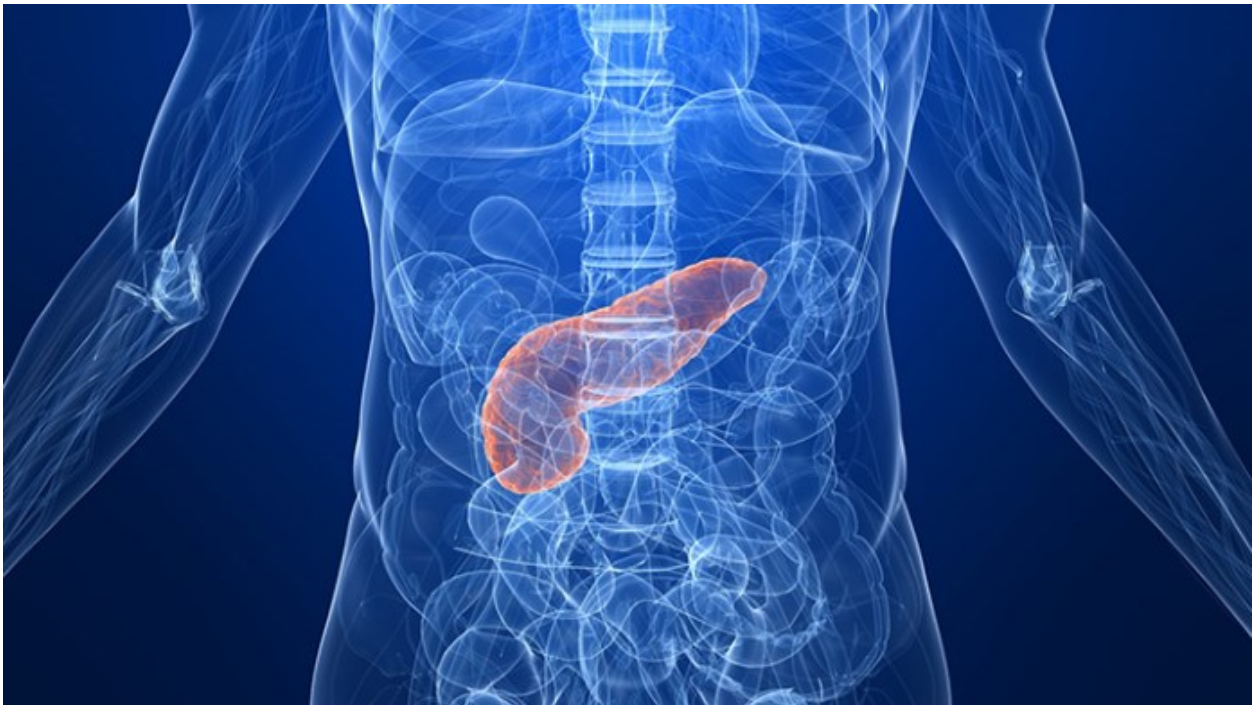
PancreasFest 2016

Abstracts



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#1 Ocular Radiation Threshold Projection Based off of Fluoroscopy Time during ERCP

Garg MS[1], Patel P[1], Blackwood, M[2], Munigala, S[3], Aoun, E[1], Kulkarni, A[1], Dhawan, M[1], Farah, K[1], Thakkar, S[1]
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Presented by **Mrinal Garg, MD** – GI Fellow, Allegheny Health Network - mrinal.garg@ahn.org

Purpose: International Commission on Radiological Protection (ICRP) guidelines suggest a threshold of ocular radiation exposure of 20 millisieverts (mSv) per year averaged over five years not to exceed 50 mSv in any one year. We analyzed the lens exposure during endoscopic retrograde cholangiopancreatography (ERCP) for attending and fellow endoscopists to determine the time of fluoroscopy needed to warrant using lens protection during ERCP.

Methods: Prospective analysis of 197 patients who underwent ERCP from January - July of 2013 at one tertiary care center endoscopy room. The fluoroscopy equipment included a GE OECTM 9800 C-arm with room setup shown in Figure 1. Patient characteristics (age/gender), anterior-posterior diameter (APD) and indications for ERCP were documented. ERCP interventions, procedure characteristics, fluoroscopy time, dose, and attending +/- fellow involvement were recorded to demonstrate the variety of cases and for comparisons to other practices. Radiation exposure was collected by three body Landauer InLight® Whole Body Basic dosimeters (BD) which calculated a projected eye lens exposure and three Landauer nanoDot® dosimeters (LD) placed directly between the eyes to accurately represent true eye exposure. Cumulative radiation doses were obtained from the dosimeters at the completion of the study and averaged over the total fluoroscopy time to determine the mSv/hour exposure.

Results: After initial calibration, 187 cases were included in the study, of which attendings wore lens dosimeters (ALD) in 178 cases and body dosimeters (ABD) in 174 cases. Fellows wore lens dosimeters (FLD) in 126 cases and body dosimeters (FBD) in 128 cases. Patient and procedural characteristics were documented. Attendings wore ALDs throughout 15.89 hours of fluoroscopy and fellows wore FLDs throughout 11.24 hours. The cumulative radiation dose absorbed was 5.35 mSv by the ALDs and 2.55 mSv by the FLDs. The projected lens absorption by the body dosimeters was 19.03 mSv by the ABDs and 5.21 mSv by the FBDs. The body dosimeters overestimated the lens dose by 13.68 mSv for the attendings and 2.66 mSv for the fellows. The hourly fluoroscopy lens exposure was 0.34 mSv/hour for attendings and 0.23 mSv/hour for fellows.

Conclusions: ERCP procedures involve increased radiation exposure to physicians. Current body radiation exposure recommendations such as the use of lead apron shielding do not account for ocular radiation exposure to endoscopists as protective eye wear is optional. This study shows the amount of fluoroscopy hours needed in this model to reach the ICRP suggested lens radiation limit of 20 mSv/year was 59.41 hours for attendings and 88.17 hours for fellows. We recommend the use of radioprotective eye wear by physicians with yearly fluoroscopy times in similarly structured practices that meet or exceed these thresholds.

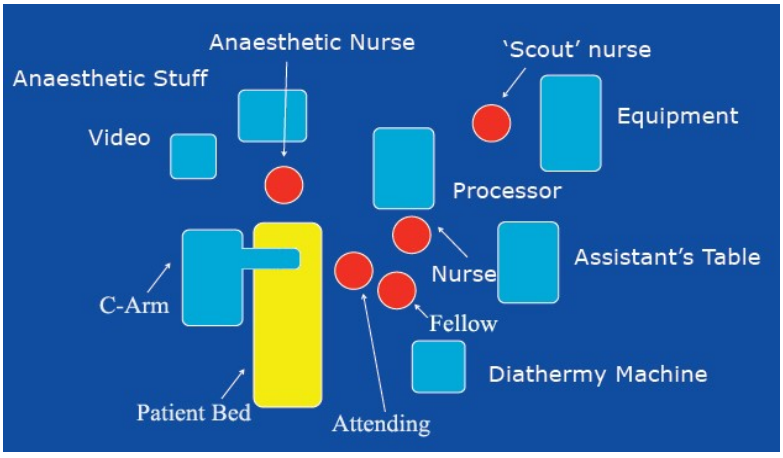

Figure 1: Endoscopy Room Setup

#2 Stellate Cells as Mediators of Immune Suppressive Features in Pancreatic Cancer

McQuinn, CW, Mace TA, Farren MR, Komar H, Kitano M, Yu L, Bloomston M, Zhong X, Zimmers T, Bekaii-Saab T, Lesinski GB.

Presented by **Christopher W. McQuinn, MD -** Post-Doctoral Research Fellow, Lesinski Laboratory **-** Ohio State University Wexner Medical Center - Christopher.mcquinn@osumc.edu

One hallmark of pancreatic ductal adenocarcinoma (PDAC) is the dense stroma that includes activated myofibroblast-like cells termed 'pancreatic stellate cells' (PSC). We hypothesized that antitumor immunity is restrained by PSC, and that key pathways can be identified to augment efficacy of immunotherapy. To gain insight into the most relevant soluble factors and pathways, primary PSC (n=10) were isolated from PDAC patients. A normal human pancreatic fibroblast (HPF) cell line was used as a control. RNA obtained from PSC or HPF underwent nanostring analysis using the nCounter PanCancer Immune Profiling panel. Cytokine and chemokine expression in supernatants was measured via bioplex analysis or ELISA. Unsupervised clustering analysis revealed the greatest fold change in IL-6 transcript between PSC and HPF, versus other cytokines in the panel. Abundant IL-6 expression was validated in supernatants by bioplex analysis, and was accompanied by other cytokines, most notably, MCP-1, VEGF and SDF-1. Supernatants from human PSC also expanded suppressive myeloid cells from bulk, human peripheral blood mononuclear cells. Analysis of a separate cohort of human pancreatic tumors (n=12) via immunohistochemistry further revealed abundant IL-6 protein in stromal regions of tumors. This prominent stromal localization of IL-6, and STAT3 phosphorylation STAT3 was also evident in pancreata from mice with mutant Kras-driven, PDAC. These data point to stromal IL-6 as a target in PDAC, and complement our data confirming plasma IL 6 as a poor prognostic factor in a large cohort (n=73) of treatment naïve PDAC patients. Ongoing studies are exploring the role of IL-6 in PSC and the effect of targeting this cytokine in combination with immunotherapy.

#3 Role of Lipocalin-2 in Obesity-Induced Pancreatic Ductal Adenocarcinoma

Cruz-Monserrate Z.

Presented by **Zobeida Cruz-Monserrate, PhD -** Assistant Professor **-** Ohio State University Wexner Medical Center – zobeida.cruz-monserrate@osumc.edu

CAPER SCHOLARSHIP

Background: Lipocalin-2 (LCN2) is a molecule known to have a pro-tumorigenic role in many cancer types and is significantly upregulated in patients with pancreatic ductal adenocarcinoma (PDAC) and in obese individuals. Obesity is a risk factor for PDAC and is associated with poor survival. We investigated whether Lcn2 depletion affected obesity-induced PDAC development and mouse survival as well as its role in the tumor microenvironment. Methods: We studied mice with acinar cell-specific expression of KRasG12D (KRasG12D/CRE) or crossed with Lcn2 knockout (Lcn2-/-) animals (Lcn2-/-/KRasG12D/CRE). Animals were fed isocaloric diets with varying amounts of saturated fat content. Moreover, the role of Lcn2 in tumor growth was tested in a syngeneic orthotopic PDAC mouse model. The pancreas of these animals were collected and analyzed for inflammation, pancreatic intraepithelial neoplasia (PanIN) and PDAC. Tumor growth in syngeneic model was measure via IVIS imaging. In addition, we studied the role of LCN2 and its specific receptor solute carrier family 22, member 17 (SLC22A17) in pancreatic stellate cells. Results: In this study, depletion of Lcn2 diminished extracellular matrix deposition, immune cell infiltration, PanIN formation, tumor growth and significantly increased survival in both an obesity-driven PDAC genetic mouse model and in a syngeneic orthotopic PDAC mouse model. In addition, we found that LCN2 modulated the secretion of pro-inflammatory cytokines in human pancreatic stellate cells, key regulators of the PDAC tumor microenvironment, via the LCN2-specific receptor, SLC22A17. Conclusions: Our results reveal a previously unknown role of LCN2 in the establishment and regulation of the PDAC tumor microenvironment, suggesting a link between LCN2, obesity, inflammation and PDAC.

#4 A Novel Pre-clinical Model for Pancreas Cancer Reveals Panitumubab Sensitivity in *KRAS* Wild-type Tumours

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Presented by **Daniel Croagh, MD -** Dept. of Surgery, Monash Health, Melbourne State, Victoria, Australia - Daniel.croagh@monashhealth.org

Background: Pancreas cancer (PC) is largely refractory to medical therapies used in unselected patients as such, personalised medicine is growing area of interest. *KRAS* wild-type tumours present as an interesting subtype of PC that can potentially be treated with Panitumumab (an epidermal growth factor receptor (EGFR) monoclonal antibody). Patient-derived xenograft (PDX) is a model well suited to testing targeted therapy as they capture the individual molecular profile of each patient's disease and maintain tumour histological architecture. To date, PDX models have used surgical resection specimens, however, in PC this excludes 80% of patients who are ineligible for surgery. By contrast fine-needle aspirate (FNA) is a biopsy offered to nearly all PC patients. Here we present a PDX using FNA samples and demonstrate treatment efficacy in *KRAS* wild-type tumours.

Aims: To establish a PDX using FNA-derived tissue and trial personalised therapy specific for *KRAS* wild-type tumours.

Methods: FNAs from PC were obtained for genetic testing (DNA for *KRAS* and RNA for RNAseq). RNAseq data was used to compare *KRAS* wild-type versus *KRAS* mutant tumours. These results were validated against The Cancer Genome Atlas which has 178 PC samples with *KRAS* mutation status and RNAseq data. FNAs were also grafted into NOD/SCID mice, a cohort of 16 mice was prepared for treatment. Four treatments were trialed for a period of 28 days: Saline, Gemcitabine, Panitumumab or Combination therapy (Gemcitabine & Panitumumab).

Results: Transcriptome profiling of *KRAS* wild-type and mutant tumours from TCGA and Monash cohorts revealed 1995 differentially expressed genes. In addition, the mutant samples show significant enrichment for *KRAS* dependency gene signature. Two FNAs were grafted using FNA samples from one *KRAS* wild-type and one with oncogenic *KRAS* mutation. The PDX with *KRAS* wild-type tumour demonstrates a significant reduction in tumour growth with Panitumumab or combination therapies compared to treatment with saline, or gemcitabine monotherapy. In addition, the PDX with *KRAS* mutant tumour showed a response to gemcitabine and combination therapy compared to saline or panitumumab treatments.

Conclusions: This study develops and validates a new PDX model for identifying and testing the treatment of novel cancer targets. This study characterises the effect of *KRAS* mutation on gene expression, the pathway enrichment analysis indicate that *KRAS* mutant tumours are driven by oncogenic *KRAS* and will be resistant to ant-EGFR therapy, which suggests this treatment strategy may be successful in *KRAS* wild-type. We show that *KRAS* wild-type tumours are responsive to Panitumumab, providing substantial evidence to support the use of Panitubumab in selected patients in the setting of a clinical trial for precision medicine.

#5 Resolution of Inflammatory Response in Endoscopic Versus Percutaneous Drainage of Necrotic Collections in Necrotising Pancreatitis

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Presented by **Daniel Croagh, MD -** Dept. of Surgery, Monash Health, Melbourne State, Victoria, Australia for **Shanan Woo, MD** Dept. of Surgery, Monash Health, Melbourne State, Victoria, Australia - Daniel.croagh@monashhealth.org

Purpose: Endoscopic and percutaneous interventions for pancreatic necrotic collections are increasingly utilised. Their relative effectiveness in reducing the systemic inflammatory response has not previously been reported. We aim to compare the effect of both modalities on the systematic inflammatory response syndrome (SIRS).

Methodology: Retrospective chart review of all endoscopic and percutaneous drainage procedures for pancreatic necrotic collections across two hospitals from 2011 to 2015. Outcomes assessed were the post-procedure reduction in C-reactive protein (CRP) levels and resolution of SIRS criteria, and length of stay (LOS) post-intervention.

Results: 46 procedures were included: 20 endoscopic and 26 percutaneous. The median pre-procedure CRP levels were similar in the endoscopic and percutaneous groups (232 vs. 206.5, P=0.169). There was a 66.8% reduction in CRP with endoscopic drainage, versus 74.5% with percutaneous drainage (P=0.448). Resolution of SIRS was defined as the post-procedure normalisation of the following parameters: white cell count (64.7% of endoscopic vs. 45.5% of percutaneous cases, P=0.232); temperature (100% of endoscopic vs. 44.4% of percutaneous cases, P=0.038); heart rate (58.3% of endoscopic vs. 8.3% of percutaneous cases, P=0.009); respiratory rate (100% of endoscopic vs. 0% of percutaneous cases, P=0.0003). Patients who had endoscopic drainage had a median post-procedure LOS of 27 days, versus 57 days in patients with percutaneous drainage (P=0.001).

Conclusion: Endoscopic drainage is associated with a greater relative reduction in SIRS and a shorter post-procedure LOS than percutaneous drainage. There was no significant difference in the relative reduction in CRP and white cell count.

#6 Microbiology of Infected Necrotizing Pancreatitis- A Systematic Review

Fargahi F.

Presented by **Farshid Fargahi, MD -** Post Doc Fellow **-** Johns Hopkins Hospital - ffargah1@jhmi.edu

Background: Infected pancreatic necrosis (IPN) has been associated with higher mortality rates among acute pancreatitis patients, thereby leading to widespread use of broad spectrum antibiotics. It is unclear if the use of antibiotics has changed the microbial profile which will likely affect the outcomes of management.

Objective: To determine the change in microbiological profile of pancreatic necrosis from 1980 to 2014.

Methods: We reviewed MEDLINE, EMBASE and Cochrane library databases for experimental and observational studies reporting the microbiology of infected pancreatic necrosis, by using 'necrotizing pancreatitis' or 'pancreatic necrosis' and 'infection or infected' as search terms. Two reviewers independently reviewed the literature for eligibility. The changes in microbiology over the time period was reported as percentage prevalence of fungal, gram positive and gram negative bacterial cultures from 1980-1999 and 2000-2014, respectively. The trend of individual microbial organism was also reviewed separately.

Results: A total of 5160 studies were reviewed of which 74 studies were included in the analysis. These included 20 multicenter and 54 single center studies, 24 were conducted at tertiary care hospitals between 1980 and 2014. 31 studies were included from the time period of 1980-1999 and 43 studies from 2000-2014. The mean duration of studies was 4.03 ± 2.74 years. There were 3649 patients with IPN included in the analysis with a mean age of 51.52 ± 9.79 years. The mean time period from the day of admission to day of diagnosis was 22.6 ± 10.54 days. 1639 (45%) specimens collected that grew gram positive bacteria of which 810 (49.4%) specimens had Streptococci, 255 (15.5%) specimens had Staphylococcus aureus and 316 (19.3%) specimens had coagulase-negative Staphylococci. 2312 (63%) specimens grew gram negative bacteria of which 796 (34.4%) had Escherichia coli, 25 (1%) Citrobacter, 225 (9.7%) Enterobacter, 354 (15.3%) Klebsiella, 432 (18.7%) Pseudomonas aeruginosa, 45 (1.9%) Acinet obacter and 119 (5.1%) had other Enterobactericieae. 402 (11%) specimens had fungi. The prevalence of gram positive organisms decreased from 54.9% to 41.2% from 1980-1999 to 2000-2014 while gram negative organisms decreased from 79.4% to 58.2%. The prevalence of fungal specimens decreased from 13.8% to 9.9% in the same time period.

Conclusion: The reduction in pathogens of infected pancreatic necrosis over two discrete time periods likely reflects increase in the use of broad spectrum antibiotics

#7 To Evaluate the Role Of Multidisciplinary Pancreatic Conference in the Management of Resectable Pancreatic Ductal Adenocarcinoma

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Presented by **Manav Sharma, MD –** Hospitalist **-** Allegheny General Hospital - Manav.Sharma@ahn.org

Introduction: Surgical resection is the most desirable treatment option for patients with pancreatic ductal adenocarcinoma (PDA). Studies have demonstrated that only 22% of patients with Stage I PDA undergo surgical resection. This may be secondary to various factors including patients being poor candidates for surgery, less aggressive approach towards resection, or delayed wait times for surgery resulting in advanced disease at the time of surgery. Identification of these potential surgical candidates in a timely manner is often challenging. The role of a multidisciplinary tumor board for PDA has been emphasized in various studies and has been shown to significantly impact patient care in other disease states by improving coordination between the teams of oncologist, gastroenterologist and surgeons.

Aim: We aim to study the effect of multidisciplinary pancreas conferences (MDPC) in patients with resectable PDA, looking at time from diagnosis to surgery and R0 resection rate as primary outcomes.

Methods: A retrospective chart review was performed of patients with PDA between 2011-2015 at our institute. Patients with resectable PDA per NCCN guidelines were included in the study. Patients were divided into 2 groups, Pre-MDPC, and MDPC. Pre-MDPC included patients prior to initiation of multidisciplinary conference from March 2011-March 2013. Group 2 (MDPC) encompassed patients from pancreatic tumor registry reviewed at bi-monthly multidisciplinary conference from April 2013-April 2015 at our institution.

Results: There were total one hundred and sixty five patients in MDPC group. 66 patients in the MDPC group were deemed resectable at the tumor board discussion. Seventy percent (n=46) of those patients were successfully resected at our institution. In Pre-MDPC group, twenty-four patients were identified who underwent successful resection for PDA. The mean age was 69 years and 68 years in MDPC and Pre-MDPC group, respectively (p= .557). Mean size of tumor was relatively larger in MDPC group as compared

to Pre-MDPC group (30mm vs. 25mm p= .01). Timing to surgery from the time of pathologic diagnosis for MDPC patients and Pre-MDPC patients was 26.3 days versus 35.5 days (p= 0.03) respectively. R0 resection rate was comparable between the two groups (87% versus 89% p= 1.00).

Conclusions: In our study, MDPC implementation was associated with significantly improved time to upfront surgery. Furthermore, 70% of resectable MDPC patients in our study underwent R0 resection at our institution, which is higher than the national average. Multidisciplinary conference significantly improves time to therapy for resectable PDA through efficient care coordination.

TABLE 1	Pre-MDPC (n=24)	MDPC (n=46)	*P*
Age (Y)	68	69	.769
Sex (%)			.570
Male	44%	39%	
Female	56%	61%	
Race (%)			.292
White	100%	91.1%	
African-American	-	8.9%	
Size of mass (mm)	24.4	30	*.01*
Mean time diagnosis to upfront surgery	35.3	26.3	*.03*
LOS	15.2	13.3	.673
R0 resection	87%	89%	1.00
NO nodal disease	47%	49%	.806
Location of mass (%)			

#8 Changes in Immunological Status are Associated with Response to Treatment in Metastatic Pancreatic Cancer Patients Treated with Chemotherapy ± Oncolytic Reovirus

Farren MR.

Presented by **Matthew R. Farren, PhD -** Postdoctoral Fellow **-** Ohio State University - matthew.farren@osumc.edu

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive cancer with a 5-year survival rate I study (NCT01280058) was conducted in treatment-naïve patients with metastatic PDAC, studying the effect of adding pelareorep (an oncolytic reovirus thought to target oncogenic RAS activity) to taxane/platinum based chemotherapy. Ultimately there was no difference in progression free survival (PFS), disease control rate (DCR), or overall survival (OS) between Arm A (pelareorep + carboplatin/paclitaxel) and Arm B (carboplatin/paclitaxel). We recently reported that pretreatment immune status was strongly associated with OS in this patient population, and we hypothesized that the failure of pelareorep to exert effective anti-tumor activity was related to continuing immunosuppression under this combination of therapeutic agents.

Plasma and PBMCs were isolated from 70 patients with evaluable pre and post-treatment samples. Bioplex assays measured the level of 32 individual cytokine/chemokine plasma biomarkers, and comprehensive phenotypes of PBMCs were generated via flow cytometry. Addition of pelareorep to carboplatin/paclitaxel led to increased levels of 14 pro-inflammatory plasma biomarkers and in cells with an immunosuppressive or exhausted phenotype (specifically TRegs and CTLA4+ T cells). Regardless of treatment arm, changes in five soluble biomarkers (Fractalkine, IL-6, IL-8, RANTES, VEGF-A) four cellular biomarkers (including T, NK, and B cell subsets) were associated with DCR and/or PFS.

These data demonstrate that changes in systemic immune status were associated with treatment outcome in metastatic PDAC patients receiving carboplatin/paclitaxel ± pelareorep and argue that pelareorep failed to improve patient outcome because oncolytic reovirus did not effectively induce antitumor immune activity and in fact apparently increased immune suppression/exhaustion. In all, these studies suggest that interventions to improve immune activity or alleviate immune suppression in combination with this or other more immunogenic chemotherapy combinations may represent actionable means of improving oncolytic virotherapy.

#9 Total Pancreatectomy with Islet Autotransplantation Resolves Pain in Young Children with Severe Chronic Pancreatitis

Bellin MD[2], Forlenza G[1], Kaustav M[2], Berger M[2], Freeman ML[4], Beilman GJ[2], Dunn TB[2], Pruett TL[2], Murati M[3], Wilhelm JJ[2], Cook M[2], Sutherland DER[2], Schwarzenberg SJ[1], Chinnakotla S[2].
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Presented by **Melena Bellin, MD** – Assistant Professor of Pediatric Endocrinology – Director of Research, Islet Autotransplant Program – University of Minnesota / Schulze Diabetes Institute - Bell0130@umn.edu

Background: Fear of diabetes and major surgery may prohibit referral of young children severely impacted by pancreatitis for total pancreatectomy and islet autotransplant (TPIAT). We evaluated outcomes in our youngest TPIAT recipients, age 3-8 years at surgery.
Methods: Medical records were reviewed for 17 children (9 female) age ≤8 years undergoing TPIAT from 2000-2014. Most (14/17) had genetic risk factors for pancreatitis. Since 2006, TPIAT recipients were followed prospectively with health questionnaires including assessments of pain and narcotic use, and scheduled HbA1c and mixed meal tolerance tests (6 mL/kg Boost HP) before surgery, and at regular intervals after. Patients are 1- 11 years post TPIAT (median 2.2 years). Data are reported as median (25th, 75th percentile).
Results: All had relief of pain, with all 17 patients off narcotics at most recent follow up. Hospitalization rates decreased from 5.0 hospitalization episodes per person-year of follow up before TPIAT, to 0.35 episodes per person-year of follow up after TPIAT. Fourteen (82%) discontinued insulin, higher than the observed insulin independence rate of 41% in 399 patients >8 years of age undergoing TPIAT over the same interval (p=0.004). Median post-TPIAT HbA1c was 5.9% (5.6, 6.3%), and within patient post-TPIAT mean HbA1c was ≤6.5% for all but 2 patients.
Conclusions: Very young children with severe refractory chronic pancreatitis may be good candidates for TPIAT, with high rates of pain relief and insulin independence, and excellent glycemic control in the majority.

#10 Upper Gastrointestinal Hemorrhage After Total Pancreatectomy, Islet Autotransplantation in Children

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Presented by **Sarah Jane Schwarzenberg, MD -** Associate Professor of Medicine – Director, Pediatric Gastroenterology, Hepatology and Nutrition, Executive Medical Director, Pediatric Ambulatory Services - University of Minnesota Masonic Children's Hospital - schwa005@umn.edu

Total pancreatectomy, islet auto-transplantation (TPIAT) successfully relieves intractable pain in children with chronic pancreatitis. We report a case series that indicates life-threatening upper gastrointestinal hemorrhage should be recognized as a potential early post-operative complication of this procedure. We reviewed 75 cases of TPIAT in individuals ≤ 18 years of age performed at the University of Minnesota Masonic Children's Hospital for episodes of serious gastrointestinal bleeding. Review of these cases showed that 4 children experienced gastrointestinal hemorrhage within 3 months after the procedure. 3/4 children were male, ages ranged from 8-18 at the time of TPIAT. 3/4 had genetic predisposing factors for CP, one was idiopathic CP. One had a pre-operative history of upper gastrointestinal hemorrhage, attributed to gastritis associated with splenic vein thrombosis. After TPIAT, all were taking proton pump inhibitor therapy and prophylactic doses of aspirin. 2/4 were on hydroxyurea for platelet counts >1,000,000. Gastrointestinal hemorrhage occurred 1-3 months after TPIAT. Prodromal symptoms were absent in 3/4; one child complained of fatigue and nausea 24 hours before bleeding was found. Hemoglobin drop ranged from 3-5 g/dL. Endoscopic evaluation demonstrated no clear cause (1), bleeding vessel at the site of gastrostomy (1), anastomotic duodenal ulcer (2). After endoscopic therapy, withdrawal of hydroxyurea and aspirin, and increased proton pump inhibitor therapy, all bleeding resolved and no re-bleeding has occurred (minimum follow-up 2 years). In conclusion, early, unexpected upper gastrointestinal hemorrhage may complicate TPIAT. A high index of suspicion is appropriate.

#11 Burden of Pediatric Acute Pancreatitis on the Healthcare System

Hornung L, Szabo F, Kalkwarf H, Abu-El-Haija M.

Presented by **Lindsey Hornung, MS –** Biostatistician **-** Cincinnati Children's Hospital Medical Center - Lindsey.Hornung@cchmc.org

Aims: The incidence of acute pancreatitis (AP) in children has increased over the past two decades and is estimated to be between 3-13/100,000 annually. The impact of rising AP incidence on the healthcare costs is unknown. The aim of this study was to examine the burden of AP on the healthcare system relative to all other pediatric admissions and trends over the past decade.

Methods: Admission and cost data of patients with the diagnosis of AP for Cincinnati Children's Hospital Medical Center (CCHMC) was extracted from the Pediatric Health Information System (PHIS) from 2004-2014. PHIS is a comprehensive database that contains clinical and financial data from 45 pediatric hospitals across the United States allowing the opportunity to study the impact of AP on the healthcare system. We determined the percentage of all admissions each year for AP. The cost for AP admissions was compared to the overall cost of all admissions to CCHMC to calculate the cost percentage of AP. We also examined the median length of stay (LOS) and daily cost for AP annually from 2004-2014 and the effect of Intensive Care Unit (ICU) admissions on these estimates.

Results: Between 2004-2014 there were 1,210 admissions to CCHMC with a diagnosis of AP of which 623 had a primary diagnosis of AP. The number of new cases with a primary diagnosis of AP significantly increased (p=0.001) during this time, from 24 cases in 2004 to 42 cases in 2014. Primary AP admissions ranged from 30 to 89 per year and constituted 0.07-0.17% of all hospital admissions. The percentage of admissions for AP significantly increased over this time period (p<0.0001). The percentage of costs for AP relative to

all admissions ranged from 0.16-0.41%. The AP cost percentage was between 1.5 to 3.7 times higher than the AP admission percentage. Overall, the median LOS for AP admissions was 4.0 days and cost per day was $3,149, however these differed if there was an ICU admission. ICU was part of the admission for AP 2-15% of the cases each year. The median LOS for those with an ICU admission was significantly higher compared to those without (11.0 vs. 3.0 days, p<0.0001). The median cost per day for those with an ICU admission also was significantly higher than those without ($4,011 vs. $3,007, p<0.0001).

Conclusions: AP admissions constitute an expensive burden on the healthcare system relative to the percentage of admissions that they comprise each year. If AP admissions continue to increase, the cost of AP admissions may pose a substantial financial burden on the healthcare system.

#12 Chronic Pancreatitis (CP) Mortality Trends in United States (US): 1983-2010

Munigala S.

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Background and Aim: Chronic Pancreatitis (CP) is an inflammatory disease characterized by irreversible morphological changes and often associated with pain and impairment of exocrine and/or endocrine function. Hospitalization is required in case of an exacerbation to control pain and for the treatment of complications such as pseudo cysts. However, most of the CP patients may not be hospitalized, hence the death rates reported using hospitalized patients and case fatality rates may be an under representation of the deaths related to CP. The aim of this study was to analyze the trends in the mortality of CP in the US using Center for Disease Control (CDC) National Vital Statistics System (NVSS).

Methods: Mortality data from NVSS was extracted using CDC Wide-ranging Online Data for Epidemiological Research (CDC WONDER) from 1983-2010 for deaths where CP was listed as a primary cause of death or any cause of death using ICD 9 codes (ICD 9: 577.1 and ICD 10: K86.1). Population mortality rates per 1,000,000 (million) population was calculated for the entire study period each year and by 4-year interval. Rates were adjusted by age and sex to 2010 US population using direct standardization and 95% confidence intervals were calculated using Poisson distribution.

Results: During the study period, there were 9,691 and 30,758 deaths due to CP as a primary cause of death and CP as any cause of death respectively which accounted for 0.02% and 0.05% of all deaths. CP Mortality (per million) due to primary cause remained stable over the years from 0.98 (95% CI 0.87, 1.09) in 1983-1987 to 1.22 (95% CI 1.09, 1.34) in 2007-2010. This trend was noted for both the sexes [males -1.23 (95% CI 1.05, 1.40) in 1983-1987 to 1.44 (95% CI 1.25, 1.64) in 2007-2010, females – 0.75 (95% CI 0.62, 0.89) in 1983-1987 to 1.00 (95% CI 0.84, 1.15). Mortality rates were negligible for patients 65 years of age. Within the age groups (25-34; 35-44; 45-54; 55-64 and > 65) there was no significant trend in mortality rates from 1983-1987 to 2007-2010. Although black race showed increased number of deaths due to CP, the rates remained stable over the years but white race showed significant increase in the death rates from 0.80 (95% CI 0.69, 0.91) in 1983-1987 to 1.21 (95% CI 1.08, 1 .35) in 2007- 2010.

Conclusions: Overall CP population mortality remained stable from 1983 to 2010. Increased mortality was observed in whites. Lack of increasing trend in the CP mortality suggests improved diagnostic evaluation and management of chronic pancreatitis over the years.

#13 Prevalence of Exocrine Pancreatic Insufficiency in US Adult Population

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Presented by **Nikhil Khandelwal, PhD, BPharm -** Associate Director, Endocrinology **-** Global Health Economics & Outcomes Research **-** AbbVie, Inc. - Nikhil.khandelwal@abbvie.com

Introduction: Exocrine pancreatic insufficiency (EPI) often remains undiagnosed due to the non-specific symptoms that mimic other gastrointestinal conditions. Reliable published estimates of the prevalence of EPI in the US are lacking. Primary goal of this study was to estimate the prevalence of EPI.

Methods: A cross-sectional online survey was completed by 100,000 adult members of an online health panel from November through December 2014. EPI patients were identified from respondents by asking if their physician ever told them that they had EPI. Frequencies and means were examined to estimate the prevalence of EPI and associated symptoms. Results were weighted to reflect US 2014 census distribution. Symptom profiles for respondents who reported having certain high-risk conditions for EPI, such as celiac disease (CeD), chronic pancreatitis (CP) and cystic fibrosis (CF), were compared.

Results: 309 respondents reported having EPI. Using weighted 2014 US census data, the EPI adult population is estimated at 1.02 million individuals. EPI patients had a mean age of 37 years and 44.0 % were male. 63.0% of the EPI patients reported their condition as moderate to severe. Among all EPI patients, 17% had CP, 8% had CeD, 8% reported CF and about 72% reported no primary underlying condition. Frequently reported symptoms included abdominal pain, bloating, diarrhea, tiredness, muscle weakness, difficulty gripping, steatorrhea and watery stools. Symptom profile distributions were similar across different disease states.

Conclusion and Discussion: EPI is often overlooked in patients with non-specific gastrointestinal symptoms, even in at risk populations. Although the study showed that EPI may occur in at least 1 million US adults, the overall prevalence could be higher as its occurrence in all at-risk population was not accounted for and confounded by certain data bias. For effective diagnosis and management of EPI, it is critical to highlight its prevalence in the general population.

Disclosures: Amit Bodhani, Nikhil Khandelwal, Mark Haupt, Beverly Johns, Siting Wang and Jane Castelli-Haley are Abbvie employees and may own Abbvie stock.

The work was funded by Abbvie. Abbvie participated in the study, design, research, data collection, analysis and interpretation of data, writing, reviewing and approving the publication.

#14 Leptin Gene Single Nucleotide Polymorphisms Do Not Alter the Incidence or Severity of Acute Pancreatitis

Evans AC.

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Aims: Acute pancreatitis (AP) is a sudden inflammatory event that originates within the pancreas and can initiate systemic inflammation with multi-organ failu re, and death. Obesity increases both susceptibility to, and severity of AP. Leptin is an adipocyte-associated peptide (adipokine) that inhibits food intake and modulates the inflammatory response. Leptin levels are increased by obesity and altered by genetic polymorphisms. The variable effects of leptin in determining pancreatitis susceptibility and severity are poorly understood in humans.

Methods: Patients with pancreatitis (n= 388) that was mild (MAP n=208), moderate (MoAP n=83) or severe (SAP n=96) enrolled in the PROOF/SAPS or NAPS2 study, and controls (n= 585) from the NAPS2 study were evaluated for genetic variations. Three functional single nucleotide polymorphisms (SNPs) in the leptin gene (LEP) (rs2167270 G/A – associated with colon cancer, rs4731427 T/C – increases IL-6 levels, and rs7799039 – associated with growth hormone deficiency) and one from the leptin receptor gene (LEPR) (rs1137101 A/G p.Gln223Arg – associated with obesity) were evaluated by TaqMan® SNP genotyping assays.

Results: Statistical analysis was done with Chi square test and student's t test. None of the leptin SNPs evaluated showed a statistically significant association with either increased susceptibility to or severity of acute pancreatitis.

Conclusions: Although leptin is an obvious target for further investigation regarding regulation of incidence or severity in acute pancreatitis, these single nucleotide polymorphisms cannot explain the variation we see in the disease course of this population. Further investigation needs to be performed on the role of leptin in acute pancreatitis.

#15 Assessing the Clinical Significance of PRSS1 Intronic Variants

Hegyi E.

Presented by **Eszter Hegyi, MD, PhD -** Post-Doc Fellow **-** Department of Molecular and Cell Biology, Boston University Medical Center - heszter@bu.edu

Background: Mutations in the serine protease 1 (PRSS1) gene encoding human cationic trypsinogen are associated with hereditary pancreatitis and sporadic chronic pa ncreatitis. The clinical relevance of the majority of exonic variants has been successfully determined and pathogenic mechanisms of the disease-causing mutations have been identified. In contrast, the role of intronic variants have 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 chronic pancreatitis (CP) highlights the need for clarifying their clinical significance. Aims: Our aim was to identify and functionally characterize PRSS1 variants in intron 3 and intron 4. We focused on these regions because splicing defects in distal introns are more likely to result in altered protein function.

Methods: 172 CP patients (cases) and 288 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. To evaluate the potential effects of PRSS1 intronic variants on pre-mRNA splicing, 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. AR42J cells were transfected with the full-length PRSS1 constructs to analyze mutational effects on mRNA splicing, protein folding and secretion of trypsinogen. Results: A variant in intron 3 was identified in one case only (c. 454-93T>C, heterozygous state). Five variants in intron 4 have been found (c.591+111C>T, c.592-79G>A, c.592-24C>T, c.592-11C>T, and c.592-8C>T), all in the heterozygous state. There was no enrichment of intronic variants in cases relative to controls. Functional analysis of variants c.592-79G>A and c.592-24C>T has been performed. S ecretion of cationic trypsinogen from transfected cells harboring full-length PRSS1 with intronic variants was unchanged relative to cells expressing the wild-type PRSS1 gene. RT-PCR analysis of total RNA showed a single transcript of similar size for both variants which was expressed at comparable levels relative to wild type.

Conclusions: Variants in intron 3 and intron 4 of PRSS1 occur rarely and are not associated with CP. In vitro analysis confirms that variants c.592-79G>A and c.592-24C>T are functionally harmless and, therefore, should have no pathological significance related to CP.

#16 A Variant (rs4680) in Catechol-O-Methyl Transferase (COMT) Gene is Associated with Variable Pain Perception in Individuals with Chronic Pancreatitis

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Presented by **V V Ravikanth, PhD –** Scientist **-** Asian Institute of Gastroenterology - ravikanth.aig@gmail.com

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Introduction: Introduction: Chronic Pancreatitis (CP) is a progressively destructive complex inflammatory disorder of the pancreas that is characterized by irreversible exocrine insufficiency and endocrine dysfunction. While the pathological hallmark is parenchymal fibrosis, the dominant clinical symptom is recurrent intractable abdominal pain of variable severity and frequency. Several mechanisms for pain in CP have been postulated, but detailed mechanisms are poorly understood. Catechol-O-methyltransferase (COMT) is an important enzyme that metabolizes catecholamine neurotransmitters involved in a number of physiological functions including pain perception. The gene coding for COMT is known to harbor functional polymorphisms that contribute to interindividual variability in phenotypes including sensitivity, severity and response to pain. A variant (rs4680; G>A) in exon 3 of the gene results in amino acid change from valine to methionine and is associated with low enzymatic activity and reduced thermal stability of the enzyme. Lesser activity of COMT causes higher pain sensitivity.

Methods: In this study, we aimed to evaluate for COMT polymorphisms in patients with CP. Materials and methods: Blood samples were collected from patients (N=114) with chronic pancreatitis and the intensity of their pain was recorded using an oral questionnaire on a scale of 1-10 (Visual Analog Scale). DNA was isolated from the blood samples and genotyping for a variant in COMT gene (rs4680) was done employing Taqman probes on the Real time PCR (Step one, Life technologies). Association between pain perception and COMT genotype was expressed as Odd's ratio (OR) with 95% confidence interval (CI) and a 'p' value of <0.05 was considered statistically significant.

Results: Of the 114 patients in the study group, 75 were males and 39 females. The mean age of male and female patients was 28±12 and 21.7± 10.8 years respectively. AA genotype was associated with increasing pain score; and based on AUROC analyses, a cut-off of VAS for pain of greater than 7 was most strongly associated with the variant. While there were a total of 25 patients with GG, 29 with GA and 6 with the AA genotypes in the below 7 pain group, the number was 18 with GG, 23 with GA and 13 with AA in the above 7 pain score group. The AA genotype was significantly (p=0.04) associated with 2.85 fold higher pain perception (OR 2.85; 95% CI-0.99 – 8.14).

Conclusions: Patients with AA mutant genotype had a significantly higher sensitivity to pain (higher pain score) compared to patients with wild type (GG) or heterozygous (GA) genotype. Given the complex biological and psychological nature of pain, it is important to identify these variants for better understanding of the contribution of these variants to pain responses and ultimately improve the diagnosis and treatment of clinical pain conditions.

#17 Carboxyl Ester Lipase Hybrid Gene and the Unfolded Protein Response: A Novel Trypsin Independent Model of Injury in Pancreatic Acinar Cells

Sunseri W.

Presented by **Whitney Sunseri, MD -** GI Fellow Currently PGY-5 **-** Children's Hospital of Pittsburgh - whitney.sunseri@chp.edu

Chronic pancreatitis (CP) is a destructive inflammatory process causing irreversible damage to the pancreas. Genetic mutations account for two-thirds of pediatric cases. Most of the known mutations are in the gene encoding trypsinogen or linked to the activation or degradation of trypsin. These findings support a trypsin-dependent mechanism of pancreatitis centered on premature trypsin activation in acinar cells and auto-digestion of the gland. The recent association of alterations in the gene encoding carboxyl ester lipase (CEL) with CP suggests that novel, trypsin-independent mechanisms can result in CP. One CEL variant associated with increased risk for CP in several European case-control studies is a product of genomic recombination between CEL and its pseudogene (CEL-HYB). As of yet, little is known about the molecular mechanism through which CEL-HYB increases risk for CP. We hypothesized that CEL-HYB has increased levels of protein misfolding resulting in defective secretion and intracellular accumulation that triggers a maladaptive up-regulation of the ER stress and unfolded protein response causing inflammation and eventual cell injury. To investigate our hypothesis, we studied the behavior of CEL-HYB protein compared to CEL WT by adenovirus transduction in AR42J cells, a rat pancreatic acinar cell line. Prior to transduction, AR42J cells were pretreated with dexamethasone to induce an acinar cell phenotype. First, the biochemical characterization of purified recombinant CEL-HYB and CEL WT showed the enzymatic properties of both proteins were similar. Second, in AR42J cells, less CEL-HYB was secreted in the medium and more CEL-HYB was retained intracellularly compared to CEL WT. A greater fraction of intracellular CEL-HYB was present as detergent-insoluble aggregates compared to CEL WT. There was no significant difference in BiP protein levels, BiP mRNA levels, XBP-1 mRNA splicing or PARP cleavage between CEL WT and CEL-HYB. In conclusion, CEL-HYB causes a reduction in CEL secretion and an increase in accumulation of insoluble protein aggregates compared to CEL WT in AR42J cells. There is no obvious increase in the investigated cell signaling pathways in response to the accumulation of CEL-HYB under our experimental setting. We plan to further investigate the cellular response of the expression of CEL-HYB in AR42J cells under various forms of metabolic stress.

#18 A Simple, Robust and Highly Productive Methodology for Mass Spectrometry Analysis of Laser Capture Microdissected Tissue from FFPE Biopsies Requiring 10,000 Cells

Shapiro J.

Presented by **John Shapiro, MS -** Senior Research Associate **-** Ohio State University - john.shapiro@osumc.edu

Aims: Archived FFPE clinical biopsies are a gold mine for understanding physiological mechanism(s) that produce disease. However, the proteomes of these biopsies are rarely characterized using laser capture microdissected (LCM) tissue, a technology that allows for collection and analysis of homogenous populations of cells. Here we present a simple, highly productive and reproducible method allowing for quantitative proteome analysis of FFPE tissue requiring 10,000 LCM isolated cells. The method was used to characterize a mouse model of pancreatitis induced with Caerulein. Mass spectrometry generated spectral count data identified in LCM isolated pancreatic acinar cells was analyzed from control vs. treated mice to demonstrate method capabilities.
Methods: Mice were injected for 1,3 and 6 weeks with 50 µg/kg intraperitoneal caerulein injections 3 days/week. FFPE sections of pancreata were deparaffinized, hematoxylin stained, dehydrated with ethanol and air dried. LCM was performed using the Zeiss LCM system. LCM acinar cell isolates were boiled 20 minutes, heated for 2 hours at 60 oC, and trypsin digested. Peptides were

analyzed using an OrbiTrap Fusion mass spectrometer (ThermoScientific). Spectral count data was analyzed for quantitative, statistically significant differences between control vs. treatment groups.

Preliminary Data: On average, 2,000 unique proteins were identified in LCM acinar cell isolates from each of the 15 mice in the study. Spectral count statistical analysis identified 142, 343 and 370 proteins with greater than 2-fold change (pvalue< 0.5) in the 1,3 and 6 week treated animals respectively. Many of the differentially up-regulated proteins detected in this mouse study are known to be associated with pancreatitis in humans including proteases thought to be key mediators of pancreatitis and as well as proteins associated with fibrosis, a common feature of pancreatitis. Additionally, LC-MS/MS identified down-regulated digestion enzymes including amylase and lipase demonstrating the diminished functional status of the pancreas.

Animal models are often used to better understand the underlying physiology in correlating human disease. Unfortunately, the reliability of these models to accurately characterize the human disease often leads to conclusions determined to be non-relevant in humans. We compared the data obtained in this study to a previously published study characterizing the proteome changes in tissue isolated from FFPE biopsies from human chronic pancreatitis patients vs. normal patients. The correlation of fold changes between mouse and human proteome was assessed comparing the 261 common proteins by the Pearson's correlation coefficient which demonstrated a high correlation (0.722, P<000.1). Thus, the data presented in this study supports the capability of this simple method requiring 10,000 LCM isolated cells to allow for greater use of archived clinical samples for better understanding of mechanisms underlying development of diseases. Additionally, the data obtained from the cerulein mouse model may provide novel insight into molecular processes of pancreatitis with diagnostic potential.

#19 Risk Factors for Asparaginase Associated Pancreatitis: A Systematic Review

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Presented by Fateema Turay Rose, MD - Pediatric Gastroenterology Fellow (PGY 6 in July 2016) - Children's Hospital of Pittsburgh, UPMC - fateema.turay@chp.edu

Background. An increasing incidence of pediatric cases of acute pancreatitis has been noted over the past two decades with recent stu dies estimating 3.6-13.2 cases per 100,000 children per year. There is a much more diverse group of etiologies of acute pancreatitis in children when compared to adults. Although the prevalence of each etiology has been difficult to define, as there have been wide ranges reported by various studies, medications have been recognized as a major cause of pediatric acute pancreatitis, resulting in greater than one-fourth of all cases. Among the medications implicated is the chemotherapeutic agent L-asparaginase. L-asparaginase has been a key component of combination chemotherapy for the treatment of acute lymphoblastic leukemia since the 1960s. Asparaginase associated pancreatitis (AAP) has been noted to have an incidence between 2-18% and is one of the most common reasons for termination of L-asparaginase treatment. Although the pathogenesis of AAP remains ambiguous, early discontinuation of L-asparaginase has been associated with inferior outcomes. To evaluate possible risk factors for the development of AAP, we present a systematic review of the current literature.

Methods. A systematic review of the current literature available through May 2015 was performed. After relevant studies were identified, two reviewers each extracted information on study characteristics, patient demographics, and clinical outcomes.

Results. After an expansive screen of 1842 citations and 59 potentially relevant articles, 10 articles were identified as eligible. Based on these 10 studies, age, ALL risk stratification, and asparaginase formulation were noted to affect risk of AAP. Two studies showed that children older than 10 years of age manifested a greater than 2-fold risk of AAP. High risk ALL patients were noted to have a

greater incidence of pancreatitis in two studies. Additionally, use of PEG asparaginase was found to result in higher incidence of AAP in one study.

Conclusion. In this extensive systematic review, age, ALL risk stratification, and asparaginase formulation are suggested to play a role in the development of AAP. The risk of asparaginase associated pancreatitis cannot be determined confidently based on the identified studies, however, proposing the potential for unknown underlying factors contributing to the phenotypic picture.

#20 A Nationwide Analysis of Venous Thromboembolism in Acute Pancreatitis Inpatients

Umapathy C.

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Background and aims: In acute pancreatitis (AP), prolonged hospitalization and the pro-inflammatory cascade serve as a milieu for the development of venous thromboembolism (VTE). Our aim was to estimate the prevalence of deep vein thrombosis/pulmonary embolism (VTE) in hospitalized patients with AP and to ascertain its impact on morbidity and mortality.

Methods: The National Inpatient Sample (2002-2011) was reviewed to identify all patients hospitalized with AP with a concomitant diagnosis of VTE. The primary clinical outcome (mortality, renal failure and respiratory failure) and secondary resources outcomes (length of stay and total hospital charges) were analyzed using univariate and multivariate comparisons. Propensity score-matched analysis (matched for patient demographics, hospital characteristics, etiology, and AHRQ-Elixhauser comorbidities) was performed to compare the outcomes in patients with and without VTE.

Results: Among 2,453,997 discharges with AP, 23, 614 (1%) were associated with VTE. Univariate analysis showed that among AP patients, VTE was more frequent in Whites (54% vs. 51%, p<0.005), morbidly obese patients (3.5% vs. 2.9%, p<0.005), and patients with more co-morbid conditions [AHRQ-Elixhauser index ☐ 3] (56.4% showed that overall, VTE in AP was independently associated with higher mortality (OR 1.4, 95% CI 1.3-1.5, p<0.005), pseudocyst (OR 2.9, 95% CI 2.8-3.0, p<0.005), longer hospitalization (9.1 days, p<0.005), and higher hospital charges ($60,585, p<0.005). A propensity score–matched cohort analysis showed that AP patients with VTE experienced more acute kidney injury (9.3% vs. 3.3%, p<0.005), respiratory failure (8.5% vs. 1.4%, p<0.005), needed more mechanical ventilation (8.3% vs. 1.9%, p<0.005), and had higher mortality (2.1% vs. 1.3%, p<0.005). On conditional logistic regression analysis, there was a trend towards increased mortality in AP-VTE (OR 1.6, 95% CI 0.7-4.0, p=0.27).

Conclusion: Presence of VTE portends poor clinical outcome in AP patients resulting in more resource utilization. VTE prophylaxis and ambulation should be strongly encouraged in AP inpatients.

#21 Detection of Elastase Isoforms by the ScheBo Pancreatic Elastase 1 Stool Test

Toth AZ.

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Background: Determination of fecal pancreatic elastase content by ELISA is a non-invasive, practical and reliable clinical test for assessing exocrine pancreatic function. However, the nomenclature of human pancreatic elastases is confusing and we do not know exactly which elastase isoforms are detected by the commercial ELISA kits.

Aims: This study was undertaken to clarify which pancreatic elastase isoforms are detected by the most widely used ELISA kit and whether naturally-occurring polymorphic variants of elastases can influence the result of this test.

Methods: Human pancreatic protease zymogens were expressed recombinantly and purified. Elastase measurements were performed with the ScheBo pancreatic elastase 1 stool test kit.

Results: Among the human pancreatic digestive enzymes tested, only chymotrypsin-like elastases 3A and 3B (CELA3A and CELA3B) were detected by the ScheBo kit. CELA3B gave approximately three times higher signal than CELA3A. Proelastases (zymogens), activated elastases and autolytically cleaved enzymes were detected with identical efficiency. CELA3B polymorphism p.W79R increased detection by 1.3-fold, while variants p.I209V, p.R210H, and p.Q134L were detected as well as wild type CELA3B.

Conclusions: The ScheBo pancreatic elastase 1 stool test is specific for human CELA3A and CELA3B elastastes, with most of the ELISA signal coming from CELA3B. Common natural variants of CELA3B have no significant effect on the results of the test.

#22 Initial Chloride Level as a Single Predictor of Morbidity in Patients with Acute Pancreatitis: A Retrospective Observational Study in Inner City Population

Chandrala CK.

Presented by **Chaitanya Krishna Chandrala, MD -** Fellow in Gastroenterology - Bronx Lebanon Hospital Center, Affiliated to Icahn School of Medicine - chaitanya.chandrala@gmail.com

Introduction: Acute pancreatitis is one of the leading gastrointestinal causes of hospitalization in North America. Also acute pancreatitis has been associated with increased morbidity and mortality due to its local and systemic complications. Several predictive models to stratify severity and predict outcomes in acute pancreatitis were developed, but most of them were complex and cumbersome. Recently single laboratory predictor models like Blood Urea Nitrogen (BUN) were studied, which appear promising. Serum chloride levels have been studied in critical care literature like septic shock to predict disease associated mortality. As acute pancreatitis is also an acute systemic process, we hypothesized that abnormal chloride levels may predict morbidity in these patients.

Methods: We conducted a retrospective observational study by including all patients admitted with acute pancreatitis to our hospital between January 2012 and January 2016. Patients who did not meet two of three criteria to diagnose acute pancreatitis have been excluded. We collected demographic, laboratory and imaging details by accessing hospital electronic medical records. We

also extracted data related to critical care admission and total hospital length of stay which indirectly measure inpatient morbidity. Data was analyzed using standard statistical methods and SAS JMP 12 software.

Results: There were a total of 323 patients who met the study criteria. We divided the patients into three groups based on initial serum chloride levels on admission to the hospital. The three groups respectively were those with normal chloride (98-108 mEq/liter), lower chloride (108 mEq/liter) levels. We observed increased total hospital length of stay in patients with higher chloride (mean 8.8 days), and lower chloride (mean 7.62 days) compared to patients with normal chloride (mean 5.71 days, p 0.015) levels. We also observed increased critical care admission rate among patients with higher and lower chloride levels (38% and 37% respectively) compared to patients with normal chloride levels (17%, p 0.0002).

Conclusion: We conclude that abnormal initial serum chloride level can predict total hospital length of stay and requirement of critical care monitoring, which indirectly measures morbidity in patients with acute pancreatitis. Our study is first of its kind in acute pancreatitis measuring association between serum chloride levels and morbidity. Future studies aiming at aggressive correction of chloride and associated reduction in morbidity and mortality would need to verify these findings.

#23 Activin as Potential Risk Stratifying Marker and Therapeutic Target in Acute Pancreatitis

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CAPER SCHOLARSHIP

Aims: Acute Pancreatitis (AP) is the sterile inflammation of the pancreas. The incidence of AP is up to 74.3 per 100,000 persons in certain regions of the world. Even though self-limiting in most cases, approximately 20% of patients will progress to severe disease and those with infected pancreatic necrosis have a 30% mortality. Currently, there is no clinical marker for risk stratification, and treatment is limited to aggressive rehydration and antibiotics in cases of secondary bacterial superinfection. Novel approaches are direly needed. The aim of this study is to elucidate the role of Activin A, a TGF-beta superfamily member and important modulator of inflammatory response, in AP.

Methods: AP was induced using two established murine models. Firstly, to investigate Activin A in a standard model of AP, male balb/c mice were treated with a single injection of cerulein i.p. or vehicle alone. Secondly, for a model of severe AP with mortality, male mice from a b6 background were fed regular chow or a high fat diet. Both groups were treated with two i.p. injections of IL-12 and IL-18 on subsequent days to developed necrotizing disease in the high fat group and edematous disease in the animals on regular diet. After sacrifice, blood and pancreas were collected. A white blood cell count was determined and serum was assessed for Activin A, Amylase, and IL-6 by ELISA. Pancreas tissue was stained by H/E and necrosis and inflammatory infiltration was individually scored by two investigators.

Results: Activin A was statistically significantly increased at early time points in both models of AP and returned to baseline with resolution of pancreatitis. Activin A was strongly correlated with both IL-6 (ρ=.751, $p<0.05$) and Amylase (ρ=.861, $p<0.05$). Elevated Activin A levels correlated with more aggressive disease in the IL-12/IL-18 induced model of AP with 4-fold higher levels in necrotizing disease. Furthermore, Activin A correlated with serum neutrophils, but not serum leucocytes.

Conclusions: We demonstrate that upregulation of Activin A correlates with disease severity in two distinct models of AP. Given its central role in other inflammatory conditions, Activin A shows promise both as a risk stratifying marker and as a potential therapeutic target.

#24 Targeted Inhibition of Pancreatic Acinar Cell Calcineurin Prevents Post-ERCP Pancreatitis in Mice

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CAPER SCHOLARSHIP

Acute pancreatitis is the most common and burdensome iatrogenic complication of endoscopic retrograde cholangiopancreatography (ERCP). There is a crucial need to devel op effective prophylactic therapies for post-ERCP-pancreatitis (PEP). In recent work, we described for the first time, that early PEP events are regulated by the calcium-activated phosphatase calcineurin (Cn) and that global Cn deletion abolishes PEP in mice. However, it is unclear whether pancreatic acinar cell Cn controls the initiation of PEP in vivo. In this study, we used two complementary genetic approaches to selectively delete the critical regulatory subunit B1 (CnB1) in pancreatic acinar cells. Firstly, we crossed a mouse line containing floxed alleles for CnB1 with a tamoxifen-inducible Cre line driven by an acinar cell specific elastase promoter. PEP was induced by retrograde pancreatic ductal infusion of normal saline at 10 µL/min for 5 min (ductal manipulated, DM) or radiocontrast infusion at 20 µL/min for 5 min (PEP). We demonstrated that pancreatic injury was reduced by 75% in CnB1 deficient mice (CnB1Δ/Δ) receiving PEP. Secondly, we used a novel approach of intra ductal adeno-associated virus (AAV) gene transfer to delete acinar cell calcineurin. The AAV contained an elastase-driven iCre (AAV6-Ela-iCre) and was infused into a CnB1 floxed mouse (CnB1f/f) line. AAV6-Ela-iCre infusion resulted in acinar cell-specific CnB1 deletion, and upon recovery from the intraductal procedure, pancreatic injury induced by PEP was reduced by 90% down to control levels. Finally, to examine the translational relevance of these findings, a single, acute intra-ductal application of the Cn inhibitors FK506 or cyclosporine (1-10 µM) was given along with the radiocontrast infusion. This novel formulation largely reduced the severity of PEP by 61% and 37%, respectively with no adverse effects observed. These data confirmed that pancreatic acinar cell Cn plays a pivotal role in PEP, and provides the impetus for launching clinical trials to test the efficacy of a novel ERCP infusion formulation containing Cn inhibitors to prevent PEP.

#25 Effect of Chymotrypsin C Deficiency on Cerulein Induced Pancreatitis in the Mouse

Jancso Z.

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Background: Human chymotrypsin C (CTRC) protects against pancreatitis by promoting proteolytic degradation of trypsinogen; thereby eff ectively curbing harmful intra-pancreatic trypsinogen activation. Loss-of-function mutations in CTRC increase the risk for chronic pancreatitis and trypsinogen mutations that block degradation by CTRC cause hereditary pancreatitis.

Aims: Our aim was to study whether inactivation of the mouse Ctrc gene results in increased severity of pancreatitis.

Methods: We identified the C57BL/6 strain as naturally deficient in Ctrc. Through crossing with the FVB strain followed by backcrossing for eight generations we restored a functional Ctrc gene in C57BL/6. Acute pancreatitis was induced by 12 hourly injections of cerulein. Chronic pancreatitis was induced by 6 hourly injections of cerulein on two days a week for 10 weeks. Pancreatitis severity was determined by histology scoring, measurement of edema, MPO and serum amylase. Chronic pancreatitis was evaluated by histology and measurement of pancreas atrophy.

Results: Severity of acute and chronic pancreatitis was attenuated in mice with restored Ctrc expression relative to the Ctrc negative C57BL/6 controls.

Conclusions. Mouse Ctrc exerts a small but significant protective effect in experimental models of acute and chronic pancreatitis.

#26 Inhibition of Jak/STAT Signaling Limits the Activation of Pancreatic Stellate Cells in Vitro and Caerulein-induced Pancreatitis in vivo

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CAPER SCHOLARSHIP

Chronic pancreatitis (CP) is a devastating disease characterized by persistent inflammation and fibrosis of the pancr eas. Unfortunately, no therapeutic options exist due to limited understanding of the cellular and molecular mediators of CP pathology. Recent findings implicate pancreatic stellate cells (PSC) as prominent mediators of the inflammatory and fibrotic phenotype observed during CP. To examine characteristics of these cells and determine appropriate therapeutic strategies targeting PSC, we utilized a variety of primary and immortalized PSC samples from backgrounds of both chronic pancreatitis and pancreatic cancer. In vitro, these cells demonstrated robust secretion of several soluble immunomodulatory factors including MCP-1, IL-6, and VEGF at levels up to 31,000, 19,000, and 800 pg/mL respectively. All cell lines displayed activation of the classically pro-survival, pro-inflammatory Jak/STAT and MAPK pathways. Treatment of PSC with the small molecule Jak1/2 inhibitor Ruxolitinib resulted in reduced STAT3 phosphorylation and decreased cell growth (40% growth after 72 hours of 50 µ M by MTT assay). Treated cells remained adherent and did not display PARP cleavage by western blot, suggesting the effects of Ruxolitinib on cell growth are not pro-apoptotic. Instead, western blot and fluorescent microscopy demonstrate a dose-dependent decrease in alpha-SMA, a marker of PSC activation. Treatment with a MAPK pathway inhibitor (MEK162) had no effect on growth or activation. These data suggest that the Jak/STAT pathway, and not the MAPK pathway, functions to limit PSC growth and activation, thereby representing a viable therapeutic target. To examine this hypothesis in vivo, we have characterized the caerulein-induced murine model of chronic pancreatitis in C57BL/6 mice. To achieve a CP-like phenotype, mice were given 50 µg/kg caerulein hourly 6X/day, 3days/week by I.P. injection. After 4 weeks mice displayed acinar cell loss, inflammation, and fibrosis as well as decreased serum amylase and lipase. For therapeutic testing, Ruxolitinib was administered at 90m g/kg twice daily by oral gavage during the final week of caerulein injections. After one week, Ruxolitinib-treated mice display increased serum amylase and lipase compared to control mice. Immunohistochemical analysis of pancreata from these animals trend toward reduced fibrosis and inflammation in trichrome and CD3-stained slides, respectively. Consistent with these observations, there was a mild reduction in acinar loss in in the pancreata from Ruxolitnib treated mice. Together these data suggest that inhibition of Jak/STAT signaling may limit caerulein-induced pancreatic damage in this model.

#27 Fat Globules Within Organized Pancreatic Fluid Collections on CT Scan Impact the Outcomes of Nonsurgical Drainage

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Aims: To assess whether the presence of fat globules in PFCs on CT scan impacts the outcomes of non-surgical drainage.

Methods: Patients with an organized PFC as well as CT scan obtained at least 4 weeks after their episode of acute pancreatitis between 1/1993 and 1/2015 were identified using an administrative database. CT scans were interpreted by single radiologist for the presence of fat globules defined as foci of fat attenuation. For those patients undergoing nonsurgical drainage (endoscopic and/or percutaneous), differences in technical and clinical success in terms of completion of procedure, resolution in PFC size (is. Fat globules were seen in 35 (45%) PFCs on CT with 21 PFCs drained endoscopically, 5 drained using both endoscopic and percutaneous approach and 2 drained percutaneously as compared to 42 (55%) PFCs with no fat on CT of which 12 were drained endoscopically, 14 were drained percutaneously and 1 was drained using both endoscopic and percutaneous drainage (p=0.03). Technical success was achieved in all PFCs. Among the PFCs with fat globules, 12 were endoscopically drained using lumen-apposing metal stents (LAMS) and 8 using double pigtail plastic stents versus 6 and 4 in PFCs without fat globules, respectively (p=0.001). There were 9 PFCs with fat globules that required reintervention as compared to 3 PFCs without fat (p=0.024). PFCs containing fat globules resolved after a mean time of 57.30± 46.81 days as compared to PFCs without fat globules which resolved after 29± 25.1 days (p=0.003)

Conclusion: PFCs containing fat globules on CT scan more commonly required LAMS, combined drainage modalities, multiple interventions, and had a significantly longer duration to resolution as compared to PFCs without fat globules. Fat globules seen within PFCs on CT scan helps endoscopists with pre-procedure planning, thereby avoiding requirement of MRI to differentiate PFCs into walled-off necrosis or pseudocyst.

#28 Effect of Size of Percutaneous Catheter Drainage on Outcome Parameters in Patients with Severe Acute Pancreatitis: A Pilot Study

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Introduction: Percutaneous catheter drainage (PCD) is an integral part of step-up approach of management of severe acute pancreatitis (SAP). However there is no consensus on size of initial PCD.

Aims: To assess the effect of initial size of PCD on outcome parameters in SAP patients.

Methods: Consecutive SAP patients with imaging evidence of drainable collection were included. Baseline demographic, clinical, biochemical and radiological evaluation was done and patients were managed with step-up approach. Image guided PCD was done and PCD size upgraded in patients not improving . Outcome parameters evaluated were hospital stay, resolution of organ

failure(OF), requirement of surgery and mortality. 28 patients with initial PCD size of 12 F were compared with 8 patients who received initial PCD of 16 F.

Results: 36 patients (mean age of 38±11.2yrs, 64%males) with SAP and fluid collections were evaluated. Early PCD (within 2 weeks) was done in 25 (65.5%) patients and beyond 2 weeks in the rest. 10 (27%) patients died during disease course. Upgradation of PCD was required in 16 (57%) of 12 F group and none of 16 F group (p=.004). Resolution of OF after PCD insertion occurred earlier in 16 F group (8.33±2.16 d) as compared to 12 F group (17.35±3.8 d,p<0.001) with shorter hospital stay (14.17±2.6 vs 23.75±6.2 d,p=.001). On subgroup analysis 16 F group compared to group requiring upgradation had earlier OF resolution (8.33±2.2 vs 19±3.5 d, p<.001) and shorter hospital stay (14.2±2.6 vs 16.9±61 d, p<.001). However no significant difference were noted between the groups in terms of mortality or surgery.

Conclusion: Upfront use of wider diameter PCD hastened OF resolution and shortened the hospital stay in patients with SAP with drainable collection.

#29 Outcomes of Endoscopic Drainage of Symptomatic Walled-Off Necrosis (WON) Using Lumen-Apposing Metallic Stents (LAMS) Compared to Fully Covered Self-expandable Metallic Stents (FCSEMS) or Double Pigtailed Plastic Stents: A 7-year Single-center Experience

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Background: Although there is consensus that minimally invasive approaches are associated with improved outcomes in WON management, there is still debate over the ideal approach. Endoscopic therapy is gaining popularity as the preferred approach however there is no consensus regarding the type of stent used for transenteric and overall management approach. The aim of this study is to report outcomes in patients (pts) treated with lumen-apposing metal stents (LAMS) compared to conventional double pigtailed plastic double pigtail (DPTS) or fully covered metallic biliary stents (FCSEMS).

Method: Data were extracted from a prospectively maintained database of necrotizing pancreatitis from 1/2009 – 11/2015, with a follow-up to 5/2016. Infected or symptomatic pts were managed using a step-up approach. Endoscopic transluminal drainage (ETD) was the primary technique with or without additional percutaneous catheter drainage (PCD) if feasible. Step up approaches of sinus tract endoscopy, video assisted retroperitoneal drainage or open surgery were used in the absence of clinical improvement despite ETN. PCD was the primary approach in pts without an adequate window for ETD. At the index ETD procedure, transgastric and/or transduodenal WON access was performed using EUS guidance. Since 4/2014 pts have been preferentially treated with a 10 Fr cystotome, placement of LAMS followed by dilation of the LAMS. Prior to 4/2014, needle guided access was obtained, followed by tract balloon dilation and placement of 1-2 10 Fr PPTS or a 10 mm FCSEMS +/- one DPTS. Pts treated using PCD or surgery as the primary approach, other transmural stents or <30 day follow-up were excluded. Baseline characteristic, short-term and long-term outcomes were compared. Primary outcomes were success rate and adverse event rates related to stents. Secondary outcomes were number of procedures, length of stay, readmissions, and deaths.

Results: 138 pts were treated endoscopically of whom 53 were treated with LAMS, 29 were treated with FCSEMS and 56 were treated with DPTS. Baseline characteristics were comparable including age, gender, ethnicity, BMI, Charlson comorbidity index,

etiology of initial pancreatitis, ICU and vasopressor requirement, BISAP and APACHE II score, although patients treated with LAMS had worse baseline ascites (p=0.002), anasarca (p <0.0001), serum albumin level (p=0.009), and larger WON sizes (mean 14.7 cm, p=0.005). Infected WON rates were similar (56.6% vs 61.2%). LAMS were associated with more rapid resolution of WON: 32.1% vs 14.3% at 1 month (p=0.03) and 90.6% vs 63.6% at 6 months (p=0.04), and time to complete WON resolution at 47 vs 85 days (p=0.04). LAMS were associated with no stent migration (0 vs 8.9%, p=0.03), higher occlusion at 1 month (22.6% vs 5.4%, p <0.0001) and less number of ETN session to achieve WON resolution (mean 2.4 vs 3.4 sessions, p=0.004). On multivariate analysis, LAMS had higher WON resolution at 1 month (OR 3.48, CI 1.06-12.67, p=0.04).

Conclusion: Compared with FCSEMS and DPTS for WON, LAMS had similar safety profile but required significantly reduced number of sessions for endoscopic necrosectomy potentially due to the larger stent lumen and no stent migration likely due to the wide anchoring flanges.

#30 Which Patients with Mild Acute Pancreatitis Require Prolonged Hospitalization?

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Background and Aims: Most patients with mild acute pancreatitis (AP) have a short hospital course. In our experience, a subset of mild AP patients stay in the hospital for longer than the expected 3-5 days. The primary aim of this study was to report the prevalence of patients with mild AP who have a prolonged length of stay (PLOS), evaluate etiology and phenotype this subgroup. Our secondary aim was to compare the demographic, clinical and laboratory variables, and outcomes between the patients with PLOS and expected LOS (ELOS). We also propose a management algorithm for such patients.

Methods: Patients admitted with AP from 2003 to 2015 were prospectively enrolled into the study. Data on demographic, clinical and laboratory variables, and outcomes was prospectively collected. AP severity was re-categorized based on the Revised Atlanta Classification (RAC). Data regarding nutrition, pain management and etiology of PLOS was collected from medical records. Fluid resuscitation and re-admissions data was collected prospectively since 2011. LOS equal or greater than 8 days was considered as PLOS and less than 8 days was considered an ELOS. Continuous variables were compared using the non-parametric t-test (Wilcoxon test) and categorical variables using the Pearson's chi-square test. P-values less than 0.05 were considered significant.

Results: 231(52.5%) out of 440 enrolled patients had mild AP based on the RAC. Among those, 46 (19.9%) patients had a PLOS and 185 (80.1%) had an ELOS. Ongoing pancreatitis-related symptoms (persistent pain, oral re-feeding intolerance) were the etiology of PLOS in 31 (67.4%) of these 46 patients followed by cholecystectomy during the same admission in 12 (26.1%) patients. There was no significant difference in age, sex, body mass index, comorbidities, etiology of AP, smoking history, alcohol consumption, lipase levels, use of narcotic pain medicines at admission or discharge, fluid resuscitation and re-admissions between the two groups. Patients with PLOS were more likely to have been transferred from community hospitals (61.3% vs 30.8%, p=0.001), have SIRS at 48hrs from admission (37% vs. 13.4%, p <0.001), havea longer fasting time (6.6 vs 2.8 days, p<0.001) and required nutritional support more frequently (30% vs 1.6%, p<0.001), compared to ELOS patients.

Conclusions: About 20% of patients with mild AP have a longer than expected hospital stay. Most of these patients have persistent pain or oral refeeding intolerance as the cause of PLOS. An early decision for enteral nutritional support in these patients may help in control of symptoms, early discharge and potentially reduce health care costs.

#31 Endoscopic Sphincterotomy (ES) May Not Alter the Natural History of Idiopathic Recurrent Acute Pancreatitis (IRAP)

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Aims: The term IRAP is used when no identifiable cause of RAP is evident. Sphincter hypertension has been postulated by some to be etiologic in IRAP, while others have suggested this to be an effect of IRAP rather than a cause. We reviewed the clinical results of ES on IRAP.

Methods: We retrospectively studied the natural course of IRAP patients enrolled in the North American Pancreatitis Study 2 between 2000-2006 from UPMC based on whether they underwent ES or were managed medically. The ES group included patients who underwent manometry or were treated empirically. We collected information on demographics, age at first AP, number of attacks, rate of attacks at baseline, and history of severe AP. Duration of follow-up was defined from the time of intervention (ES or decision for medical management) until last contact. During follow-up, we recorded occurrence of any subsequent AP attack, rate of AP attacks (primary outcomes) and diagnosis of definitive chronic pancreatitis (CP) (secondary outcome). Similar data was abstracted for medically managed patients with alcoholic RAP.

Results: Of 53 IRAP patients, 29 (55%) underwent ES (lone biliary, lone pancreatic, dual sphincterotomy in one-third each). Among IRAP patients, 17 (32%) underwent manometry. Of these patients, 14 had abnormal studies and received ES, and 3 had normal studies and did not receive ES. When compared with medically managed IRAP patients, those who underwent ES were similar in age, sex, prior severe AP, and rate of AP attacks (1.57 vs. 1.41 per year, p=0.84), but had significantly more AP attacks at baseline (median 3 vs 2, p=0.03). During follow-up (median 7 years, IQR 4.1, 10.1), when compared with medically managed patients, those who underwent ES had a similar risk of any subsequent AP (33 vs. 55%, p=0.11) and number of AP attacks (median 1 vs 0, p=0.19). Rate of AP attacks during follow-up decreased significantly overall and was not significantly different between the two groups (median 0.15 vs. 0, p=0.33). From Poisson regression analysis, significant predictors for rate of AP attac ks during follow-up were sex and rate of AP attacks at baseline, but not ES (Table 1). When compared with IRAP, alcoholic RAP patients had a lower rate of AP attacks at baseline, but a higher risk of subsequent AP and rate of AP attacks during follow up. Overall, 14% progressed to CP - 24% with IRAP and ES, 8% medically managed IRAP, and 27% with alcoholic RAP (p=ns).

Conclusions: ES, chosen in patients with higher burden of attacks, does not seem to impact the natural history of IRAP. Alcoholic RAP has a more aggressive course than IRAP. Progression to CP is higher in IRAP patients with more aggressive baseline course and alcoholic RAP. Our findings call for an appropriately powered randomized trial to definitively answer the role of ES in IRAP.

#32 Can Development of Acute Kidney Injury in Acute Pancreatitis be Predicted?

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Introduction: Acute kidney injury (AKI) is an important cause of morbidity and mortality in severe acute pancreatitis (AP).Cytokines play an important role in the pathophysiology of AP and AKI.

Aims & Methods: To study the predictive role of inflammatory cytokines in development of AKI in patients with AP. In this prospective study between July 2013 and December 2014 consecutive eligible patients of AP underwent complete demographic, clinical, biochemical and radiological evaluation. Severity classification was done using revised Atlanta classification and systemic inflammatory response score (SIRS) , Bedside Index of Severity of Acute Pancreatitis (BISAP), CT Severity Index (CTSI) and APACHE II scores were calculated. Organ failure was defined according to modified Marshall Score . Development of AKI was monitored in all the patients. Serum levels of interleukin (IL)-6, IL-8, IL-10, IL-1b and TNFα were measured at baseline (day 1) for all patients and on day 3 in those who had AKI. For comparative analysis patients were divided into 2 groups: with and without AKI. The AKI cohort was further subdivided into persistent AKI (P-AKI) and transient AKI (T-AKI). Statistical analysis was done using SPSSv20.0 to study the predictive value of different cytokines for development of AKI.

Results: Of the 107 patients (mean age of 38.4 yrs, 64.5% males, etiology: alcohol 36.4% gallstone disease 26.2% and others 51.4%), AKI developed in 20 (18.7%). T-AKI was seen in 7 (35%) while 13 (65%) had P-AKI. Patients with AKI had significantly higher IL-6 ($p=0.004$), IL-8 ($p<0.0001$) and TNFα ($P=0.05$) levels on day 1 when compared to non-AKI group. In the AKI group, day 3 levels of TNFα ($p=0.010$) were significantly higher than day 1 levels whereas IL-10 ($p=0.04$) levels were significantly lower than day 1 levels. Significant rise on day 3 of TNFα ($p=0.004$) was observed in the P-AKI group. Day 1 levels of IL-6 and IL-8 had strong positive correlation with severity indices such as SIRS ($p<0.001$), BISAP ($p<0.001$) and CTSI ($p<0.0001$) as also with outcome measures such as need for intervention ($p<0.0001$), hospital stay ($p<0.0001$) and intensive care stay ($p<0.0001$).

Conclusion: IL-6 and IL-8 levels at admission were significantly associated with development of AKI in AP. Rising levels of TNFα suggested development of persistent AKI.