STUDY TITLE: Incorporating Endoscopic Ultrasound and Elastography towards improving outcomes of Pediatric Pancreatitis Management

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BACKGROUND/PURPOSE:
EUS is well established as a diagnostic tool in the adult population, introduced clinically in the 1980s,[1] but its uses in pediatrics are still emerging. In children EUS is primarily used as a diagnostic tool for evaluation of pancreaticobiliary disease.[2-6]

Pancreatitis has been increasing in incidence in both adult and pediatric populations, requiring providers to increasingly recognize, accurately diagnose and care for patients with ARP and CP[7, 8]

To maximize the success of interventions aimed at slowing or stopping disease progression and ameliorating the deleterious downstream effects of pancreatic insufficiency, techniques capable of identifying the early stages of chronic pancreatic disease are urgently needed.

The advantage of EUS over other diagnostic techniques is the high detail characterization of parenchymal and duct findings of pancreatitis. While adult Rosemont or conventional criteria are in use for EUS diagnosis of CP in adults, validated pediatric criteria do not exist.[9-12] The Rosemont and conventional criteria are nonetheless used for pediatric patients, as there are no reasonable alternatives. To date, EUS findings of CP in children have not been systematically studied.

In addition to grayscale characterization, ultrasound provides the opportunity to quantify tissue stiffness as a biomarker of fibrosis using elastography. Shear wave elastography (SWE) provides operator independent, true quantitation of tissue stiffness and is available on both EUS and transabdominal ultrasound (TUS) systems. Both TUS and EUS SWE have been studied for diagnosis of CP in adult patients,[13-17] however they have not been studied in pediatric pancreatitis.

The Pancreas Care Center at Cincinnati Children's Hospital Medical Center (CCHMC) and the large population it serves places us in a unique position to study EUS and ultrasound elastography in pediatric patients and address these gaps in the literature.

SPECIFIC AIMS
The aims of the proposed study are as follows:

Aim 1: Characterize endoscopic ultrasound (EUS) findings of pediatric acute recurrent pancreatitis (ARP) and chronic pancreatitis (CP).
Adult criteria for EUS diagnosis of CP exist, but no such criteria exist for children. As such, the applicability of current diagnostic criteria to pediatric patients is unknown.

1.1: Catalogue grayscale EUS findings of ARP and CP in a pediatric cohort and compare to healthy controls. *Hypothesis*: EUS findings of ARP and CP in pediatric patients will differ from those of adult ARP and CP and will be characteristically different

from healthy controls. *Exp1***:** We will catalogue grayscale EUS findings in 40 pediatric patients with known history of ARP or CP undergoing clinically indicated EUS and will compare those with findings in 20 patients without a history of pancreatitis who are undergoing EUS for other indications.

1.2: Benchmark grayscale EUS against other imaging modalities for diagnosis of CP, particularly early CP, in children. *Hypothesis:* Grayscale EUS findings will be more sensitive than other imaging modalities in all stages of CP. *Exp2:* We will test associations, in blinded fashion, of grayscale EUS findings catalogued under S.A1.1 in enrolled children with findings on alternative pancreas imaging modalities performed for clinical indications. Specifically, we will correlate to endoscopic retrograde cholangiopancreatography (ERCP), magnetic resonance cholangiopancreatography (MRCP) and computed tomography (CT) performed for clinical indications within +/- 3 months of the EUS.

Aim 2: Define the diagnostic performance of ultrasound elastography for CP and pancreatic stiffness as a measure of fibrosis in pediatric patients.

2.1: Define the diagnostic performance of EUS and TUS elastography for pediatric CP. *Hypothesis:* EUS and TUS elastography will have high specificity for CP with increased stiffness in patients compared to controls. *Exp 1:* Patients enrolled under Aim 1 will undergo shear wave elastography (SWE) measurement of the pancreas during EUS. These same patients will undergo research TUS with SWE of the pancreas. SWE results by both EUS and TUS will be evaluated for diagnostic performance for CP.

2.2: Define agreement between EUS and TUS measurement of pancreatic parenchymal stiffness in pediatric patients. *Hypothesis:* EUS and TUS measures of pancreatic parenchymal stiffness will agree with minimal bias. *Exp2:* EUS and TUS SWE data obtained under S.A2.1 will be evaluated for agreement and divergent cases will be investigated to define causes.

2.3: Define the diagnostic performance of elastography for pancreatic fibrosis. *Hypothesis:* SWE is a sensitive indicator of pancreatic fibrosis as identified by histology. *Exp3:* Patients undergoing clinically indicated total pancreatectomy and islet auto transplant (TPIAT) or other pancreatic surgical resection at our institution (approximately 20 per year) will be approached to undergo pre-operative TUS SWE. These SWE measurements, along with EUS SWE measurements obtained preoperatively, will be compared to binary and semi-quantitative assessments of pancreatic parenchymal fibrosis by histology.

STUDY DESIGN:
This will be a single center prospective study to assess the role of EUS and ultrasound elastography in patients with ARP and CP. This pilot study will catalogue EUS and elastography findings in children with ARP and CP and compare with healthy controls.

Additionally, we plan to evaluate sonographic markers for pancreas fibrosis in children, including EUS elastography which we will compare to transabdominal ultrasound elastography for assessment of pancreatic parenchymal stiffness. Elastography and grayscale EUS findings will be benchmarked against parenchymal histology for patients undergoing pancreatic surgery (e.g. total pancreatectomy with islet Autotransplantation).

Data derived from this study including EUS findings in pediatric patients with ARP and CP, and US markers of pancreatic fibrosis, will serve as the foundation for more extensive studies of pediatric pancreatitis with EUS. Additionally, this may serve as preliminary data for establishment of pediatric EUS criteria for CP and early CP.

STUDY PROCEDURES:

Approximately 60 participants will be recruited to enroll in the study. Forty participants will have ARP or CP as defined by the International Study Group of Pediatric Pancreatitis: In search for a cure (INSPPIRE)[18]. Twenty participants from this cohort will be undergoing TPIAT or other pancreatic resection. Another twenty participants will be controls with no history of pancreatic disease undergoing EUS for other clinical indications.

Procedures and Imaging:

EUS will be performed as part of routine clinical care using a GF-UCT180 curvilinear array ultrasound gastrovideoscope (Olympus America Inc; Center Valley, PA). Grayscale findings (Table 1) will be recorded and documented for clinical care. Research EUS SWE measurements will be obtained using the Aloka Arietta 850 AT processor (Olympus America Inc; Center Valley, PA) with SWE measurements taken from each of the head, genu, body and tail of the pancreas. Research TUS SWE will be performed using a Canon Aplio i800 ultrasound system and a curved 1-6 MHz transducer. 2D SWE will be performed with measurement of shear wave speed in the head, body and tail of the pancreas.

Modality	Findings
EUS	Rosemont and Conventional Criteria
MRI	Atrophy T1 signal (signal intensity ratio, relaxometry) Enhancement Cambridge Criteria
CT	Atrophy Calcifications Duct dilation
ERCP	Cambridge Criteria

Table 1: EUS and other imaging findings to be catalogued and compared for diagnosis of CP

MRCP or CT imaging within 3 months of the EUS will be reviewed blinded to EUS and SWE findings for findings of CP (Table 1). Fluoroscopic pancreatogram images from patients with an ERCP within this time frame will be scored using Cambridge Criteria.[19]

Research EUS SWE measurements are anticipated to add approximately 5 minutes to the total procedure time. Research TUS SWE will take no more than 20 minutes and may or may not occur on the same day as the EUS procedure.

Specimen histology: A small core of pancreatic tissue is routinely collected from all patients undergoing TPIAT at our institution and a similar sample would be obtained from patients undergoing other resections. Findings from enrolled participants' samples will be reviewed for the presence of fibrosis using a four-stage scoring system adopted by Wellner et al.[22]

Data collected from Epic may include: patient age, sex, height/ weight, relevant lab values, results of imaging modalities (MRCP, CT, US, or ERCP, EUS), relevant genetic testing results, pancreatic function testing results, medications, hospital stay, complications, clinical course, interventions/surgical procedures, and other relevant clinical data.

STUDY POPULATION:
There will be two cohorts for the study.

Pancreatitis Cohort:
Inclusion criteria:

- Confirmed diagnosis of ARP or CP by INSPPIRE criteria
- ≤ 21 years of age, male and female
- Children undergoing EUS for clinical care
- For Aim 2.3 only: Children undergoing TPIAT or other pancreatic resection

Exclusion criteria:

- Children <15 kg who cannot accommodate the size of endoscope
- Children with acute pancreatitis (AP) <6 weeks prior to EUS

Control Cohort:
Inclusion criteria:

- Children without a history of pancreatic disease undergoing EUS for other clinical indications
- ≤ 21 years of age, male and female

Exclusion criteria:

- Children <15 kg who cannot accommodate the size of endoscope
- Children with AP, ARP or CP

Definitions:
Acute pancreatitis (AP): The presence of at least 2 out of 3 criteria: 1) abdominal pain (acute onset, epigastric, possibly radiating to the back); 2) serum amylase and/or lipase of at least 3 times greater than the upper limit of normal; and 3) characteristic findings of acute pancreatitis on imaging such as ultrasound, computed tomography, magnetic resonance imaging (i.e. pancreatic edema, areas of pancreatic or peripancreatic necrosis, peripancreatic inflammation).[18]

Acute Recurrent Pancreatitis (ARP): The presence of at least 2 distinct episodes of AP as defined above, along with 1) complete resolution of pain and a >1 month pain-free interval between diagnoses of AP; or 2) complete normalization of serum amylase and lipase before the subsequent episode of AP is diagnosed, along with complete resolution of pain, irrespective of a specific time interval.[18]

Chronic Pancreatitis (CP): The presence of at least one **irreversible structural change*** in the pancreas with or without abdominal pain +/- exocrine pancreatic insufficiency +/- diabetes.[18]

irreversible structural changes:

- *Ductal calculi, dilated side branches, parenchymal calcifications found in any imaging (abdominal ultrasound (abd US), magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP), computerized tomography (CT), endoscopic retrograde cholangiopancreatography (ERCP), endoscopic US (EUS).*

- *Ductal obstruction or stricture/dilatation/irregularities that are persistent (for >2 months) on any imaging.*
- *Parenchymal atrophy, irregular contour, accentuated lobular architecture, cavities alone are not diagnostic findings for CP.*
- *Surgical or pancreatic biopsy specimen demonstrating histopathologic features compatible with CP (acinar atrophy, fibrosis, protein plugs, infiltration with lymphocytes, plasma cells, macrophages).*

RECRUITMENT AND CONSENT*:*

Subject Recruitment:

Recruited subjects will be identified through review of patients presenting for EUS for clinical care. Potential participants for the pancreatitis cohort will be reviewed to confirm diagnosis of ARP or CP by INSPPIRE criteria. We are requesting a waiver of consent for chart review to confirm eligibility of the subjects for the study.

Potential participants for the control cohort will be identified by the primary investigator at the time of scheduling. These control patients will be undergoing EUS for other clinical indication. Following screening, patients will be enrolled by the research staff after informed consent is obtained through the informed consent process mentioned below. We plan to approach for enrollment, all pediatric patients that meet inclusion criteria during the funding period and anticipate no difficulty achieving our recruitment targets based on the robust referral base for our pediatric Pancreas Care Center.

Process of obtaining Consent (including eConsent):

Consent, parental permission and/or assent will be obtained from all patients (pancreatitis cohort and control cohort) before any study-related procedures are performed. Written assent will be obtained from participants 11 years of age and older. The investigator will be available to answer any questions that the participant or parent may have regarding procedures, risks, and alternatives. The consent process will be documented on the informed consent progress note.

Consent may take place by several methods: in-person paper consent, in-person electronic consent (using REDCap for the eConsent) or over the phone (via paper or REDCap for eConsent). Signatures of the subject and study staff may not always occur on the same date depending on how and when the subject returns the signed consent. No matter the consenting process, study procedures will not occur prior to a fully executed consent form. Consent will be obtained following the CCHMC consenting SOP. REDCap eConsent will not replace the consenting method, it will be used as an additional resource for signing the consent form. A copy of the consent form will either be given to the subject in paper form or emailed to them via REDCap depending on how the consent is completed. In all cases, the consent process will be documented on the informed consent process note and a copy of the signed consent(s) will be kept in the patient's medical record.

Staff will make sure that the eConsent database is updated as soon as possible after a new version of the paper consent is approved. Staff will also make sure paper consents are used to consent eligible subjects in the event that the eConsent database is not updated prior to eligible subjects being available for consent approach by a member of the study staff. For the reasons described, the eConsent will not be submitted to the IRB for approval.

Subjects will be reminded that participation in research is completely voluntary. Coercion is eliminated by having the subjects sign an assent document and the parent/guardian signs the consent document. We will give potential subjects time to read the consent form, consent them in a private setting, and answer any questions they may have. Potential subjects (or parents) will be told that the subject's (parent's) decision to participate will not affect the clinical care received.
If patients do not want to participate, at any time, they are instructed to call the Research Coordinator to opt out. The study consent process will ensure that potential subjects will be adequately informed about the study and will have an opportunity to ask questions.

DATA MANAGEMENT & ANALYSIS:

1. Data will be stored in password-protected files at CCHMC. Study data will be restricted to study personnel only after all research training is complete.
2. Once data is collected, a code will be created. The identifying information will be removed from the data file and replaced with the code. Codes will be stored in a separate file. Only research personnel will have access to the passwords and data.
3. Once the study is complete, data will be retained in a coded state for potential future currently unspecified research. Future research will require IRB approval prior to utilizing this dataset.

Statistical analysis:
Power calculation: Given that this is a pilot and feasibility study, a power calculation was not performed. We plan to approach for enrollment all pediatric patients that meet inclusion criteria during the funding period and anticipate no difficulty achieving our recruitment targets based on the robust referral base for our pediatric Pancreas Care Center.

Aim1: Frequencies will be used to describe the presence of EUS findings in patients with ARP, CP and controls. Groups will be compared using Fisher's exact and Chi-square tests as appropriate. These tests will also be used, as appropriate to compare the relationship between EUS and other imaging findings.

Aim2: Means, standard deviations, 95% confidence intervals will be used to describe TUS and EUS SWE results for patients with ARP, CP and for controls. Agreement between TUS and EUS SWE will be analyzed using Pearson correlations, intraclass correlation coefficients and Bland-Altman analyses. Sensitivity and specificity and 95% confidence intervals will be calculated for diagnosis of CP by SWE using INSPPIRE criteria and for prediction of the presence of fibrosis on histology.

POTENTIAL RISKS & BENEFITS:
Potential Risks:
The risk category for all subjects who choose to participate in the study will fall into the minimal risk category. Participating in the study will add no additional risks to the clinically indicated EUS procedure. There is no known risk from TUS procedure.

Data Safety Monitoring Plan:
This study is a non-intervention study. Therefore, no formal data safety monitoring board will be appointed. Adverse events related to the study procedures will be monitored by the study coordinator and reported to the PI. The PI will then report any adverse events in writing to the CCHMC IRB within the time frame specified in the IRB guidelines. These procedures should be highly effective in minimizing risk to study participants.

Potential Benefits:
There is no direct benefit to the study subject. However, future patients may benefit due to the knowledge gained from this study that may direct future patient care.

PRIVACY & CONFIDENTIALITY:
Each subject will be assigned a study ID number. A password-protected table will be maintained that links the study ID number to the medical record number. This table will be maintained on a secure server and/or in a locked file cabinet, as appropriate. The password-protected database containing the research data will be maintained on a secure server with access limited to study personnel. Identifying data will be saved in a password-protected database. No primary data or patient identifiers will be published.

Once the study is complete, data will be retained in a coded state for potential future currently unspecified research. Future research will require IRB approval prior to utilizing this dataset.

COST OF PARTICIPATION:
There is no cost to participate in this study.

PAYMENT FOR PARTICIPATION:
We will provide each participant/family with a $75 gift card (Clincard) for reimbursement of patient time and effort to participate in the study and attain the research measurements.

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