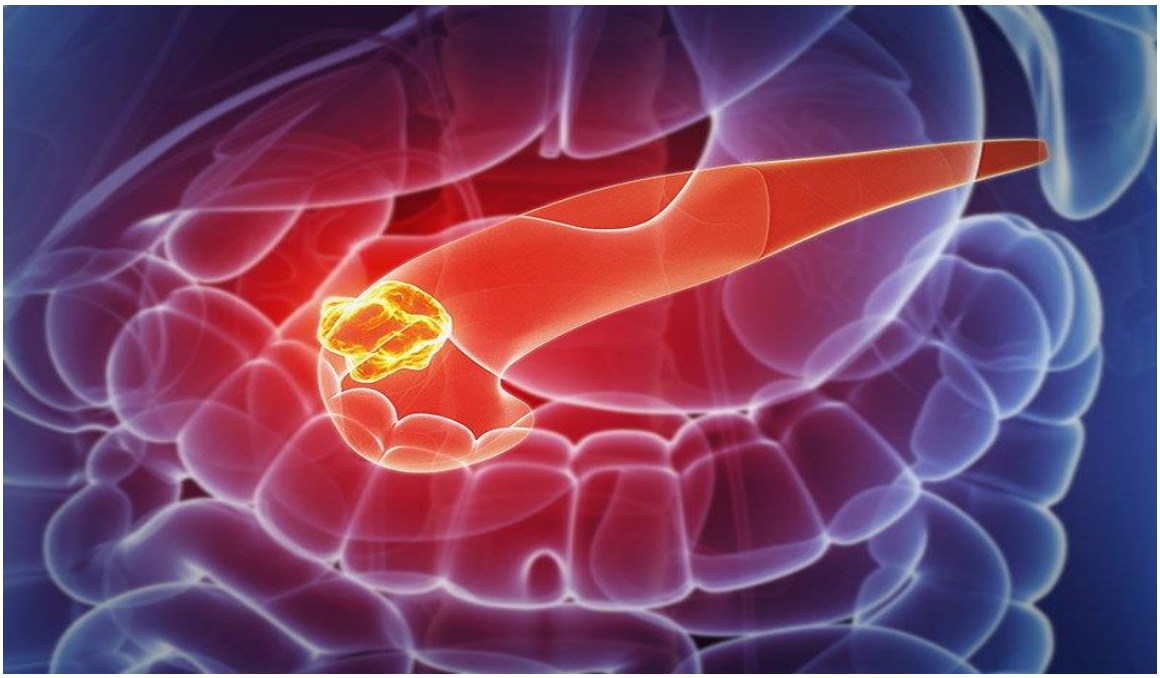
PancreasFest 2019

Abstracts



Posters Displayed: Ballroom

from 7:00 am to 4:00 pm on Thursday July 25, 2019
from 7:00 to 11:30 am on Friday July 26, 2019

Poster Reception & Discussion:

Thursday, July 25 – 4:00 to 5:30 pm

PancreasFest 2019

Abstracts

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1

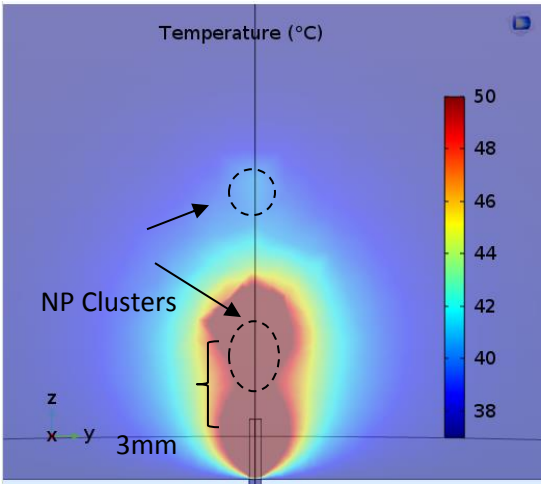
Computational Modeling of Plasmonic Heating: A Computerized Approach Towards Plasmonic Photothermal Therapy for Pancreatic Cancer

Santiago Manrique-Bedoya[1], Chris Moreau[2], Sandeep Patel[2], Kathryn Mayer[1], Yusheng Feng[1].
CAPER Scholarship Recipient- University of Texas, San Antonio
[1]The University of Texas at San Antonio, [2]UT Health San Antonio

Introduction: Endoscopic therapy for non-resectable pancreatic cancer has historically consisted of palliative stenting. Recent advancements in EUS-guided devices have created an opportunity to treat the tumor directly. Therapeutic modalities such as radiofrequency ablation (RFA) and laser interstitial thermal therapy (LITT) have emerged as potential tumor debulking tools. Predictability of diseased tissue treatment in-vivo is challenging to assess due to visualization constraints, causing a reduction in specificity and increasing pancreatitis risk. Photodynamic therapy (PDT) has been proposed to increase specificity but requires systemic photosensitizer which may be intolerable for patients in sunny climates. We propose nanoparticle-mediated (plasmonic) photothermal therapy (PPTT) which can be locally administered and stimulated with a wavelength of laser that is harmless to tissue at low power.

Methods: The computational analysis was carried out in COMSOL Multiphysics 5.3™ using a cylindrical section of pancreatic tissue with optical and thermal tissue properties obtained from literature. Clusters of nanoparticles were introduced into the tissue as point sources along the laser beam path. The heat equation for homogeneous and isotropic medium was solved throughout the entire 3D geometry using the finite element method (FEM) via Multifrontal Massively Parallel Sparse Direct Solvers and others to converge a solution.

Results: A 20 mW, 808 nm laser was used to simulate the effect of PPTT on pancreatic tissue. The laser was delivered through a 400 μm fiber and two nanoparticle clusters were included in the model, one 3 mm away from the fiber tip and the other at 7 mm from the tip. The temperature distribution plot shows the minimal effect induced by the laser fiber and the maximized effect of nanoparticle clusters close to the light source. At this power level, clusters above 5 mm away from the light source are less likely to show prominent effects due to the light propagation decay through tissue. Additional power levels were analyzed and improved penetration depth.



Conclusions: This computational model allows for parameter optimization such as nanoparticle concentration and distribution, as well as laser power and wavelength so that therapy effects are maximized in tumor site and minimized in surrounding areas. Optical and thermal properties are easily modifiable to account for tumor tissue and healthy tissue effects. The values obtained and the model created could then be used as the foundation for developing a tool to aid physicians in the assessment of treatment.

2

Diagnostic Imaging in Pancreatic Ductal Adenocarcinoma

Laurel Branch
CAPER Scholarship Recipient- Medical University of South Carolina

Introduction: Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer related death in the United States due in large part to its late clinical presentation and challenges in diagnosis at an early stage.[1,2,3] Endoscopic ultrasound (EUS) with fine needle aspiration or biopsy (FNA/FNB) is highly sensitive, but there is often a delay in reaching this step.[4] Since many patients diagnosed with PDAC often present with nonspecific symptoms, we hypothesized that a substantial proportion undergo multiple diagnostic imaging studies before achieving a definitive diagnosis. A secondary aim of this project was to define patient and tumor characteristics associated with high utilization of diagnostic imaging studies.

Methods: This is a retrospective cohort study which includes all patients diagnosed with PDAC at a single tertiary referral center between July 1, 2014 and September 30, 2018. A definitive diagnosis of PDAC required cytopathologic confirmation of PDAC via EUS-FNA or EUS-FNB. Patients were excluded if no medical records were available for review during the 12-month antecedent period leading up to the diagnosis of PDAC. Medical records were abstracted for relevant patient, radiologic, and tumor characteristics;

medical record review included those from referring facilities prior to referral for EUS. Diagnostic imaging studies included computed tomography, magnetic resonance imaging, positron emission tomography, transabdominal ultrasound, EUS, and endoscopic retrograde cholangiopancreatography (ERCP). Studies performed purely for cancer staging or palliation of obstructive jaundice were excluded. Based on the distribution of the number of antecedent imaging studies across the cohort, patients were classified as high or low utilizers. High utilizers were defined as patients who underwent 3 or more imaging studies prior to the diagnostic EUS. Patient and tumor characteristics were compared between groups.

Results: A total of 397 cases of PDAC meeting the study enrollment criteria were included, (mean age 68.3 $\pm$ 10.6, 43.8% female). Not including the EUS procedure when a definitive diagnosis was made, the median number of diagnostic imaging studies performed prior to the confirmatory biopsy was 2 (range 0-10). A substantial (n=158, 39.8%) of patients underwent three or more imaging studies ("high utilizers") prior to referral for EUS ***(figure 1)***. Patient characteristics associated with use of more antecedent imaging studies included younger age at presentation, male sex, a history of acute or chronic pancreatitis, and clinical presentation with jaundice ***(table 1)***. Tumors located in the pancreatic head were more common among high utilizers of antecedent imaging; as expected, high utilizers experienced a longer delay between their first imaging study and definitive EUS (median 27 vs. 10 days, p<0.0001, ***table 2***), with 25% of high utilizers taking 75 days or longer.

Conclusion: A substantial number of patients diagnosed with PDAC undergo three or more imaging studies prior to referral for definitive EUS-guided tissue sampling, leading to delays in diagnosis and excess resource utilization. These observations suggest a need for increased physician education regarding the diagnostic value of EUS, particularly in challenging cases such as concomitant acute or chronic pancreatitis, and for less invasive and more widely available diagnostic tests.

Table 1: Patient Characteristics

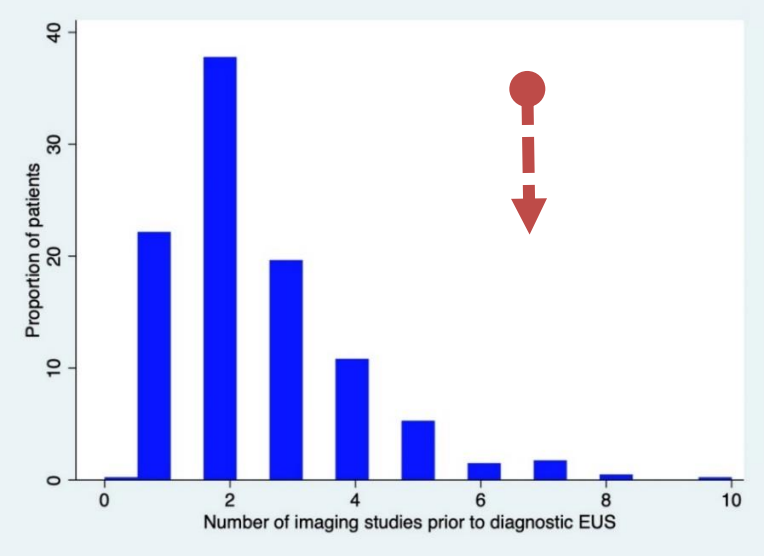
Variable	Low utilizer (n=239)	High Utilizer (n=158)	P value
Age (Mean +/- SD)	69.3 (10.4)	66.8 (10.8)	0.02
Female sex, n (%)	116 (48.5)	58 (36.7)	0.02
Race, n (%)			0.28
White	167 (71.1)	101 (64.7)	
Black or African American	67 (28.5)	71 (32.9)	
Asian	1 (0.4)	0 (0.0)	
Smoking Status			0.08
Never	111 (46.4)	56 (35.4)	
Former	88 (36.8)	73 (46.2)	
Current	40 (16.7)	29 (18.4)	
Alcohol Use			0.74
Never	138 (57.7)	96 (60.8)	
Former	12 (5.0)	9 (5.7)	
Current	89 (37.2)	53 (33.5)	
Current acute pancreatitis	26 (10.9)	27 (17.1)	0.08
Prior acute pancreatitis	7 (2.9)	16 (10.1)	0.003
Chronic pancreatitis	5 (2.1)	11 (7.0)	0.02
Diabetes Mellitus	98 (41.0)	73 (46.2)	0.31
• Recent Onset Diabetes Mellitus	15 (6.3)	9 (5.7)	0.81
Presenting Symptoms			
Jaundice or Abnormal LFTs	119 (49.8)	108 (68.4)	<0.001
Abdominal Pain	167 (69.9)	115 (72.9)	0.53
Weight Loss	135 (56.5)	84 (53.2)	0.52
Back Pain	47 (19.7)	35 (22.2)	0.55

Numbers may not add up to 100% due to rounding.

Table 2: Tumor Characteristics

Variable	Low Utilizer	High Utilizer	P value
Tumor Size, median (range)	3.0 (1.0 – 10.0)	3.0 (1.0 – 7.2)	0.05
Tumor Location			0.008
Head/Neck	156 (65.3)	126 (79.8)	
Body	50 (20.9)	19 (12.0)	
Tail	33 (13.8)	13 (8.2)	
Metastatic Disease	77 (32.2)	44 (27.9)	0.36
Median days from first imaging to diagnostic EUS, median (range)	10 (1 – 365)	27 (1 – 382)	< 0.0001

Figure 1: Number of imaging studies prior to diagnosis of pancreatic cancer



Based on the observed distribution, patients undergoing three or more imaging studies before the diagnostic EUS were classified as high utilizers.

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3

Feasibility and Performance of a Protein Signature Assay in EUS-FNA of Suspected Pancreatic Adenocarcinoma

Patrick Underwood
CAPER Scholarship Recipient- University of Florida

Background: Endoscopic ultrasound (EUS) with fine-needle aspiration (FNA) or core biopsy (FNB) is routinely used for the diagnosis and staging of pancreatic cancer (PDAC) given its proven accuracy and favorable safety profile. However, EUS with FNA fails to make a diagnosis nearly 25% of the time. Accurate diagnosis is imperative given the clinical ramifications. We had previously demonstrated that PDAC has a distinct intratumoral inflammatory milieu. A 41-proteinmultiplex panel revealed that 14 analytes had an area under the curve of > 0.75. Penalized logistic regression analysis revealed 12 analytes with predictive capability. A risk score generated from this model had an accuracy, sensitivity, and specifity of 94.3%, 92.9%, and 96.0%, respectively.

Aim: The aim of this pilot prospective study is to evaluate the feasibility and performance of the optimized protein signature assay in EUS-FNA/FNB obtained tissue specimens.

Methods: Single-arm prospective pilot study of EUS-FNA/FNB aspirate analysis for the diagnosis of PDAC. All adult subjects with suspected PDAC who are undergoing EUS-FNA will be included, with the exclusion of those with cystic lesions, possible metastatic disease or currently undergoing neoadjuvant therapy. At the time of EUS-FNA, a single extra pass is performed by the endoscopist using the same technique as for obtaining the clinical specimen. After needle removal from the endoscope, the stylet is passed through the needle to obtain tissue. The tissue is weighed and snap frozen in liquid nitrogen. For analysis, the tissue is thawed and suspended in 500 µL per 30 mg of tissue. It then undergoes bead homogenization. Lysates are collected and undergo assay for total protein. Lysates will then be assayed with a 41 protein multiplex assay to probe for 41 unique proteins which may be indicative of PDAC.

Results: To date, a total of seven patients (mean age 70.2 years) have been enrolled and underwent EUS-guided biopsy (median of 4.5 passes; range 3 to 5) of a pancreas mass (median size 24 mm; range 11-90 mm). Six patients underwent EUS-FNB using a 20-gauge core biopsy needle whereas FNA with a 22-gauge needle was performed in one patient. Final cyto-histopathological diagnosis included:

5 patients with pancreatic adenocarcinoma, 1 patient with metastatic small cell lung cancer, and one patient with no evidence of malignancy. The first five patients underwent immediate homogenization and lysis of tissue to ensure adequate protein was being obtained. The mean total protein concentration was 14.9±9.5 mg/mL. No samples contained <1 mg/ml which is the lower limit of the multiplex assay. There were no immediate or delayed post-procedural adverse events.

Conclusions: The current standard operating procedure has been implemented seamlessly in the workflow of patients undergoing EUS-FNA/FNB as part of their clinical care. Our preliminary findings suggest that the current study protocol is associated with a high tissue procurement yield for protein multiplex assay analysis in patients undergoing EUS-FNA or FNB for suspected PDAC. Once the target goal of patient enrollment (n=40) has been met, the next phase of this pilot study will involve evaluating the tissue samples with the optimized protein multiplex assay to further corroborate its performance as a potential adjunct novel diagnostic tool.

4

Differentiating Pancreatic Ductal Adenocarcinoma (PDAC) from individuals with symptoms suggestive of PDAC, including type II diabetes, with ROC AUC values above 0.95

Payam Delfani[2], Anders Carlsson[2], ,**Thomas King[2]**, Alexander Ney[1], Stephen P Pereira[1], Linda Dexlin Mellby[2]
[1] University College London, UK [2] Immunovia, Lund, Sweden and Marlborough, USA

Background: Discriminating PDAC from non-PDAC symptomatic individuals represents a more challenging task than distinguishing PDAC from healthy controls. Current available tests have been shown to be inadequate to deliver clinically actionable result, e.g. CA19-9 cannot alone discriminate between PDAC and other disease conditions in the gastrointestinal tract. This study aimed to evaluate if IMMray PanCan-d could, with high accuracy, separate patients with PDAC (stage I-IV) from individuals with various non-specific but concerning symptomatic conditions not caused by PDAC, which mirrors the clinical setting for gastrophysicians.

Methods: Patient samples from 150 PDAC (stage I-IV), 570 non-PDAC symptomatic individuals and 217 healthy individuals were tested, using IMMray PanCan–d as well as a CA19-9 ELISA assay. To minimize confounding, pre-analytical variables, all patient samples were collected and processed using the same standard operating procedures, stored at -80°C and tested within a year after collection. Data analysis was performed using Immunovia software algorithms and SVM ROC AUC-values were determined for the different groups.

Results: In total, 937 individuals were analyzed. Combining IMMray PanCan-d with CA19-9, the results showed SVM ROC AUC-values of 0.97, 0.98 and 0.96 differentiating PDAC vs. non-PDAC symptomatic individuals, healthy controls and type II diabetes, respectively. Similar results were achieved for all stages of PDAC.

Conclusion: The current study showed for the first time that IMMray PanCan-d has the capacity to differentiate between symptomatic, non-PDAC individuals, including type II diabetes, and all different stages of PDAC. These findings have significant clinical implications for individuals attending primary and secondary care units with non-specific but concerning symptoms where PDAC may be suspected.

5

The Impact of Adjuvant Chemotherapy for Resectable Pancreatic Cancer

Aslam Syed, MD[1]; Neil Carleton[1]; Annika Dhawan[1]; Zachary Horne, MD[2]; Gursimran Kochhar MD[1]; Suzanne Morrissey, MD[1]; Harry Williams, MD[3]; Donald Atkinson, MD[3]; Suzanne Schiffman, MD[3]; Dulabh Monga, MD[4]; Anthony Lupetin, MD[5]; Alexander Kirichenko, MD[2]; Marcia Mitre, MD[1]; Manish Dhawan, MD[1]; Abhijit Kulkarni, MD[1]; and Shyam Thakkar, MD[1]
[1] Division of Gastroenterology, Allegheny Health Network, Pittsburgh, PA, [2] Department of Radiation Oncology, Allegheny Health Network, Pittsburgh, PA, [3] Department of Surgery, Allegheny Health Network, Pittsburgh, PA, [4] Department of Hematology/Oncology, Allegheny Health Network, Pittsburgh, PA, [5] Department of Radiology, Allegheny Health Network, Pittsburgh, PA

Introduction: Surgical resection with chemotherapy remains the preferred treatment for pancreatic ductal adenocarcinoma (PDA). Data remains limited regarding survival rates for resectable PDA with adjuvant chemotherapy treatment when managed by a multidisciplinary team. The objective of this study is to assess survival rates and outcomes of adjuvant chemotherapy for resectable PDA following presentation at a multidisciplinary pancreas conference (MDPC).

Methods: All patients presented at a tertiary care center from April 2013 to August 2016 with PDA were discussed at the MDPC and were followed prospectively until November 2018. Patients were included in the study if the MDPC determined they had resectable PDA. Resectable PDA was defined as no involvement or abutment of regional vascular structures and no extra-pancreatic disease as determined by radiologic imaging. Patients underwent attempted upfront surgery and were followed until the end of the study timepoint.

Results: A total of 278 patients were presented at the MDPC during the study period. The MDPC determined that 91 patients met criteria for resectable disease and 70 were fit for surgery. A total of 64 patients underwent successful surgery, as 6 patients had metastatic disease upon laparotomy (91.4% resection rate). Of the 64 patients that underwent surgery, 37 (58%) started adjuvant chemotherapy with only 16 (25%) completing treatment. Patients who completed their adjuvant chemotherapy had a significantly prolonged survival time versus those who did not complete all cycles (36.9 months vs. 18.8 months, *P* = 0.014) (Figure 1). Reasons for patients who did not receive adjuvant chemotherapy included debilitation and post-operative complications (Table 1). Patients receiving any adjuvant chemotherapy had a median overall survival of 34.8 months versus a median overall survival of 17.1 months for those that did not (*P* = 0.43). Each additional cycle of chemotherapy conferred a relative survival advantage of 13.7% (P = 0.016).

Conclusions: Our data suggest that successful completion of adjuvant chemotherapy has better survival outcomes, specifically for those who completed 4-6 cycles versus those that completed 1-3 cycles. Given that only 25% of patients in this study completed adjuvant chemotherapy due to debilitation, operative complications, family issues, etc., consideration should be given for optimizing fitness or providing pre-operative neoadjuvant therapy in resectable PDA. Further studies are warranted.

Figure 1: (A) Kaplan-Meier curves for overall survival based on adjuvant chemotherapy (P = 0.43) and (B) number of adjuvant chemotherapy cycles received (P = 0.014).

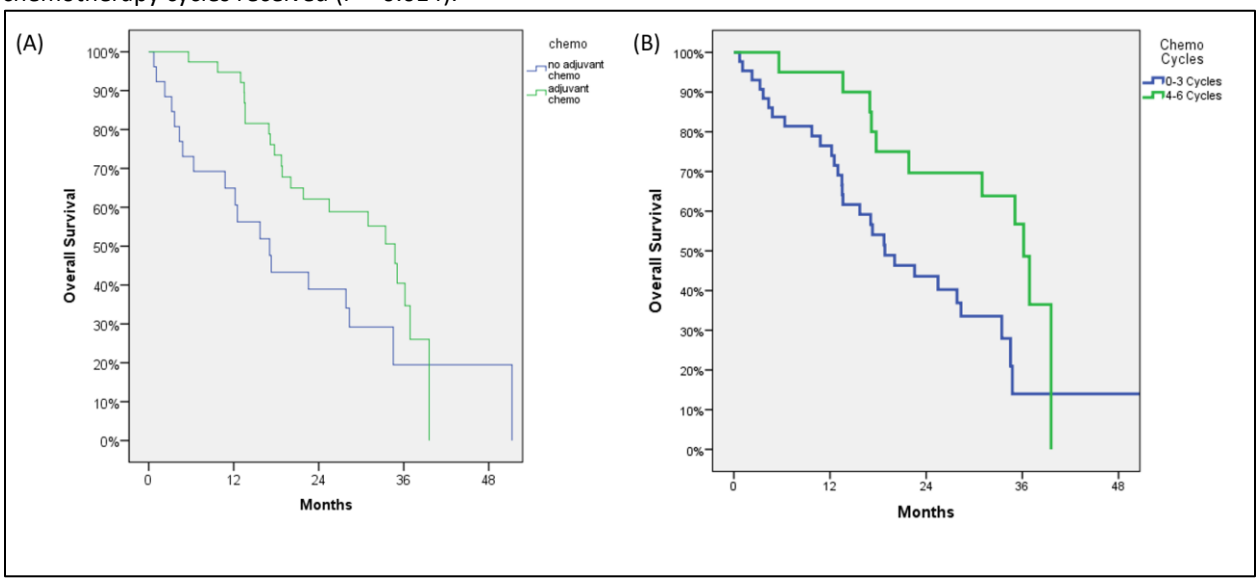

Table 1: Reasons detailing why patients either did not start or did not complete adjuvant chemotherapy

Table 1A: Reasons for Not Starting Chemotherapy

Event	Number of occurrences
Post-operative complications	7
Debilitation, advanced age, could not tolerate chemotherapy	5
Prolonged post-operative ICU episode	3
Found to have metastatic disease and/or tumor recurrence	3
Loss of follow-up; patient transferred outside health system to be close to family	2
No longer a chemotherapy candidate due to prolonged post-operative recovery	1
Surgical resection curative, chemotherapy not needed	1
Unknown	5

Table 1B: Reasons for Not Completing Chemotherapy

Event	Number of occurrences
Significant side effects (pneumonia, neutropenia, thrombocytopenia, pain, diarrhea, etc.)	8
Recurrence of disease and/or metastatic disease	4
Stopped due to debilitation and hospitalizations related to post-operative complications	3
Intermittent therapy due to cellulitis, eventually not able to tolerate	1
Unknown	5

6

Depression as a Symptom and Effect of Pancreatic Cancer: a Bidirectional Relationship

Talal Seoud MD, Hassan Quershi, **Aslam Syed MD**[1,*]; Gursimran Kochhar MD; Katie Farah MD, Suzanne Morrissey MD; Marcia Mitre MD; Manish Dhawan MD; Abhijit Kulkarni MD; Shyam Thakkar MD

[1] Division of Gastroenterology, Allegheny Health Network, Pittsburgh, PA, [2] Department of Internal Medicine, Case Western University, Cleveland, OH

Introduction: Pancreatic cancer (PaC) is the third leading cause of all cancer related deaths with a high mortality rate and poor prognosis. Depression is known to precede a diagnosis of pancreatic cancer in approximately 33-45% of patients who've had a diagnosis of PaC. Moreover, depression often occurs in patients diagnosed with cancer, and is prevalent in up to 50-78% of patients diagnosed with PaC. The study aims at evaluating the diagnosis of depression in patients prior to a diagnosis of PaC, as well as the development of depression in patients after a diagnosis of PaC is made.

Methods: A population-based study, using an IBM platform called Explorys was used to collect de-identified data. Over 50 million patients, spanning nationally in over 40 healthcare systems' electronic medical records are in this cloud-based, HIPPA-enabled platform. Data was obtained using SNOMED/ICD-9 code criteria with search terms "malignant tumor of the pancreas" and "depressive disorder." A temporal analysis was conducted to evaluate a timeline of a depression diagnosis preceding PaC. A temporal relationship was also established to evaluate the relationship of depression occurring after a diagnosis of PaC. Demographics and associated findings of depression were compared to a control cohort of patients diagnosed with depression without diagnosis of PaC using odds ratio (OR) with 95% confidence intervals (CI).

Results: A total of 58,140 patients were found to have diagnosis of PaC, 11,690 (20.1%) had concomitant diagnosis of depression in their EHR. Patients with PaC and depressive disorder that were referred to a mental health professional had a lower rate of all-cause mortality when compared to patients without a referral (42% vs. 37%, P = 0.009). A total of 59, 310 patients with diagnosis of PaC were identified, of which 11,730 (19.8%) had preceding depressive disorder. Factors associated with a diagnosis of depression included being male, African-American, age >65 and symptoms of weight loss and fatigue. 83.1% of patients developed PaC diagnosis within 6 months of depression diagnosis. Over 90% of patients developed PaC within 3 years of being diagnosed with depression.

Conclusions: Depression has a bidirectional relationship with PaC. In addition to having a high prevalence in patients with PaC, it is found in patients preceding the diagnosis of PaC. Based on the analysis, it is likely that clinicians are underdiagnosing depression in patients with pancreatic cancer. Clinicians should remain vigilant in patients with a new diagnosis of depression especially in those above the age of 65, males, and who have depression related findings including weight loss, fatigue, agitation, and anxiety. Additionally, Identifying and treating symptoms of PaC is associated with improved survival. More studies are warranted to evaluate the effects of referral or screening as a part of multidisciplinary team in the management of pancreatic cancer and whether it influences morbidity and mortality.

Table 1:

	PaC with Depressive Disorder [N = 11,690]	PaC without Depressive Disorder [N = 46,450]	*P*
Gender, n [%]			
Male	4,870 [42]	24,870 [54]	< 0.001
Female	6,820 [58]	21,560 [46]	< 0.001
Race, n [%]			
Caucasian	9,410 [80]	33,470 [72]	< 0.001
African-American	1,420 [12]	5,890 [13]	0.0038
Hispanic	90 [1]	380 [1]	1.000
Age, n [%]			
18 – 65	4,020 [34]	13,450 [29]	< 0.001
> 65	7,630 [65]	32,670 [70]	< 0.001
All-Cause Mortality, n [%]	4,920 [42]	17,430 [38]	< 0.001

Table 2:

	Depression and PaC [N = 11,730]	Control [N = 5,290,190]	OR [95% CI]	*P*
Gender, n [%]				
Male	4,890 [41.7]	1,707,420 [32.3]	1.50 [1.45, 1.56]	< 0.0001
Female	6,840 [58.3]	3,582,770 [67.7]	0.67 [0.64, 0.69]	< 0.0001
Ethnicity, n [%]				
Caucasian	9,440 [80.5]	4,187,610 [79.2]	1.09 [1.04, 1.14]	0.0004
African-American	1,420 [12.1]	548,350 [10.4]	1.19 [1.13, 1.26]	< 0.0001
Hispanic	90 [0.8]	50,910 [1]	0.80 [0.65, 0.98]	0.0310
Age, n [%]				
18-65	4,030 [34.4]	3,674,020 [69.4]	0.23 [0.22, 0.24]	< 0.0001
> 65	7,650 [65.2]	1,523,850 [28.8]	4.63 [4.46, 4.81]	< 0.0001
Findings, n [%]				
Anxiety	5,080 [43.3]	2,200,320 [41.6]	1.07 [1.03, 1.11]	0.0002
Sleep Disorder	4,470 [38.1]	1,613,450 [30.5]	1.40 [1.35, 1.46]	< 0.0001
Agitation	170 [1.4]	40,270 [0.8]	1.92 [1.85, 1.99]	< 0.0001
Suicidal Thoughts	380 [3.2]	388,670 [7.3]	0.42 [0.41, 0.44]	< 0.0001
Weight Loss	3,580 [30.5]	353,210 [6.7]	6.14 [5.92, 6.37]	< 0.0001
Fatigue	5,470 [46.6]	1,463,100 [27.7]	2.29 [2.20, 2.37]	< 0.0001

Table 3:

Timeline to PaC	Depression and PaC [N = 11,730]	Rate (%)
6 months	9,750	83.1
1 year	10,140	86.4
3 years	10,970	93.5

7

Iron Levels and Lipocalin 2 Expression Modulate Responses of Cells in the Tumor Micro-environment of Pancreatic Ductal Adenocarcinoma

V Pita Grisanti,[1,2,3] A.W. Dangel,[1,2] A Ludwig, O Ueltschi,[1,2] X Mo,[4] M Pietrzak,[4] A Hite,[4] R.F. Hwang,[5] M Traczek,[1,2] N Badi,[1,2] Z Cruz-Monserrate.[1,2,#]

Oral Presentation, Session VIII-C

[1]Division of Gastroenterology, Hepatology, and Nutrition, Department of Internal Medicine, Wexner Medical Center; [2]The Comprehensive Cancer Center–Arthur G. James Cancer Hospital and Richard J. Solove Research Institute; [3] Interdisciplinary Nutrition program; [4] Department of Biomedical Informatics, The Ohio State University, Columbus, OH; [5] Department of Surgical Oncology, University of Texas, MD Anderson Cancer Center, Houston, Texas.

Background: Pancreatic Ductal Adenocarcinoma (PDAC) is the third leading cause of cancer-related death in the US. Cancer cells uptake high iron levels that can potentially promote cell invasion by inducing an epithelial-to-mesenchymal transition (EMT). Intracellular iron levels can be regulated by lipocalin-2 (LCN2), a secreted protein that chelates iron in the tumor microenvironment (TME) and promotes PDAC by modulating pro-inflammatory responses in pancreatic stellate cells (PSCs). The objective of this study was to determine how iron levels and LCN2 expression affected PDAC cell proliferation and metastasis.

Methods: Human PDAC cell lines BXPC3 (KRAS-wild-type) and Panc-1 (KRAS-mutant) and PSCs were treated with various doses of iron and the iron chelator deferoxamine (DFO). Cell proliferation was measured via MTT assays. Changes in the expression of the pro-

inflammatory cytokines, the LCN2 receptor SLC22A17, and the iron storage gene Ferritin (FTH1) were measured via RT-qPCR. Invasion assays were performed to assess the migratory potential. The expression of EMT markers and the anti-metastatic gene N-myc downregulated gene 1 (NDRG1) were quantified. The Lcn2 gene was deleted via CRISPR in mouse PDAC cells, and RNA sequencing analyses were done to assess differences in gene expression. Moreover, the expression of NDRG1, LCN2, and FTH1 were measured after various iron and DFO treatments in the parental and Lcn2-KO cell lines via RT-qPCR.

Results: Iron and DFO regulated PDAC cell proliferation in a dose-dependent manner, determined by KRAS mutation status. Increased iron treatments upregulated the expression of pro-inflammatory cytokines. In addition, iron chelation augmented the expression of SLC22A17 and decreased the expression of pro-inflammatory cytokines in PSCs. Elevated iron doses increased the expression of EMT markers and invasion in BXPC-3 compared to Panc-1 cell lines and reduced NDRG1 expression. Deletion of Lcn2 in mouse PDAC cells modified the expression of extracellular matrix (ECM) genes, increased the expression of NDR1 which was downregulated after iron treatment. Iron chelation increased Ndrg1 and Lcn2 expression at high doses in parental mouse PDAC cells.

Conclusion: Iron responses in PDAC TME cells are dependent on KRAS mutation status. Lack of Lcn2 expression might have protective effects against metastasis. Further studies will determine the role of iron intake modulation and Lcn2 blockade in PDAC.

8

Incidence of Pancreatitis with the use of Immune Checkpoint Inhibitors (ICI) in Advanced Cancers: A Systematic Review and Meta-Analysis

John George
CAPER Scholarship Recipient- Yale New Haven Health

Background: Systemic immune side effects including pancreatitis have been reported with the use of Immune Checkpoint Inhibitors (ICI) (CTLA-4, PD-1 and PDL-1). However, the true incidence, risk, causes (tumor or drug specific) of pancreatitis and relation to other immune side effects, especially diabetes mellitus (DM) are unknown.

Methods: We performed a systematic review and meta-analysis of all clinical trials using ICI for the incidence of any grade lipase elevation, pancreatitis or DM.

Results: The incidence of asymptomatic lipase elevation after ICI use is 2.7% (211/7702) and grade 2 pancreatitis is 1.9% (150/7702). No pancreatitis related mortality has been reported in these clinical trials. Patients treated with CTLA-4 inhibitors have increased incidence of pancreatitis when compared to patients treated with PD1 inhibitors 3.98% (95% CI: 2.92 to 5.05) vs 0.94% (95% CI: 0.48 to 1.40); P value < 0.05. Patients treated with ICI for melanoma have increased incidence of pancreatitis when compared to non-melanoma cancers. We also noted an additive increase in incidence of pancreatitis with combination of CTLA4 and PD-1 inhibitors (10.60; 95% CI: 7.89 to 13.32) compared with either CTLA-4 or PD-1 inhibitors alone.

Conclusions: Our study provides precise data for the incidence of pancreatitis among patients using ICI based on tumor types and ICI regimens. ICI use for solid tumors is associated with increased incidence of all grades of lipase elevation and pancreatitis, especially for CTLA-4 agents and ICI combination. Although it does not appear to be associated with mortality, ICI related pancreatitis should be recognized early for appropriate treatment and to potentially reduce long term complications.

9

Incidence of Pancreatitis with the use of Immune Checkpoint Inhibitors (ICI) in Advanced

Ridwaan Albeiruti MD, Fahad Chaudhary MD, Justin Kupec MD
West Virginia University

Background: Acute pancreatitis (AP) is the most common gastrointestinal cause of admission in the United States. Diabetes mellitus (DM) is one of the most common diseases worldwide. In this study, we examine the incidence and in-hospital outcomes associated with uncontrolled hyperglycemia (DKA and hyperosmolar hyperglycemic state (HHS)) among patients hospitalized with AP using discharge data from the Nationwide Inpatient Sample (NIS).

Methods: We utilized the NIS of the Healthcare Cost and Utilization Project (HCUP) to identify adult patients admitted with acute pancreatitis between 2003-2015. Patients were identified using ICD-9-CM codes. Patient characteristics included age, sex, race, insurance status, and income. Hospital characteristics included bed size, location, and weekend admission. In-hospital complications studied included mortality, urinary tract infections, acute kidney injury, acute dialysis requirement, septic shock, respiratory failure, length of stay and cost. Weighted national estimates were used in all statistical analyses. Baseline characteristics were compared using Pearson-chi-squared test and Fisher's exact test for categorical variables and an independent-samples t-test for continuous variables.

We then compared in-hospital complications, length of stay, and cost of hospitalization using univariate and multivariate logistic regressions.

Results: The final sample included 6,516,654 pancreatitis hospitalization. Acute pancreatitis patients with uncontrolled hyperglycemia were younger (43 vs 53, p<0.001), male (59.6% vs 40.4%, p<0.001), black (24.3% vs 17.5%, p<0.001), and of a lower socioeconomic status (37.5% vs 32.1%, p<0.001). Comorbidities associated with uncontrolled hyperglycemia in patients with AP include depression/psychosis (8.3% vs 5.8%, p<0.001), tobacco use (25.9% vs 22.5%, p<0.001), alcohol use (26.6% vs 25.8%, p<0.001). In a multivariate logistic regression analysis, biliary etiology of AP (OR 0.26, 95% CI 0.25-0.28, p<0.001), presence of inflammatory bowel disease (OR 0.34, 95% CI 0.28-0.39, p<0.001) and cirrhosis (OR 0.89, 95% CI 0.86-.0.93, p<0.001) carried a decreased risk of DKA/HHS. Patients admitted with AP developing uncontrolled hyperglycemia were more likely to have AKI (10.8% vs 33%, p<0.001), dialysis (3.2% vs 4.1%, p<0.001), respiratory failure (4.6% vs 9.1%, p<0.001), gastrointestinal bleeding (GIB) (2.9% vs 4.1%, p<0.001) and septic shock (1.7% vs 3.6%, p<0.001). While the length of stay were significant (4 days), total charges of hospitalization were increased nearly 29%. Although the increase in mortality was statistically significant in those with uncontrolled hyperglycemia, this difference was not clinically significant (2.2% vs 2.4%, p<0.001).

Conclusions: Patient admitted with AP complicated by uncontrolled hyperglycemia (DKA/HHS) have no clinically significant difference in mortality or length of stay despite having increased morbidities of AKI, respiratory failure, GIB, and cost.

10

Dynamic Analysis of Patients with Acute Pancreatitis: Validation of a New Predictive Tool for Severity Assessment in a Large Prospective Cohort

Pedram Paragomi MD[1], Dan Spagnolo PhD[2], Cameron Breze[2], Amir A. Gougol MD[1], Mark Haupt MD[2], David C. Whitcomb MD PhD[1], Georgios I. Papachristou MD PhD[1,3]

CAPER Scholarship Recipient- University of Pittsburgh

[1]Division of Gastroenterology, Hepatology and Nutrition, University of Pittsburgh Medical Center, Pittsburgh, PA, [2]Ariel Precision Medicine,

4638 Centre Avenue, 2nd Floor Pittsburgh, Pittsburgh, PA 15213, USA, [3]Division of Gastroenterology and Hepatology, Veterans Affairs Pittsburgh Health System, Pittsburgh, PA

Background: Acute pancreatitis (AP) is an inflammatory response to pancreatic injury. Variable responses to injury result in mild, moderate or severe acute pancreatitis (SAP). Early detection of the systemic inflammatory response syndrome (SIRS) and multi-organ dysfunction syndrome (MODS) in SAP followed by prompt intervention may improve outcomes. Numerous scoring systems attempt to classify patients into severity levels, but their clinical utility is limited due to incomplete data, incomplete analysis, and *post hoc* analyses providing unclear treatment guidance. A simple, accessible, and dynamic tool is needed for evidence-based guidance at the point of care in AP patients.

Aim: Test the accuracy and utility of an automated system to classify severity of AP cases.

Methods: 163 AP patients prospectively ascertained at UPMC using the APPRENTICE protocol were used in a validation study of a new severity calculator (Ariel Precision Medicine, Pittsburgh, PA). Data from admission was sufficient to calculate SIRS score, HAPS (Harmless Acute Pancreatitis Score), Panc 3 score, and BISAP (Bedside Index of Severity in Acute Pancreatitis). Data from 24 / 48 / 72 hrs, and hospital day 7 was used to track outcomes (Table 1). Each scoring system was tested for association with patient outcomes, including transient (sustaining < 48 hrs) and persistent (sustaining > 48 hrs) organ failure, and ICU admission using a χ^2 independence test. Models were tested for association with outcomes using combinations of clinical scoring systems to observe performance.

Results: After adjudication, 100% concordance between automated clinical scoring metrics and their true values was observed for SIRS, HAPS, Panc 3, and BISAP at admission. SIRS score ≥ 2 was significantly associated with OF onset within the first 24 hrs (p-value=0.023). Using a SIRS threshold of 3 yielded improved positive and negative predictive values. SIRS ≥ 3 was significantly associated with OF onset within the first 48 hrs (p-value<0.00001, and OF occurrence throughout length of stay (p-value<0.01). SIRS ≥ 2 and ≥3 at admission were both associated with elevated rate of ICU admission (p-value<0.00001 and p-value=0.0002 respectively). Further results are delineated in Table 2.

Conclusions: A new predictive tool designed to utilize data from health information systems accurately calculates the scores believed to be important in the APPRENTICE study. The severity scores on admission proved to be useful in predicting future outcomes, and therefore may help identify patients with predicted SAP early in the course. Prospective multicenter studies are warranted to determine if access to guidance tools at the point of care improve outcomes.

Table 1: Characteristics of study population collected by UPMC as part of the Acute Pancreatitis Patient Registry to Examine Novel Therapies in Clinical Experience (APPRENTICE) study.

Patients' Characteristics	
Age, Mean ± SD	53 ± 16
Female	78 (47.8%)
Caucasian	135 (82.8%)
African American	20 (12.2%)
Hispanic	1 (<1%)
BMI, Mean ± SD	31 ± 10
Transfer from outside hospital (OSH)	77 (47.2%)
Active Smoking	47 (28.8%)
Active Drinking	81 (49.7%)
Etiology	
♦ Gallstone	59 (36.2%)
♦ Alcohol	36 (22.1%)
♦ Hypertriglyceridemia	15 (9.2%)
♦ POST-ERCP	11 (6.7%)
♦ Idiopathic	31 (19.0%)
ICU admission	31 (19.0%)
Mortality	1 (<1%)
Length of hospital stay (days), Median (IQR)	7 (4-11)
Revised Atlanta Classification	
♦ Mild Acute Pancreatitis	109 (66.9%)
♦ Moderately-Severe Acute Pancreatitis	37 (22.7%)
♦ Severe Acute Pancreatitis	17 (10.4%)

Table 2: χ^2 independence test for clinical scoring systems and patient outcomes. SIRS, HAPS, Panc 3, and BISAP were tested for association with transient and persistent organ failure.

	Persistent OF (POF)	Transient OF (TOF)	No OF (NOF)	P-value (any OF vs. NOF)	P-value (POF vs. TOF vs. NOF)
SIRS (First 24h)					
SIRS score ≥ 3 within first 24h	9	2	27	**0.003**	**0.007**
SIRS score<3 on admission and at 24h	8	4	113		
HAPS					
HAPS admission ≥1	12	3	59	0.064	0.112
HAPS admission = 0	5	1	67		
PANC3					
PANC-3 admission ≥1	10	3	68	0.95	0.745
PANC-3 admission = 0	8	1	54		
BISAP					
BISAP admission ≥1	14	3	63	**0.001**	**0.0005**
BISAP admission = 0	0	0	63		
HAPS-BISAP-Panc-3					
H-B-P positive (≥1)	16	5	106	0.303	0.3563
S (=0)	2	0	27		
Admission SIRS-HAPS-BISAP					
S-H-B positive (≥1 index positive)	12	4	52	**0.002**	**0.007**
S-H-B negative (no positive index)	4	2	88		
Admission SIRS-HAPS-BISAP-PANC3					
S-H-B-P Positive (≥1 index positive)	13	5	110	0.947	0.936
S-H-B-P Negative (no positive index)	3	1	30		

11

Utility of Presepsin for Diagnosis of Infected Acute Necrotizing Pancreatitis

Oleksandr Rotar[1*], Igor Khomiak[2], Michail Nazarchuck[3], Vasyl Rotar[1], Andrii Khomiak[2]

[1]Bukovinian State Medical University, Chernivtsi, Ukraine, [2]O.O. Shalimov National Institute of Surgery and Transplantology, Kyiv, Ukraine, [3]5th City Clinical Hospital, Minsk, Belarus

Context: Purulent complications worsens prognosis in patients with acute necrotizing pancreatitis (ANP). Early diagnosis of infection development can improve results of their management.

Objective: Aim of our research was to establish utility of presepsin for diagnosis of local and system infected complications during ANP.

Methods: Prospective study of 70 patients with severe ANP in a single intensive care department of regional hospital have been performed. Levels of presepsin before any invasive treatment were determined and compared with results of bacteriological investigation of pancreatic tissue.

Findings: The positive results of bacteriological examination were obtained in 43 patients. The rate of presepsin was three-four times higher in the patients with infected complications than those in the individuals with sterile pancreatic necrosis. Increasing the presepsin rate above 632 pg / ml allows confirming the presence of both local and systemic infection with high sensitivity and specificity. ROC AUC of presepsin diagnostic utility for all types of infected complications of ANP reached 0.956, CI 0.883-0.972, $p<0.01$.

Conclusion: Presepsin concentration is early highly sensitive and specific marker for all kind of infected complications of ANP.

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Development, Validation of a Post-ERCP Pancreatitis Risk Calculator and Machine Learning Based Decision Making Tool for Prophylaxis Selection

Ayesha Kamal[1*], Venkata S. Akshintala[1*], Albert Kuo[2], B. Joseph Elmunzer[3], Hui Luo[4], D. Nageshwar Reddy[5], Mahesh K. Goenka[6], Rakesh Kochhar[7], Erwin van Geenen[8], Ludmila Danilova[9], Saowanee Ngamruengphong[1], Anthony N. Kalloo[1], Mouen A. Khashab[1], Vikesh K. Singh[1], Cristian Tomasetti[2,9]

CAPER Scholarship Recipient- Johns Hopkins University

[1]Division of Gastroenterology, Johns Hopkins Hospital, Baltimore, MD, [2]Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, [3]Division of Gastroenterology and Hepatology, Medical University of South Carolina, Charleston, SC, [4]Xijing Hospital of Digestive Diseases, Fourth Military Medical University, Xi'an, China, [5]Department of Gastroenterology, Asian Institute of Gastroenterology, Hyderabad, India, [6]Department of Gastroenterology, Apollo Gleneagles Hospital, Kolkata, India, [7]Department of Gastroenterology, Postgraduate Institute of Medical Education & Research, Chandigarh, India, [8] Department of Gastroenterology and Hepatology, Radboud University Medical Center, Nijmegen, Netherlands, [9]Division of Biostatistics & Bioinformatics, Department of Oncology, Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD

Background: While patient and procedural risk factors for the development of post-ERCP pancreatitis (PEP) have been described in numerous prior prospective studies, a validated risk estimation tool is not available. Stratification based on such risk estimation will allow appropriate patient selection and utilization of appropriate prophylactic measures to prevent PEP.

Methods: Feature selection, model training and its validation were based on patient-level data from 3 recent multi-center, randomized controlled trials (RCT) evaluating PEP prevention in high and average risk patients. Data pertaining to patient and procedural risk factors of PEP and PEP preventive strategies were obtained. Study participants were randomly assigned to training and test cohorts in a 4:1 ratio. The important predictors of PEP were identified using backward selection via random forest (RF), a machine learning method which adjusts for interaction among the predictors. The RF model was subsequently trained using these predictors and model performance in estimating PEP risk was evaluated using area under the receiver operating curve (AUC) with 10-fold cross validation as well as on an independent test set. PEP reduction with prophylaxis was estimated with the random forest model. The RF model was translated to a computer based, risk calculator and decision making tool. Pancreatic duct (PD) stent could not be included in the decision making model as its use was not randomized in the source RCTs and its estimated effect could therefore be subjected to endoscopist bias.

Results: A total of 3853 patients (mean age 56.2±16.3 years; 42.3% females) were included in the RF model among whom 7.2% developed PEP. 69.3% patients received rectal indomethacin and 15.9% received prophylactic PD stent placement, respectively. Fifteen variables were identified as important, independent predictors of PEP (Figure 1). After evaluating the model performance via 10-fold cross-validation, the discriminatory power of the PEP risk classification model was tested on an independent validation set, resulting in a 78% prediction accuracy (80% specificity, 49% sensitivity, 0.67 AUC: Figure 2). The model showed similar accuracy in

estimating PEP risk reduction with rectal indomethacin use. In prospective evaluation of patients, the model identifies patients with similar characteristics from the training cohort and estimates PEP risk and PEP risk reduction with rectal indomethacin use (Figure 1). Conclusions: This machine learning based PEP risk estimation tool can provide a real-time, personalized and objective risk of PEP. Furthermore, this tool could assist in PEP prophylaxis decision making by predicting PEP risk reduction with rectal indomethacin use. Thereby, indirectly identifying patients who are not likely to benefit from rectal indomethacin prophylaxis and may require PD stent placement.

Figure 1: Screen-shot of the computer based, real time risk-calculator and decision making tool. The risk factors of post-ERCP pancreatitis (PEP) are listed to the left and a graphical representation of PEP risk without prophylaxis and with rectal indomethacin prophylaxis is presented to the right.

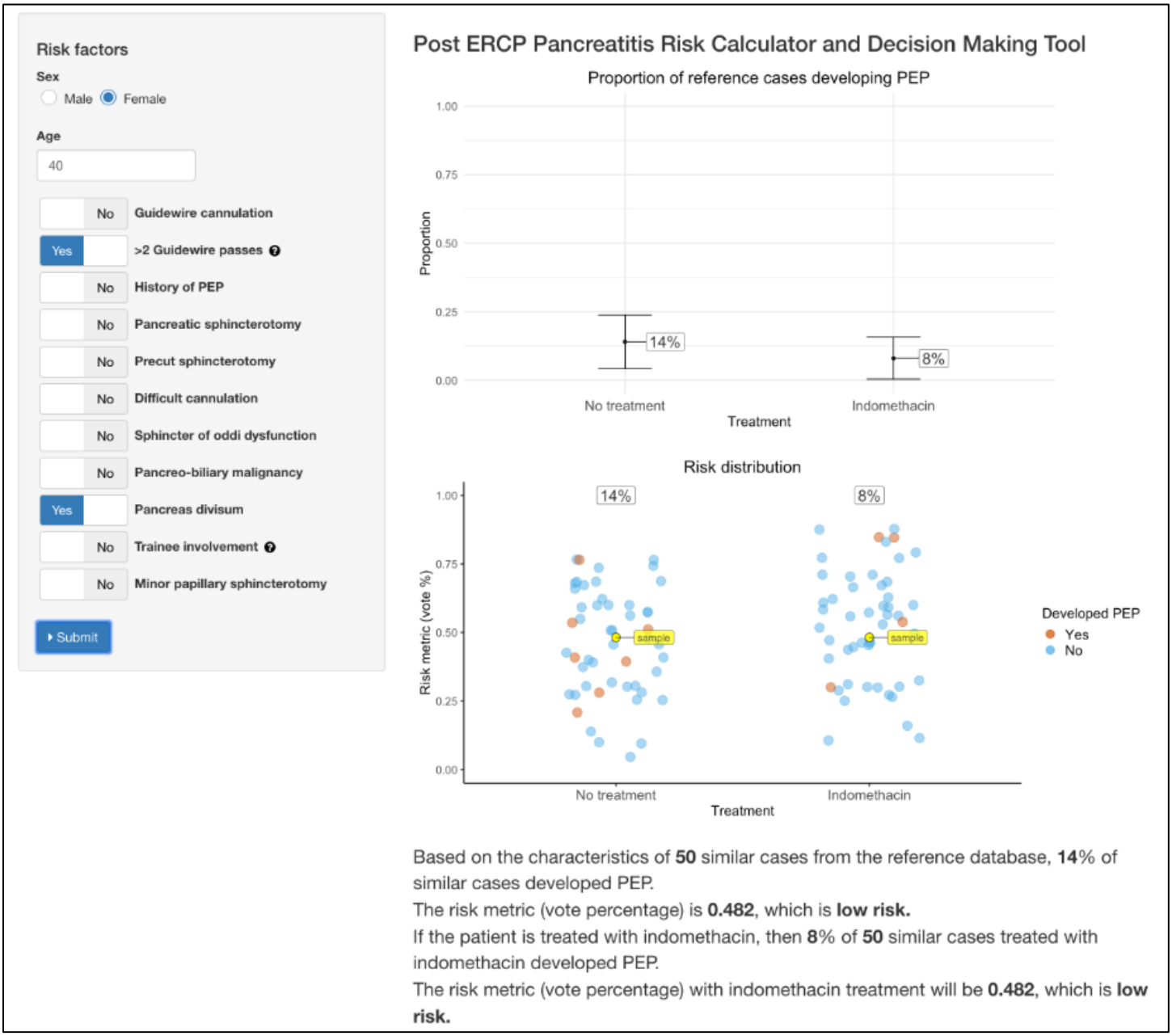
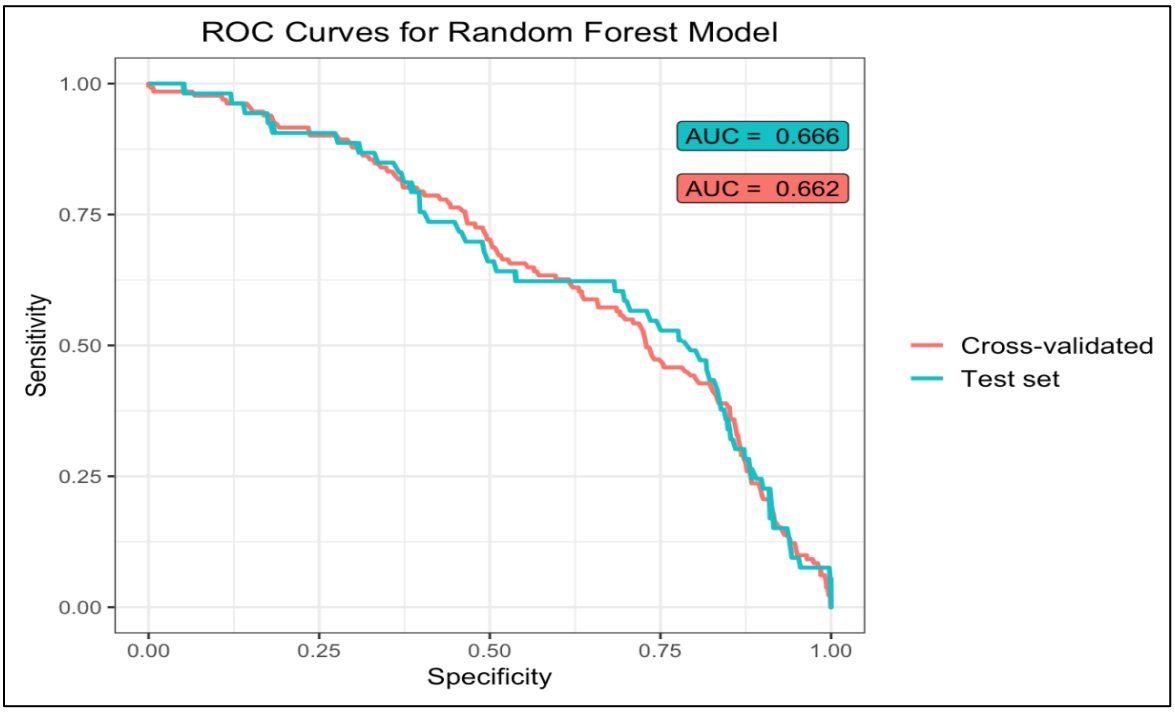


Figure 2: Area under the receiver operating curve (AUC) with 10-fold cross validation (green) and in an independent test cohort (red) for post-ERCP pancreatitis (PEP) risk estimation and decision making.



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What is the Impact of a Delayed Presentation on Outpatients with Post-ERCP pancreatitis?

Benjamin L. Bick, MD, Evan L. Fogel, MD, Suzette Schmidt, RN, BSN, Badih Elmunzer, MD, MSc, Yan Tong, PhD, Mark A. Gromski, MD, Stuart Sherman, MD, Glen Lehman, MD, James L. Watkins, MD, Gregory A. Cote, MD, MS, Paul Tarnasky, MD, Richard Kwon, MD, Nalini Guda, MD, Douglas Pleskow, MD, Jeffrey J. Easler, MD

Background: Post-ERCP pancreatitis (PEP) occurs in up to 15% of high risk patients. Symptoms after ERCP are common and usually determine admission. However, discharge of outpatients at risk for PEP is frequent after ERCP. In retrospective studies, discharged PEP patients are at increased risk for severity, possibly due to delays in IV fluid therapy. The aim of this study is to evaluate clinical predictors and outcomes in patients discharged and later admitted with delayed presentation of PEP.

Methods: We identified consecutive outpatients with PEP enrolled in a prospective study designed to evaluate the optimal rectal Indomethacin dose for prevention of PEP in high-risk patients. All patients received Indomethacin and were observed for at least 4 hours post-ERCP per protocol. All clinical data except IV fluids, recovery medications, and pain scores were collected prospectively. Diagnosis and severity of PEP was defined by Cotton criteria.

Results: 107/720 (14.9%) developed PEP. 135/720 (18.8%) were directly admitted after ERCP. While the direct admission rate in patients that developed PEP was higher ($p<0.001$), 58/107 (54.2%) were discharged and had a delayed presentation of PEP. Median time to presentation was 24 hours (IQR 15-31.75 h). Discharged patients were older (age 47.7 vs 41.1, $p=0.026$), more often had a morning procedure (59.2% vs 39.7%, $p=0.044$), less often had pancreatic stent placement (82.8% vs 95.9%, $p=0.032$), spent less time in recovery (261 vs 312 minutes, $p=0.004$), required less IV opioids (6.4 vs 17.3 MME, $p<0.001$) and had lower pain scores (2.8 vs 6.5, $p<0.001$) (Table 1). On multivariable analysis, an afternoon procedure (OR 4.00, $p=0.016$) and pain score >3 (OR 1.37, $p=0.001$) were associated with admission. While discharged patients were more likely to present with SIRS on admission (43.1% vs 10.2%, $p<0.001$), a delayed presentation was not associated with severe PEP.

Discussion: Delayed presentation of PEP after discharge of high-risk patients is frequent, but not associated with adverse outcomes or severe PEP. Systematic deployment of PEP prophylaxis with rectal Indomethacin, pancreatic stents, and IV fluids may attenuate the impact of delayed presentation on outcomes. Afternoon procedure time and increased pain appear to influence decisions to admit. However, given the frequency of delayed presentation of PEP, accurate and early diagnostic tests for PEP may be of clinical value.

Table 1. Characteristics of outpatients with post-ERCP pancreatitis who were either directly admitted or discharged with a delayed admission for PEP

	Direct admission (n=49)	**Discharge with delayed admission** (n=58)	**p value**
Demographics and baseline history			
Age, mean (SD)	41.1 (14.7)	47.7 (15.5)	**0.026**
Gender, F (%)	44 (89.8%)	45 (77.6%)	0.093
BMI, mean (SD)	29.0 (8.1)	30.5 (8.2)	0.342
Charlson Comorbidity Index (age-adjusted), mean (SD)	1.3 (1.7)	1.7 (1.6)	0.258
Suspicion of SOD (%)	37 (75.5%)	41 (70.7%)	0.576
History of PEP (%)	12 (24.5%)	14 (24.1%)	0.966
History of RAP (%)	20 (40.8%)	27 (46.6%)	0.551
Home distance from ERCP site (miles), mean (SD)	178.0 (231.4)	263.9 (456.6)	0.235
Peri-procedural data			
Time of day, PM (%)	29 (59.2%)	23 (39.7%)	**0.044**
Duration of ERCP (min), mean (SD)	45.5 (21.3)	39.7 (20.3)	0.154
IV fluids (mL) during ERCP, mean (SD)	655.5 (289.0)	660.8 (217.9)	0.914
Weight based IV fluid rate during ERCP (mL/kg/h), mean (SD)	13.9 (8.5)	16.3 (10.7)	0.212
Pancreatic sphincterotomy (%)	31 (63.3%)	31 (53.4%)	0.305
Pancreatic sphincterotomy, minor (%)	6 (12.2%)	11 (19.0%)	0.343
Pre-cut access (%)	4 (8.2%)	7 (12.1%)	0.507
>8 cannulation attempts (%)	17 (34.7%)	19 (32.8%)	0.833
Ampullectomy (%)	1 (2.0%)	1 (1.7%)	0.904
>3 pancreatic injections (%)	15 (30.6%)	12 (20.7%)	0.239
Pancreatic acinarization	2 (4.1%)	3 (5.2%)	0.79
Pancreatic stent (%)	47 (95.9%)	48 (82.8%)	**0.032**
Recovery room data			
Duration in recovery (min), mean (SD)	312.1 (118.9)	261.0 (52.1)	**0.004**
IV fluids (mL) given in recovery, mean (SD)*	398.9 (362.3)	301.0 (318.9)	0.179
Weight based IV fluid rate in recovery (mL/kg/h), mean (SD)*	1.5 (2.5)	0.9 (0.9)	0.112
IV Morphine milligram equivalent (MME) (grams), mean (SD)	17.3 (20.0)	6.4 (7.1)	**<0.001**
Likert pain score (1-10) at decision to discharge/admit, mean (SD)	6.5 (2.8)	2.8 (2.7)	**<0.001**
Benzodiazepines received in recovery (%)	10 (20.4%)	10 (17.2%)	0.675
Anti-emetics received in recovery (%)	41 (83.7%)	42 (72.4%)	0.164
Outcomes			
Post-ERCP pancreatitis severity			0.807
Mild	30 (61.2%)	36 (62.1%)	
Moderate	17 (34.7%)	18 (31.0%)	
Severe	2 (4.1%)	4 (6.9%)	
Organ failure during hospitalization (%)	5 (10.2%)	6 (10.3%)	0.981
Pancreatic necrosis (%)	2 (4.1%)	0	0.207
ICU during hospitalization (%)	0	3 (5.2%)	0.248
Duration of hospitalization (days), mean (SD)	4.6 (4.0)	4.1 (2.6)	0.449
SIRS on admission (%)	5 (10.2%)	25 (43.1%)	**<0.001**
SIRS during hospitalization (%)	19 (38.8%)	32 (55.2%)	0.091
Persistent SIRS, lasting >48 hours (%)	9 (18.4%)	16 (27.6%)	0.262
Readmission within 30 days (%)	3 (6.1%)	0	0.0928

*Recovery room IV fluid data available for 44 patients directly admitted and 45 patients discharged.

14

Impact of Image Quality on Single-Operator Pancreatoscopy Guided Intraductal Lithotripsy for the Treatment of Pancreatic Ductal Stones

Feenalie Patel, MD, Jeffrey J. Easler, MD, Stuart Sherman, MD, James L. Watkins, MD, Benjamin L. Bick, MD

Background: Obstructing main pancreatic ductal stones (MPDS) are sequela of chronic pancreatitis, and can cause pain through increased intraductal pressure. Large MPDS (≥5 mm) are often managed with extracorporeal shock wave lithotripsy (ESWL). Single-operator pancreatoscopy (SOP) with intraductal lithotripsy (SOPIL) is increasingly utilized due to multiple logistic advantages. SOP has been refined with interval advances in image quality, evolving from a fiberoptic (F-SOP) to a digital (D-SOP) (Figure 1) platform. The

aims of this study are 1) to report our center's experience in terms of effectiveness and safety of SOPIL for MPDS and 2) assess for technical benefits of the advances in image quality for this procedure.

Methods: This is a retrospective case series of Indiana University Medical Center patients who underwent SOPIL for the treatment of large MPDS from 2012 to 2018. Electrohydraulic lithotripsy was used. Large MPDS were defined as stones ≥5 mm obstructing the main pancreatic duct. Technical success was defined as complete or near complete stone clearance based on final pancreatogram. Clinical success was measured by improvement in pain or improvement in exocrine insufficiency (no longer requiring pancreas enzymes).

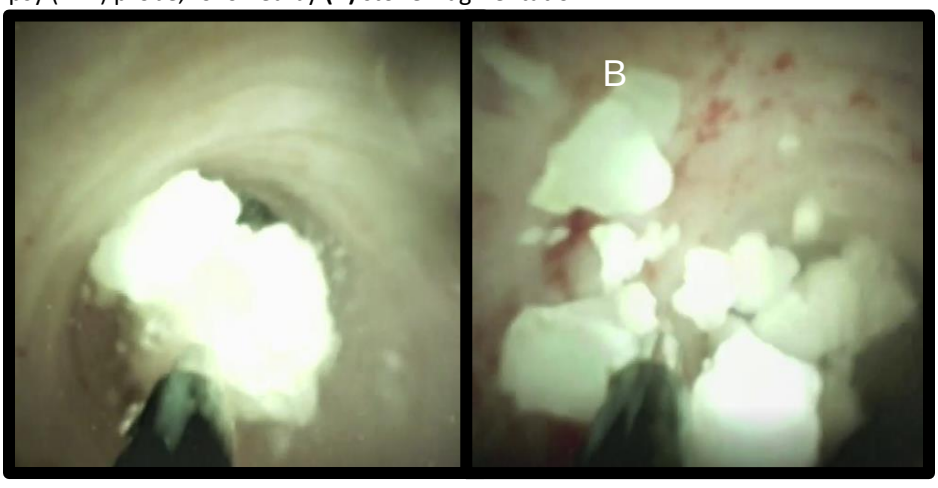
Results: 14 patients underwent SOPIL. Baseline characteristics, intra-procedural therapies, and outcomes are included in table 1. Symptoms prompting SOPIL included chronic pain (92.9%), recurrent acute pancreatitis (7.1%), and exocrine pancreatic insufficiency (71.4%). 13 of 14 (92.9%) patients had prior ERCP with unsuccessful stone clearance and 7/14 (50%) had prior unsuccessful stone fragmentation with ESWL. The majority of patients had a single, large (64%, N=9/14) versus multiple (46%, n=5) MPDS. Patients underwent a mean of 1.6 SOPIL procedures and 2.0 ERCP procedures for stone clearance with an average 3,339 (range 244-15,498) shocks. The overall rate of technical success was 85.7% with a100% (7/7) rate of successful SOPIL salvage treatment after ESWL failure. Of patients with pain indication and technical success for SOPIL (n=11), satisfactory pain improvement was seen in 10/11 (90.9%). Exocrine insufficiency resolved in 40% (4/10). First generation (F-SOP) equipment was used in 8/14 (57.1%) and included the 2 technical failures. Cited reasons for technical failure included difficulty visualizing the stone to perform therapy and large stone size (33 mm). Technical successes compared to failures had fewer EHL sessions (1.3±0.5 vs 3.5±2.1, p=0.003) and a lower total procedure duration (82.8±24.4 vs 243±138.6 minutes, p=0.001). On univariate analysis, no characteristics were associated with an increased risk of technical failure. After excluding technical failures, D-SOP compared to F-SOP platform was associated with fewer shocks (1207.7±907.7 vs 2829.7±646.2, p=0.029) and trended towards a lower procedure time (70.5±23.9 vs 95±19.5 minutes, p=0.08). One patient (7.1%) developed mild post-ERCP pancreatitis.

Conclusion: SOPIL is a safe and effective method of MPDS stone clearance that also results in clinical improvement in pain and exocrine insufficiency. Second generation (D-SOP) compared to first generation (F-SOP) platform is associated with fewer total shocks and a shorter procedure time. Our data suggests that improved imaging of the stones and pancreatic duct with a digital platform improves procedure efficiency and may equate an increased rate of technical success.

Table 1: Characteristics of patients who underwent single-operator pancreatoscopy (SOP) with electrohydraulic lithotripsy (EHL)

Baseline Characteristics	
Demographics	
Age, mean	59.5 years
Gender, %F	50.0% (7/14)
Ethnicity	
Caucasian	92.9% (13/14)
African American	7.1% (1/14)
Chronic Pancreatitis Characteristics	
Etiology	
Alcohol use only	7.1% (1/14)
Tobacco use only	21.4% (3/14)
Tobacco and Alcohol use	50.0% (7/14)
Idiopathic	21.4% (3/14)
Chronic pain	92.9% (13/14)
Chronic Narcotic Use	53.8% (7/13)
Exocrine Insufficiency	71.4% (10/14)
Prior therapies	
History of prior ERCP	92.9% (13/14)
History of prior ESWL	50.0% (7/14)
Number of ESWL sessions, mean	1.57
Number of shocks, mean	16,214
Stone characteristics	
Stone location	
Head	92.9% (13/14)
Neck	14.3% (2/14)
Body	35.7% (5/14)
Number of stones, mean	1.6
Stone size (mm), mean [range]	11 [5-33]
Intraprocedural Therapies	
Number of EHL sessions, mean	1.6
Number of EHL shocks, mean	3,339
Number of EHL/ERCP sessions, mean	2
Combined procedure time of EHL/ERCP (min), mean	106
Stone Extraction Techniques	
Stricture dilation	64.2% (9/14)
Balloon sweep	100% (14/14)
Basket sweep	57.1% (8/14)
Forceps	14.3% (2/14)
Outcomes	
Technical Success	85.7% (10/12)
Pain improvement	90.9% (10/11)
Improvement of exocrine insufficiency	40.0% (4/10)
Post-procedure admission	28.5% (4/14)
Average length of stay (days)	1.75
Admission for pain management	75.0% (3/4)
Admission for mild post-ERCP pancreatitis	25.0% (1/4)

Figure 1: (A) Digital single-operator pancreatoscopy (D-SOP) demonstrating a main pancreatic duct stone with the electrohydraulic lithotripsy (EHL) probe, followed by **(B)** stone fragmentation.



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Reviving the Rendezvous Technique: A Novel Approach in ERCP

Irma Hashmi, DO, Joan Kheder, MD, Christopher Marshall, MD

Background: The development of a pancreatic duct (PD) leak is a rare and serious complication of acute necrotizing pancreatitis. Patients may require endoscopic management with endoscopic retrograde cholangiopancreatography (ERCP) and sphincterotomy with stent placement. We discuss the case of a patient who underwent a major to minor papilla rendezvous technique of a non-dilated pancreatic duct (PD) without the use of endoscopic ultrasound (EUS), which is a technique cited only a few times in the literature.

Results: The patient is a 63-year-old female with history of Celiac disease and chronic pancreatitis who presented with subacute, diffuse abdominal pain. Laboratory findings revealed lipase 357 (normal less than 50 units/ liter) with normal liver function tests. Computed tomography scan showed atrophic pancreatitis, acute on chronic pancreatitis complicated by peripancreatic pseudocysts, walled off necrosis and perihepatic ascites. EUS revealed an 81 mm x 33 mm pseudocyst in the pancreatic body and tail with necrotic material with developing wall. The patient was initially managed conservatively with intravenous fluids and antibiotics. However, magnetic resonance cholangiopancreatography (MRCP) revealed discontinuation of the pancreatic duct and therefore an ERCP was performed. The bile duct and ventral pancreatic duct were successfully cannulated with brisk flow of contrast through the ducts. Contrast extravasated from the pancreatic duct indicating a pancreatic duct leak. However, both the guide wire, a straight Hydra Jagwire, and Hydratome sphincterotome could not pass from the ventral duct to the distal pancreatic duct due to tortuosity of the ventral duct. The guide wire was exchanged for a Nova Gold wire and sphincterotome exchanged for a 3-4-5 taper tip catheter without successful cannulation. A NaviPro wire was tried next which reentered the duodenum through the minor papilla; the guidewire was changed to a NovaGold wire. This too passed from the minor papilla to the duodenum. At this point, the wire was captured with forceps and pulled through the accessory channel and the cannula passed over the wire through the minor ampulla to the main PD. The tract was dilated, and a 5 French by 12 cm stent was placed across the area of bile duct leak successfully. The patient's abdominal pain improved dramatically following the procedure, and she was discharged to a rehabilitation center without further complications.

Conclusion: The major to minor rendezvous technique allows for successful cannulation of the PD when selective cannulation is unsuccessful. While traditional endoscopic technique enters the PD by way of the major duodenal papilla and ventral pancreatic duct, the rendezvous procedure reaches the PD via the minor duodenal papilla and dorsal pancreatic duct. Complications of necrotizing pancreatitis and chronic pancreatitis including stricture or calculi can lead to difficulty in PD access via the ventral duct. As imaging was without such findings in our patient, we suspect that she likely had an incomplete pancreas divisum. Literature review reveals the first case report of this technique performed in 1999; subsequent case reports have cited movement from fluoroscopy-assisted ERCP to EUS-guided approach. However, we did not use EUS and did not have a dilated PD, making the approach more difficult and unique as literature cites novelty in one or the other but not both.

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Tacrolimus and Indomethacin are Safe and Effective at Reducing Post-ERCP Pancreatitis in Orthotopic Liver Transplant Patients Undergoing ERCP

Nikhil Thiruvengadam, MD

CAPER Scholarship Recipient- University of California, San Francisco

Background & Aims: Biliary complications following orthotopic liver transplantation (OLT) are managed primarily by ERCP. Post-ERCP pancreatitis (PEP) is the most common procedural adverse event (AE). Mouse studies have suggested that transient pancreatic duct obstruction leads to calcineurin activation and pancreatitis, a process that tacrolimus may prevent. However, there are no large studies evaluating this in humans. Furthermore, rectal indomethacin reduces PEP but has not been studied in OLT patients due to concerns with renal dysfunction. We sought to: 1) determine the incidence of procedural AEs post-OLT; 2) determine the effectiveness of tacrolimus at reducing risk of PEP; 3) examine the effectiveness and safety of indomethacin; and 4) examine the interaction between tacrolimus and indomethacin.

Methods: We performed a retrospective cohort study of 337 post-OLT patients who underwent 937 ERCPs. After June 2012, 100 mg rectal indomethacin was routinely administered. Demographic and clinical variables, pre-procedural tacrolimus troughs, PEP, and AEs were collected. We used a data-driven approach to identify an optimal cut-point for the analysis of tacrolimus troughs and their association with PEP. Locally weighted scatterplot smoothing was used and an inflection point of 2.5 ng/mL was identified. Adjusted

odds ratios (ORs) for the association between risk factors and complications as well as use of indomethacin and tacrolimus trough > 2.5 ng/dL and risk of PEP were determined using mixed-effects multivariable logistic regression.

Results: There were 21 (2.2%) cases of PEP, 7 (0.7%) bleeding events and 6 (0.6%) cases of cholangitis. No perforations occurred. 848 procedures had a tacrolimus trough > 2.5 ng/mL while 54 had a trough <= 2.5 ng/mL. A tacrolimus trough > 2.5 ng/mL was associated with 77% lower odds for PEP (OR 0.23 95%-CI 0.07-0.78, p=0.02, Figure 1). 286 patients were exposed to indomethacin while 651 were not. Indomethacin was associated with a 90% reduction in risk of PEP (OR 0.10 (95%-CI 0.01-0.75;p=0.02, Figure 2). No difference in rates of bleeding, cholangitis or decline in GFR was associated with rectal indomethacin. In patients with a tacrolimus trough > 2.5 ng/mL, indomethacin additionally reduced the odds of PEP by 88% (OR 0.12 95%-CI 0.02–0.88; p=0.03).

Conclusions: We demonstrated: 1. Post-OLT patients have a low rate of post-ERCP AEs. 2. A tacrolimus trough > 2.5 ng/dL was associated with a significantly lower rate of PEP. 3. Rectal indomethacin significantly decreased rates of PEP and its usage did not worsen renal function in a cohort with CKD. 4. Concurrent usage of indomethacin offered an additional risk reduction for PEP in patients with a tacrolimus trough > 2.5 ng/dL. 5. Future prospective studies are needed to study the role of tacrolimus in prophylaxis of PEP and its role when rectal indomethacin is administered.

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Practices and Barriers for Prophylactic Rectal Indomethacin for Post-ERCP Pancreatitis in the United States: A 2018 National Survey Study

Sailesh Kandula[1], Gregory A. Cote[2], Evan Fogel[1,], Stuart Sherman[1], Mark Gromski[1],
Glen Lehman[1], James L. Watkins[1], and Jeffrey J. Easler[1].
[1] Division of Gastroenterology and Hepatology, Indiana University School of Medicine, Indianapolis, IN, United States, [2] Division of Gastroenterology & Hepatology, Department of Medicine, Medical University of South Carolina, Charleston, SC, United States.

Background: Post ERCP Pancreatitis (PEP) is the most frequent complication of endoscopic retrograde cholangiopancreatography (ERCP) and accounts for substantial procedure related morbidity and health care expenditures. Prophylactic pancreatic stent placement and rectal indomethacin (IND) prevent PEP, decrease severity and are endorsed as standard of care by GI societies. It is unclear the extent to which these interventions are practiced throughout the United States (US). The impact of such factors such as ERCP operator training, experience and practice setting on the use PEP prophylaxis interventions is unclear.
Aims: 1. Describe the utilization patterns of IND for PEP prophylaxis throughout the US. 2. Identify factors that impact the deployment of IND for post-ERCP pancreatitis 3. Characterize barriers toward deployment of IND for PEP prophylaxis.

Methods: A 27-question self-administered survey was distributed using an electronic cloud based survey tool (Qualtrics). Questions assessed ERCP operator training, practice setting, experience, practice patterns for PEP prophylaxis and perceptions regarding PEP prophylactic interventions. Endoscopists with practices based in the US and listed in the American Society for Gastrointestinal Endoscopy (ASGE) directory received the survey invitation via e-mail. The invitation outlined the study and offered a link to complete the voluntary survey if they had an active ERCP practice. Data was de-identified for the purposes of analysis.

Results: Survey response rate was 5% (n=319/6276). Of respondents, 46.4% reported formal therapeutic endoscopy training and 37% practiced in a GI fellowship based program. (Table 1) Annualized volumes of >100 ERCP procedures per year were reported by 47.1%, with pancreatic ERCP comprising ≤ 5% of procedures in the majority, 62%. At 94.7%, the vast majority of respondents reported IND as part of their practice with 53.9% systematically administering IND regardless of patient risk profile. The most common indications for administering IND were: difficult cannulation, multiple pancreatic duct injections and history of PEP. Of physicians that do not use IND in their practice, no single factor appeared to be dominant. Recent entry into ERCP practice (<10 yrs, p=0.055) and any use of prophylactic pancreatic stents (p=0.001) were associated with use of IND. (Table 2) A higher annualized procedure volume (>100, p=0.036) and frequent deployment of pancreatic stents (p=0.004) were associated with frequent use of IND.

Discussion: While the frequent use of IND associates with practices with higher ERCP procedure volumes and that regularly deploy prophylactic pancreatic stents, our findings suggest almost universal acceptance of IND for PEP prophylaxis regardless of practice type or operator experience. IND for PEP prophylaxis is accessible, accepted and perceived to be an effective form of PEP prophylaxis by physicians that perform ERCP.

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Multi-Organ Failure is the Strongest Determinant of Poor Clinical Outcomes in Acute Pancreatitis. (APPRENTICE Study Group)

Amir Gougol, Pedram Paragomi, Xiaotian Gao, Ioannis Pothoulakis, Rupiyoti Talukdar, Rakesh Kochar, Mahesh Kumar Goenka, Aiste Gulla, Jose A. Gonzalez, Vikesh K. Singh, Miguel Ferreira, Tyler Stevens, Sorin T. Barbu, Haq Nawaz, Silvia C. Gutierrez, Narcis O. Zarnescu, Gabriele Capurso, Jeffrey Easler, Konstantinos Triantafyllou, Mario Pelaez-Luna, Shyam Thakkar, Carlos Ocampo, Enrique de-Madaria, Gregory A. Cote, Bechien U. Wu, Ayesha Kamal, Livia Archibugi, Subhash Tiwari, Gong Tang, Anna Evans Phillips, & Georgios I. Papachristou.

CAPER Scholarship Recipient- University of Pittsburgh

Background: According to the revised Atlanta classification, severe acute pancreatitis (AP) is defined by the development of persistent organ failure (OF); however, there is remarkable heterogeneity within this group of patients. In this study, we aim to assess the impact of multi-organ failure (MOF) with its various presentations on clinical outcomes in patients with severe AP.

Methods: Data was collected from multinational, prospective cohort of AP patients (APPRENTICE Study). Enrollment was conducted between May 2015 to November 2017. There were 22 international centers who participated from 4 different continents. Renal, pulmonary, and cardiovascular failure were defined by the modified Marshall Score ≥2. Isolated organ failure (IOF) involved a single failing organ; multi-organ failure (MOF) was defined by the failure of ≥2 organs. Patients with MOF were categorized based on the type of organ, which failed first. Early OF was defined as the development of OF within the first 24 hours of admission.

Results: In total, 1585 patients were enrolled; median age was 49.8, 47% were female and biliary was the most common etiology (45.3%). Overall, 39 (2.5%) patients died during hospitalization. Persistent OF developed in 188 (11.8%) patients. Of them, 89 (47.3%) patients developed MOF, whereas 99 (52.6%) patients were classified as IOF. Mortality was significantly higher in patients with MOF compared to IOF (37.5% vs. 7.1%, p-value<0.01). Of patients with IOF, the renal system was involved in 20.2%, pulmonary in 74.7%, and cardiovascular in 5% of patients. Overall, the mortality among patients with IOF was relatively low (7.1%) and similar between isolated renal and pulmonary failure (5% vs. 4.1%, p-value=0.8).

Among patients with MOF, the first failing organ was renal in 24 (27%), pulmonary in 25 (28%), and cardiovascular in 4 (4.5%) patients. In 36 (40.5%) subjects, OF started in multiple organs concurrently (concurrent OF). OF onset varied based on the type of first failing organ. Development of early OF occurred less frequently in patients with pulmonary as the first failing (37.5%), compared to patients with renal (71%) or concurrent (73%) as the initial failing organ (p-value=0.01). After controlling for the number of failing organs, mortality was significantly higher in patients with pulmonary as the first failing organ compared to patients with renal as the first failing organ (62.5%, vs. 25%, p-value=0.01).

Conclusions: Using a large, international, prospective cohort of AP patients, we demonstrated heterogeneous outcomes in patients with severe AP; MOF had highest impact on mortality. The clinical course of patients with MOF appeared to varied based on the type of first failing organ.

Table 1: Comparison between isolated versus multiple organ failures among patients with severe acute pancreatitis.

	All Patients with Persistent OF (N=188)	Isolated Organ Failure (N=99)	Multi-organ Failure (N=89)	P-value*
Age, median (IQR)	49 (35-63)	45 (29-60)	51 (40-65)	0.04
Gender, female (%)	56 (29.8)	36 (36.4)	20 (22.5)	0.04
BMI, median (IQR)	26.4 (23.4-30)	25.7 (22.7-29.4)	26.8 (23.9-31.3)	0.19
Active alcohol drinking (%)	99 (52.7)	42 (42.4)	57 (64)	0.003
Smoking (%)	60 (31.9)	25 (25.3)	35 (39.3)	0.04
BUN ≥20 (%)	126 (68.5)	52 (54)	74 (84.1)	<0.01
Hct ≥44 (%)	74 (40.2)	29 (30.2)	45 (51.1)	0.004

SIRS ≥2 (%)	141 (77)	76 (79.2)	65 (74.7)	0.47
Etiology				0.12
- Biliary	64 (34)	40 (41)	24 (27)	
- Alcoholic	71 (37.8)	32 (32.3)	39 (43.8)	
- Others	53 (28.2)	27 (27.3)	26 (29.2)	
Pancreatic Necrosis (%)	116 (74.4)	60 (72.3)	56 (76.7)	0.25
- Extensive Necrosis (%)	51 (45.1)	28 (48.3)	23 (41.8)	0.7
LOS, median (IQR)	20 (13-30)	17 (12-26)	27 (21-39)	<0.01
Mortality (%)	40 (21.4)	7 (7.1)	33 (37.5)	<0.01

Extensive necrosis was defined as involvement of equal or greater than 50% of the pancreas.
IQR, interquartile range; BMI, body mass index; BUN, blood urea nitrogen; Hct, hematocrit; SIRS, systemic inflammatory response syndrome; OF, organ failure; LOS, length of stay.
*P-values for continuous and categorical variables were calculated with Kruskal-Wallis, and Chi Square tests, respectively.

Table 2: Comparison of acute pancreatitis patients with multi-organ failure based on the type of first failing organ.

	Renal Failure as First (N=24)	Pulmonary Failure as First (N=25)	Concurrent Failures as First (N=36)	p-value*
Age, median (IQR)	46.5 (41.7-68.7)	40 (30-49.5)	51 (44-62)	0.06
Gender, female (%)	8 (33.3)	4 (16)	8 (22.2)	0.35
BMI, median (IQR)	26 (23.5-29.2)	25 (23-42.7)	26.8 (24.2-30.3)	0.38
Etiology (%)				0.8
- Biliary	8 (33.3)	5 (20)	9 (25)	
- Alcoholic	9 (37.5)	12 (48)	18 (50)	
- Others	8 (32)	7 (29.2)	9 (25)	
Pancreatic Necrosis (%)	15 (75)	14 (73.7)	27 (90)	0.26
BUN ≥20 on admission (%)	21 (87.5)	16 (66.7)	33 (91.7)	**0.03**
Hct ≥44 on admission (%)	9 (37.5)	9 (36)	27 (75)	**0.003**
SIRS (%)	17 (71)	15 (65.2)	32 (88.9)	0.07
OF Onset within first 24 hours (%)	17 (70.8)	9 (37.5)	25 (73.5)	**0.01**
OF-Death Interval, median days (IQR)	20.3 (5-29.1)	9.6 (5.4-28.3)	6.8 (3.2-20.8)	0.3
LOS, median (IQR)	30 (20-45)	21 (17-27)	28 (21-38)	0.25
Mortality (%)	6 (25)	15 (62.5)	11 (30.6)	**0.01****

Cardiovascular failure as the first failing organ was not included into analysis due to low number of cases.
IQR, interquartile range; BMI, body mass index; BUN, blood urea nitrogen; Hct, hematocrit; SIRS, systemic inflammatory response syndrome; OF, organ failure; LOS, length of stay.
*P-values for continuous and categorical variables were calculated with Kruskal-Wallis, and Chi Square tests, respectively.
**The difference in mortality was compared using multivariate regression analysis.

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Multi-Organ Failure is the Strongest Determinant of Poor Clinical Outcomes in Acute Pancreatitis. (APPRENTICE Study Group)

Ioannis Pothoulakis[1], Pedram Paragomi[1], Livia Archibugi[2], Marie Tuft[1], Rupiyoti Talukdar[3], Rakesh Kochar[4], Mahesh Kumar Goenka[5], Aiste Gulla[6,7], Vikesh K. Singh[8], Jose A. Gonzalez[9], Miguel Ferreira[10], Sorin T. Barbu[11], Tyler Stevens[12], Haq Nawaz[13], Silvia C. Gutierrez[14], Narcis O. Zarnescu[15], Jeffrey Easler[16], Konstantinos Triantafyllou[17], Mario Pelaez-Luna[18], Shyam Thakkar[19], Carlos Ocampo[20], Enrique de-Madaria[21], Bechien U. Wu[22], Gregory A. Cote[23], Anna E. Phillips[1], Gong Tang[1], Georgios I. Papachristou[1], Gabriele Capurso[2]

CAPER Scholarship Recipient- University of Pittsburgh

[1] University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA, [2]Digestive and Liver Disease Unit, S. Andrea Hospital, Sapienza University of Rome, Rome, Italy, [3] Asian Gastroenterology Institute, Hyderabad, India, [4] Postgraduate Institute of Medical Education and Research, Chandigarh, India, [5] Apollo Gleneagles Hospitals Kolkata, Kolkata, India, [6] Georgetown University Hospital, Washington, DC, USA, [7] Lithuanian University of Health Sciences, Kaunas, Lithuania, [8] John Hopkins Medical Institution, Baltimore, Maryland, USA, [9] Universidad Autónoma de Nueva León, Monterrey, Mexico, [10] Hospital Nacional de Itaguá, Itagua, Paraguay, [11] University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj-Napoca, Romania, [12] Cleveland Clinic Foundation, Cleveland, USA, [13] Eastern Maine Medical Center, Maine, Bangor, USA, [14] Hospital Nacional "Profesor Alejandro Posadas", Buenos Aires, Argentina, [15] University of Medicine and Pharmacy, Bucharest, Romania, [16] Indiana University School of Medicine, Indianapolis, Indiana, USA, [17] Attikon University General Hospital, Athens, Greece, [18] Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán-Universidad Autónoma de Mexico, Mexico City, Mexico, [19] Allegheny General Hospital, Pittsburgh, Pennsylvania, USA, [20] Hospital General de Argudos "Dr. Cosme Argerich", Buenos Aires, Argentina, [21] Investigación Sanitaria y Biomédica de Alicante (ISABIAL – Fundación FISABIO), Alicante, Spain, [22] Kaiser Permanente, Pasadena, California, USA, [23]Medical University of South Carolina, Charleston, South Carolina, USA

Background: Severe hypertriglyceridemia is an established cause of acute pancreatitis (AP). Previous data on incidence, concomitant risk factors, and severity of hypertriglyceridemia-induced acute pancreatitis (HTG-AP) in comparison to the other etiologies is limited and mainly obtained from small, retrospective and heterogenous studies.
Aim: To examine the prevalence, patient characteristics, and clinical outcomes of patients with HTG-AP compared to other etiologies from a large, international prospective study.

Methods: Acute pancreatitis patient registry to examine novel therapies in clinical experience (APPRENTICE) is a global, multicenter consortium prospectively enrolling AP patients from 22 international centers (United States: 8, Europe: 5, Latin America: 6, India: 3). Data was collected via standardized questionnaires and registered in REDCap (Research Electronic Data Capture). Revised Atlanta Classification (RAC) definitions were used to determine AP severity. Patients were diagnosed with primary HTG-AP when serum triglycerides levels were >500 mg/dl in the absence of other common etiologies. Pearson chi-square test and t-test were used to compare categorical and continuous variables, respectively. Multivariable logistic regression model was used with severe/moderate condition as the outcome.

Results: Overall, 1478 patients were prospectively enrolled. HTG-AP was diagnosed in 69 patients (prevalence=4.6%), of which 33.3% were male. HTG-AP patients were younger (40.4 vs 50 years; p<0.0001), had a higher BMI (30.4 vs 27.5 kg/m^2; p=0.0002), were more likely to be active alcohol users (70.6% vs 48.9%; p<0.0001), diabetic (59.4% vs 15.3%; p<0.0001), and were more likely to be enrolled on a recurrent episode of AP than during their index attack (40.6% vs 24%; p=0.002) compared to other etiologies. Median TG level was 1675 mg/dl (739-3927) in HTG-AP patients, and 133 mg/dl (91-193) in the others (p=0.0001). In respect to clinical outcomes, a significantly higher number of patients in the HTG-AP group required ICU admission (26.2% vs 16.4%; p=0.036), however length of hospital stay (8 vs 8 days; p=0,7541), and mortality (1.5% vs 2.6%; p=0.566) were similar between the two groups. Comparison of severity in HTG-AP compared to other causes with multivariable logistic regression controlling for age, gender, race, BMI, active smoking, alcohol use, and diabetes showed a trend for higher severity in HTG-AP that did not reach statistical significance.

Conclusion: This multinational prospective cohort found distinct baseline characteristics in HTG-AP patients, similar to what is reported in previous smaller, retrospective studies. Furthermore, there was a trend for increased severity in the HTG-AP group, with a significantly higher rate of ICU admission.

HTG-primary vs non-HTG:

	Univariable		Multivariable	
	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
Age	0.99 (0.99, 1.00)	.005	1.00 (0.99, 1.01)	.826
Gender, male	2.0 (1.6, 2.5)	<.001	1.8 (1.4, 2.3)	<.001
Race, white	0.5 (0.4, 0.6)	<.001	0.5 (0.4, 0.6)	<.001
BMI	0.99 (0.97, 1.00)	.255	1.01 (0.99, 1.03)	.447
Active alcohol use	1.3 (1.1, 1.7)	.009	1.2 (0.9, 1.5)	.206

Active smoking	1.2 (0.9, 1.5)	.209	1.0 (0.7, 1.3)	.805
Diabetes	1.0 (0.8, 1.4)	.890	1.0 (0.7, 1.4)	.799
HTG-AP	1.4 (0.9, 2.3)	.168	1.3 (0.8, 2.2)	.330

Univariable and Multivariable HTG model for severity:

	HTG-AP (n=69)	Non HTG-AP (n=1,409)	p-value
Age, mean (SD)	40.4 (9.7)	50.0 (18.6)	<.001
Gender, male (%)	23 (33.3)	674 (47.8)	.018
Race, white (%)	35 (50.7)	693 (49.2)	.803
BMI, mean (SD)	30.4 (5.6)	27.5 (6.4)	.0002
Alcohol use, No. (%)	48 (70.6)	683 (48.9)	<.001
Active smoker, No. (%)	19 (27.9)	319 (22.9)	.331
Diabetes, No. (%)	41 (59.4)	216 (15.3)	<.001
Recurrent AP, No. (%)	28 (40.6)	338 (24.0)	.002
TG level, median (IQR)	1675.2 (739-3927)	133 (91-193)	.0001
Severity, No., (%)			.166
Mild	40 (58.0)	931 (66.1)	
Moderate/Severe	29 (42.0)	478 (33.9)	
SIRS, No. (%)	42 (60.9)	687 (48.8)	.049
LOS, median (IQR)	8 (5-12)	8 (5-13)	.7541
ICU Admission, No. (%)	18 (26.1)	231 (16.4)	.036
Organ failure, No. (%)			
Cardiac	3 (4.3)		
Renal	7 (10.1)	))	
Respiratory	11 (15.9)	.7)	
rgan failure, No. (%)	6 (8.7)	78 (5.5)	.268
ty, No. (%)	1 (1.5)	36 (2.6)	.566

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Early Rapid Fluid Therapy is Associated with Increased Risk of Persistent Organ Failure in Acute Pancreatitis Patients with Hemoconcentration after Initial Management

L. Li[1], T. Jin[1], S. Wen[2], R. Zhang[1], N. Shi[1], P. Zhu[1], L. Lan[3], Z. Lin[1], K. Jiang[1], J. Guo[1], T. Liu[1], A. Philips[4], L. Deng[1], X. Yang[1], V. K. Singh[5], R. Sutton[6], Y. Kang[7], J. A. Windsor[8], W. Huang[1], Q. Xia[1]

CAPER Scholarship Recipient- West China Hospital

1Department and Laboratory of Integrated Traditional Chinese and Western Medicine, Sichuan Provincial Pancreatitis Center and West China-Liverpool Biomedical Research Center, West China Hospital, Sichuan University, Chengdu, China; 2Department of Endocrinology, Chengdu University of Traditional Chinese Medicine, Chengdu, China; 3West China Biomedical Big Data Center, West China Hospital, Sichuan University, Chengdu, China; 4Applied Surgery and Metabolism Laboratory, School of Biological Sciences, University of Auckland, Auckland, New Zealand; 5Pancreatitis Center, Division of Gastroenterology, Johns Hopkins Medical Institutions, Baltimore, USA; 6Liverpool Pancreatitis Research Group, Royal Liverpool University Hospital and Institute of Translational Medicine, University of Liverpool, Liverpool, United Kingdom; 7Department of Critical Care Medicine, West China Hospital, Sichuan University, Chengdu, China; 8Surgical and Translational Research Center, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand

Background: Recent studies related to early rapid fluid therapy (ERFT) in acute pancreatitis (AP) focused on the population who admitted primarily in Emergency Department (ED) without any fluid therapy before and did not progress to organ failure on admission, or those who directly admitted to Intensive Care Unit (ICU). To our knowledge, the characterization of patients with AP and their fluid therapy in general wards after initial management have never been clearly defined and studied.

Objectives: To investigate the relationship between ERFT, hematocrit, and clinical outcomes in patients with AP after initial fluid therapy in ED and to identify risk factors for persistent organ failure.

Design: Retrospective cohort study.

Patients: Consecutive AP patients admitted to general wards ≤ 48 hours of symptom onset after initial management in ED.
Interventions: None.

Measurements and Main Results: 'Early' was first 6 hours after admission to general wards and 'rapid' fluid rate was ≥ 3 ml/kg/h. Patients were stratified into 3 groups according to hematocrit level at admission of wards and 24 hours thereafter: Group 1, hematocrit < 44% at admission and at 24 hours; Group 2, hematocrit increased and > 44% at 24 hours; Group 3, hematocrit > 44% on admission and decreased at 24 hours. A total of 628 patients were included. Group 3 had a higher hematocrit on admission, greater baseline predicted severity, more patients received ERFT in first 6 hours and larger fluid volume during first 24 hours compared with Group 2 and Group 1. Group 3 had an increased risk for persistent organ failure (odds ratio 2 [95% CI, 1.1-3.8], p = 0.03) after adjusting for baseline parameters and predicted severity scores compared with Group 1, whereas there was no significant difference between Group 2 and Group 1. Multivariate logistic regression analyses revealed hemoconcentration at admission and ERFT were significant risk factors for persistent organ failure (both p < 0.001) and mortality (both p < 0.05).

Conclusions: ERFT and hemoconcentration are associated with persistent organ failure in AP patients after initial management in ED. Restricting fluid rate in the first 6 hours of these patients may represent a beneficial fluid management strategy which merits validation in randomized clinical trials.

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Clinical and Endosonographic Factors Related to Recurrence in Idiopathic Acute Pancreatitis

Francisco Valverde-López, MD, PhD
CAPER Scholarship Recipient- "La Merced" Hospital

Introduction: Natural history of idiopathic acute pancreatitis (IAP) is complex and it usually needs a thorough study that includes endoscopic ultrasound (EUS) in order to find the etiology and prevent further episodes. The efficacy of EUS as a diagnostic tool to establish etiology has been proven in many studies but its role as a predictor of recurrence has not been deeply assessed.
Aim: To assess the prediction ability of EUS and several clinical factors on recurrent episodes of acute pancreatitis.

Methods: We retrospectively analyzed data such as sex, age, liver enzymes (ALT and ALP) on hospital admission in the index episode, previous cholecystectomy or not, smoker condition and recurrence rates from patients referred to our unit for EUS after a first episode of IAP or recurrent IAP. Patients were considered to have IAP after an initial normal study including abdominal ultrasound, a clinical history with no evidence of alcohol consumption and smoking, triglyceride levels out of an acute episode, and blood tests. Either ERCP with sphincterotomy or cholecystectomy were performed when stones were found in EUS in common bile duct or gallbladder respectively. When EUS findings suggested chronic pancreatitis or other etiology, patients underwent conservative management and clinical follow up. Patients were followed until death. Patients lost to follow up were excluded.

Results: We recruited 106 patients from 2010 until 2016 and they were followed until 2018 with a mean follow up of 53.59 ± 27.79 months. Patient characteristics, EUS findings, need of MRCP, ERCP or cholecystectomy after EUS, as well as recurrence rates are shown in table 1. When addressing the relation between clinical and laboratory factors and recurrence we found that normal ALT or ALP by the time of admission and a previous cholecystectomy raised the probability of having a new episode of AP (p=0.04, p < 0.01 respectively). Patients aged below 65 years old showed higher recurrence rate than older ones with a p value almost significant (p=0.06). Furthermore, findings different than lithiasis in biliary tract on EUS also had a higher probability of a relapse (p < 0.01 respectively). Results are detailed in table 2. When logistic regression was performed, we found that age under 65 years old (OR 3.56; CI 95% 1.21-10.44; p = 0.02), previous cholecystectomy (OR 3.19; CI 95% 1.11- 9.17; p = 0.03) and normal EUS or findings different than lithiasis in gallbladder or common bile duct (OR 2.87; CI 95% 1.04 - 7.87; p = 0.04) were all independent risk factor of recurrence.

Discussion: Far beyond sheer endosonographic findings, physicians performing EUS for IAP assessment might be concerned about etiological diagnosis and also about prognosis and future management. EUS is necessary to identify biliary findings that can lead to an ERCP or cholecystectomy, and findings suggestive of chronic pancreatitis leading to a closer clinical follow-up and further tests to assess pancreatic function. Furthermore, in combination with other factors such as age or the presence of a gallbladder in situ, EUS can provide predictive information about recurrence. Our study shows that patients aged under 65 years old, with a previous cholecystectomy and no stones on EUS entail a high risk of relapse. All this information should be taken into account by pancreatologists in order to decide whether a closer clinical monitoring is needed or if some patients could be spared from follow-up, although further multicenter studies should be done in this setting.

Table 1. Patient Characteristics

	Total
N	106
Age, (mean±SD)	56.4 ±17-66
Male, n (%)	52 (50)
Gallbladder in situ, n (%)	78 (73.6)
EUS FINDINGS	
- Normal or incomplete	24 (22.6)
- Biliary	*52 (49.1)*
- Suggestive of CP (Rosemont), n (%)	14 (13.2)
- Pancreatic mass, n (%)	2 (1.9)
- Suggestive of CPN, n (%)	3 (2.8)
- Congenital anomalies, n(%)	2 (1.9)
- Other	9 (8.5)
EUS diagnostic yield (%)	67
MRCP, n (%)	38 (35.8)
ERCP, n (%)	19 (18.1)
Cholecystectomy, n (%)	43 (55.1)
Recurrence during follow-up, n (%)	29 (27.4)
Follow up in months, mean ± SD)	53.59 ± 27.79

Table 2. Factors Related with Recurrence

	Total	Recurrence	No recurrence	P
N	*106*	29 (27.4)	77 (72.6)	
Normal ALT/ALP, n (%)	56	20 (68.9)	36 (46.7)	0.04
Male sex, n (%)	**52**	**16 (55.1)**	**36 (46.75)**	**n.s.**
No lithiasis in EUS, n (%)	**54**	**21 (72.4)**	**33 (42.8)**	**<0.01**
Age < 65, n (%)	**65**	**22 (75.8)**	**43 (55.8)**	**0.06**
Current or previous smoker, n (%)	**37 (3.1)**	**10 (34.4)**	**27 (35)**	**n.s**
Previous cholecystectomy, n (%)	**28 (4.9)**	**13 (44.8)**	**15 (19.4)**	**< 0.01**

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Persistent SIRS and Non-Alcohol Etiology of AP are associated with Oral Feeding Intolerance in AP: Results From an International, Multicenter, Prospective Cohort Study

A. Phillips[1], I. Pothoulakis[1], P. Paragomi[1], K. Jeong [2], K. Ooka[3], R. Talukdar[4], R. Kochar[5], M. Kumar Goenka[6], A. Kielate-Gulla[7,8], V. Singh[9], J. Gonzalez[10], M. Ferreira[11], S.T. Barbu[12], T. Stevens[13], S. Gutierrez[14], N. Zarnescu[15], G. Capurso[16], J. Easler[17], K. Triantafyllou[18], M. Pelzez-Luna[19], S. Thakkar[20], C. Ocampo[21], E. DeMadaria[22], B. Wu[23], G. Cote[24], G. Papachristou[1], H. Nawaz[25]

CAPER Scholarship Recipient- UPMC

[1]University of Pittsburgh School of Medicine, Division of Gastroenterology, Hepatology, and Nutrition, Pittsburgh, United States, [2]University of Pittsburgh School of Medicine, Pittsburgh, United States, [3]University of Pittsburgh Medical Center, Division of Gastroenterology, Hepatology, and Nutrition, Pittsburgh, United States, [4]Asian Gastroenterology Institute, Hyderabad, Inda, [5]Postgraduate Institute of Medical Education and Research, Chandigarh, India, [6]Apollo Gleneagles Hospitals Kolkata, Kolkata, India, [7]Georgetown University Hospital, Washington, DC, United States, [8]Lithuanian University of Health Sciences, Kaunas, Lithuania, [9]Johns Hopkins Medical Institution, Baltimore, United States, [10]Universidad Autonoma de Nueva Leon, Monterrey, Mexico, [11]Hospital Nacional de Itagua, Itagua, Paraguay, [12]University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj-Napoca, Romania, [13]Cleveland Clinic Foundation, Cleveland, United States, [14]Hospital Nacional "Profesor Alejandro Posadas", Buenos Aires, Argentina, [15]University of Medicine and Pharmacy, Bucharest, Romania, [16]Saint Andrea Hospital, Sapienza University of Rome, Digestive and Liver Disease Unit, Rome Italy, [17]Indiana University School of Medicine, Indianapolis, United States, [18]Attikon University General Hospital, Athens, Greece, [19]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran-Universidad Autonoma d Mexico, Mexico City, Mexico, [20]Allegheny General Hospital, Pittsburgh, United States, [21]Hospital General de Argudos "Dr. Cosme Argerich", Buenos Aires, Argentina, [22]Investigacion Sanitaria y Biomedica de Alicante (ISABIAL-Fundacion FISABIO), Alicante, Spain, [23]Kaiser Permanente, Pasadena, United States, [24]Medical University of South Carolina, Charleston, United States, [25]Eastern Main Medical Center, Bangor, United States.

Background and Objectives: Inability for patients to advance to an oral diet, or Oral Feeding Intolerance (OFI), occurs in 1 in 5 patients with acute pancreatitis (AP) and results in slow clinical recovery and increased health care resource utilization. Occurrence of OFI is unpredictable, and there is lack of validated criteria to assist with diet advancement. We aim to determine clinical predictors of OFI.

Materials and Methods: Patients were enrolled in the Acute Pancreatitis Patient Registry to Examine Novel Therapies in Clinical Experience (APPRENTICE), a 22-center international, multicenter, prospective cohort study. Patients with diagnosis of AP and at least one feeding attempt by mouth during admission were eligible. Occurrence of OFI was determined by the primary clinician. Demographic and clinical data were collected prospectively. Severity of AP was determined using Revised Atlanta Classification (RAC). Clinical parameters were investigated for association with OFI. Timing of initial feeding attempt was stratified based on day of hospitalization. Pearson's chi-square and Wilcoxon rank-sum test were used for categorical and continuous variables respectively. Multivariate logistic regression was performed controlling for age, gender, active alcohol use, active tobacco use, admission lipase, etiology, blood urea nitrogen (BUN), hematocrit, SIRS score ≥ 2, 48hour SIRS ≥ 2, transfer status, and prior history of AP.

Results: Of 1,233 patients (50.1% male) included in the study, 160 (12.9%) experienced OFI. Incidence of OFI was similar irrespective of timing of initial feeding attempt relative to hospital admission day (p = 0.41). In univariate analysis, patients with OFI were more likely to be younger (45 v 50 yrs; p=0.018), male (61% v 49%; p=0.004), transferred from outside hospital (38% v 29%; p=0.02), have more comorbidities (Charlson Comorbidity Index ≥ 2, 27% v 39%; p=0.007), alcohol etiology of AP (48% v 30%; p<0.001), SIRS ≥ 2 on admission (49% v 35%; p<0.001), SIRS ≥ 2 at 48hrs (50% v 26%; p<0.001), develop moderate/severe AP (41% v 24%; p<0.001), and have a longer hospital stay (10 v 6 days; p<0.001). Multivariate logistic regression showed SIRS ≥ 2 at 48h (OR 3.33; 95% CI 0.18, 0.50) and non-gallstone AP etiology (OR 1.75; 95% CI 0.35, 0.94) were independent predictors of OFI.

Conclusion: AP patients with SIRS ≥ 2 at 48h or with non-gallstone etiology may require a modified protocol for oral refeeding. Further research is required to develop personalized nutrition management plans in AP patients to prevent OFI.

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Mild Chronic Pancreatitis Caused by Persistent ER Stress in AT-1 KO Mice Progresses to Severe Disease with Acute Pancreatitis Induction

M. M. Cooley[1], D.D.H. Thomas[1], K. Deans[1], Y. Peng[2], A. Lugea[3], S. Pandol[3], L. Puglielli[2], G. E. Groblewski[1]

Oral Presentation, Session VIII-C

[1] Department of Nutritional Sciences, University of Wisconsin – Madison, Madison, WI, United States, [2] Department of Medicine, University of Wisconsin – Madison, Madison, WI, United States, [3] Pancreatic Research Group, Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA, United States

Background: Unfolded protein response (UPR) activation occurs in response to accumulation of unfolded proteins in the endoplasmic reticulum (ER) and is observed in experimental models of both acute (AP) and chronic (CP) pancreatitis. Acetylation of newly translated

ER proteins is necessary for protein folding, mediated by the ER-associated acetyl-CoA transporter AT-1. We produced acinar-specific AT-1 knockout mice to activate chronic ER stress and induce chronic pancreatitis.

Methods: Tamoxifen-inducible, acinar-specific AT-1 KO mice were generated by crossing AT-1 floxxed mice with Ela-CreERT2 mice. Tamoxifen was administered at 2 months and tissues collected 2-3 months post treatment. Pancreatitis parameters – including UPR activity, autophagic activity, inflammation, and fibrosis – were assessed by immunoblotting, qPCR, H&E staining, Sirius red staining, and immunofluoresence. AP was induced for two consecutive days by 7 hourly injections of caerulein, followed by 1 week recovery period.

Results: Ela-Cre AT-1 KO pancreas exhibited signs of mild to moderate chronic pancreatitis, with elevation of UPR markers sXBP1, p-eIF2α, ATF4, and CHOP. Autophagic inhibition was present as indicated by increased LC3-II accumulation and decreased LAMP2 levels. AT-1 KO pancreas displayed significant immune cell infiltration and inflammation as well as collagen deposition and α-smooth muscle actin expression. Interestingly, increased amylase expression and decreased lipase and elastase expression was observed with AT-1 loss, and trypsin activation was increased. Stimulated amylase secretion in AT-1 KO was enhanced over 3-30pM CCK. AT-1 KO pancreas failed to recover after AP induction, with significant acinar cell loss and overall 40% reduction in total pancreatic weight.

Conclusions: Loss of AT-1 activity promotes a phenotype consistent with mild to moderate chronic pancreatitis that progressed in severity with AP induction. This study contributes to the understanding of the importance of ER acetylation on protein folding and ER stress responses. Further investigation into the acetylation of acinar-specific proteins will reveal additional insights.

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Cystic Fibrosis Transmembrane Conductance Regulator Modulators Reduce the Risk of Recurrent Acute Pancreatitis Among Adult Patients with Pancreas Sufficient Cystic Fibrosis

Venkata S. Akshintala[1], Ayesha Kamal[1], Mahya Faghih[1], Garry R. Cutting[2], Liudmila Cebotaru[2], Natalie E. West[2], Mark T. Jennings[2], Rebecca Dezube[2], David C. Whitcomb[3], Noah Lechtzin[2], Christian A. Merlo[2], Vikesh K. Singh[1]

CAPER Scholarship Recipient- Johns Hopkins Hospital

[1] Pancreatitis center, Division of gastroenterology, Johns Hopkins Hospital, Baltimore, MD, [2] Adult cystic fibrosis center, Division of pulmonary and critical care medicine, Johns Hopkins Hospital, Baltimore, MD, [3] Division of gastroenterology, hepatology and nutrition, University of Pittsburgh Medical Center, Pittsburgh, PA

Background: Approximately 1 in 5 patients with pancreas sufficient cystic fibrosis (PS-CF) will develop acute pancreatitis (AP). The cystic fibrosis transmembrane conductance regulator (CFTR) modulator, ivacaftor, was shown in a recent case series of 6 patients with PS-CF and AP to reduce the risk of recurrent AP over a 12 month follow-up period (Carrion A. *et al*. Journal of Pediatric Gastroenterology and Nutrition. 2018). However, all 6 had at least one ivacaftor responsive mutation. It is not known whether ivacaftor alone or in combination with other CFTR modulators (tezacaftor or lumacaftor) can reduce the risk of AP in a larger number of patients with PS-CF and AP.

Methods: The CF registry at our institution was queried for adult patients with PS-CF, a documented history of AP and use of CFTR modulators (ivacaftor alone or lumacaftor/ivacaftor or tezacaftor/ivacaftor). Patient characteristics including demographics, CFTR genotype, pancreatitis risk factors and number of AP episodes, pancreatic exocrine function and other relevant laboratory, imaging parameters were obtained from the time of CF diagnosis as well as sentinel AP episode to the follow-up period after CFTR modulator initiation. Patients without documented evidence of AP and those with other risk factors of pancreatitis were excluded.

Results: A total of 15 adult CF patients were identified with documented evidence of AP and on CFTR modulators (Table 1). Seven of these patients were female and the mean age was 44.1 (SD± 13.8). Mean age at first pancreatitis episode was 32.2 (SD± 17.1), while mean age at the time of CFTR modulator initiation was 42.5 (SD± 14.1). Six of these patients had at least 1 episode of AP in 24 months preceding CFTR modulator initiation with a median of 2 episodes [1.75, 2.5] (Table 2). None of the patients had CT imaging evidence of pancreatic calcifications at the time of CFTR modulator initiation. The mean duration of follow-up after CFTR modulator initiation was 22.9 months (SD± 18.7). None of the patients who remained on CFTR modulators developed any episode of AP or required hospitalization for AP related abdominal pain during follow up. However, there was one patient (ID# 12) who developed AP only during times when she had to discontinue CFTR modulator use due to problems with insurance coverage.

Conclusions: CFTR modulators, alone or in combination, substantially reduce the risk of recurrent AP over a mean follow-up period of 2 years in adult patients with PS-CF and a history of prior AP. These data suggest that any augmentation of CFTR function can reduce the risk of pancreatitis. A controlled trial is warranted to confirm these findings.

Table 1: Patient demographics, CF genotype and CF modulator used
(M=Male, F = Female, CF = cystic fibrosis, CFTR = Cystic fibrosis transmembrane conductance regulator)

Patient ID	Age	Gender	CFTR Mutation #1	CFTR Mutation #2	CFTR Modulator Regimen
1	38	M	F508del	2789+5G->A	Ivacaftor transitioned to tezacaftor / ivacaftor combination
2	39	F	R1162X	2789+2insA	Ivacaftor
3	44	F	F508del	G551S	Ivacaftor
4	47	F	F508del	3849+10kbC->T	Tezacaftor / ivacaftor combination
5	47	M	F508del	2789+5G->A	Ivacaftor transitioned to tezacaftor / ivacaftor combination
6	30	M	2183AA->G	S945L	Ivacaftor transitioned to tezacaftor / ivacaftor combination
7	32	M	2789+5G->A	duplication exons 8-10	Tezacaftor / ivacaftor combination
8	38	F	F508del	R352Q	Tezacaftor / ivacaftor combination
9	76	F	R117H	TG12/T5	Ivacaftor
10	59	M	F508del	3272-26A->G	Ivacaftor transitioned to tezacaftor / ivacaftor combination
11	50	F	F508del	R352Q	Ivacaftor transitioned to tezacaftor / ivacaftor combination
12	29	F	4251delA	G551D	Ivacaftor
13	64	M	3849+10kbC->T	3849+10kbC->T	Ivacaftor transitioned to tezacaftor / ivacaftor combination
14	27	M	2789+5G->A	E60X	Tezacaftor / ivacaftor combination
15	41	M	F508del	R117H	Ivacaftor

Table 2: Acute pancreatitis and CF characteristics
(CF = cystic fibrosis, CFTR = Cystic fibrosis transmembrane conductance regulator, * = Data not available)

Patient ID	Age at first pancreatitis episode	Age at CFTR modifier initiation	Number of pancreatitis episodes in 24 months prior to CFTR modifier initiation	Number of pancreatitis episodes documented after CFTR modifier initiation	Duration of follow-up since CFTR modifier initiation (in months)
1	19	37	2	0	11
2	35	38	2	0	22
3	*	43	0	0	19
4	39	46	0	0	15
5	39	46	0	0	15
6	23	28	1	0	25
7	8	32	0	0	8
8	24	37	0	0	22
9	75	75	2	0	11
10	54	58	0	0	12
11	35	46	0	0	48
12	21	23	4	5	74
13	27	63	0	0	13
14	15	27	0	0	5
15	37	38	2	0	44

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Risk and Outcomes of Clostridium Difficile Infection with Chronic Pancreatitis in the United States

Adeyinka Adejumo, MD, MS

Background and aims: Diseases associated with recurrent antibiotic use, hospitalizations, and exposure to healthcare care system increases the risk of acquiring clostridium difficile infection (CDI). In addition to these factors, chronic pancreatitis (CP) alters intestinal immunity and gut microbiome, which may further elevate the risk of CDI. Despite these connections between CP and CDI, no study has evaluated the risk and outcomes of CDI with CP. This study investigates the trends, odds and outcomes CDI from CP in a nationally representative sample of hospitalized patients.

Methods: We initially performed a cross-sectional analysis on the 2014 Nationwide Inpatient Sample (NIS) adult discharge records to estimate the crude and adjusted odds ratio (cOR & aOR) of CDI with CP as the outcome and predictor respectively. We then pooled data of patients hospitalized primarily for CP from the 2012-2014 years of NIS, and estimated the impact of CDI on mortality and outcomes. Finally, using the 2007-2014 years of NIS, we calculated the trends in prevalence of CDI, stratified by concomitant CP, and estimated the mediating effect of concomitant CP on the trends of CDI (SAS 9.4).

Results: In the 2014 NIS (n=5,950,391), CP was associated with increased odds of CDI (cOR: 2.10[1.95-2.26]) which persisted after multivariate adjustment for demographic-, hospital- and comorbid- factors (aOR: 2.01[1.87-2.19]).
Among patients hospitalized primarily for CP from 2012-2014 (n=32,614, unweighted:163,070), 886 (2.7%) had CDI. After multivariate adjustment, CP patients with CDI had higher odds of acute kidney injury (AOR:2.57[2.11-3.13]), longer length of stay (13.3- vs. 7.4-days), higher hospital charges (US$127,496 vs. US$72,767), discharge to another acute care or rehabilitation facility vs. home (1.79[1.49-2.16]), but not mortality (AOR:0.93[0.28-3.05]).
From 2007 to 2014, the rate of CDI was 106.4/10,000 hospitalizations, increasing steadily at a rate of 3.7/10,000 hospitalizations/year from 95.4/10,000 (2007) to 118.4/10,000 (2014) hospitalizations. Compared to patients without CP, those with CP had both a 2x higher rate of CDI (201.3/10,000 vs. 105.9/10,000 hospitalizations), and 3x higher increase in CDI/hospitalization per year (13.5 vs. 3.7 per 10,000 hospitalizations/year).

Conclusions: CP is a risk factor for CDI and CDI is associated with poorer outcomes among patients with CP. If these findings are confirmed in prospective studies, research on the role of anti-CDI prophylactic measures on CP patients may be needed given the poor outcomes associated with CDI.

Keywords: Mortality, Odds, Risk, Length of stay; Cost; National Inpatient Sample, Acute kidney failure

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Exocrine Pancreatic Function, Genetic Variants, and Risk Factors in a Cohort of Subjects with Chronic Pancreatitis

Jefferson N. Brownell, Mark Haupt, Katya Orlova, Joan I. Schall, Virginia A. Stallings
CAPER Scholarship Recipient- Childrens Hospital of PHL

Background: Chronic pancreatitis (CP) is an inflammatory disease leading to pancreatic parenchymal fibrosis and destruction. Genetic variants in multiple pathways leading to pancreatic inflammation have been identified, including abnormal trypsin activity, duct function, and endoplasmic reticulum stress. Patients with CP often develop exocrine pancreatic insufficiency (EPI) resulting in fat malabsorption.

Methods: Genetic testing was conducted on an adult cohort of subjects with CP undergoing tests of fat and energy malabsorption, including the coefficient of fat absorption (CFA), malabsorption blood test (MBT), and stool bomb calorimetry (BC), as well as substance use and medical history questionnaires. Saliva was collected for next-generation DNA sequencing (Ariel Precision Medicine, Pittsburgh, PA) of all exons and intronic junctions of major genes associated with pancreatitis and CP. ANOVA was used to compare racial and genetic group means for fat malabsorption.

Results: 21 subjects with CP (age 33-66, mean 50±10 years; 52% female; 52% European ancestry, 43% African ancestry, 5% South Asian ancestry [SA], 5% East Asian ancestry [EA], and 5% Latin American ancestry) underwent genetic testing. Past or present tobacco use was reported in 86%, while 95% reported past or present alcohol use. One subject was diagnosed with pancreas divisum, consistent with expected prevalence. A total of 372 variants were noted in targeted genes; 38 were known or suspected pancreatitis risk factors.

Two subjects had no known significant variants. Ten subjects had variants in two or more etiologic CP pathways. One subject had the pathogenic p.Asn29Ile (N29I) variant in *PRSS1* associated with hereditary pancreatitis. Of the 10 males, eight had at least one X-linked risk-increasing variant. The male of SA descent had a *CLDN2-MORC4* variant associated with CP and alcohol use in SA men. Comparisons of fat malabsorption are presented in **Table 1**. Of the 7 subjects of African descent, 6 had significant EPI (fecal elastase <200µg/g) despite detection of only mild to moderate risk alleles. While subjects of African descent had a greater degree of energy lost in stool when compared to those of European descent for each measure, there were no associations among specific alleles or duration of disease and degree of EPI.

Conclusion: In a small cohort of subjects with a history of CP, variants were found in all known pathways for development of pancreatitis. Though subjects of African descent had milder risk alleles, they demonstrated a greater prevalence of EPI, suggesting additional risk factors in this population. Furthermore, specific variants may confer varying levels of risk in different populations.
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Table 1: Measures of fat malabsorption in subjects with chronic pancreatitis (n=21)

Ancestry	Fecal Elastase-1 (µg/g stool)	Coefficient of fat absorption (%)	Malabsorption Blood Test (HA AUC, mg*h/dL)	Bomb Calorimetry (cal/g stool)
Caucasian (n=12)	238±154	92.4±8.6	9.2±4.4	5309±582
African (n=7)	134±190	80.4±22.1	5.8±2.1	6009±751*
East Asian (n=1)	45	88.6	14.2	6127
South Asian (n=1)	17	94.5	9.6	5069

HA AUC = heptadecanoic acid area under the curve.
* Bomb calorimetry was significantly higher in subjects of African descent than those of Caucasian descent, t test $p<0.05$. Differences between these two groups in coefficient of fat absorption and HA AUC were significant at $p=0.05$. Normal values have not been established for the malabsorption blood test or stool bomb calorimetry. East Asian and South Asian subjects were not included in this analysis.

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Chronic Pancreatitis is Associated with Increased Cardiovascular Mortality: A Population-Based Analysis

Aslam Syed MD, Shyam Thakkar MD, Manish Dhawan MD, Marcia Mitre MD, Abhijit Kulkarni MD, Katie Farah MD, Suzanne Morrissey MD; Gusimran Kochhar MD
CAPER Scholarship Recipient- Allegheny Health Network
Division of Gastroenterology, Allegheny Health Network, Pittsburgh, PA

Introduction: Chronic pancreatitis (CP) is associated with high morbidity and mortality. Chronic inflammatory changes leading to systemic atherosclerosis can cause ischemic heart disease (IHD). Studies observing this relationship are limited, particularly describing associated epidemiological relationships, mortality rates, and the role of statin therapy. This study aims to analyze variables that pose a risk of IHD development in patients with chronic pancreatitis, and report the role of statin use.

Methods: A population-based study was conducted using a cloud-based, HIPPA-enabled web platform called Explorys (IBM, New York) to collect aggregated de-identified electronic health records. At the time of the study, Explorys had access to over 62 million unique records. Data was obtained using ICD-9 code criteria for chronic pancreatitis, ischemic heart disease, and HMG-CoA reductase inhibitors (statins). Patient characteristics and all-cause mortality rates were compared with patients of IHD after a diagnosis of CP as a first time event using relative risk (RR) with 95% confidence interval (CI) in a random-effect model.

Results: Chronic pancreatitis was found in 81,820 patients, of which 14,500 (17.7%) had subsequent development of IHD. The RR of IHD was significantly higher in patients with prior CP vs. the control population in our registry [RR 7.50 (95% CI: 7.37-7.63), P<0.0001]. Family history of cardiac disease, tobacco use, obesity, and aspirin use were higher in the CP with IHD population. Patients that were elderly (> 65), male, and African-American were at higher risk of IHD with prior CP. Also, there was a higher rate of all-cause mortality in patients with CP and IHD vs. patients with CP alone. The younger population (18 – 65) and African-Americans with CP on statins had a beneficial effect in the prevention of IHD. Statins did not affect all-cause mortality in patients with CP and IHD vs. patients on statins with CP with subsequent IHD (P=0.3338).

Conclusions: Patients at higher risk of IHD post CP diagnosis include being elderly, male, and African-American. Mortality is significantly increased in patients with CP and IHD vs. CP alone. Statins had a beneficial effect in decreasing the rates of IHD in patients that were less than 65 and African-Americans.

Table 1:

Characteristic	CP [N = 81,820]	CP subsequent IHD [N = 14,500]	Relative Risk [95% CI]	*P*
Age, *n* [%]				
18-65	53,640 [66]	6,870 [47]	0.47 [0.46, 0.49]	< 0.0001
> 65	27,740 [34]	7,590 [52]	2.14 [2.08, 2.20]	< 0.0001
Male, *n* [%]	42,390 [52]	8,290 [57]	1.24 [1.21, 1.28]	< 0.0001
Ethnicity, *n* [%]				
Caucasian	58,240 [71]	10,340 [71]	1.01 [0.97, 1.04]	0.7039
African-American	16,670 [20]	3,500 [24]	1.24 [1.20, 1.29]	< 0.0001
Hispanic	4,390 [5]	740 [5]	0.95 [0.89, 1.01]	0.1246
Baseline Comorbidities, *n* [%]				
Family history of cardiac disease	11,620 [14]	2,410 [17]	1.20 [1.16, 1.25]	< 0.0001
History of tobacco use	31,770 [39]	6,450 [44]	1.26 [1.23, 1.30]	< 0.0001
BMI > 30	47,300 [58]	11,210 [77]	2.48 [2.40, 2.58]	< 0.0001
Aspirin use, *n* [%]	32,600 [40]	10,710 [74]	4.26 [4.12, 4.42]	< 0.0001
All-Cause Mortality, *n* [%]	10,670 [13]	3,160 [22]	1.86 [1.80, 1.92]	< 0.0001

Table 2:

Characteristic	CP subsequent IHD [N = 14,500]	CP on Statin and subsequent IHD [N = 9,440]	Relative Risk [95% CI]	*P*
Age, *n* [%]				
18-65	6,870 [47]	4,110 [44]	0.86 [0.84, 0.88]	< 0.0001
> 65	7,590 [52]	5,320 [56]	1.18 [1.15, 1.20]	< 0.0001
Male, *n* [%]	8,290 [57]	5,480 [58]	1.04 [1.01, 1.06]	0.0037
Ethnicity, *n* [%]				
Caucasian	10,340 [71]	7,030 [74]	1.17 [1.14, 1.21]	< 0.0001
African-American	3,500 [24]	2,160 [23]	0.93 [0.91, 0.96]	< 0.0001
Hispanic	740 [5]	480 [5]	0.99 [0.94, 1.05]	0.8892
All-Cause Mortality, *n* [%]	3,160 [22]	2,080 [22]	1.01 [0.99, 1.04]	0.3338

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National Estimates of the Trends and Outcomes of Protein-Energy Malnutrition Among Patients with Chronic Pancreatitis

Adeyinka Adejumo, MD, MS
CAPER Scholarship Recipient- North Shore Medical Center, MA

Background: In chronic pancreatitis (CP), the continuous inflammatory destruction of pancreatic tissue results in decreased digestive enzyme secretion with impaired digestion and absorption, which ultimately predisposes to Protein Energy Malnutrition (PEM). Studies to quantify the risk of clinically diagnosed PEM with CP and its impact on CP are lacking in the US.

Aims: We investigate the frequency, trends, patient characteristics and the impact of PEM on clinical outcomes of patients hospitalized primarily for CP.

Methods: From the Nationwide Inpatient Sample (NIS), years 2007-2014, we estimated the frequency and trends of PEM among the entire population of hospitalized adult (aged:18-90-years) patients, stratified by CP. We tested the impact of CP on the trends of PEM. Afterwards, we selected records with CP from the recent years of NIS (2012-2014), and identified the factors associated with PEM. Finally, we propensity-matched PEM to non-PEM (1:1) and estimated the impact of comorbid PEM on the healthcare utilization and outcomes of patients with CP (SAS 9.4).

Results: From 2007-2014, the prevalence of PEM was 506 per 10,000 hospitalizations increasing from 337/10,000 (2007) to 626/10,000 (2014) at a rate of 41 PEM cases/10,000 hospitalizations/year. The prevalence of PEM was 2.8x higher among patients with CP (1,388/10,000 vs. 502/10,000; p-value<0.0001). Furthermore, patients with CP had a higher rate of increase in PEM cases per year (93 vs. 41 new PEM case/10,000 hospitalizations/year; p<0.0001), compared to patients without CP. From 2012-2014, there were 32,024 hospitalizations primary for CP, with 11.5% (3,694) having concomitant PEM. PEM cases were more likely to be White, advanced age, Medicare-insured, low-income earners, non-Northeastern regions, and patients with multiple co-morbidities. After propensity-matching, concomitant PEM was associated with higher risk of mortality (RR: 3.55[1.73-7.31]), acute kidney injury (1.48[1.28-1.70]), parenteral nutrition (5.58[4.47-6.97]), longer hospital stay (8.3- vs. 4.8-days), higher charges (US$59,334 vs. US$33,249) and higher discharge to secondary facilities (1.74[1.53-1.97]).

Conclusions: The frequency of PEM is higher and increasing at a faster rate among patients with CP compared to those without the disease. Given the poor outcomes and higher resource utilization among CP patients with PEM, routine and regular outpatient screen and treatment of PEM among patients with CP may curtail this ominous trend and outcomes.

Keywords: Mortality, Odds, Risk, Length of stay; Cost; National Inpatient Sample, Acute kidney failure

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National Prevalence, Trends and Healthcare Burden of Different vs. Same Hospital 30- and 90-day Readmissions in Patients Hospitalized for Chronic Pancreatitis

Adeyinka Adejumo, MD, MS

Background: Chronic pancreatitis (CP) is associated with frequent hospitalizations. Readmissions to a different vs. same health facility has been implicated to elevate the risk of suboptimal health delivery and poor outcomes in different diseases. The impact of readmissions in different health center on outcomes in CP has not been studied.
Aims: We sought to evaluate the prevalence and trends of different hospital readmissions on CP patients, and its impact on healthcare burden during readmissions.

Methods: We extracted index adult (age>=18-years) hospitalizations for CP from the Nationwide Readmissions Database (NRD) 2010-2014. We followed CP patients surviving at discharge for 3 months, and recorded the proportion, yearly trends and predictors of different hospital readmissions at 30- and 90-days after discharge. We then calculated the effect of different hospital readmissions on the healthcare burden during 30- and 90-day readmissions (mortality, length of stay and charges) (SAS 9.4).

Results: There were 22,405 CP hospitalizations surviving at discharge from 2010-2014, of which 27% and 46% (6,340 and 10,508) were readmitted in 30- and 90-days respectively. At 30- and 90-day readmissions, the frequency of different hospital readmissions were similar at 28.6% and 28.3%, and were relatively unchanged from 2010-2014. Factors associated with different hospital readmissions

in a multivariate analyses include: younger age category (age: 18-45- vs. 46-65- vs. >65-years); having a diagnosis of cholangitis, acute pancreatitis or multiple comorbidities during index hospitalization; and hospitalization in non-teaching hospitals.
During 30-day readmissions, different hospital readmissions was associated with higher hospital charges ($115,585 vs. $95,882; aMR: 1.21[1.11-1.31], p<0.0001), but no difference in mortality (1.6% vs. 1.4%; aOR: 1.17[0.62-2.24], p=0.63) nor length of stay (9.2- vs. 8.6-days; aMR: 1.07[0.99-1.15], p=0.08) in multivariate models. Additionally, different hospital hospitalizations during 90-day readmissions was associated with higher risk of mortality (1.0% vs. 0.6%; aOR: 1.68[1.06-2.65], p=0.03) and higher charges ($72,480 vs. $60,315; aMR: 1.20[1.12-1.29], p<0.0001), but no difference in length of stay (6.5- vs. 6.1-days; aMR: 1.06[0.99-1.13], p=0.12).

Conclusions: Different hospital readmissions is high among patients with CP and is associated with higher mortality and cost. Studies to identify the reason for presentation to different hospitals and interventions focused on younger patients may ameliorate the problems of different hospital readmissions.

Keywords: Mortality, Odds, Risk, Length of stay; Charges; Nationwide Readmissions Database, Cholangitis

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Care Fragmentation Increases the Risk of Inferior Outcomes During 30- and 90-day Readmissions After Hospitalization for Acute Pancreatitis

Adeyinka Adejumo, MD, MS

Background: Patients with acute pancreatitis (AP) often require recurrent hospitalizations at the same or different health facilities. Re-hospitalization in different center (care fragmentation), impedes adequate longitudinal follow-up of patients by previous health care providers, and may be associated with unnecessary re-ordering of previously performed investigations, resource wastages and higher charges. However, studies on the occurrence of care fragmentation is lacking among patients with AP in the US.
Aims: We investigate the frequency, trends, and predictors of care fragmentation among AP patients, and its impact on healthcare burden during readmissions.

Methods: From the Nationwide Readmissions Database (NRD) 2010-2014, we calculated the prevalence, annual trends and predictors of care fragmentation among adult patients surviving an index hospitalization of AP at 30- and 90-days of readmission after initial discharge. We estimated the impact of care fragmentation on the healthcare burden during 30- and 90-day readmissions (mortality, length of stay and charges) (SAS 9.4).

Results: From 2010-2014, there were 422,950 hospitalizations of which 15% and 26% (63,627 and 110,178) were readmitted in 30- and 90-days respectively. Among readmitted patients, the percentage of care fragmentation were similar at 26.2% and 26.3% (30- and 90-day), and were stable over the years from 2010-2014 (25.4-27.3% and 25.8-27.1%). During both 30- and 90-day readmissions, the predictors of care fragmentation were similar. There was higher odds of care fragmentation among patients within the younger age category (age: 18-45- vs. 46-65- and >65-years), with substance abuse (alcohol, tobacco and other substances), and liver cirrhosis. Alternatively, there were lower odds of care fragmentation among patients with multiple comorbidities, hospitalizations in teaching hospitals, and those who underwent cholecystectomy and pancreatectomy during their index hospitalizations. During 30-day readmissions, care fragmentation was associated with a higher risk of mortality (4.0% vs. 2.9%; aOR: 1.39[1.19-1.63], p<0.0001), longer hospital stay (7.7- vs. 6.4-days; aMR: 1.20[1.15-1.25], p<0.0001) and higher charges ($56,899 vs. $42,012; aMR: 1.35[1.30-1.41], p<0.0001). Similarly during 90-day readmissions, care fragmentation was associated with higher risk of mortality (3.5 vs. 2.3%; aOR: 1.48[1.30-1.69], p<0.0001), longer hospital stay (6.9 vs. 5.8-days; aMR: 1.18[1.14-1.22], p<0.0001) and higher charges ($51,015 vs. $38,292; aMR: 1.33[1.29-1.38], p<0.0001).

Conclusions: The frequency of care fragmentation is high among patients with AP, and it is associated with poorer outcomes. Targeted measures towards individuals with high risk of care fragmentation (age<45 years, substance abuse) may alleviate the associated healthcare burden.

Keywords: Mortality, Odds, Risk, Length of stay; Cost; Nationwide Readmissions Database, Acute kidney failure

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Pain "Burn-out" During the Natural Course is Independent of the Duration of Chronic Pancreatitis (CP)

Kishore Vipperla, MD

CAPER Scholarship Recipient - University of Pittsburgh MC

Background and Aims: Classic natural history studies, published before year 2000, suggest two specific pain patterns in CP: patients with Type A pain have uncomplicated disease; those with Type B pain have complicated disease needing surgery to relieve pain. Pain "burn-out" during the clinical course in both groups is suggested, however data on this issue remains conflicting. Our aim was to describe the natural history of pain in a well-phenotyped cohort of CP in the modern era with specific attention to the duration of CP and role of intervention (endotherapy and/or surgery).

Methods: Records of 279 patients enrolled from 2000-2014 in the North American Pancreatitis Study 2 from the University of Pittsburgh were retrospectively reviewed to collect relevant data to compliment detailed information collected at enrollment. Specific attention was paid to pain (at any time, at enrollment, during follow-up, at end of study), treatment received including narcotics, interventions, hospitalizations, diabetes, pancreatic enzyme (PERT) use, and mortality. Mean duration of observation for primary analysis calculated from the ages at first diagnosis of acute (AP) or CP to the last contact until 11/2017 was 9.4±6.7 yrs.

Results: Data on select clinical and pain-related variables are shown in Table 1 and 2. Any intervention during the clinical course was required in 67.3% patients (endotherapy alone 32.6%, surgery alone 6.3%, and both 28.3%). When compared with patients in medical group, those in the intervention group were significantly ($p<0.05$) younger at diagnosis, had a higher prevalence of AP, RAP, diabetes and PERT use. Patients in intervention group were significantly ($p<0.05$) more likely to have any pain (98% vs. 75%), report severe (71% vs. 64%) pain at enrollment, have Type B pain during clinical course and require narcotics as outpatient. Although attenuation of pain was observed in a subset, 34% of medical group and 60% of intervention group still had pain at the end of study. On regression analysis, after controlling for demographics, smoking, etiology, diabetes, PERT use, and duration of CP, the odds of being in pain at any time (OR 14.4, 95% CI 4.5-46.5) and at the end of study (OR 2.6, 95% CI 1.43-4.72) was significantly higher in the intervention group when compared with medical group. Moreover, there was no association between the duration of CP with any pain, severe pain at enrollment and pain at the end of study period.

Conclusions: Patients who require an intervention for CP have more aggressive phenotype than patients managed medically. Although pain burn-out is seen in a subset, patients achieve pain relief at different times, which is independent of the duration of disease. These data suggest that better strategies are needed for pain assessment and to identify patients likely to benefit from interventions for CP.

Table 1. Descriptive Characteristics of patients with Chronic Pancreatitis

	All Patients (n=279)	Medical (n=101)	Any Intervention (n=178)	p-value
Age at Enrollment	48.6 ± 15.4	52.7 ± 15.8	46.3 ± 14.8	<0.001
Male	150 (53.8)	58 (57.4)	92 (51.7)	0.355
White	233 (83.5)	83 (82.2)	150 (84.3)	0.451
Age at AP/CP Diagnosis	40.7 ± 18.0	46.3 ± 18.9	37.5 ± 16.7	<0.001
Age at Last Contact	54.3 ± 15.3	58.0 ± 15.4	52.2 ± 15.0	0.002
Acute Pancreatitis ever	208 (74.6)	64 (63.4)	144 (80.9)	<0.001
Recurrent Acute Pancreatitis	144 (51.6)	42 (41.6)	102 (57.3)	0.012
Smoking history				0.034
Never	80 (28.7)	27 (26.7)	53 (29.8)	
<1 pack per day	91 (32.6)	34 (33.7)	57 (32.0)	
>1 pack per day	97 (34.8)	38 (37.6)	59 (33.1)	
Unknown	11 (3.9)	2 (2.0)	9 (5.1)	
Very Heavy drinker	104 (37.3)	31 (30.7)	73 (41.0)	0.345
Etiology				0.920
Alcohol	133 (47.7)	48 (47.5)	85 (47.8)	
Idiopathic	89 (31.9)	34 (33.7)	55 (30.9)	
Genetic	31 (11.1)	11 (10.9)	20 (11.2)	

Other	26 (9.3)	8 (7.9)	18 (10.1)	
Diabetes (At any time)	138 (49.5)	41 (40.6)	97 (54.5)	0.026
Pancreatic Enzyme Use (Ever)	205 (73.5)	63 (62.4)	142 (79.8)	<0.001
Pancreatic Enzyme Use (End of Study)	189 (67.7)	52 (51.5)	137 (77.0)	<0.001
Duration of observation (years) – from CP diagnosis to end of study	9.4 ± 6.7	7.8 ± 5.3	10.3 ± 7.4	0.002
Duration of observation (years) – from AP/CP diagnosis to end of study	13.9 ± 9.7	11.7 ± 9.7	15.2 ± 9.5	0.004
Alive at last follow-up	199 (71.3)	68 (67.3)	131 (73.5)	--

Categorical variables presented as n (%); continuous variables presented as mean ± SD

Table 2. Pain and other relevant outcomes in patients with Chronic Pancreatitis

	All Patients (n=279)	Medical (n=101)	Any Intervention (n=178)	p-value
Abdominal Pain (Ever)	250 (89.6)	76 (75.2)	174 (97.8)	<0.001
Pain (Enrollment)				0.011
No Pain	56 (20.1)	26 (25.7)	30 (16.9)	
Usually Pain Free, Episodes of Mild to Moderate Pain	27 (9.7)	16 (15.8)	11 (6.2)	
I have constant mild to moderate pain	24 (8.6)	10 (9.9)	14 (7.9)	
I am usually free of abdominal pain but have episodes of severe pain	64 (22.9)	21 (20.8)	43 (24.2)	
I have constant mild to moderate pain plus episodes of severe pain	100 (35.8)	25 (24.8)	75 (42.1)	
I have constant severe pain	8 (2.9)	3 (3.0)	5 (2.8)	
Pain at End of Study	130 (52)	26 (34.2)	104 (59.7)	<0.001
Pain Pattern*				<0.001
Type A	85 (34)	41 (53.9)	44 (25.3)	
Type B	132 (52.8)	30 (39.5)	102 (58.6)	
Mixed	33 (13.2)	5 (6.6)	28 (16.1)	
Total Number of Hospitalizations	12.4 ± 18.9	6.8 ± 11.0	15.6 ± 21.6	<0.001
Ever used Narcotics for Pain as Outpatient*	189 (75.6)	46 (60.5)	143 (82.2)	<0.001

Categorical variables presented as n (%); continuous variables presented as mean ± SD
*Calculated among those who had pain

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Pain Modulatory Phenotypes Differentiate Chronic Pancreatitis Patients with Distinct Clinical Pain Profiles

Faghih M, Phillips AE, Larsen IM, Drewes AM, Singh VK, Yadav D, Olesen SS
CAPER Scholarship Recipient- Johns Hopkins

Background and Aims: Pain is a common problem in patients with chronic pancreatitis (CP) and effective therapy remains a considerable challenge. Methods based on quantitative sensory testing (QST) provide information on pain modulation and have demonstrated promise in predicting future pain status and the efficacy of analgesics. The aims of this study were to explore the existence of CP subgroups with different pain modulatory phenotypes and to investigate associations with patients' clinical pain and psychological profiles.

Methods: This was a cross-sectional, multicentre study of CP patients. Patients completed a number of questionnaires including the modified Brief Pain Inventory short form, the Hospital Anxiety and Depression Score as well as measures of conditional and situational Pain Catastrophizing. Using a standardized QST protocol, we recorded pain detection thresholds (PDTs) to static muscle pressure

stimulations at the ´pancreatic dermatomes´ on the upper abdomen and back (dermatomes that share spinal segmental innervation with the pancreas) and at three control areas. The ratio between pancreatic and control PDTs were calculated (PDT-index) to offset interindividual differences in absolute thresholds. The PDT-index was used in conjunction with repetitive pinprick stimulations (temporal summation) applied at the abdominal pancreatic dermatome to obtain a measure of segmental hyperalgesia (a proxy of central sensitization). A conditioned pain modulation (CPM) paradigm was performed to investigate descending pain modulation. Patients were grouped based on normative QST reference values and questionnaire scores were compared across subgroups to investigate associations between patients` pain modulatory phenotypes and clinical pain and psychological profiles.

Results: A total of 91 patients were enrolled in the study. The mean age was 53.1±12.7 Years, 62% were men, and 65% had toxic etiology. Four distinct pain modulatory phenotypes were found: group 1 (n=34) had normal pain modulation; group 2 (n=27) had impaired CPM; group 3 (n=14) had segmental hyperalgesia; and group 4 (n=16) had impaired CPM and segmental hyperalgesia (Figure). Significant differences in average clinical pain scores, as well as BPI pain and interference scores were observed across subgroups ($p<0.05$), with higher pain scores observed for patients in group 4 (Table). In contrast, anxiety, depression and pain catastrophizing scores were comparable across subgroups, implying that QST profiles were not associated with psychiatric comorbidity.

Conclusion: Patients with segmental hyperalgesia and impaired CPM have significantly more pain compared to their counterparts with normal QST profiles. As psychological profiles were not dependent on pain modulatory phenotypes, QST provides an unbiased mean for characterization of pain on an individual patient level. This information can be used for prognostication and tailoring of management strategies.

Clinical pain and psychological variables in the total patient cohort. The patient subgroups stratified by pain modulatory phenotype

BPI; Brief Pain Inventory, HADS; Hospital Anxiety and Depression Score
[#]P-value across patient subgroups
Significance of the difference between patients with normal pain modulatory phenotype (Group 1) and the other patient subgroups;
[*]$P_{adjusted}<0.05$

	All patients (n=91)	Group 1 (n=34)	group 2 (n=27)	Group 3 (n=14)	Group 4 (n=16)	P-value[#]
Clinical pain variables						
Average pain	5.0 (3.0–7.0)	4.0 (2.0-5.0)	5.0 (4.0-7.9)	3.5 (1.0-6.0)	5.5 (4.5-8.0) *	**0.046**
Maximal pain	6.0 (4.0–8.0)	5.0 (2.0-8.0)	6.5 (5.0-8.0)	5.5 (0-8.0)	8.0 (6.5-8.0)	0.11
BPI pain score	4.5 (2.3-6.3)	4.0 (2.0-5.0)	5.5 (3.8-6.8)	3.6 (0.5-7.3)	5.9 (4.3-7.4) *	**0.02**
BPI interference score	4.1 (1.3-6.3)	3.4 (0.6-5.7)	4.3 (1.4-6.1)	2.1 (0-5.7)	6.4 (4.8-7.6) *	**0.02**
Psychological variables						
Pain catastrophizing						
Conditional	26.0 (15.0-33.0)	23.5 (17.0-32.0)	23 (13.0-31.0)	32.0 (16.0-40.0)	27.0 (14.5-37.0)	0.40
Situational	22.0 (11.0-33.0)	22.0 (9.0-34.0)	20.0 (8.0-30.0)	30.0 (16.0-34.0)	23.0 (14.0-37.0)	0.43
HADS						
Depression score	7.0 (4.0-10.0)	7.5 (3.0-10.0)	6.0 (4.0-9.0)	7.5 (2.0-10.0)	8.0 (5.5-10.0)	0.62
Anxiety score	8.0 (5.0-12.0)	7.0 (5.0-10.0)	8.0 (4.0-12.0)	7.0 (4.0-11.0)	10.5 (7.0-12.5)	0.24

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Mutations in the 5' Upstream Region of Chymotrypsinogen C Gene are not Associated with Chronic Pancreatitis

Balázs Csaba Németh[1,2], Réka Madarász[1], Adrienn Nagy[1], Máté Sándor[1], Tamás Takács[1], Gyula Farkas Jr.[3], Ferenc Izbéki[4], László Czakó[1], Richárd Szmola[5], Judit Gervain[4], Szilárd Gódi[6], Andrea Szentesi[1,7], Ákos Szücs[8], Miklós Sahin-Tóth[9,10], Péter Hegyi[2,6,7], Hungarian Pancreatic Study Group

CAPER Scholarship Recipient- University of Szeged

[1] First Department of Medicine, University of Szeged, Szeged, Hungary [2] Momentum Gastroenterology Multidisciplinary Research Group, Hungarian Academy of Sciences University of Szeged, Szeged, Hungary, [3] Department of Surgery, University of Szeged, Szeged, Hungary, [4] Szent György University Teaching Hospital of County Fejér, Székesfehérvár, Hungary, [5] Department of Interventional Gastroenterology, National Institute of Oncology, Budapest, Hungary, [6] First Department of Medicine, Medical School, University of Pécs, Pécs, Hungary, [7] Institute for Translational Medicine, Medical School, University of Pécs, Pécs, Hungary, [8] First Department of Surgery, Semmelweis University, Budapest, Hungary, [9] Center for Exocrine Disorders, Department of Molecular and Cell Biology, Boston University Henry M. Goldman School of Dental Medicine, Boston, MA, USA, [10] University of California Los Angeles, Department of Surgery, Los Angeles, CA, USA

Introduction: Chymotrypsinogen C (*CTRC*) plays a significant role in regulating trypsinogen activation. Early activation of trypsinogen inside the pancreas is a key molecular mechanism in the pathogenesis of pancreatitis that results in self-digestion and local inflammation of the organ. Loss-of-function mutations in the *CTRC* gene encoding Chymotrypsinogen C impair either the catalytic activity or the expression of the enzyme. Impaired expression of *CTRC* might be caused by variants in the 5' upstream region, however,

this region of the gene was not investigated yet. Our aim was to sequence the 5' upstream region of the *CTRC* gene in patients and controls in order to identify variants that may predispose to chronic pancreatitis.

Patients and methods: We selected 117 patients with non-alcoholic (NACP), 147 patients with alcoholic chronic pancreatitis (ACP) and 263 controls recruited by the Hungarian Pancreatic Study Group (HPSG – www.pancreas.hu). Mutations within the ~1.4 kb CTRC 5' upstream region were analyzed by Sanger sequencing.

Results: We found 2 common polymorphisms (c.-913A>G and c.-811G>A) and 4 further variants (c.-993G>T, c.-314AAAT[5], c.-92C>T and c.-59C>T) in the ~1.4 kb long 5' upstream region of the *CTRC* gene. However, we found that the variant c.-913A>G slightly accumulated in patients compared to controls, genotype and allelic distribution of the identified variants were generally comparable between each group of patients and controls.

Conclusion: Based on our preliminary results, the identified mutations in the 1.4 kb long 5' upstream region of the *CTRC* gene are not associated with chronic pancreatitis.

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Assessing the Clinical Significance of PRSS1 Intronic Variants

Eszter Hegyi[1,2], Anna Zsófia Tóth[2], Andrea Szentesi[1,3], Gyula Farkas Jr[4], Ferenc Izbéki[5], Bálint Erőss[1], László Czakó[3], Áron Vincze[6], Péter Hegyi[1,3,7], Miklós Sahin-Tóth[2]

CAPER Scholarship Recipient- University of Pécs

[1] Institute for Translational Medicine, Medical School, University of Pécs, Pécs, Hungary, [2] Center for Exocrine Disorders, Department of Molecular and Cell Biology, Boston University Henry M. Goldman School of Dental Medicine, Boston, MA, [3] First Department of Medicine, University of Szeged, Szeged, Hungary, [4] Department of Surgery, University of Szeged, Szeged, Hungary, [5] Szent György University Teaching Hospital of Fejér County, Székesfehérvár, Hungary, [6] Division of Gastroenterology, First Department of Medicine, University of Pécs, Pécs, Hungary, [7] Division of Translational Medicine, First Department of Medicine, Medical School, University of Pécs, Hungary

Background: The clinical relevance of the majority of *PRSS1* (serine protease 1 gene encoding human cationic trypsinogen) exonic variants in chronic pancreatitis (CP) has been successfully determined and pathogenic mechanisms of the disease-causing mutations have been identified. The role of intronic variants has not been characterized well so far, presumably due to difficulties in studying their functional effects. However, the increasing number of reported *PRSS1* intronic variants in patients with CP highlights the need for clarifying their clinical significance.

Aims: To identify and functionally characterize *PRSS1* intronic variants. We focused on intron 3 and intron 4 because splicing defects in distal introns are more likely to result in altered protein function.

Methods: 223 CP patients (cases) and 271 controls with no pancreatic disease from the Hungarian National Pancreas Registry were enrolled. Direct sequencing of intron 3 and intron 4 of *PRSS1* has been performed. The entire genomic sequence of the *PRSS1* with the intronic variants has been cloned into a low-copy number variant of the pcDNA3.1 (-) plasmid. HEK293T and AR42J cells were transfected with the full-length *PRSS1* constructs to analyze mutational effects on mRNA expression, protein folding, secretion and activity.

Results: A heterozygous intron 3 variant (c. 455-93T>C) was identified in one case only. Six variants in intron 4 have been found (c.591+111C>T, c.592-79G>A, c.592-38T>C, c.592-24C>T, c.592-11C>T, and c.592-8C>T), all in the heterozygous state. There was no significant enrichment of intronic variants in cases relative to controls. Functional analysis of all intronic variants has been performed. Secretion of cationic trypsinogen from transfected cells harboring full-length *PRSS1* with intronic variants was unchanged relative to cells expressing the wild-type *PRSS1* in both cell lines. Trypsin activity in the conditioned medium and mRNA expression levels were analyzed in HEK293T cells. None of the variants exhibited a substantially decreased (i.e., more than 50%) or increased (i.e., more than twofold) activity compared to the wild type. The mRNA expression levels correlated with the secreted protein amounts.

Conclusions: Variants in intron 3 and intron 4 of *PRSS1* occur rarely and are not associated with CP. In vitro analysis confirms that these intronic variants are functionally harmless and, therefore, should have no pathological significance related to CP.

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Identification of Pancreatitis Risk Genotypes in Patients of Non-European Ancestry

Daniel M Spagnolo PhD,[1] Mitchell A. Ellison,[1] David C. Whitcomb, MD PhD,[2] Jessica LaRusch PhD,[1] Celeste Shelton, MS CGC PhD,[1] Ekaterina Orlova MPH MS CGC,[1,3] **Mark Haupt MD**[1]

[1]Ariel Precision Medicine, Pittsburgh, PA. [2]Division of Gastroenterology, Hepatology and Nutrition, [3]Department of Human Genetics; University of Pittsburgh, Pittsburgh, PA.

Background: Differences in pancreatitis etiology and outcomes are reported in patients of differing race and ancestry. For example, black pancreatitis patients are more likely to be male, have a history of smoking, and physician-defined alcohol etiology. Morphologic differences also exist, with black patients having higher rates of calcifications, changes in ductal morphology and pancreatic atrophy. A recent description of Chilean patients with pancreatitis identified higher rates of severe morphologic changes but less pain compared to those of a North American Cohort. Evaluation of *PRSS1*, *SPINK1*, *CFTR* and *CTRC* variants in NAPS2 patients suggested different pathogenic variant frequencies between patients of European and African ancestry. Similar differences in susceptibility variant prevalence is described in Asian populations. The purpose of this study was to explore and describe differences in the prevalence of pancreatitis susceptibility variants in patients of different self-reported ethnicities undergoing clinical genetic testing.

Methods: One hundred consecutive pancreatitis patients undergoing genetic evaluation with a deep sequencing pancreatitis panel (*PRSS1, PRSS2, PRSS1-2 risk haplotype, CPA1, CEL, CFTR, SPINK1, CTRC, UBR1* and *GGT1)* were evaluated. Patients were categorized as Caucasian and non-Caucasian. Variants were classified according to ACMG guidelines. Prevalence was compared to population allele frequencies in gnomAD.

Results: The following ancestries were reported: 2% East Asian, 3% South Asian, 7% Black or African American, 1% Central-South American, 8% Jewish-Ashkenazi, 1% Middle Eastern, 4% Native American, 51% White-European, 42% White-Other. 69% (58/84) of Caucasians and 62.5% (10/16) of non-Caucasians were reported by their referring physician to have idiopathic pancreatitis. A higher percentage of Caucasian patients were found to have variants (pathogenic, risk, or uncertain significance) in *CEL* and *SPINK*1 (7% and 9%) than those of non-Caucasian ancestry (1% and 5%). A higher percentage of patients of non-Caucasian ancestry had variants in *GGT1* (33% v 22%). Caucasian patients were found to have a higher rate of *CFTR* variants (100% vs. 64%). In total, 14 pathogenic variants and 15 risk variants were found in the Caucasian population. 4 pathogenic variants and 7 risk variants were found in the non-Caucasian population.

Conclusions: Differences in risk factors, symptoms, severity and outcomes exist between pancreatitis patients of different ancestries. This preliminary analysis highlights differences in patterns of risk variants between patients with different self-reported ancestries. Further genetic analyses of ancestry group differences may provide greater insight into the different phenotypes of pancreatitis. Additional work is required to further understand and replicate these preliminary findings in a larger population, particularly to identify population-specific variants that contribute to pancreatitis development and expression.

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Complex Pancreatitis Genetics: Comprehensive Genetic Evaluation Reveals High Prevalence of Risk Variants

Daniel M Spagnolo PhD,[1] Mitchell A. Ellison,[1] David C. Whitcomb, MD PhD,[2] Jessica LaRusch PhD,[1] Celeste Shelton, MS CGC PhD,[1] Ekaterina Orlova MPH MS CGC,[1,3] **Mark Haupt MD**[1]

[1]Ariel Precision Medicine, Pittsburgh, PA. [2]Division of Gastroenterology, Hepatology and Nutrition, [3]Department of Human Genetics; University of Pittsburgh, Pittsburgh, PA.

Background: Chronic pancreatitis (CP) is a syndrome resulting from persistent inflammation of the pancreas due to multiple genetic, metabolic, and environmental factors and their interactions. Traditionally, genetic testing for pancreatitis has focused on evaluation for Hereditary Pancreatitis (HP), a rare autosomal dominant form of pancreatitis. HP accounts for approximately 2% of all cases of pancreatitis. Evidence now suggests the genetic etiology of a significant proportion of CP is complex, often involving variation within several genes through multiple mechanisms. Here we describe the clinical genetic testing results of a pancreatitis-specific DNA sequencing panel for Mendelian and complex forms of pancreatitis.

Methods: A multiethnic cohort of one hundred consecutive pancreatitis patients undergoing genetic evaluation with a deep sequencing pancreatitis panel (*PRSS1, PRSS2, PRSS1-2 risk haplotype, CPA1, CEL, CFTR, SPINK1, CTRC, UBR1* and *GGT1)* were evaluated. Variant classification was made according to ACMG guidelines. Variant frequencies were compared to population allele frequencies in gnomAD.

Results: The most common physician-reported etiologies of pancreatitis were idiopathic (68%: 39% early, 29% late), toxic (18%) and obstructive (18%). A total of 242 genetic variants were identified and evaluated according to ACMG criteria. Of those, 53 met clinical reporting standards: 16 pathogenic variants (*CFTR* 11, *PRSS1* 3, *SPINK1* 1, *CTRC* 1), 17 risk variants, 20 variants or factors of uncertain significance. All patients had at least 1 variant meeting ACMG clinical reporting criteria. 54% of patients had at least 1 risk variant identified. Variants were most commonly identified in *CFTR* (52.8% of variants), followed by *SPINK1* (9.4%) and *CTRC* (9.4%). Consistent with previous reports, *PRSS1* variants associated with Hereditary Pancreatitis were identified in 3% of patients. Established combinations of risk variants were identified, such as those in *CFTR* with those in *SPINK1*.

Conclusions: Variants in known genes associated with pancreatitis were commonly identified in this population. The prevalence of Hereditary Pancreatitis variants was as expected. Most patients were found to harbor multiple risk variants that impact different mechanistic pathways. Specific combinations of known common risk variants in patients with pancreatitis supports the role of complex genetics in pancreatitis. Pancreatitis is a complex disorder in which various etiologies contribute to the severity and progression of the disease. A comprehensive, mechanistic evaluation of variants and risk factors that contribute to disease is necessary to fully understand the biological basis of a patient's condition and make improvements to personalized management and risk prediction. Additional work is ongoing to further understand and quantify the combinatorial effects of the risk variants of small effect size.

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Temporal Trends and Predictors of Pancreatitis Patients Who Leave Against Medical Advice: A Nationwide Analysis

Fahad Chaudhary MD, Ridwaan Albeiruti MD, William Hutson MD
West Virginia University

Background: Acute pancreatitis is the leading gastrointestinal cause of hospital admissions in the United States. Nearly half of all readmissions are related to pancreatitis. Our study aims to determine the prevalence, trends, and predictors of discharge against medical advice (AMA) in this cohort.

Methods: We utilized the Nationwide Inpatient Sample (2003-2016) of the Healthcare Cost and Utilization Project (HCUP) to identify patients admitted with pancreatitis. We compared in-hospital complications and costs and then determined predictors of discharge AMA using univariate and multivariate logistic regressions.

Results: A total 7,158,894 patients were admitted with pancreatitis during our study period. Of those, 199,351 (2.8%) left AMA. Discharge AMA increased over time from 2.3% in 2003 to 3.2% in 2016 ($p<0.001$). Patients who left AMA were more likely to be younger (49.4% vs 5.8%, $p<0.001$), male (68.2% vs 50.2%, $p<0.001$), black (24.4% vs 17.5%, $p<0.001$), and of a lower socioeconomic status (38.6% vs 14.7%, $p<0.001$). They had a greater prevalence of depression (10.6% vs 7.1%, $p<0.001$), cirrhosis (10.9% vs 8.6%, $p<0.001$), smoking (44.4% vs 22.6%, $p<0.001$), drug abuse (18.4% vs 6.8%, $p<0.001$), and HIV (3.0% vs 1.4%, $p<0.001$). Alcohol use was the most likely etiology of pancreatitis among those leaving AMA (52.3% vs 23.5%, $p<0.001$). In a multivariate regression, patients more likely to leave AMA included: age 18-44 (OR 4.14, 95% CI 4.04-4.24, $p<0.001$), male (OR 1.58, 95% CI 1.56-1.60, $p<0.001$), and black (OR 1.06, 95% CI 1.05-1.07, $p<0.05$). Patients with alcoholic pancreatitis were more likely to leave AMA (OR 1.81, 95% CI 1.79-1.83, $p<0.001$). Patients with a history of depression (OR 1.05, 95% CI 1.03-1.07, $p<0.001$), drug abuse (OR 1.44, 95% CI 1.42-1.46, $p<0.001$) and HIV (OR 1.25, 95% CI 1.21-1.29, $p<0.001$) were also more likely to be discharged AMA.

Conclusion: The number of discharges AMA increased over time from 2003-2016. Nearly 1 in 36 pancreatitis admissions leave AMA. Predictors of AMA include patients who are younger, male, black, lower socioeconomic status, and have a history of depression, HIV, alcohol and drug use. Future studies are necessary to examine the reasons for discharge AMA among this population.

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Probiotic use may Increase the Odds of Hospital Readmission for a Chronic Pancreatitis Flare

Jose R. Aponte-Pieras, PGY-3, MD, ScB, Wahid Wassef, MD, MPH, FACP
University of Massachusetts Medical School

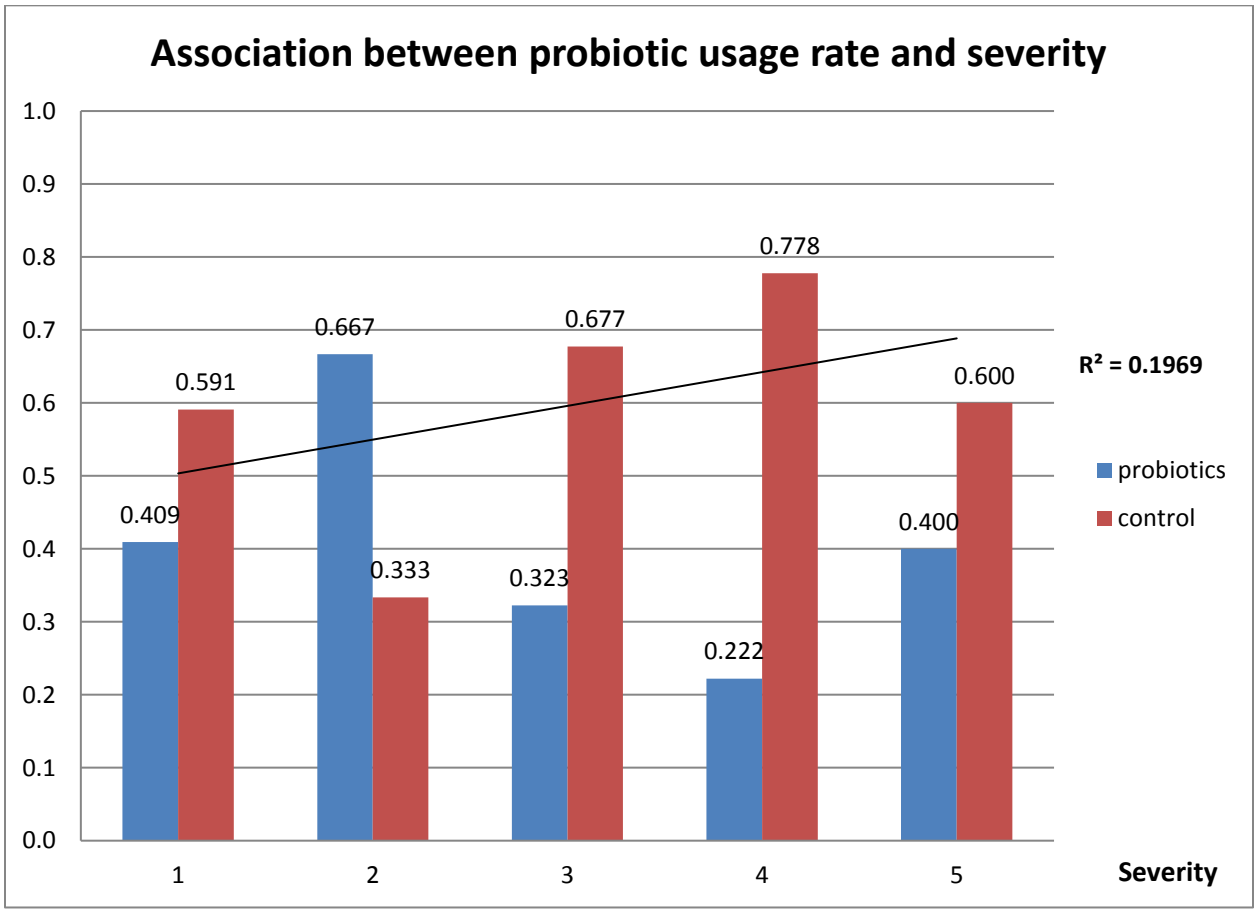
Introduction: Chronic pancreatitis is a debilitating condition that develops following recurrent episodes of pancreatitis. It increases morbidity, affects quality of life, and leads to high usage of medical resources. Studies suggest that dysbiosis may play a role in pancreatitis with bacterial and endotoxin translocation contributing to severity. Bacteria such as lactobacillus and bifidobacterium have been found in chronic pancreatitis at lower concentrations, while others such as Enterobacteriaceae were higher in concentration. Probiotics may increase concentrations of beneficial bacteria such as lactobacilli, preventing overgrowth of non-commensals. The goal of our research is to assess the role of probiotics in patients with chronic pancreatitis.

Method: We conducted a retrospective chart review of a chronic pancreatitis patient database (n = 88) and evaluated prior probiotic use. Cohorts were based on severity as rated on a scale of 1-5 (correlating with “mild”, “mild-moderate”, “moderate”, “moderate-severe”, and “severe”); based on the ACG practice guidelines’ 9-point EUS criteria for diagnosis. We collected data on initial diagnostic EUS, initial mention of probiotic use, and admission data related to chronic pancreatitis. We chose a null of 0.05 with a 95% confidence interval for statistical significance.

Results: Our results revealed that following EUS diagnosis of chronic pancreatitis 38% of patients had used probiotics. The rate of probiotic use for each severity rating (1-5) decreased with increasing severity of disease as noted by a positive linear relationship (R of 0.4437; p = 0.00002). Further analysis demonstrated an average hospital length of stay of 48.09 days for probiotic users compared to 11.11 for non-users. The odds of re-admission given probiotic use overall were 3.08 (95% CI: 1.17-8.11; p = 0.023). This effect was preserved regardless of whether patients were designated as having severe disease (presence of calcifications or rating of 4-5) or lack of severe disease.

Discussion: We found a linear relationship between severity and lack of probiotic use. The majority of patients with higher severity rating were primarily non probiotic users. The use of probiotics was linked to increased hospital length of stay, and was associated with increased odds of readmission for pancreatitis flares. Although our analysis suggested a potential association between worsening severity and lack of probiotic use, we failed to find a positive effect from probiotic use. Probiotics were associated with worse outcomes when compared to placebo. Overall, probiotics were found to be more likely associated with readmission for an active pancreatitis flare than placebo. Increased disease severity was not found to be a factor confounding this effect. In conclusion, we were unable to find a protective role for probiotics. We may have data to suggest a strong association for probiotics to increased length of stay and hospital re-admission. We suspect that this result may be attributable to the fact that patients with worse outcomes are treated more aggressively with therapies yet to derive a protective effect. There is not enough evidence to suggest probiotics are a potential source of harm to patients with chronic pancreatitis, but their use may be associated with worse outcomes.

Figure 1



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Association of Autoimmune Diseases in Children with Acute Recurrent or Chronic Pancreatitis

Yuhua Zheng, Sohail Z. Husain, Bridget Zimmerman, Douglas S. Fishman, Brian McFerron, Uzma Shah, Michael Wilschanski, Steven L. Werlin, David Troendle, Sarah Jane Schwarzenberg, Sue Rhee, John Pohl, Emily R. Perito, Chee Y. Ooi, Jaimie D. Nathan, Veronique D. Morinville, Maria Mascarenhas, Asim Maqbool, Quin Liu, Tom K. Lin, Ryan Himes, Melvin B. Heyman, Tanja Gonska, Matthew J. Giefer, Cheryl E. Gariepy, Steven D. Freedman, Melena Bellin, Bradley Barth, Maisam Abu-El-Haija, Mark E. Lowe, Aliye Uc

Background: An association has been reported in children with autoimmune diseases and pancreatitis. Little is known about the characteristics of children with an autoimmune disorder who present with acute recurrent pancreatitis (ARP) or chronic pancreatitis (CP).

Objective: To determine the frequency and associations of autoimmune diseases and patient characteristics in the well-phenotyped INSPPIRE (International Study group of Pediatric Pancreatitis: In search for a cuRE) cohort.

Methods: We reviewed the INSPPIRE database for autoimmune diseases in 447 children enrolled from August 2012 to August 2017. We excluded children with autoimmune pancreatitis (n=13). Twelve had inflammatory bowel diseases (IBD) (5 Crohn's disease, 4 ulcerative colitis, 3 indeterminate colitis), 5 type 1 diabetes mellitus, 2 overlap syndrome, 3 celiac disease, 1 systemic lupus erythematosus, 3 Hashimoto thyroiditis, 2 juvenile idiopathic arthritis and 1 dermatomyositis. Patient demographics, and clinical information were compared between children with autoimmune diseases (n=29) to those without (n=415). Differences between groups were tested using two-sample t-test for continuous variables, Wilcoxon rank-sum test for ordinal variables, Pearson Chi-square test or Fisher's exact test for categorical variables. $P < 0.05$ was considered statistically significant.

Results: Children with autoimmune diseases were significantly older at the first acute pancreatitis attack compared to those without (12.8 ± 4.2y vs 8.5 ± 4.7y, p< 0.0001). There was no significant difference in CP diagnosis (34% in autoimmune vs 47% in others, p=0.2). Genetic risk factors, specifically *PRSS1* and *CFTR* variants were less common in the autoimmune group (p<0.01 and p<0.05 respectively). There was significantly more common usage of azathioprine (AZA)/6-mercaptopurine (6-MP) (p<0.0001) or steroids (p<0.01) in children with autoimmune diseases, probably due to their primary illness. Abdominal pain related to pancreatitis was less common in children with autoimmune diseases than those without (63% vs 82%, p<0.019). The frequency of emergency room visits, hospitalizations, school attendance were not different between the groups. Pancreatic duct obstruction/stricture was seen exclusively in non-autoimmune group (0% vs 23% p<0.01); gallstones/sludge (17% vs 6%, p=0.06) and common bile duct dilatation (42% vs 15% p=0.001) were more common in children with autoimmune disorders.

Conclusions: Autoimmune diseases (IBD in particular) is an uncommon risk factor of pediatric ARP or CP. These children tend to have later disease onset, similar health-related quality of life, but abdominal pain unrelated to pancreatitis. A larger and longitudinal study is needed to better demonstrate a temporal association of medication usage with ARP or CP and whether these children develop CP over time.

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Validation and Optimization of an Early Predictor Model for Pediatric Acute Pancreatitis

Peter R Farrell[1,3] MD,MS; Lindsey Hornung[2] MS; Peter Farmer[3,4] MD, Angelica W DesPain[5] MD, Esther Kim[6] MD, Ryan Pearman[5] BA, Beemnet Neway[5] BS, Ashley Serrette[7] MD, , Sona Sehgal[8] MD, Tom K. Lin[1,9] MD, Jaimie D. Nathan[1,9] MD, David S Vitale[1,9] MD, Maisam Abu-El-Haija[1,9] MD

CAPER Scholarship Recipient- Cincinnati Children's Hospital

[1] Division of Gastroenterology, Hepatology and Nutrition, Cincinnati Children's Hospital Medical Center, [2] Division of Biostatistics and Epidemiology, Cincinnati Children's Hospital Medical Center, [3] Pediatric Residency Program, Children's Hospital of the King's Daughters, [4] Department of Pediatrics, Eastern Virginia Medical School, [5] Division of Emergency Medicine, Children's National Medical Center, [6] Pediatric Residency Program, Children's National Medical Center, [7] Division of Emergency Medicine, Cohen Children's Medical Center, [8] Division of Gastroenterology, Hepatology and Nutrition, Children's National Medical Center, [9] Department of Pediatrics, University of Cincinnati

Introduction: Acute pancreatitis (AP) is increasing in the pediatric population but there remain limited pediatric data regarding optimal management. In 2017, severity classification guidelines for pediatric AP were published defining mild, moderately severe, and severe AP. Following these guidelines, Vitale et al developed a model to predict severity utilizing internal data from Cincinnati Children's Hospital Medical Center (CCHMC). The model used admission Blood Urea Nitrogen (BUN) level as a significant predictor of severe disease (AUROC 0.75, 95% CI 0.61 – 0.89).

Objectives: To validate and optimize the predictive value and performance of the previous model designed to predict severity of AP in the pediatric population by using data from two other medical centers.

Study Design: Pediatric patients (age <19 years) with primary diagnosis of first time AP were included in this study. Patients were retrospectively examined at Children's Hospital of the Kings Daughters (CHKD, Norfolk, VA) based on ICD-9 or ICD-10 codes during a 5 year period. Patients prospectively enrolled in an ongoing study of first time AP at Children's National Medical Center (CNMC, Washington, DC) were included (ClinicalTrials.gov ID NCT03242473). Permission was granted by respective local IRBs. Differences in lab values at admission between the groups of mild and both moderately severe and severe AP (combined were called SAP) were analyzed using Wilcoxon-Mann-Whitney tests and logistic regression models.

Results: At CHKD, 57 patients were identified with a first time episode of AP. At CNMC, 16 patients were enrolled, for a total of 73 primary AP patients for analysis. Of those, 22 (30%) met either the criteria for severe or moderately severe AP and were included in the SAP group. Patients who developed SAP had significantly higher BUN (p=0.002) and lower albumin (p=0.005) levels. Validation of the BUN model was done, and confirmed to be a significant predictor (p=0.005) of development of any form of SAP (AUROC 0.73, 95% CI 0.60 – 0.86, sensitivity 68%, specificity 73%, PPV 52%, NPV 84%) as previously described. When combined in a multivariable model, BUN (p=0.005) and albumin (p=0.004) combined created a better predictive model for SAP (AUROC 0.83, 95% CI 0.72 – 0.94, sensitivity 71%, specificity 79%, PPV 60%, NPV 86%).

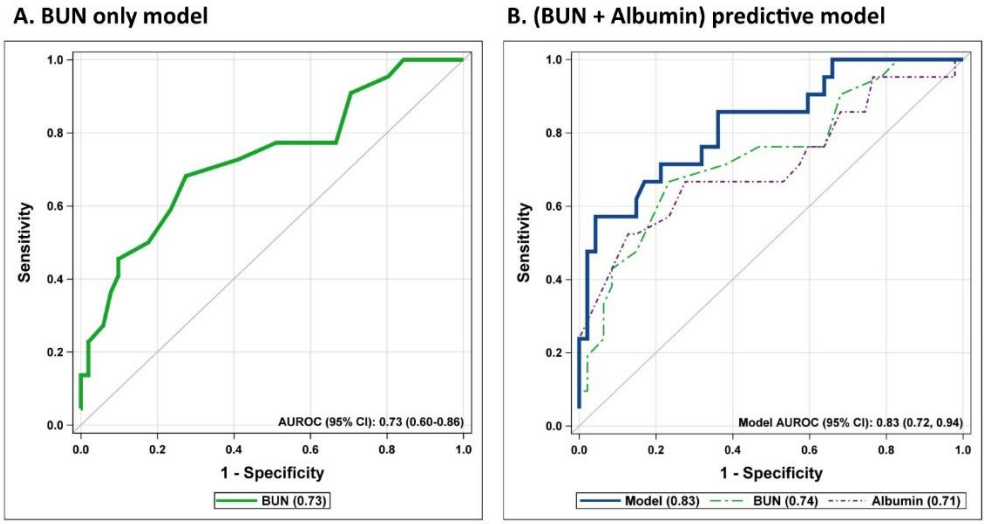
Conclusion: This study validates the previously described model using a validation cohort from two distinct pediatric hospitals, and demonstrates that BUN on admission is a significant predictor of the development of moderately severe or severe AP. Our data suggest albumin further optimizes the predictive model. This could allow for early identification of patients at highest risk for progression to any form of severe AP. Future studies should be directed towards creating a clinical tool for SAP prediction.

Table 1. Admission values and biochemical characteristics of patients with first time pediatric AP.

	SAP (n=22)	**Mild AP (n=51)**	**P-value**
Lipase x ULN	23.8 (5.6-45.9) *n=21*	12.3 (6.9-42.9) *n=48*	0.66
Amylase x ULN	4.1 (2.4-10.5) *n=19*	2.2 (1.4-7.1) *n=40*	0.15
Albumin, g/dL	3.3 (3.1-4.2) *n=21*	4.0 (3.6-4.6) *n=47*	**0.005**
Anion Gap, mmol/L	12.0 (8.0-16.0) *n=21*	12.0 (10.0-15.0) *n=51*	0.74
WBC, 10^3/microL	13.1 (5.8-17.3) *n=19*	9.8 (6.5-13.8) *n=39*	0.38
Creatinine, mg/dL	0.5 (0.4-0.7) *n=22*	0.5 (0.4-0.7) *n=51*	0.94
Calcium, mg/dL	9.2 (8.8-9.5) *n=22*	9.3 (8.9-9.7) *n=51*	0.29
AST, Unit/L	32.0 (24.0-63.0) *n=21*	38.0 (22.0-80.0) *n=47*	0.69
ALT, Unit/L	29.0 (21.0-57.0) *n=21*	31.0 (24.0-135.0) *n=47*	0.39
Hematocrit, %	39.4 (33.2-41.9) *n=19*	37.3 (34.4-39.8) *n=39*	0.53
Hemoglobin, g/dL	13.7 (11.0-14.5) *n=19*	12.9 (11.7-14.1) *n=39*	0.89
BUN, mg/dL	14.5 (11.0-19.0) *n=22*	11.0 (8.0-13.0) *n=51*	**0.002**
Alk Phosphatase, Unit/L	163.0 (137.0-207.0) *n=21*	138.5 (91.0-225.0) *n=46*	0.54
Glucose, mg/dL	97.5 (80.0-138.0) *n=22*	99.0 (89.0-118.0) *n=51*	0.75
Triglyceride, mg/dL	49.5 (35.0-69.0) *n=10*	68.0 (50.0-115.0) *n=21*	0.06
Sodium, mmol/L	138.5 (136.0-140.0) *n=22*	140.0 (138.0-142.0) *n=51*	0.11
Chloride, mmol/L	103.5 (101.0-106.0) *n=22*	104.0 (101.0-106.0) *n=51*	0.91
Total Bilirubin, mg/dL	0.5 (0.4-0.9) *n=21*	0.6 (0.4-1.1) *n=47*	0.50
CRP, mg/dL	1.3 (0.5-6.6) *n=11*	1.1 (0.6-3.0) *n=29*	0.83
Potassium, mmol/L	4.1 (3.9-4.6) *n=21*	4.1 (3.7-4.4) *n=51*	0.64
Total protein, g/dL	6.6 (5.9-7.6) *n=21*	7.1 (6.5-7.5) *n=47*	0.20
Platelet count, 10^3/microL	288.0 (154.0-393.0) *n=19*	261.0 (219.0-326.0) *n=39*	0.67
CO2, mmol/L	24.5 (18.0-27.0) *n=22*	24.0 (22.0-25.0) *n=51*	0.93

Wilcoxon-Mann-Whitney analysis, data presented as median (25th-75th percentile). AP= Acute Pancreatitis. SAP = Moderately Severe and Severe Acute Pancreatitis combined

Figure 1: Receiver operating characteristic curves for prediction of moderately severe and severe AP (SAP)
A: BUN alone validation model (AUROC 0.73, 95% CI 0.60 – 0.86, sensitivity 68%, specificity 73%, PPV 52%, NPV 84%)
B: BUN and Albumin combined optimized the previously generated model (AUROC 0.83, 95% CI 0.72 – 0.94, sensitivity 71%, specificity 79%, PPV 60%, NPV 86%).



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Factors Associated with Prolonged Length of Stay in Pediatric Acute Pancreatitis in a Single Tertiary Pediatric Care Center in Mexico City, Mexico

Rivera Suazo, Yunuen[1] MD; Vázquez Frías, Rodrigo[1] MD, PhD.
[1] Children's Hospital of México Federico Gómez, Division of Pediatric Gastroenterology and Nutrition.

Background: Specific factors have been associated with prolonged length of stay (PLOS) for pediatric acute pancreatitis (AP).[1, 2]

Objective: To identify factors associated with PLOS for pediatric patients hospitalized with AP.

Methods: *Study design.* Data were obtained by using the retrospective investigation system, of patients discharged from Hospital Infantil de México Federico Gómez with an ICD-10 (K85.9) code for AP from January 1, 2017 to March 31, 2019.
Inclusion criteria. AP was confirmed by manual chart review, as requiring 2 of the following: abdominal pain compatible with AP, serum amylase and/or lipase values $\geq$ 3 times upper limits of normal, and imaging findings of AP, according to the criteria of the INSPPIRE group, in a patient < 18 years of age at the time of admission, discharged with a primary discharged diagnosis of AP.
Exclusion criteria. The exclusion criteria included pancreatic tumors, chart with missing information and AP during hospitalization.
Data collection. Demographic, clinical, nutritional status, laboratory, and management data were collected. LOS $\geq$ 7 days was considered as PLOS.
Statistical Analysis. All of the factors for PLOS were assessed individually using x^2 or Fisher exact tests for qualitative data and Student t test and Mann-Whitney U for continuous variables. Results are expressed as numbers (%) or mean $\pm$ SD. P values <0.05 were considered statistically significant. We used multivariate logistic regression analysis to calculate the adjusted OR for the development of PLOS. Data were compiled and analized with SPSS for Windows version 20.0 (IBM Corp, Armonk, NY).

Results : For the 51 discharges, mean LOS was 11.76 $\pm$ 13.45 days and mean age was 10.83 $\pm$ 4.42 years. Discharges were primarily female (51%, n=26). The most frequent symptoms were abdominal pain with vomiting (49%, n=25). 62.7% (n=32) cases were mild, 29.4% (n=15) were moderately severe, and 7.8% (n=4) were severe. There was one death (1.9%). The most common etiology was anatomy/obstructive (58.8%, n=30). For pain management 49% (n=25) received both non-opioids and opioids. The common modality of nutrition after NPO was clear liquids (76.4%, n=39) and 15.6% (n=8) normal diet. 19.6% (n=10) of cases received parenteral nutrition. Antibiotics were used in 49% (n=25). 21.5% (n=11) received fluid resuscitation on admission, all with lactated Ringer's solution (Table 1).
On multivariate analysis of factors associated with PLOS, use of antibiotics was the only variable significantly associated with outcome of interest (OR 31.71; 95% CI 2.71-370.65; P = 0.006) and early nutrition (within 72 hours of admission) was independently associated with a decreased LOS (OR 0.05; 95% CI 0.001-0.63; P = 0.02).

Conclusions: Early nutrition showed a protective power against PLOS and who require antibiotics are at the highest risk of PLOS in pediatric patients admitted with AP.

References
1. J Pediatr 2015;167:397-402
2. JPGN 2018;67:e30-e35

Table 1. Demographic characteristics of pediatric acute pancreatitis episodes discharges in the study population

	Prolonged length of stay		
	Yes	No	*P*
n	27	24	
Age, y	9.99 ± 4.67	11.76 ± 4.01	0.15*
Sex			
Male, n (%)	12 (44.4%)	13 (54.2%)	0.48°
Female, n (%)	15 (55.6%)	11 (45.8%)	
Weight, kg	34.08 ± 18.16	38.17 ± 17.04	0.41*
Height, cm	132.9 ± 26.72	140.85 ± 23.84	0.26*
BMI	17.7 ± 4.18	18.3 ± 4.23	0.63*
Recurrent (2 or more episodes), n (%)	13 (48.2%)	19 (79.2%)	0.02°
Severity			
Mild, n (%)	10 (37 %)	22 (91.7%)	0.001°
Moderately severe, n (%)	13 (48.2%)	2 (8.3%)	
Severe, n (%)	4 (14.8%)	0	
Etiology			
Idiopathic, n (%)	6 (22.2%)	3 (12.5%)	0.07°
Anatomy/Obstructive, n (%)	12 (44.4%)	18 (75%)	
Trauma n (%)	2 (7.4%)	3 (12.5%)	
Toxic, n (%)	5 (18.5%)	0	
Toxic/Metabolic, n (%)	2 (7.4%)	0	
Comorbidity, n (%)	16 (59.3%)	21 (87.5%)	0.03°
Complications chronic pancreatitis, n (%)	5 (18.5%)	12 (50%)	0.02°
Chronic pancreatic damage	7 (75%)	12 (100%)	0.25°
Endocrine pancreatic insufficiency	1 (25%)	0	0.25°
Fluid resuscitation, n (%)	11 (40.7%)	0	0.0001°
Pain management, n (%)	25 (92.6%)	22 (91.7%)	1°
Non-opioids, n (%)	7 (28%)	8 (36.4%)	0.23°
Opioids, n (%)	2 (8%)	5 (22.7%)	
Non-opioids/opioids, n (%)	16 (64%)	9 (40.9%)	
Antibiotics, n (%)	20 (74.1%)	5 (20.8%)	0.0001°
Time to nutrition after NPO			
Early < 48 h	5 (18.5%)	16 (66.7%)	0.0001°
Early < 72 h	5 (18.5%)	6 (25%)	
Late > 72 h	17 (63%)	2 (8.3%)	
Modality of nutrition after NPO			
Oral, n (%)	24 (88.9%)	23 (95.8%)	0.61°
Enteral, n (%)	3 (11.1%)	1 (4.2%)	

Type of nutrition after NPO			
Normal	3 (11.1%)	5 (20.8%)	0.61°
Clear liquids	24 (88.9%)	15 (62.5%)	
Low fat	0	4 (16.7%)	
Parenteral nutrition	9 (33.3%)	1 (4.2%)	0.01°°
Lipase, U/L	1634.5 (673.5-5134.7)	3331 (1139-5442)	0.22+
Amilase, U/I	232.5 (102-959.25)	271 (152.5-785.5)	0.71+
Creatinine, mg/dL	0.69 ± 0.34	0.58 ± 0.20	0.14*
BUN, mg/dL	19.93 ± 20.51	11.56 ± 5.19	0.05*
Total bilirubin, mg/dL	1.71 ± 1.59	0.58 ± 0.30	0.001*
AST, U/L	73.5 (22.5-185.75)	21 (16-28)	0.02+
ALT, U/L	95 (28.5-201.5)	25 (18-29)	0.03+
Albumin, g/dL	3.26 ± 0.86	4.08 ± 0.47	0.0001*
Hemoglobin, g/dL	13.12 ± 2.56	14.24 ± 1.85	0.08*
Hematocrit, %	39.45 ± 7.63	42.36 ± 5.61	0.13*
Leukocytes, $10^3/\mu L$	12.12 ± 7.48	11.89 ± 4.60	0.89*
Platelets, $10^3/\mu L$	250.31 ± 130.38	319.0 ± 93.67	0.04*
Calcium, mg/dL	8.98 ± 0.81	9.32 ± 0.51	0.07*
LDH, U/L	396 (232-479)	215 (172.5-303.5)	0.008+
BMI = body mass index; NPO = non per os; BUN = blood urea nitrogen; AST = aspartate aminotransferase; ALT = alanine aminotransferase; LDH = lactate dehydrogenase. * Student t test; * Chi-square; °° Fisher exact test; + Mann-Whitney U.			

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Secretin Improves Visualization of Non-Dilated Pancreatic Ducts in Children Undergoing Magnetic Resonance Cholangiopancreatography

Yinan Li, MD, Jonathan R. Dillman, MD MSc, Christopher G. Anton, MD, Eric J. Crotty, MD, Ethan A. Smith, MD, Maisam Abu-El-Haija, MD, Andrew T. Trout, MD

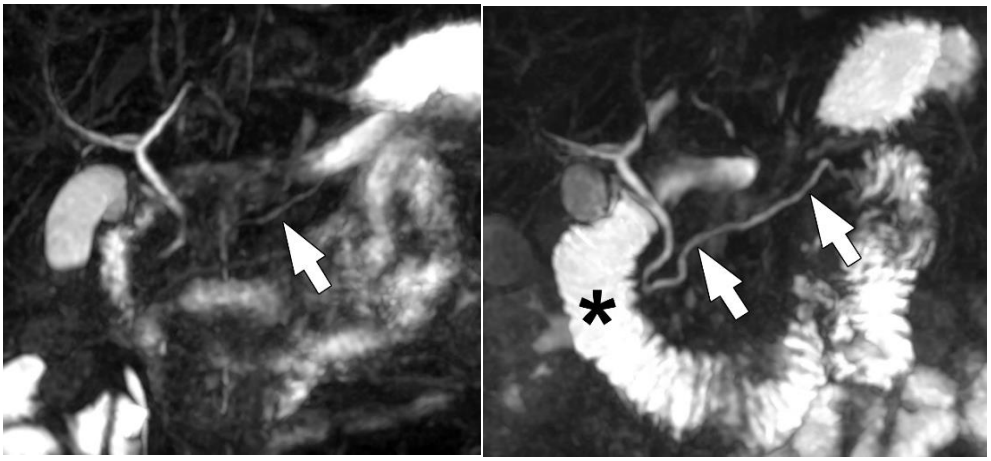
Objective: The diagnostic contribution of secretin to pediatric magnetic resonance cholangiopancreatography (MRCP) is debated. The purpose of this study was to assess whether secretin improves visualization of a non-dilated pancreatic duct and whether it increases identification of variant duct anatomy.

Materials and Methods: Retrospective review of MRCP images obtained in 50 volunteers aged 6-15 years without history of pancreatic disease. Pre- and post-secretin images (coronal 3D FSE MRCP, coronal SSFSE fat-saturated sequences) were separated for review by three radiologists (R1, R2, R3) who were blinded to the purpose of the study and to secretin administration. Reviewers ranked subjective image quality (Likert 1-5) and reported pancreaticobiliary duct anatomy and duct visibility (yes/no).
Paired t-tests were used for comparison of means, and chi-square or Fisher exact test were used for comparison of frequencies. Sensitivity and specificity of pre-secretin images was judged against post-secretin images as the reference standard.

Results: The frequency of image quality scores ≥4 assigned to 3D MRCP images was significantly greater post-secretin for R2 ($p<0.0001$) and R3 ($p=0.005$) and approached significance for R1 ($p=0.052$). Mean number of visible pancreatic duct segments (head, body, tail) was significantly greater on the post-secretin images for all reviewers (R1:1.9 vs. 1.3, R2:1.9 vs. 1.2, R3:1.4 vs. 0.8; all $p<0.01$).
For all three reviewers, pre-secretin image sensitivity was poor for variant pancreatic ductal anatomy (R1: 37.5%, R2: 50%, R3: 40%).

Conclusions: Secretin improves subjective MRCP image quality, visualization of the pancreatic duct, and provides greater sensitivity for anatomic variants such as pancreas divisum in children with non-dilated pancreatic ducts.

Figure 1 – Oblique coronal 3D MRCP maximum intensity projection (MIP) images before (a) and after (b) secretin. Image (a) depicts a non-dilated, barely conspicuous pancreatic duct (arrow) while the post-secretin image (b) shows increased conspicuity of the entire pancreatic duct (arrows). Each of the three reviewers reported no visibility of any segment of the pancreatic duct before secretin (a) and visibility of all 3 pancreatic duct segments after secretin (b). Note also duodenal filling with fluid on the post secretin image consistent with a normal exocrine response (asterisk).



a. b.

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Drug-Induced Pancreatitis (DIP) in a Pediatric Patient Following Acetaminophen Overdose

Oriana G Vanegas Calderon, Chinenye R Dike, Warren Bishop, Aliye Uc

Introduction: Drug-induced pancreatitis (DIP) remains a poorly defined cause of acute pancreatitis (AP). Although acetaminophen is a commonly used over-the-counter medication and a moderate risk for DIP, it is not known whether a true association exists between acetaminophen and pancreatitis. Most acetaminophen-induced AP cases have been described in adults and along with multi-organ failure. Recording latency (time frame between the initiation of medication to the onset of AP) and ruling out other causes are important concepts in developing a classification system for pediatric DIP. Here we report an adolescent with a well-described latency who developed AP during the recovery period of acetaminophen overdose.

Case report: A 16-year-old female was admitted following a large intentional acetaminophen overdose (~1 g/kg). Immediately after ingestion, she developed severe periumbilical abdominal pain and vomiting, followed by bilious emesis and hematemesis. She presented to the local hospital emergency department 14 hours post-ingestion with an initial acetaminophen level of 152µg/ml. She was started promptly on intravenous N-acetyl cysteine and transferred to our hospital. On admission, transaminases were mildly elevated and peaked on post-ingestion day (PID) 3. Her PT and INR were elevated and corrected after 3 doses of IV vitamin K. Acetaminophen level was undetectable on PID 3. On PID 4 she developed epigastric pain and tenderness with anorexia. Transaminases were improving but serum amylase and lipase were elevated (Table 1). Abdominal ultrasound showed a normal pancreas, gallbladder and biliary tract. Her serum calcium and glucose were normal. She was treated with IV fluids; her pain was controlled with morphine as needed. Abdominal pain resolved in 2 days and she quickly was advanced to full general diet.

Table 1. Laboratory values and pain scale

Lab values /Pain scale	PID1	PID2	PID3	PID4	PID5	PID6	PID7
Acetaminophen (□g/mL)	152	4.6	<1.2	-	-	-	-
AST (Ref. range: 10-35 U/L)	51	228	5434	2800	-	281	66
ALT (Ref. range: 5-20 U/L)	79	277	6846	5428	3429	2351	1352
Amylase (Ref. range: 0-100 U/L)	-	-	-	172	114	105	-
Lipase (Ref. range: 13-60 U/L)	23	-	-	210	155	159	-
Abdominal pain (0-10)	2	2	5	8	2	0	0

Summary and Conclusion: Here we report an acetaminophen-induced acute pancreatitis in an adolescent four days after ingestion, during the recovery phase of her overdose. Clinicians should consider acute pancreatitis if a child with acetaminophen toxicity develops

abdominal pain, nausea and/or vomiting after initial recovery. This case also highlights the importance of clinical history including recording the latency period and ruling out other causes of acute pancreatitis to better understand the true prevalence of drug-induced pancreatitis.

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Changes in Inflammatory Cytokine Levels in the Acute and Subacute Phases of Islet Engraftment After Total Pancreatectomy and Islet Autotransplantation (TPIAT).

KR McEachron, GJ Beilman, S Chinnakotla, TL Pruett, TB Dunn, V Kirchner, MD Bellin
CAPER Scholarship Recipient- University of Minnesota
Oral Presentation, Session VIII-C
University of Minnesota Medical School, Department of Surgery

Background: Total pancreatectomy with islet autotransplantation (TPIAT) offers the potential for improved quality of life and reduced opioid dependence for patients with painful chronic pancreatitis. However, only 30-40% eventually wean completely off insulin (1, 2), with the islet mass transplanted (IEQ) as the strongest predictor of insulin independence (2-4). The islet infusion procedure is complicated by inflammatory insults which limit islet survival and future function (5-8); the inflammatory cytokines TNF and Interferon-γ-induced protein 10 (IP-10/CXCL10) are proposed to be directly damaging to islets (9-11) and have negative effects on transplant outcomes (12). Inflammatory cytokines in this setting represent a potential target for clinical intervention. We sought to characterize the cytokine response profiles of TPIAT patients during the acute transplantation and engraftment phases.

Methods:Plasma levels of six known inflammatory cytokines (IL-6, IL-8, IP-10, MCP-1, TNF, and IL-) were collected in a pilot cohort of 25 patients undergoing TPIAT at these timepoints: prior to surgery, after pancreatectomy but before islet infusion, then 15 min, 30 min, 60 min, 3 hours, 6 hours, 12 hours, 24 hours, 3 days, 5 days, 7 days, 14 days, 21 days, 30 days, and 90 days post-infusion of islets. Area under the curve (AUC) for cytokine exposure was calculated using the trapezoidal method including the baseline pre-islet infusion level. Cytokine status at 90 days was classified as returned to baseline or elevated. Diabetes outcomes and islet graft function were assessed at day 90 by: insulin dose, mixed-meal tolerance testing (MMTT), intravenous glucose tolerance testing (IVGTT), and glucose-potentiated arginine stimulating testing (AST). Multiple linear regression was used to measure and test associations between predictors and the potentiated acute insulin response to glucose (AIRpot). Total IEQ transplanted was also converted into a categorical variable (<299,999 IEQ = low (n=9), 300,000-399,999 = medium (n=8), >400,000 = high (n=8)) and ANOVA was used to compare the cytokine trends between these categorical groups.

Results: After infusion of islets during TPIAT, mean IP-10 levels increased to greater than twice-baseline immediately following islet infusion (15- and 30-minute timepoints), then returned to baseline by 3 hours post-infusion, followed by a slow but lesser trend upward through 90 days post-transplant (Figure 1a). On average, elevations in TNF levels were seen later, not exceeding baseline levels until 5-7 days post-transplant, and only exceeding baseline levels by 1.3 times (Figure 1b). Notably, most patients had elevations also observed in MCP-1, IL-8, and IL-6. When adjusted for transplanted IEQ, neither the AUC IP-10 nor AUC TNFwere associated with the acute insulin response to glucose potentiation (AIRpot) at 90 days post-transplant, or the insulin dose at 90 days ($p>0.1$ for all models). Those with persistently elevated cytokine levels at day 90 did not show differences in metabolic outcomes ($p>0.05$). There was no significant difference in the total AUC of either cytokine between the categorical groups of IEQ transplanted (low, medium, or high; all $p>0.5$).

Conclusions: There is a general increase in inflammatory cytokine levels following islet autotransplant, with some patients having persistently high inflammatory markers, as long as 90 days post-transplant. The latter is unlikely a consequence of the infusion, but rather may represent a pro-inflammatory milieu maintained by ongoing illness, infection, or other stressors in this population. IP-10 rose more quickly and to a greater magnitude than TNF following islet infusion, suggesting IP-10 might be considered as a potential therapeutic target. However, in this small cohort, we did not observe any association of cytokine levels with islet mass infused or the diabetes outcomes at 3 months. Given the multiple patient and islet graft variables that can impact diabetes outcomes, our cohort may have been too small to detect these associations.

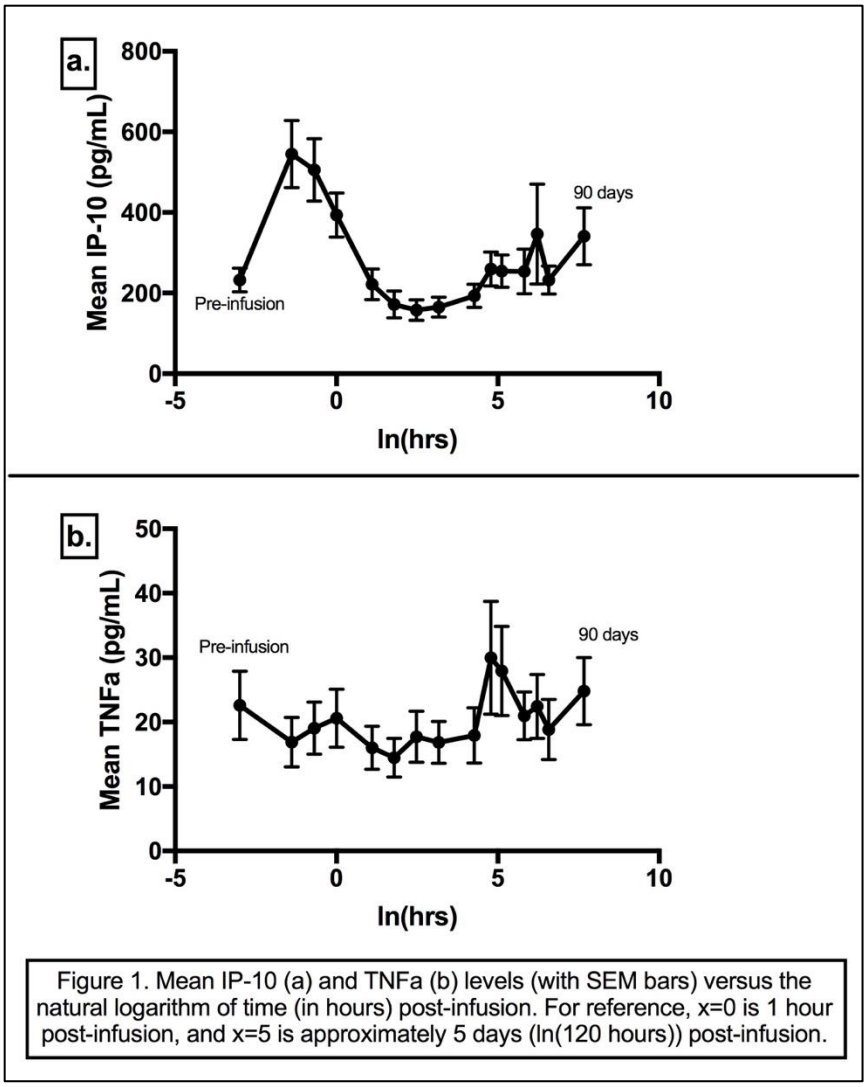

Figure 1. Mean IP-10 (a) and TNFa (b) levels (with SEM bars) versus the natural logarithm of time (in hours) post-infusion. For reference, x=0 is 1 hour post-infusion, and x=5 is approximately 5 days (ln(120 hours)) post-infusion.

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Measures of Fecal Fat Absorption with Current Methods in a Healthy Population

H. Bashaw, J. N. Brownell, J. I. Schall, V. A. Stallings

CAPER Scholarship Recipient- Children's Hospital of Philadelphia

Children's Hospital of Philadelphia, Roberts Center for Pediatric Research, Philadelphia, United States

Background and Objectives: Fecal measures of nutrient malabsorption are a cornerstone of nutritional studies and coefficient of fat absorption (CFA) is considered a gold standard. The reference value for CFA was established in the mid-1900s using gravimetric methods with subjects on high-fat test diets (100-200 g fat/d). Currently, CFA is determined by nuclear magnetic resonance (NMR) spectroscopy and subject test diets often contain only moderate amounts of fat (<100 g/d). Reference values for CFA have not been confirmed using NMR spectroscopy analysis in a healthy population consuming a moderate fat test diet. The aim of this study was to determine the range and distribution of CFA in a healthy population eating a moderate fat test diet using current analysis techniques.

Materials and Methods: The present study is a secondary analysis of a healthy control group of participants in a cohort study comparing fat absorption in healthy subjects to fat absorption in subjects with chronic pancreatitis. All subjects were instructed to eat a moderate fat diet (minimum 80 g fat/day). Participants recorded prospective, weighed dietary intake and collected stool for the 72-hour study period. Dietary records were analyzed for average dietary fat intake (fat g/d). Stool samples were analyzed by NMR spectroscopy (Mayo Medical Laboratories, Rochester, MN) to measure average fat content (fat g/d). CFA was calculated for each subject ([dietary fat - stool fat]/dietary fat x100) and results were compared to the historical reference value of ≥93% determined on higher fat diets with the original gravimetric methods.

Results: 19 subjects (age 30-61 years, mean 41.6±9.6; 37% male, 58% Caucasian) fulfilled criteria for secondary analysis (>18y old, generally healthy, no medications that interfere with gastrointestinal transit). Subjects consumed a median of 98 g fat/d (range 45-196 g fat/d) and median stool fat output was 4.0 g/d (range 1-11 g/d). Median CFA for the group was 96.5% (range 91.9 to 98.7%). Of note, one subject had a CFA of 91.9%, below the reference value of 93% for normal absorption established by previous methods.

Conclusion: Our findings confirmed that the historical reference value for CFA is acceptable for new analytical methods in a contemporary subject sample consuming a moderate fat test diet. Seventy-two hour stool collections and weighed dietary records, however, remain cumbersome and challenging. Work to develop less burdensome testing for macronutrient malabsorption must continue.

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The Impact of Faculty Ratio and Region on Advanced Endoscopy Fellow EUS and ERCP Procedure Participation

Mishel Malik[1], **Chris Moreau BS[2]**, Ailene Alcaraz[2], Hari Sayana MD[2], Sandeep Patel DO[2], Laura Rosenkranz MD[2]
[1]Johns Hopkins University, [2]UT Health San Antonio

Introduction: Advanced Endoscopy fellows consider procedure volume to be an important factor when choosing their match, but there are differences in hands-on involvement across the United States. Student to teacher ratio is known to impact student involvement at all educational levels, and regional differences may also play a role. These factors are recorded in self-reported data from advanced endoscopy training programs, but their impact on fellow procedural involvement have not been thoroughly analyzed in literature.

Methods: Data was collected from self-submitted annual reports of Advanced Endoscopy programs provided to the American Society for Gastrointestinal Endoscopy Training Committee. For regional analysis, program data was grouped based on U.S. Census Bureau major region assignments. For faculty ratio analysis, program data was placed into 5 groups based on both the ratio and group size. Half values were rounded up to the nearest whole, and ratios above 5 were grouped together. Mann-Whitney U test was used to compare groups for two-tailed hypothesis testing with a significance level of 0.05.

Results: A total of 65 training programs were analyzed. Regional distribution of programs was: Northeast-35.4% (n=23), South-29.2% (n=19), Midwest-23.1% (n=15), and West-12.3% (n=8). The average percentage of fellow participation for all centers was 60.6% for ERCP and 58.0% for EUS. The average fellow participation by region for ERCP was: Northeast-67.7%, South-63.3%, Midwest-56.8%, and West-41.1%. There was a statistically significant difference in participation between the West and both the Northeast (p=0.010) and South (p=0.028). The average fellow participation for EUS was: Northeast-61.7%, South-58.0% (n=19), Midwest-54.1%, and West-55.1%. There was no statistical difference in fellow participation in EUS between regions. The average faculty to fellow ratio for all centers was 4.20 for ERCP and 3.94 for EUS. Participation percentages were compared based on Faculty to Fellow ratio groups of: 2 or less, 2.5 to 3, 3.5 to 4, 5, and 6 or more. In the ERCP group, facilities with 2 or less faculty per fellow had significantly higher (p=0.00044) fellow participation than facilities with 6 or more faculty per fellow. In the EUS group, facilities with 2 or less faculty had higher participation (p=0.076) than facilities with 6 or more faculty per fellow. When one facility with both high participation and high faculty to fellow ratio was excluded, the difference was significant (p=0.01). The middle groups were not statistically different in ERCP.

Conclusion: Though fellow involvement in EUS and ERCP procedures is similar on average, programs with the highest number of teaching faculty had significantly less fellow ERCP involvement than those with the least. Programs in the West tended to have much lower fellow ERCP involvement than the other regions. Fellow EUS involvement was not significantly different across the regions but was slightly higher in programs with less faculty. More detailed information is needed to determine the impact of involvement on post-graduate fellow performance.

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Genetics of INSPPIRE Subjects

Mark E. Lowe MD, PhD

The International Study Group of Pediatric Pancreatitis: In search for a cure (INSPPIRE) has collected 2 databases of well phenotyped patients with acute recurrent pancreatitis (ARP) and chronic pancreatitis (CP) for INSPPIRE-1 and INSPIRRE-2. The data includes information on the analysis of genetic risk variants for ARP and CP done as part of the subjects' clinical evaluation. For INSPPIRE-1, clinical genetic data is available for 346 patients for variants of *PRSS1*, *CFTR*, *CTRC* and *SPINK1* although not all patients had every gene tested. The genetic data was collected to determine the proportion of children who have genetic risk factors contributing to the

pathogenesis of their disease. Just under 70% of children harbor one or more known genetic risk factors. In comparison, only 20% of adults have genetic risk variants. Of the subjects who were tested, variants were found in *PRSS1* (30%), *CFTR* (31%), *SPINK1* (20%) and *CTRC* (7%). 10% of patients with ARP and 15% of patients with CP had 2 or more genetic risk factors. Patients with CP were more likely to have *PRSS1* and *SPINK1* variants. Children who presented before 6 y of age were more likely to have variants of *PRSS1* or *CTRC*. Variants of *CFTR* and *SPINK1* were evenly spread across all pediatric age groups. Children progressed from ARP to CP in a median of 3.8 years. Patients with *PRSS1* variants progressed to CP faster than patients who did not have PRSS1 variants. None of the genetic variants interacted with pancreas divisum to increase risk for ARP or CP. Patients with PRSS1 variants were less likely to have PD. More extensive genetic analysis by targeted next generation sequencing of 155 subjects confirmed that the main genetic variants are found in *PRSS1*, *CFTR*, *CTRC* and *SPINK1*. About 2% had variants in *CASR* or *CPA1*. No known pathological variants were found for *CEL*, *CLDN2* or *PRSS2*. 15% of the subjects had risk variants in 2 or more genes. Only 7% had no genetic risk factors. The INSPPIRE-2 database now has 389 subjects with clinical genetic data on 286. The distribution of genetic variants is similar to that reported for INSPPIRE-1. In conclusion, genetic risk variants are major contributors to the pathogenesis of ARP and CP in pediatrics. Larger numbers and additional analysis will be necessary to determine if certain genetic risk variants tend to occur together and to define the impact variants have on the natural history of ARP and CP.

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A National Survey on the Management of Acute Necrotizing Pancreatitis in China

Xiaowu Dong, Wenjian Mao, Zhihui Tong, Weiqin Li, **Lu Ke**
Center of Severe Acute Pancreatitis (CSAP), Jinling Hospital, Medical School of Nanjing University, Nanjing, China

Background: The optimal treatment strategy of acute necrotizing pancreatitis (ANP) is a controversial issue and it remains unclear which strategies the Chinese doctors are using. Therefore, we performed a national survey amongst a group of Chinese doctors from different departments and hospitals to assess current clinical practice in China.

Methods: An online questionnaire consisting of 12 choice questions designed to evaluate the diagnosis and treatment strategy during different phases of ANP was sent to 394 doctors through a national collaborative network focusing on the management of acute pancreatitis.

Results: The response rate was 81% (n = 321) covering 30 regions across the country. The survey results revealed that a step-up approach has been widely adopted in patients with infected pancreatic necrosis (IPN) in China (91%). For the timing of initial intervention, when IPN cannot be confirmed or suspected, most respondents (71%) chose to determine whether to intervene according to clinical conditions. A lack of consensus can be clearly seen in terms of early diagnosis of IPN as the respondents chose to judge this depending on clinical symptoms (22%), organ failure (26%), imaging changes (26%), and results from fine needle aspiration (16%), respectively. On suspicion or diagnosis of IPN, the Chinese doctors preferred a relatively early (approximately less than 4 weeks) and aggressive strategy like intervention even before capsulation of the acute necrotic collection (ANC) as 50% of the respondents chose immediate drainage rather than wait-and-see, which would increase to 78% after the development of walled-off infected necrosis.

Conclusion: The step-up approach is the preferred treatment strategy in IPN patients who needed intervention amongst Chinese doctors. There is a great diversity regarding the diagnosis of IPN and optimal timing of initial intervention for ANC.

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Goal Directed Fluid Therapy in Spontaneously Breathing Patients with Predicted Severe and Moderately Severe Acute Pancreatitis: A Prospective Pilot Study of Passive Leg Raising Test

T. Jin,[1] L. Li,[1] L. Deng,[1] Z. Lin,[1] K. Jiang,[1] C. Hu,[1] X. Zhang,[1] N. Shi,1 Q. Tan,[1] C. Cheng,[1] R. Zhang,[1] X. Zhou[1], W. Yu,[1] P. Zhu,[1] T. Liu,[1] A.R. Philips,[2] G. Jia,[1] X. Yang,[1] R. Sutton,[3] J.A. Windsor,[4] **W Huang**,[1] Q Xia.[1]
[1]Department of Integrated Traditional Chinese Medicine and Western Medicine, Sichuan Provincial Pancreatitis Center and West China-Liverpool Biomedical Research Centre, West China Hospital, Sichuan University, Chengdu, China; [2]Applied Surgery and Metabolism Laboratory, School of Biological Sciences, University of Auckland, Auckland, New Zealand; [3]Liverpool Pancreatitis Research Group, Royal Liverpool University Hospital and Institute of Translational Medicine, University of Liverpool, Liverpool, United Kingdom; [4]Surgical and Translational Research Centre, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand.

Background: Fluid therapy (FT) is key to early management of acute pancreatitis (AP), but there is no agreement on how to determine if volume expansion (VE) is required. This study aimed to investigate predicting response to VE (RVE) by passive leg raising test (PLRT) and change in stroke volume (△SV).

Methods: Patients with predicted severe or moderately severe AP were recruited <72 hours of pain onset and assessed at 0, 4, 8, 12, 18-20, 24 hours by objective clinical assessment (OCA; heart rate, hematocrit, urine output and mean arterial pressure), standardized PLRT (at 30, 60 and 120 seconds) and PLRT/ΔSV (blinded to OCA) using arterial line (Edwards EV1000A™, Irvine). If OCA <2, no VE given and FT rate was 1-3 ml/kg/h. If OCA ≥2, VE was given (250 ml normal saline over 10 min). The RVE determined the FT rate: responders (ΔSV >10%, 5-10 ml/kg/h) and non-responders (ΔSV ≤10%, 1-3 ml/kg/h). Clinical outcomes recorded. The prediction of RVE by OCA and PLRT/ΔSV were compared using Receiver Operating Characteristic analysis.

Results: Sixty-two patients (41 severe, 18 moderately severe) were recruited with median 31 hours from symptom onset. Overall median length of hospital stay was 13 days (IQR 9-21), 12 admitted to ICU, 4 had necrosectomy, and 4 died. Responders received significantly more fluid between different intervals up to 12 hours than non-responders, but there was no difference in clinical outcome. Compared with OCA, PLRT/ΔSV at 60s and 120s was better at predicting RVE at 0 and 4 hours, and was the best at 8 hours [AUC for OCA 0.563 vs. 0.773 (ΔSV-60s) vs. 0.835 (ΔSV-120s) and equivalent at 12 hours.

Conclusion: This prospective blinded goal directed FT study is the first to evaluate PLRT in spontaneously breathing patients with AP and demonstrated it was superior to OCA in predicting RVE.

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Effectiveness and Safety of Prophylactic Anticoagulation for Preventing Splanchnic Thrombosis in Patients with Acute Necrotizing Pancreatitis

Jing Zhou, Wenjian Mao, Lu Ke, Zhihui Tong, Gang Li, Bo Ye, **Weiqin Li**
Center of Severe Acute Pancreatitis (CSAP), Jinling Hospital, Medical School of Nanjing University, Nanjing, China

Background: Splanchnic venous thrombosis (SVT) is a covert but clinically relevant complication in patients with acute necrotizing pancreatitis (ANP). SVT often involves portal vein (PV), splenic vein (SplV) and superior mesenteric vein (SMV) either separately or in combination. So far, there are no studies appraising the effect of prophylactic anticoagulation on preventing development of SVT.

Methods: Patients with ANP admitted to our Intensive Care Unit (ICU) within 7 days from onset of abdominal pain between January 2013 and December 2018 were retrospectively analyzed. Baseline parameters and clinical outcomes were compared between patients who received conventional therapy (no or occasional anticoagulant administration) and those who received prophylactic anticoagulation (mostly low-molecular-weight heparin twice a day) during their ICU stay. The primary outcome measure was incidence of SVT and its subtypes.

Results: Of the 273 patients (median age 46 years) included, 84 (31%) developed SVT during index hospital stay or the first month of follow-up. SplV was the most commonly affected site, accounting for 60% (84/273) of SplVT, follow by 9% (24/273) SMV and 5% (14/273) PV. There were 92 patients managed conventionally and 181 patients received prophylactic anticoagulation, respectively. Compared with convention therapy group, patients received prophylactic anticoagulation experienced significantly lower incidence of SVT (22% [40/181] versus 48% [44/92], $P < 0.01$) that was most attributed by isolated SplV thrombosis (12% [22/181] versus 30% [28/92], $P < 0.001$). There were no significant differences in the rate of bleeding events, multiple organ dysfunction syndrome, mortality, duration of ICU stay and length of index hospital stay.

Conclusions: Prophylactic anticoagulation appears to reduce the incidence of SVT without increasing the risk of bleeding. Randomized clinical trials are warranted to confirm our preliminary findings.

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Rectally Administered Indomethacin to Prevent Post-ESWL Pancreatitis (RIPEP): The Analysis of 700 Patients

Yang-Yang Qian[1,2], Nan Ru[1], Hui Chen[1], Wen-Bin Zou[1,2], Hao Wu[1,2], Lei Xin[1] , Ji-Yao Guo[1], Xin-Ying Tang[1] , Bo Li[3], Liang-Hao Hu[1] , Zhao-Shen Li[1,2] and Zhuan Liao[1,2]
[1] Department of Gastroenterology, Digestive Endoscopy Center, Changhai Hospital, the Second Military Medical University, Shanghai, China; [2] Shanghai Institute of Pancreatic Diseases, Shanghai, China; [3] Department of Anesthesiology, Changhai Hospital, the Second Military Medical University, Shanghai, China

Background: Pancreatic extracorporeal shock wave lithotripsy (P-ESWL) is the first-line therapy for large pancreatic duct stones. Although highly effective and safe for the fragmentation of pancreatic stones, it is not complication-free. Similar to endoscopic retrograde cholangiopancreatography (ERCP), pancreatitis is the most common complication. To date, nonsteroidal anti-inflammatory drugs (NSAIDs) have been proven to be the only effective prophylactic medication for post-ERCP pancreatitis. Given the little research about effective prevention for post P-ESWL pancreatitis, we aim to determine whether rectally administered indomethacin can reduce post-ESWL pancreatitis.

Methods/design: The RIPEP study is a prospective, randomized, double-blinded, placebo controlled trial. Patients with chronic pancreatitis (CP) and pancreatic stones (>5 mm in diameter) treated with P-ESWL at Changhai Hospital will be randomly allocated to rectally administer indomethacin or glycerin suppository 30 min before the procedure. The primary endpoint is the incidence of post-ESWL pancreatitis. Secondary endpoints include the severity of pancreatitis, occurrence rate of asymptomatic hyperamylasemia, other complications and subgroup analysis.

Results: Seven hundred patients diagnosed with CP scheduled to undergo ESWL is prospectively enrolled in the study after eligibility screening from May 1st 2011 to December 15th 2017. According to the random number table, 354 patients are allocated to the control group and 346 patients to the experimental group. As for the demographic and clinical characteristics, there exist no significant differences. The incidence of post-ESWL pancreatitis ranks the first among post-ESWL complications and rectally administered indomethacin can greatly reduce the incidence (12.4 vs. 7.5%, P=0.030, RR 1.70, 95%CI 1.02-2.84). However, the prophylaxis does not exert its effect on improving the severity of post-ESWL pancreatitis (P>0.05). The incidence of the other complications including bleeding, steinstrasse, infection and perforation are similar between the two groups. Asymptomatic hyperamylasemia is the most common among adverse events with an incidence of 27.4% in the control group and 27.7% in the experimental group, followed by hematuria. Also, no significant difference of the incidence of adverse events exists (P>0.01). The risk factors of post-ESWL pancreatitis include female (P=0.011) and pancreas divisum (P=0.014), while patients with diabetes (P=0.021), steatorrhea (P=0.007) display a greatly lower incidence (P=0.028), and the incidence decreased significantly with disease progression (P=0.020).

Conclusion: The RIPEP trial is the largest and first prospective study to show that rectally administered indomethacin is safe and effective in reducing the development of post-ESWL pancreatitis. The prophylaxis can especially benefit female patients with pancreas divisum and intact pancreatic function.
Trial registration: ClinicalTrials.gov, ID: NCT02797067, registered on 17 November 2016.

KEYWORDS: Chronic pancreatitis, ERCP/ESWL, Complications, Indomethacin, Risk factor, Prophylaxis

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Single-Cell Transcriptome Profiling of the Pancreas in Caerulein-Induced Chronic Pancreatitis Mouse

Xiao-Tong Mao[1], Wen-Bin Zou[1,2], Shun-Jiang Deng[1,2], Xin-Ying Tang[1], Yue Wang[3], Zhao-Shen Li1,[2] and Zhuan Liao[1,2]
[1] Department of Gastroenterology, Digestive Endoscopy Center, Changhai Hospital, the Second Military Medical University, Shanghai, China; [2] Shanghai Institute of Pancreatic Diseases, Shanghai, China; [3] Research Center of Developmental Biology, the Second Military Medical University, 800th Xiangyin Road, Shanghai 200433, China

Background: Single-cell RNA sequencing is a promising method to identify gene expression changes at single-cell resolution. A single-cell transcriptomic map of the normal human and mouse pancreas has been reported in 2016. Chronic pancreatitis (CP) is a long-standing inflammatory disease of the pancreas. Herein, we firstly investigated the single-cell mRNA profiling of the pancreas in CP mouse.

Methods: CP was induced in one C57/BL mouse by repetitive intra-peritoneal injections of caerulein for 6 weeks, whereas the control mouse received a comparable amount of normal saline. Hematoxylin-eosin staining and Masson's trichrome staining were used to evaluate pancreatic histological injury. Pancreatic tissues were dissociated into single cells. We used the BD Rhapsody system (BD Genomics) to capture transcriptomic information of single cells from the whole pancreas cell suspensions derived from one mouse with CP and one control. Principal component and t-SNE analysis was applied for dimension reduction base on the high variable genes.

Results: Massive collagen deposition, pancreatic atrophy and infiltration of inflammatory cells were observed in CP mice. After stringent quality control filtering, we retained and transcriptionally profiled 3,825 single cells in total (1,645 in CP and 2,180 in control). Visualizing these data using t-SNE revealed 15 transcriptionally unique subtypes (2 clusters of ductal cells, 2 clusters of mesenchymal cells, 3 clusters of endothelial cells, the cluster of acinar cells, the cluster of endocrine cells, and 6 clusters of immune cells). Compared with control group, acinar cells, mesenchymal cells and endothelial cells were significantly reduced and inflammatory cells increased in CP group. Pancreatic cells of the CP and healthy mouse were distinct in the t-SNE map and showed different transcriptional characteristics. In the CP mouse, we identified one sub-population of pancreatic duct cells with over-expression of Mmp-7 indicating the occurrence of acinar-to-ductal metaplasia, and with over-expression of Cldn2 indicating the tight junction between pancreatic duct cells had changed.

Conclusion: This single-cell analysis uncovered different cell-type compositions of the pancreas and transcriptional signatures of pancreatic duct cells in healthy and CP mice.

KEYWORDS: chronic pancreatitis, single-cell analysis, transcriptome, pancreatic duct cells, caerulein

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Enhanced Recovery After Surgery Program Implementation for Pancreatic Surgery in a High-volume Center in China

Nan Lyu, Qiang Li, Feng Guo, Zipeng Lu, Kuirong Jiang, Cuncai Dai, Junli Wu, Wentao Gao, Jishu Wei, Jianmin Chen, **Yi Miao**
The First Affiliated Hospital of Nanjing Medical University, Nanjing, China

Background: There is no widespread application of Enhanced Recovery After Surgery (ERAS) program in pancreatic surgery due to lack of prospective studies to provide evidence. We sought to appraise the role of ERAS in pancreatic surgery in a high-volume pancreas center in China.

Methods: This was a prospective observational study comparing post-operative events of patients undergoing pancreatic surgery received ERAS with those who received conventional management between January 1, 2015 to September 30, 2017 in our unit. The ERAS program was a unique institutional protocol developed according to our current practice, international ERAS guideline and the most updated evidence covering the following key aspects: patient education, pre-operative optimization of major organ functions, early removal of drainage tubes, strict pain-control, early mobilization, early post-operative oral nutrition support, prophylactic anti-coagulation, enhanced glycemic control and near-zero fluid balance. Meanwhile, several measures were taken to improve its implementation, monitor its running, and assess the clinical results. Achievement of management goals, short-term post-operative complications, post-operative length of hospital stay (LOHS) and costs were analyzed.

Results: During the study period, 1081 patients were implemented with ERAS program. The percentage of goal achievements varied from 43% to 100% for different ERAS items, while more than 80% of the ERAS items (14/17) can be accomplished with an acceptable percentage (>60%). When compared with a historical control of conventional postoperative management (n=88), implementation of ERAS resulted in an earlier recovery of oral feeding (1.3 days vs. 5.4 days, $p<0.01$), mobilization (1.5 days vs. 2.5 days, $p<0.01$), nasal-gastric tube removal (3.0 days vs. 5.3 days, $p<0.05$), and urethral catheter removal (2.2 days vs. 3.3 days, $p<0.01$), and were further associated with reduced post-operative LOHS (14.0 days vs. 19.6 days, $p<0.05$) and hospitalization cost (80,000 Chinese yuan vs. 86,000 Chinese yuan, $p<0.05$), compared with conventional care There were no differences in overall morbidity, major complications and morality between the two groups (all $p>0.05$).

Conclusion: ERAS program is safety and feasible in an unselected patient population undergoing pancreatic surgery with significantly enhanced post-operative recovery in our experience. Monitoring of program running and appropriate interventions offers indispensable assistance to ensure implementation efficacy.