consortium development was to iteratively improve our questionnaires. Within the first year, the INSPPIRE group identified sections of the Physician and Patient Questionnaires that needed modification (See Supplemental Digital Content: Questionnaires Content).

D. Database Initiation and Functioning

Data Management—Subject data for the INSPPIRE study was stored electronically in the REDCap™ platform at UI. The Biomedical Informatics team at the Institute for Clinical and Translational Science (ICTS) managed the REDCap™ platform. All relevant study site personnel were provided with accounts within the University of Iowa ITS (Information Technology Services) identity management framework, including remote access to study data through secure encrypted connections. Only IRB-approved research team members had access to the REDCap™ data platform. Each non-UI team member's access was limited to instruments and data from their location. Each team member was granted access to the system through a secure login.

Physical Data Safety and Security—In the REDCap™ data platform, primary data were secured in the Healthcare Information Systems Data Center. Data backups were secured in the main Information Technology Services Data Center. Both physical locations were two-factor authenticated. Operating system security included secure logins, data encryption at rest, remote system logging and configuration, and change management. Data backups were encrypted both in flight and at rest. Copies of data were replicated to the remote data center every 15 minutes. Disaster recovery was tested, and at any time, 100+ point-in-time copies of data were available.

Due to the differing requirements of the IRBs from each institution, an individual project for each institution was implemented. Another single project was created to house the merged data from all of the institutions. To maintain security and IRB requirements only the UI team had access to this merged project and the data contained within.

To accomplish the merging of data, custom coding was required and a separate REDCap™ plugin was developed. The resultant merged data maintained the data integrity but also allowed for the primary site to easily view and analyze the data from all projects in one place.

Periodic reviews of the timeliness, completeness and accuracy of the data were conducted by the ICTS team and communicated to each site via standardized reports and e-mail. Conference calls were held every 1 to 2 months to share information, monitor progress, improve efficiency, and encourage consistent practices across centers. Reports regarding enrollment numbers, types of patients enrolled, and completeness and accuracy of data were provided to the clinical centers on a regular basis. Whenever possible, calculated measures were generated within REDCap™, in order to improve both data collection efficiency and accuracy. The REDCap™ team and the PI at the University of Iowa examined frequencies and reasons for missing data, both programmatically and manually across the entire cohort and within individual sites. The team at the University of Iowa identified and minimized overlapping or duplicative patient information obtained from study sites. In cases where multiple partially completed surveys existed for a single patient, the REDCap™ team and PI at the University of Iowa scrutinized each individual data point, and worked within their site and the individual sites to verify and adjudicate the data.

DISCUSSION

The INSPPIRE Consortium represents the first initiative to create a multi-center approach to systematically characterize pancreatitis in children. Although pediatric AP, ARP, and CP are more common than previously estimated, they are not common enough for a single center to make significant progress in developing a registry of patients. This reality has hampered progress in the field of pediatric pancreatology for decades. A novel multi-center collaboration, as described in this manuscript, was required to overcome this barrier.

Our current work demonstrates the success of the INSPPIRE endeavor. Our early results reflect the largest and most diverse group of children with ARP and CP ever assembled. We have established the feasibility of 14 centers spread over 4 countries and 3 continents working together collaboratively and for the goal of progress in the understanding of pediatric pancreatitis. Detailed analysis of data gathered to date and ongoing data collection will help improve our understanding of the epidemiology, etiology, diagnostic measures, therapeutic interventions, outcomes, and disease burden including effects on quality of life and the economic impact in pediatric patients with ARP and CP.

Several important lessons may be extracted from our consortium's experience. At its onset, the group was unfunded and meetings were held at members' own expense. It was a necessity to acquire funding to support further research. The formalization of the consortium greatly helped secure funding. Seeking expert opinion from previously formed and functioning consortia was invaluable. These experienced investigators made us aware of the "growing pains" inherent in developing a consortium. They also provided advice on the need and effective processes to remove and add consortium members over time. Their expertise helped us develop a well-defined administrative structure, which was necessary to

ensure the overall stability of the consortium, and to set rules of engagement. Even if individual consortium members changed over time, the structure of the consortium could be maintained.

The development of pediatric-specific pancreatitis questionnaires provided several challenges. Of central concern in the development of questionnaires was the issue of initially not knowing *what* was important and thus weighing the inherent desire to collect all possible pertinent data versus feasibility constraints for data entry, patient contact and patient involvement. Despite using previously-developed data points from the adult study (13, 16–21), multiple elements had to be altered for the pediatric population to be more reflective and relevant of current clinical practice and to gather more detailed information. For example, prior questionnaires only asked about self-history of smoking, a pro-fibrotic factor that hastens the progression of CP (22–24) and possibly increases the risk of AP (25). Because most of our patients would not be expected to have significant firsthand exposure to cigarettes but might have significant second-hand exposure in their household, we added a section to capture information about second-hand smoke exposure.

A key aspect in the development and use of the database questionnaire was that the process would be dynamic with refinements made as necessary. During the first year of use, minor amendments were made to the original questionnaires reflecting a feedback mechanism to continuously improve the information gathered, including methods of asking questions and ensuring that all relevant data was captured in the most simple and consistent manner across the consortium sites. Ongoing critique and review of the questionnaires by the consortium members ensured that most appropriate and complete data would be captured.

The actual implementation and use of the electronic database provided a few challenges. One of the issues that arose was in the analysis of multiple entry questions for listing medications. For ease of use, free text would have been the easiest for the data entry teams, but this method of entry would have added a layer of complexity to data analysis. The balance between the ease of data entry and ease of data analysis led to a consensus by the study team to select a limited set of medications relevant to this study that were strictly coded. Strict coding of this type of questions allowed the team to ensure that data would be measured in the exact same manner across institutions. It also reduced the chance to introduce errors by coding responses after they were submitted.

Collecting information into an electronic database in our multicenter consortium has limitations. At the initiation of this study, most of the captured data was retrospective, although newly-diagnosed patients were actively sought (for example, diagnosis of second episode of AP). “Follow-up” questionnaires to be completed annually by physicians and participants will help establish the natural history of pediatric ARP and CP by capturing prospective data. As with any study involving questionnaires, the quality of the data entered depends heavily on the participants, and in particular, study coordinators supplying and entering the data. Family or patient recall of prior events and variability in quality and completeness of data within patient charts revealed important challenges in efforts to include all relevant and accurate information. To improve the quality of our data, we required

adherence to a strict data entry process that provided multiple checks on the accuracy and completeness of the data.

Future aims and goals include analysis of the wealth of information already collected within the database. The registry provides a cohort of well-phenotyped patients for future studies of pathogenesis and the development of novel therapies. A prime example of its utility is that the creation of this cohort leads to exciting genomic possibilities. Never before has such a large group of pediatric pancreatitis patients been assembled with such a high likelihood of having genetic factors and modifiers involved in their disease process. In the next phase of the study, we will begin to collect DNA samples for genetic analysis and serum samples for biomarker analyses to enable investigations for the presence of previously-described pancreatitis genetic markers (8–13) and to search for unknown factors that might contribute to the pathogenesis of ARP or CP in pediatric patients.

In summary, the INSPPIRE Consortium experience has demonstrated the feasibility and success of constructing and running a multi-center study protocol to study a relatively rare pediatric diagnosis. The network provides a robust international collaboration of pediatric centers to engage in prospective studies and analyses of children with ARP and CP. The INSPPIRE database currently includes data on 194 children diagnosed with ARP and CP in 14 centers in 4 countries. Analysis of collected data will provide a greater understanding of epidemiology, etiology, diagnostic measures, management, complications, and quality of life in pediatric pancreatitis and create opportunities for therapeutic interventional studies – all impossibilities without a multi-center approach.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by National Institute of Health (NIH) DK096327 (AU).

We would like to thank Debra Pfab, Ethan Valentine, Katherine Lilly, Rebecca Beek, Donna Smith, Katherine Keenan, Vikki Scaini, Nick Peterson, Christina Gorges, Shannon Riggs, Elizabeth Garnett, Tiffanie Hales, Thea Pugatch, Roxanne Strachan, Vanessa Bonett, Lily Nahidi, and Kara Cooper for enrolling patients into the study, entering data into the database, for IRB and administrative support.

References

1. Lopez MJ. The changing incidence of acute pancreatitis in children: a single-institution perspective. J Pediatr. 2002; 140(5):622–624. [PubMed: 12032533]
2. Werlin SL, Kugathasan S, Frautschy BC. Pancreatitis in children. J Pediatr Gastroenterol Nutr. 2003; 37(5):591–595. [PubMed: 14581803]
3. Nydegger A, Heine RG, Ranuh R, Gegati-Levy R, Crameri J, Oliver MR. Changing incidence of acute pancreatitis: 10-year experience at the Royal Children's Hospital, Melbourne. J Gastroenterol Hepatol. 2007; 22(8):1313–1316. [PubMed: 17489962]
4. Sanchez-Ramirez CA, Larrosa-Haro A, Flores-Martinez S, Sanchez-Corona J, Villa-Gomez A, Macias-Rosales R. Acute and recurrent pancreatitis in children: etiological factors. Acta Paediatr. 2007; 96(4):534–537. [PubMed: 17306005]

5. Park A, Latif SU, Shah AU, Tian J, Werlin S, Hsiao A, et al. Changing referral trends of acute pancreatitis in children: A 12-year single-center analysis. J Pediatr Gastroenterol Nutr. 2009; 49(3): 316–322. [PubMed: 19503003]
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(1):5–8. [PubMed: 19752770]
7. Corfield AP, Cooper MJ, Williamson RC. Acute pancreatitis: a lethal disease of increasing incidence. Gut. 1985; 26(7):724–9. [PubMed: 4018637]
8. Wang W, Liao Z, Li ZS, Shi XG, Wang LW, Liu F, et al. Chronic pancreatitis in Chinese children: etiology, clinical presentation and imaging diagnosis. J Gastroenterol Hepatol. 2009; 24(12):1862–1868. [PubMed: 19793170]
9. Lucidi V, Alghisi F, Dall'Oglio L, D'Apice MR, Monti L, De Angelis P, et al. The etiology of acute recurrent pancreatitis in children: a challenge for pediatricians. Pancreas. 2011; 40(4):517–21. [PubMed: 21499205]
10. Sultan M, Werlin S, Venkatasubramani N. Genetic prevalence and characteristics in children with recurrent pancreatitis. J Pediatr Gastroenterol Nutr. 2012; 54(5):645–50. [PubMed: 22094894]
11. Minen F, De Cunto A, Martelossi S, Ventura A. Acute and recurrent pancreatitis in children: exploring etiological factors. Scand J Gastroenterol. 2012; 47(12):1501–4. [PubMed: 23016884]
12. Chowdhury SD, Chacko A, Ramakrishna BS, Dutta AK, Augustine J, Koshy AK, et al. Chronic Pancreatitis In Children. Indian Pediatr. 2013
13. Whitcomb DC, Yadav D, Adam S, Hawes RH, Brand RE, Anderson MA, et al. Multicenter approach to recurrent acute and chronic pancreatitis in the United States: the North American Pancreatitis Study 2 (NAPS2). Pancreatology. 2008; 8(4–5):520–31. [PubMed: 18765957]
14. Morinville VD, Husain SZ, Bai H, Barth B, Alhosh R, Durie PR, et al. Definitions of Pediatric Pancreatitis And Survey Of Current Clinical Practices: Report From Insppire (International Study Group Of Pediatric Pancreatitis: In Search For A Cure). J Pediatr Gastroenterol Nutr. 2012
15. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009; 42(2):377–81. [PubMed: 18929686]
16. Yadav D, Hawes RH, Brand RE, Anderson MA, Money ME, Banks PA, et al. Alcohol consumption, cigarette smoking, and the risk of recurrent acute and chronic pancreatitis. Arch Intern Med. 2009; 169(11):1035–45. [PubMed: 19506173]
17. Yadav D, Slivka A, Sherman S, Hawes RH, Anderson MA, Burton FR, et al. Smoking is underrecognized as a risk factor for chronic pancreatitis. Pancreatology. 2010; 10(6):713–9. [PubMed: 21242712]
18. Burton F, Alkaade S, Collins D, Muddana V, Slivka A, Brand RE, et al. Use and perceived effectiveness of non-analgesic medical therapies for chronic pancreatitis in the United States. Aliment Pharmacol Ther. 2011; 33(1):149–59. [PubMed: 21083584]
19. Amann ST, Yadav D, Barmada MM, O'Connell M, Kennard ED, Anderson M, et al. Physical and mental quality of life in chronic pancreatitis: a case-control study from the North American Pancreatitis Study 2 cohort. Pancreas. 2013; 42(2):293–300. [PubMed: 23357924]
20. Clarke B, Slivka A, Tomizawa Y, Sanders M, Papachristou GI, Whitcomb DC, et al. Endoscopic therapy is effective for patients with chronic pancreatitis. Clin Gastroenterol Hepatol. 2012; 10(7): 795–802. [PubMed: 22245964]
21. Cote GA, Yadav D, Slivka A, Hawes RH, Anderson MA, Burton FR, et al. Alcohol and smoking as risk factors in an epidemiology study of patients with chronic pancreatitis. Clin Gastroenterol Hepatol. 2011; 9(3):266–73. quiz e27. [PubMed: 21029787]
22. Law R, Parsi M, Lopez R, Zuccaro G, Stevens T. Cigarette smoking is independently associated with chronic pancreatitis. Pancreatology. 2010; 10(1):54–59. [PubMed: 20332662]
23. van Geenen EJ, Smits MM, Schreuder TC, van der Peet DL, Bloemena E, Mulder CJ. Smoking is related to pancreatic fibrosis in humans. Am J Gastroenterol. 2011; 106(6):1161–6. quiz 1167. [PubMed: 21577244]
24. Alexandre M, Pandol SJ, Gorelick FS, Thrower EC. The emerging role of smoking in the development of pancreatitis. Pancreatology. 2011; 11(5):469–74. [PubMed: 21986098]

25. Sadr-Azodi O, Andren-Sandberg A, Orsini N, Wolk A. Cigarette smoking, smoking cessation and acute pancreatitis: a prospective population-based study. Gut. 2012; 61(2):262–7. [PubMed: 21836026]

26. Trivedi CD, Pitchumoni CS. Drug-induced pancreatitis: an update. J Clin Gastroenterol. 2005; 39(8):709–716. [PubMed: 16082282]

27. Spanier BW, Tuynman HA, van der Hulst RW, Dijkgraaf MG, Bruno MJ. Acute pancreatitis and concomitant use of pancreatitis-associated drugs. Am J Gastroenterol. 2011; 106(12):2183–8. [PubMed: 21912439]

28. Nitsche C, Maertin S, Scheiber J, Ritter CA, Lerch MM, Mayerle J. Drug-induced pancreatitis. Curr Gastroenterol Rep. 2012; 14(2):131–8. [PubMed: 22314811]

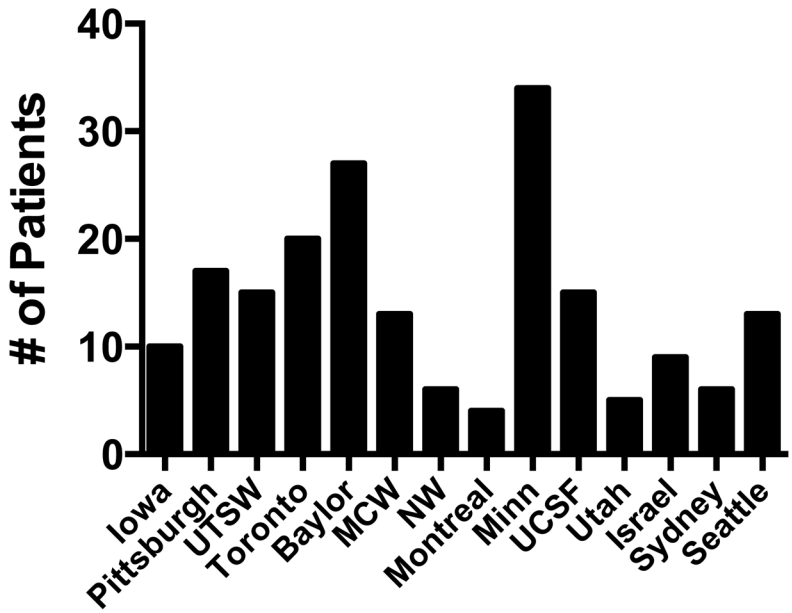

Figure 1. Number of patients enrolled per INSPPIRE centers

The figure shows the distribution of 194 patients enrolled between September 1, 2012 and August 31, 2013 across INSPPIRE centers. UTSW: University of Texas Southwestern Medical School, MCW: Medical College of Wisconsin, NW: Nationwide Children's Hospital, Minn: University of Minnesota; UCSF: University of California at San Francisco.

Table 1

Demographics of the INSPPIRE Cohort

	N
Female	105 (54%)
Age (Years±SDV)	12.4±4.7
Ethnicity	
Non-Hispanic	159 (82%)
Hispanic	35 (18%)
Race	
Caucasian	139 (72%)
Black/African-American	7 (3.5%)
Hispanic	13 (7%)
Native American	7 (3.5%)
Asian	10 (5%)
More than one race	7 (3.5%)
Other, or unknown	11 (5.5%)

N= number

SDV= Standard Deviation