KU School of Medicine

DEPARTMENT OF INTERNAL MEDICINE

RESEARCH DAY

November 16th, 2022

This event is partially sponsored by the Bohan Visiting Professor Program

Internal Medicine Research Day 2022 Schedule

Wednesday, November 16th, 2022	
9:00AM – 11:30AM	Morning Poster Sessions **Ad Astra Room, Health Education Building, HEB 5202** Judging Session 1 – 9:00 a.m. - 10:00 a.m. Judging Session 2 – 10:00 p.m. - 11:00 a.m.
11:30AM	Lunch catered by *The Russell* **School of Nursing Auditorium Lobby**
11:45AM–12:45PM	Internal Medicine Research Day Plenary Address/Grand Rounds: **Heidi Crane, MD, MPH:** "***Lessons Learned from a Career in HIV Research"*** **School of Nursing Auditorium, SON G013**
12:45PM–1:00PM	Q&A Session **School of Nursing Auditorium, SON G013**
1:30PM–4:00PM	Afternoon Poster Sessions **Ad Astra Room, Health Education Building, HEB 5202** Judging Session 3 – 1:30 p.m. - 2:30 p.m. Judging Session 4 – 2:30 p.m. - 3:30 p.m.
3:30PM-5:30PM	Reception **Ad Astra Room, Health Education Building, HEB 5202** Open bar and appetizers catered by *Brancato's*
4:30PM	Presentation of Awards **Ad Astra Room, Health Education Building, HEB 5202**

2022 Research Showcase Abstracts

1

Biopsy-Derived Human Barrett's Esophagus Organoids Express Phenotypic Markers of Columnar, Intestinal, and Esophageal Submucosal Gland Cells

Authors: Zhang, Qiuyang D.; Bansal, Ajay; Dunbar, Kerry B.; Chang, Yan; Balaji, Uthra; Gu, Jinghua; Zhang, Xi; Pan, Zui; Spechler, Stuart J.; Souza, Rhonda F.

Author Affiliations: Department of Medicine, Center for Esophageal Diseases, Baylor University Medical Center at Dallas, Center for Esophageal Research, Baylor Scott & White Research Institute; Department of Gastroenterology and Hepatology, University of Kansas Medical Center and the Kansas Cancer Institute, Kansas City, Kansas; University of Texas Southwestern Medical Center/Dallas VA Medical Center, Dallas, Texas; College of Nursing and Health Innovation[8], the University of Texas at Arlington, Arlington, TX; Biostatistics Core, Baylor Scott & White Research Institute, Dallas, TX

Introduction:
Barrett's esophagus (BE), the condition in which a metaplastic mucosa with gastric and intestinal features replaces esophageal squamous mucosa damaged by GERD, is the precursor of esophageal adenocarcinoma. Tissue-relevant organoids are preferred models for studying human disease processes, but the extent to which these organoids recapitulate their tissue of origin is a critical factor for their utility. Few studies have used human BE organoids and, in those that have, the BE organoids were incompletely characterized. Now, we have established human BE organoids from endoscopic biopsies, and have carefully characterized their growth, differentiation, and phenotype

Methods:
Endoscopic biopsies from 6 BE patients (all male Caucasians; mean age 62 years; mean BE length 4 cm) were minced into ≤0.3 mm fragments, rinsed in PBS containing antibiotics and digested using collagenase A. Aggregates >70 μM were removed by filtration and cells were plated in 25μl Matrigel with supplemented advanced DMEM/F12. We evaluated organoid: 1) morphology by optical microscopy, 2) formation rate (organoids at day 7 per number of cells plated), 3) growth by diameter, 4) histology by H&E and Alcian blue staining, and 5) stem cell and differentiation marker expression by qPCR and immunofluorescence

Results:
Biopsy-derived BE organoids were generated from all 6 patients. Average organoid formation rate was 10%; organoid size significantly increased from days 3-16 ($p<0.0001$). Organoids were grown for >5 passages, frozen and, after thawing, organoids reformed. Three distinct morphologies were seen during organoid development: 1) cystic (days 3-7), 2) ellipsoid with crypt-like buds (days 9-12), and 3) glandular-appearing (days 14-21; Figure 1). H&E staining on day 12 demonstrated a single layer of mucin-producing columnar cells, and Alcian blue staining confirmed the presence of acidic mucins (Figure 1). mRNA expression patterns revealed that, during organoid development, developmental stem cell markers like SOX2, OCT4, and KLF4 declined while expression of columnar/intestinal stem cell markers like SOX9 and LGR5 increased, as did expression of columnar/intestinal differentiation markers (MUC2, TFF3, villin) (Figure 2). Interestingly, BE organoids expressed mRNA and protein for LEFTY1 and OLFM4, which are putative markers of esophageal submucosal glands

Conclusion:
Using endoscopic biopsies, we have successfully established BE organoids that contain both columnar and goblet cells typical of BE. Progression from the cystic to organoid stage was associated with upregulation of stem cell and differentiation markers of columnar, intestinal, and esophageal submucosal gland cells. Thus, our BE organoids recapitulate the histologic and molecular features of BE tissue, and could serve as high-fidelity models for studying the biology and pathophysiology of human BE

Funding Sources: Funded by NIH R01DK124185 and Department of Veteran Affairs CX001668 to RFS and the American College of Gastroenterology Clinical Research Award to AB

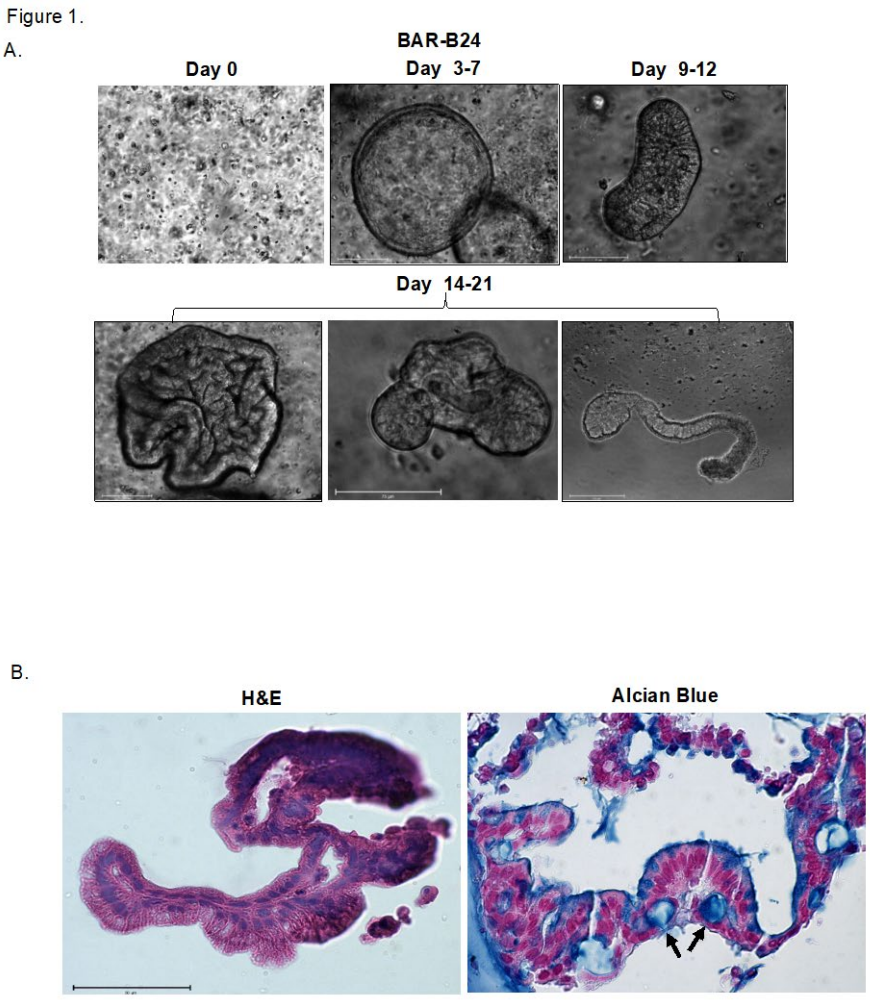
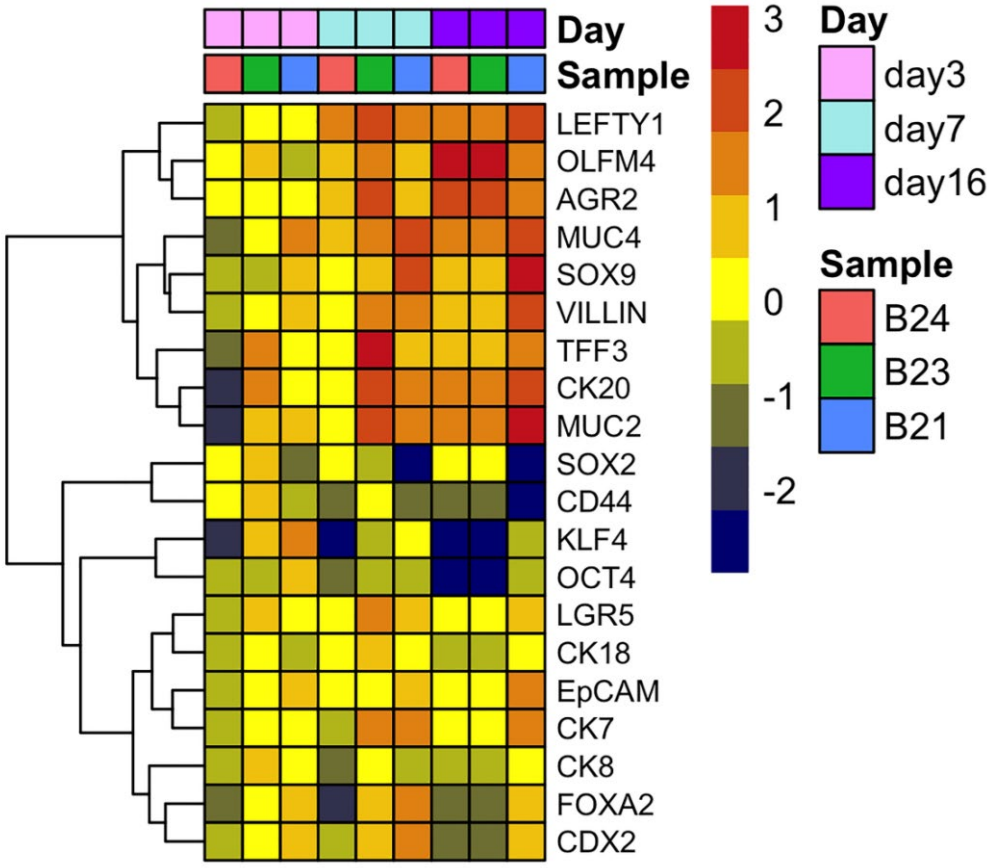


Figure 1. (A) Optical Microscopy demonstrating the three distinct morphologies seen during BE organoid development. (B) H&E and Alcian blue staining of a BE organoid at day 12. Black arrows indicate goblet cells. Scale bar = 75 μm

Figure 2: Heat-map and hierarchical clustering with dendrogram generated from qPCR gene expression data of 3 BE organoids at days 3, 7, and 16 of development. Note the relative reduction of developmental stem cell markers like SOX2, OCT4, and KLF4 and the relative upregulation of columnar/intestinal stem cell markers like SOX9 and LGR5 from days 3-16. Relative upregulation of expression of columnar/intestinal differentiation markers was also seen. Red color corresponds to high relative expression and blue color corresponds to low relative expression.



2

Inflammatory cell-cell crosstalk can be altered by exosome cargo reprogramming

Authors: Priyanka Ghosh[1,2], Kyo Sasaki[1,2], Kayla E King[1,2], Steven A Weinman[1,2], and Ann L. Wozniak[1,2]

Author Affiliations: [1]Department of Internal Medicine, University of Kansas Medical Center, Kansas City KS, 66160, U.S.A
[2]Liver Center, University of Kansas Medical Center, Kansas City KS, 66160, U.S.A

Background:

Macrophage-derived exosomes play key roles in intercellular communication. Within the liver, they have been linked to several inflammatory diseases including nonalcoholic fatty liver disease (NAFLD).

Methods & Results:

In this study we found that inflammatory macrophages cause injury to hepatocytes, in part by a cell-cell cross talk phenomenon, involving the secretion of exosomes containing pro-inflammatory cargos. Incorporation of these inflammatory signals into exosomes requires the cleavage of the trafficking adaptor protein RILP, which, as previously shown, results from inflammasome-induced caspase 1 activation. RILP cleavage mediated inflammatory cell-cell communication can be altered by overexpressing a dominant negative, non-cleavable form of RILP (ncRILP). ncRILP exosome preparations, by themselves, are sufficient to suppress inflammatory effects in hepatocytes. We also examined RILP cleavage in peripheral blood monocytes isolated from both NAFLD and NASH patients by measuring the cellular localization of Rab7. Rab7 is a RILP binding protein that co-localizes with and follows RILP (cleaved and non-cleaved) throughout the cell. When RILP is not cleaved, Rab7 localizes in a tight vesicular structure near the perinuclear region while the cleaved form of RILP re-distributes Rab7 throughout the cytoplasm. For NAFLD patients, Rab7 appeared in a condensed, peri-nuclear area while in NASH patients, the Rab7 distribution was throughout the cell periphery. This indicates that patients with NASH have a higher level of RILP cleavage and thus, increased baseline inflammation.

Conclusion:

Together this suggests that both direct RILP manipulation and/or supplying ncRILP-modified exosomes could be used as a novel therapy for the treatment of inflammatory liver diseases, and the Rab7 distribution pattern could be a potential non-invasive diagnostic marker for the detection of NAFLD and NASH.

3

The nicotine metabolite cotinine causes mucociliary dysfunction

Authors: Price, Michael[1]; Baumlin, Nathalie[2]; Yoshida, Makoto[2]; Chiu, Alexander[1]; Salathe, Matthias[2]; Kim, Michael[2]

Author Affiliations: [1]University of Kansas Medical Center, Department of Otolaryngology; [2]University of Kansas Medical Center, Department of Internal Medicine, Division of Pulmonary, Critical Care and Sleep Medicine

Introduction:

Electronic nicotine delivery systems (ENDS) have been widely adopted as an alternative to traditionally smoked combustible cigarettes. Recent data suggest that vaping delivers a much higher level of airway nicotine compared to traditional cigarettes. Moreover, recent data demonstrate that nicotine causes mucociliary dysfunction by disrupting ion channel function and ciliary beat frequency. Nicotine itself is metabolized in the airway, but the relationship between nicotine metabolites and mucociliary dysfunction is unknown. We hypothesized the nicotine metabolite cotinine causes mucociliary dysfunction.

Methods:

We exposed primary human bronchial epithelial cells (HBECs) cultured at air-liquid interface (ALI) to biologically relevant concentrations of the nicotine metabolite cotinine and measured ciliary beat frequency (CBF) using high speed video microscopy. Cystic fibrosis transmembrane conductance regulator (CFTR) and large conductance, Ca(2+)-activated, and voltage-dependent K(+) (BK) channel functions were recorded in Ussing chambers.

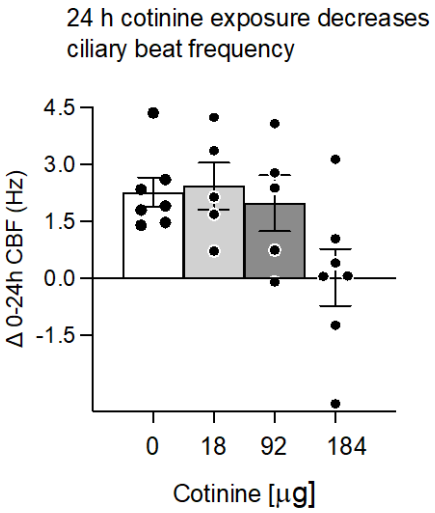
Results:

24-hour cotinine exposure (0-184 µg) caused dose-dependent decreases in CBF (control, delta 2.26 Hz vs 184 µg cotinine, 0.02 Hz; $P < 0.05$; $n = 7$) and CFTR (control, 17.9 ± 2.6 µA / cm^2 vs 184 µg cotinine, 11.8 ± 1.4 µA / cm^2; $P < 0.05$; $n= 7$), and trending decreased BK (control, 30.7 ± 3.9 µA / cm^2 vs 184 µg cotinine, 22.7 ± 2.9 µA / cm^2; $P = 0.3$; $n= 4$) activities.

Conclusion:

Our findings are the first to demonstrate cotinine causes decreased CBF and CFTR dysfunction. These data suggest that airway levels of nicotine associated with ENDS may result in cotinine production with deleterious effects on the mucociliary apparatus. Thus, cotinine-levels derived from ENDS may be harmful to lung function. Ongoing studies are aimed at elucidating the mechanisms of cotinine-induced mucociliary dysfunction.

Funding Sources: FAMRI (CIA #130033 to M.S.); James and Esther King Florida Biomedical Research Program (Grant #5JK02 to M.S.); and NIH (HL139365, HL157942 and HL133240 to M.S.).



4

Risk stratification of patients who present with chest pain and have normal troponins using a machine learning model

Authors: Shafiq, Muhammad[1]; Mazzotti, Diego[1]; Gibson, Cheryl[1]

Author Affiliations: [1]The University of Kansas Medical Center

Introduction:

Risk stratification tools exist for patients presenting with chest pain to the emergency room and have achieved the recommended negative predictive value (NPV) of 99%. However, due to low positive predictive value (PPV), current tools result in unwarranted serial laboratory tests and cardiac stress tests (CSTs). This study aimed to create a machine learning model (MLM) for risk stratification of chest pain with a better PPV.

Methods:

This retrospective cohort study used de-identified hospital data from January 2016 until November 2021. Inclusion criteria were patients >21 years who presented to the emergency room, had at least two serum troponins measured, were subsequently admitted to the hospital, and had a CST within 4 days of presentation. Exclusion criteria were elevated troponin (>0.05 ng/mL) and missing body mass index data. The primary outcome was abnormal CST. Demographics, coronary artery disease history, and cardiovascular risk factors were evaluated as predictors of abnormal CST. Patients were categorized into a high-risk (coronary artery disease history or more than two risk factors) or low-risk group (all other patients). Bivariate analysis was performed using a χ^2 test or Fisher's exact test. Age was compared by *t* test. Binomial regression, random forest, and XGBoost were used for prediction. Binomial regression was also used for inference.

Results:

The final cohort of the study included 2328 patients, of which 245 (10.52%) patients had abnormal CST. When adjusted for covariates in the binomial regression model, male sex (risk ratio (RR): 1.52, 95% confidence interval (CI): 1.2-1.94, $P < 0.001$), coronary artery disease history (RR: 4.46, 95%CI: 3.08-6.72, $P < 0.001$), and hyperlipidemia (RR: 3.87, 95%CI: 2.12-8.12, $P < 0.001$) were associated with CST. Incidence of abnormal CST was 12.2% in the high-risk group and 2.3% in the low-risk group (RR: 5.31, 95%CI: 2.75-10.24, $P<0.001$). The XGBoost model had the best PPV of 24.33%, with an NPV of 91.34% for abnormal CST.

Conclusion:

The XGBoost model provided a better PPV than the widely used history, electrocardiogram, age, risk factors, and initial troponin pathway (HEART) score for stratification (24.33% *vs* 13.00%). This highlights the beneficial potential of MLMs in clinical decision-making.

Funding Sources:

This work was supported by a CTSA grant from NCATS awarded to the University of Kansas for Frontiers: University of Kansas Clinical and Translational Science Institute (# UL1TR002366) The contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH or NCATS.

Table 1: Comparison of the models for the prediction of an abnormal cardiac stress test

Feature	BR	RF	XGBoost
Prediction cutoff value	0.20	0.18	0.27
Sensitivity (95%CI)	45.06 (44.23, 45.88)	13.92 (13.50, 14.33)	30.54 (29.30, 31.79)
Specificity (95%CI)	80.46 (80.14, 80.79)	93.66 (93.53, 93.80)	88.51 (88.15, 88.86)
PPV (95%CI)	21.34 (21.09, 21.60)	20.55 (20.05, 21.04)	24.33 (23.46, 25.20)
NPV (95%CI)	92.55 (92.42, 92.69)	90.24 (90.14, 90.35)	91.34 (91.12, 91.56)

BR: Binomial regression; CI: Confidence interval; NPV: Negative predictive value; PPV: Positive predictive value; RF: Random forest.

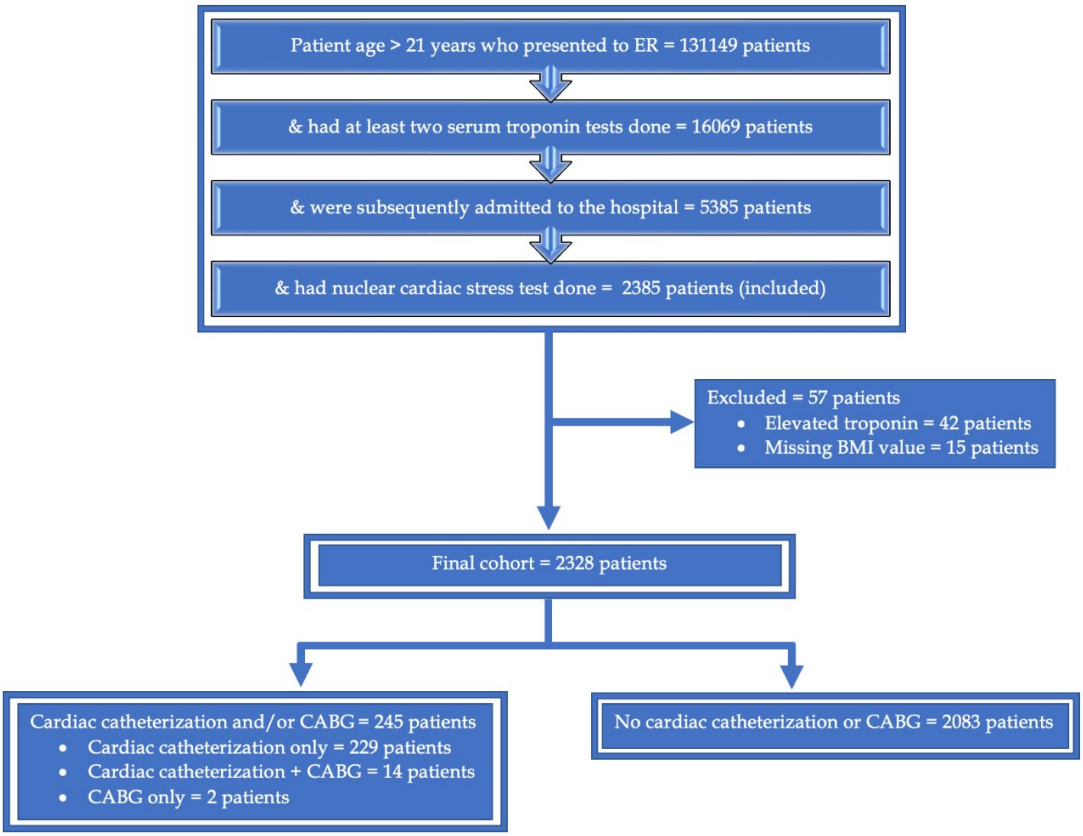


Figure 1: Flowchart of the cohort selection. BMI: Body mass index; CABG: Coronary artery bypass graft; ER: Emergency room.

5

Method of Referrals for Clinical Research Trials and their Impact on Participant Motivations

Authors: Holden, Rachel[1]; Flores, Erica[1]; VanSciver, Angela[1,2]; Clutton, Jon[1,2]; Finley, Katrina[1,2]; Watts, Amber[1,2]; Szabo-Reed, Amanda[1,3]

Author Affiliations:
The University of Kansas Medical Center, KU Alzheimers Disease Research Center[1]
The University of Kansas, Psychology[2]
The University of Kansas Medical Center, Department of Internal Medicine, Division of Physical Activity and Weight Management[3]

Introduction:
The MOTIVES study was developed to capture any patterns in motivations for those who were physician referred via Epic-based Best Practice Advisory (BPA), as compared to those who were self-referred to the physical health intervention trial, LEAP! Rx. LEAP! Rx is an on-going 12-month randomized, controlled study with two groups. The intervention group receives regulated exercise and education as compared to a waitlist control.

Methods:
219 total participants, 118 physician referred and 101 self-referred were randomized for LEAP! Rx. 160 total participants consented to complete the MOTIVES survey at baseline and end of intervention. MOTIVES is a ten-section survey assessing motivations to participate in the intervention using a Likert scale. Within the MOTIVES subsample, 98 participants were physician referred and 62 were self-referred. The responses in the MOTIVES survey will be analyzed at a future date to compare recruitment mode, response on the MOTIVES questionnaire and study adherence. Demographics are included in Table 1. Patterns related to age, gender, race, ethnicity, or education will also be explored.

Results:
Preliminary analysis focused on demographics by method of referral. 160 participants consented to do the MOTIVES survey, 18 physician referred were males with 14 males self-referred. The average age of all participants was 71.856 +/- 4.886 years old and average years of education is 21.406 +/- 2.313 years, respectively. In the total sample, 22, or 13.6%, of the participants identified as a minority race with 5 participants reporting to be of Hispanic ethnicity. Only 2 of the 22 participants identifying as minorities were self-referred, the other 20 were referred by a physician.

Conclusions:
We expect participants that are physician referred to report increased motivation from their physician while those who are self-referred will have more motivation centered around their personal health or desire to help others through research. We also hypothesize that those who are self-referred will have greater study adherence. Future studies can conform their recruitment efforts to better meet the motivations for the target population being recruited.

Funding: Grant #R01AG052954

Table 1. Baseline Demographics

	Physician-Referred	Self-Referred	Total Sample
Referral Method	98 physician referred pts completed MOTIVES	62 self-referred pts completed MOTIVES	160 consented (subset of those enrolled)
Age	71.500 +/- 4.521 yo	72.419 +/- 5.404 yo	71.856 +/- 4.886 yo
Gender	80 Females	48 Females	128 Females
Race	White: 78 (79.6%) Minority: 20 (20.4%)	White: 60 (96.8%) Minority: 2 (3.2%)	White: 138 (86.3%) Minority: 22 (13.6%)
Ethnicity (Hispanic/Latino)	2 Hispanic Reported	3 Hispanic Reported	5 Hispanic Reported
Years of Education	21.439 +/- 2.479 yrs	21.355 +/- 2.041 yrs	21.406 +/- 2.313 yrs

7

Role of Commensal *Bifidobacterium* Derived Extracellular Vesicles in Modulating Immune Response in Context with Anti-PD-1 therapy

Authors: Preet, Ranjan [1]; Vishwakarma, Vikalp [2]; Choudhary, Sonali[3]; Dai, Qun[1;] Thomas, Sufi[3,4]; Shahid, Umar [5]; Anant, Shrikant[3]; Sun, Weijing [1]; Zhang, Jun[1,3]

Author Affiliation: [1]Division of Medical Oncology, Department of Internal Medicine, University of Kansas Medical Center, Kansas City, KS 66160, USA.

[2]Department of Pathology and Laboratory Medicine University of Kansas Medical Center Kansas City, KS 66160, USA.

[3]Department of Cancer Biology, University of Kansas Cancer Center, Kansas City, KS 66160, USA.

[4]Departments of Otolaryngology, University of Kansas Medical Center, Kansas City, KS 66160, USA.

[5]Department of Surgery, University of Kansas Medical Center, Kansas City, KS 66160, USA.

Introduction:

Lung cancer is the leading cause of cancer-related deaths worldwide and one of the greatest challenges in cancer treatment. Although, immunotherapy is now a standard of care for patients with advanced/metastatic non-small cell lung cancer (NSCLC), many patients do not derive benefit directly. Several studies have elucidated new strategies to improve antitumor immune response via modulation of gut microbiome. Recently, it has been published that commensal *Bifidobacterium* can promote antitumor immunity and facilitates response to anti-PD-L1 therapy. However, it remains largely unknown how gut microbiota can remotely affect lung cancer microenvironment and subsequently modulate immune response. Here, we are demonstrating the role of commensal *Bifidobacterium*-derived extracellular vesicles (BEVs) in modulating therapeutic efficacy of anti-PD-1 therapy in NSCLC.

Methods:

Bifidobacterium probiotic cocktail from SeekingHealth company was grown in Bifidus Selective Medium (BSM) broth at 37°C for 48h in an anaerobic chamber. BEVs were prepared by ultracentrifugation method. C57BL/6J mice were used to perform all the *in-vivo* experiments. Several methods were adopted such as scanning electron microscopy, Transmission electron microscopy. western blot analysis, fluorescent microscopy, confocal microscopy, immunogold labelling, *in-vivo* imaging, Ki -67 staining, cytokine analysis and immunohistochemistry to complete the study.

Results:

To test the effect of BEVs, human (A549, H460) and mouse (LL-2) lung cancer cells were treated with BEVs. BEV uptake resulted in a significant upregulation of PD-L1 (~2-3-fold) expression. BEVs were also taken up by organoids from C57BL/6J mouse intestine and human lung cancer tissue. BEVs administered via oral gavage were up-taken in grafted LL-2 tumors. Along with anti-PD-1, BEVs can synergistically reduce tumor growth (~2.2 fold) in LL-2 syngeneic tumor mouse model. Ki67 staining showed that BEVs and anti-PD-1 therapy mitigated tumor cell proliferation with significant changes in cytokine (TNF-α, IFN-γ and IL-2) expression. The number of CD3+ (~4-fold) and CD8+ (~5-fold) tumor-infiltrating lymphocytes were significantly increased when mice were treated with combinatorial treatment.

Conclusions:

This work has identified a novel connection between bacteria derived EVs and tumor immune microenvironment along with providing preclinical evidence that bacterial EVs can play important role in modulating immunotherapy.

Funding: The startup funds GR13525 and KUCC E3DT Pilot Grant GR13945 to J.Z. were used to perform this study.

8

A Phase II Study of Perioperative Pembrolizumab plus mFOLFOX Combination in Patients with Potentially Resectable Adenocarcinoma of the Esophagus, Gastroesophageal Junction (GEJ) and Stomach

Authors: Sun, Weijing; Saeed, Anwaar; Veeramachaneni, Nirmal; Al-Rajabi, Raed; Kasi, Anup; Al-Kasspooles, Mazin; Baranda, Joaquina; Phadnis, Milind; Godwin, Andrew K; Olyaee, Mojtaba; Madan, Rashna; Streeter, Natalie; Nagji, Alykhan; Williamson, Stephen

ABSTRACT NOT AVAILABLE

9

Increased Depression and Anxiety Symptoms are Associated with Higher Nightmare Frequency within the Wisconsin Sleep Cohort

Authors: Gratton, Matthew K.P. [1,2]; Mazzotti, Diego R.[1]; Hamilton, Nancy A.[2]

Author Affiliations: [1]Department of Internal Medicine, University of Kansas Medical Center, [2]Social and Behavioral Sciences, Psychology, University of Kansas

Introduction:
Nightmare frequency is thought to be common in people with psychiatric disorders. While research has shown that increased nightmare severity is strongly associated with high negative affect, little is known about the direction of the relationship between nightmare frequency and other depression or anxiety symptoms. As nightmares may put patients at higher risk of development or exacerbation of such symptoms, understanding whether depression and anxiety are risk factors for increased nightmare frequency is imperative. This study sought to examine the association of depression and anxiety with incidence of higher nightmare frequency.

Methods:
Using cross-sectional and longitudinal data from the Wisconsin Sleep Cohort, accessed through the National Sleep Research Resource, we conducted an analysis of demographics, co-occurring sleep disturbances, mental health measures and nightmare frequency. The study sample included 1051 Wisconsin state employees with a baseline assessment. All participants were screened for depression and anxiety symptoms using the Zung Depression Scale, and the State-Trait Anxiety Inventory. Nightmares were measured using an ordinal variable capturing nightmare frequency per month. Using a theory based clinical cutoff, anxiety, depression, and nightmare measures were split into binary variables representing higher risk and lower risk for incidence of symptoms. Inclusion criteria of low nightmares at baseline was used to correct for the preexisting association between frequent nightmares and anxiety and depression. Sleep disturbances, medication use, nightmares and insomnia were based on self-report instruments. Associations were assessed using logistic regression adjusted for age, body mass index, and sex.

Results:
From the baseline sample, 714 participants had a follow-up assessment (68%; mean [SD] follow-up time 4.5 [1.7]). After adjusting for confounders, more severe anxiety at baseline was associated with increased incidence of higher frequency of nightmares at follow-up (OR=1.36; 95%CI=0.44-3.12, p <0.001), however more severe depression was not (OR=2.62; 95%CI=1.00-6.86; p = 0.051).

Conclusion:
Participants with higher risk of anxiety experienced higher incidence of frequent nightmares upon a 4-year follow-up, independent of confounders. Depression risk was not independently associated with nightmare frequency. Further research should be targeted at gaining a better understanding of the potential mechanisms explaining this relationship.

Funding Sources: This Wisconsin Sleep Cohort Study was supported by the U.S. National Institutes of Health, National Heart, Lung, and Blood Institute (R01HL62252), National Institute on Aging (R01AG036838, R01AG058680), and the National Center for Research Resources (1UL1RR025011). The National Sleep Research Resource was supported by the U.S. National Institutes of Health, National Heart Lung and Blood Institute (R24 HL114473, 75N92019R002)

10

Positive Airway Pressure Utilization, Major Adverse Cardiovascular Events Incidence Risk and Mortality in Medicare Beneficiaries with Obstructive Sleep Apnea

Authors: Mazzotti, Diego R[1]; Waitman, Lemuel R[2]; Gozal, D[2]; Song, Xing[2]

Author Affiliations: [1]University of Kansas Medical Center, [2]University of Missouri School of Medicine

Introduction:

Positive airway pressure (PAP) is the first line treatment for moderate-severe or symptomatic obstructive sleep apnea (OSA). Randomized controlled trials have established that PAP therapy has beneficial impact on cardiovascular and metabolic functions. However, evidence on the benefits of PAP for preventing major adverse cardiovascular events (MACE) is limited. We aimed to determine the association between PAP utilization and incidence of MACE and all-cause mortality in a large sample of Medicare beneficiaries.

Methods:

Medicare beneficiaries (>65 years) with at least 5 years of consecutive enrollment to part A and B and ≥2 distinct OSA claims were collected from multi-state (Kansas, Missouri, Iowa, Wisconsin, Nebraska, Minnesota, Texas, Utah, North Dakota, South Dakota and Indiana), multi-year (2011-2017) Medicare fee-for-service claims data. We further required at least 1-year enrollment before the first OSA claim. Evidence of PAP utilization and index date was defined based on the first Healthcare Common Procedure Coding System PAP initiation codes (E0601, E0470, E0471) after first OSA diagnosis. MACE was defined as the first occurrence of myocardial infarction, coronary revascularization, stroke, or heart failure (identified by diagnostic and procedure code claims) after PAP initiation. Analyses were adjusted by age at initial OSA diagnosis, sex, race and presence of hypertension, type 2 diabetes, obesity, and evidence of MACE prior to the index date.

Results:

Our sample included 212,445 eligible Medicare beneficiaries with evidence of OSA diagnosis (mean [SD] age 75 [5.7] years; 45.2% women; median [Q1, Q3] follow-up 4 [2.0, 4.9] years at censoring). Five-year MACE cumulative incidence rate was 59.3% and the mortality rate was 17.8%. In adjusted analyses, OSA patients with evidence of PAP utilization (50.8%) had significantly lower MACE incidence risk (HR=0.812; 95%CI=0.803-0.822; p<0.0001) when compared to those without evidence of using PAP. OSA patients with evidence of PAP utilization also had significantly lower mortality risk (HR=0.575; 95%CI=0.560-0.591; p<0.0001). Pre-existing hypertension, type II diabetes and obesity were also significantly associated with increased mortality and MACE risk.

Conclusion:

PAP utilization based on device initiation derived from claims data is associated with lower MACE incidence and mortality in older adults that are Medicare beneficiaries.

Funding Sources:

American Heart Association (20CDA35310360), Patient-Centered Outcomes Research Institute (RI-CRN-2020-003-IC); NIH CTSA NCATS Frontiers: University of Kansas Clinical and Translational Science Institute (UL1TR002366); Tier 2 grant, University of Missouri.

11

Non-steroidal anti-inflammatory drugs (NSAIDs) for Chemoprevention in Patients with Familial Adenomatous Polyposis: a systematic review and meta-analysis

Authors: Farooq, Umer; Alayli, Abdallah El; Duvvuri, Abhiram; Teja, Ravi; Sahithi, Razan; Mansour, Razan; Mustafa, Reem A.; Bansal, A

Author Affiliations: Department of Internal Medicine, Outcomes and Implementation Unit, University of Kansas Medical Center, Kansas City, KS, USA

Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, ON, Canada

Division of Gastroenterology and Hepatology, the University of Kansas Medical Center, Kansas City, KS and the University of Kansas Cancer Center, Kansas City, KS.

Introduction:

Published literature shows mixed reports of the benefits of non-steroidal anti-inflammatory drugs (NSAIDs) in colon cancer prevention in patients with familial adenomatous polyposis (FAP). We conducted a systematic review and performed a meta-analysis to assess the impact of NSAIDs on polyp burden and progression in patients with FAP.

Methods:

We searched PubMed, EMBASE, Google Scholar, and Cochrane for randomized controlled trials (RCT) reporting effects of NSAIDs on colorectal polyp regression in patients with FAP (Prospero ID: CRD42021247683). All trials compared the use of NSAIDs (selective or non-selective) versus placebo in 1:1 or 2:1 ratio. The primary endpoints were mean percent change in a) polyp number and b) polyp size. Mean differences (MD) between the two study arms were pooled using random effects model using RevMan and the quality of the evidence was assessed using the Cochrane Risk of Bias tool for RCT and the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology.

Results:

Over 718 citations were screened, and 4 trials fit the inclusion criteria (1-4). The trials included 181 and 55 patients in the NSAIDS and placebo groups respectively (49.7% females, mean age 33 ± 5.4years, mean duration of follow-up 8.25 ± 2.49 months). The mean duration of NSAIDs treatment was 7.5 ± 2.37 months. The risk of bias was low for all studies. Treatment with NSAIDs reduced both polyp number (MD -24.68% (95% CI -39.45%, -9.1%) (Low certainty)(**Figure 1A**) and polyp size (MD -21.69% (95% CI -44.76%, 1.34%) (Low certainty) when compared to placebo (**Figure 1B**). The most common gastrointestinal adverse events reported in the studies were stomatitis, diarrhea, abdominal pain, while side effects leading to drug discontinuation included gastroenteritis and drug allergy without significant differences in adverse event between two groups.

Conclusion:

Low certainty evidence showed that short-term NSAID use reduced polyp number by ~25% and polyp size by ~22%. Further studies are needed before NSAIDs can be universally recommended for colon cancer chemoprevention in FAP**.**

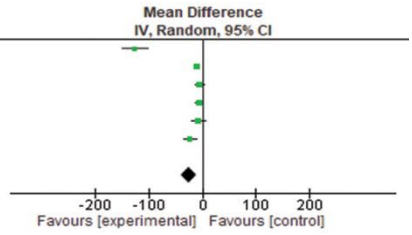
Funding Sources: n/a

Figure 1: Forest Plots.

A

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Giardiello (1993) (Sulindac 150 mg)	-56	10	11	70	40	11	12.5%	-126.00 [-150.37, -101.63]
Higuchi (2003) (Rofecoxib 25 mg)	-6.8	2.6	12	3.1	2.7	9	18.8%	-9.90 [-12.20, -7.60]
Iwama (2006) (Tiracoxib 150 mg)	1	9	21	6	17	20	17.8%	-5.00 [-13.39, 3.39]
Iwama (2006) (Tiracoxib 200 mg)	0	7	19	6	17	20	17.9%	-6.00 [-14.09, 2.09]
Steinbach (2000) (Celecoxib 100 mg)	-11.9	30.3	32	-4.5	16.4	15	16.3%	-7.40 [-20.78, 5.98]
Steinbach (2000) (Celecoxib 400 mg)	-28	24	30	-4.5	16.4	15	16.8%	-23.50 [-35.44, -11.56]
Total (95% CI)			**125**			**90**	**100.0%**	**-24.68 [-39.45, -9.91]**

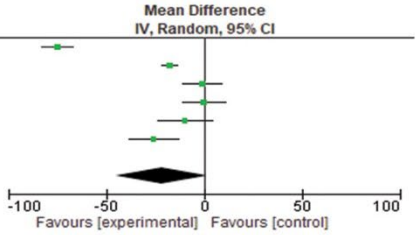
Heterogeneity: Tau² = 300.99; Chi² = 94.18, df = 5 (P < 0.00001); I² = 95%
Test for overall effect: Z = 3.28 (P = 0.001)



B

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Giardiello (1993) (Sulindac 150 mg)	-65	9	11	10	10	11	16.9%	-75.00 [-82.95, -67.05]
Higuchi (2003) (Rofecoxib 25 mg)	-16.2	4.2	12	1.5	5.2	9	17.2%	-17.70 [-21.85, -13.55]
Iwama (2006) (Tiracoxib 150 mg)	3	15	21	4	18	20	16.7%	-1.00 [-11.17, 9.17]
Iwama (2006) (Tiracoxib 200 mg)	4	16	19	4	18	20	16.6%	0.00 [-10.68, 10.68]
Steinbach (2000) (Celecoxib 100 mg)	-14.6	31.7	32	-4.9	17.3	15	16.2%	-9.70 [-23.75, 4.35]
Steinbach (2000) (Celecoxib 400 mg)	-30.7	25.7	30	-4.9	17.3	15	16.4%	-25.80 [-38.50, -13.10]
Total (95% CI)			**125**			**90**	**100.0%**	**-21.69 [-44.76, 1.39]**

Heterogeneity: Tau² = 803.48; Chi² = 209.96, df = 5 (P < 0.00001); I² = 98%
Test for overall effect: Z = 1.84 (P = 0.07)



12

Kupffer cell ablation induces liver failure in a mouse model of alcohol-associated liver disease

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Introduction:

Kupffer cells (KCs) are the resident macrophages of the liver, and their properties change depending on environmental conditions. They are diverse, distinct from infiltrating macrophages (IMs), and their gene expression patterns fall outside the M1-M2 framework. During alcohol associated liver disease (ALD), KCs are thought to become “activated” but their function is uncertain. The **AIM** of this study was to selectively ablate KCs in a mouse model of mild-moderate alcohol-associated steatohepatitis (ASH) and assess the impact on inflammation and liver function.

Methods:

C57BL/6J-Clec4f-DTR mice expressing human diphtheria toxin (DT) receptor specifically in KCs were fed either chow or high fat western diet chow with 10-20% alcohol in the drinking water for 16 weeks (WDA diet). DT (400 ng/mouse) was administered IP every 3 days from 12-16 weeks. Impact on KC populations was assessed by flow cytometry.

Results:

WDA diet for 16 weeks produced steatohepatitis and pericellular fibrosis, but mice appeared healthy. DT injection resulted in complete loss of all KCs but no immediate effect on IMs. Repeat DT injection every 3 days resulted in extended loss of mature KCs and their replacement by “neo-KCs” which expressed normal amounts of F4/80 but lacked most other Kupffer cell proteins such as Clec4f, Timd4 or Cd163. Chow fed mice remained healthy during KC depletion, but alcohol-fed mice became ill with >20% weight loss, elevated PT and reduced expression of albumin, Hnf4a, Cyp2c37 and clotting factor 12. This liver failure-like phenotype was associated with only mild increases in ALT (25 to 60 IU/ml), less than 2x increases in inflammatory cytokines, and no histological inflammation by H&E. Ki-67 staining, however, showed marked hepatocyte proliferation and GSEA analysis of whole liver mRNA showed marked similarly to reported gene sets of liver failure associated with human alcoholic hepatitis. Finally, IV injection of bone marrow monocytes from WT donors without DTR expression restored mature KCs in spite of the repeat DT injections and corrected the liver failure phenotype.

Conclusion:

This work demonstrates that KCs are primarily protective to the liver and are necessary to preserve hepatocellular function during ASH. Ablation of KCs during alcohol exposure causes hepatocytes to transition to a de-differentiated, progenitor-like state that closely resembles the liver failure phenotype seen in severe alcohol-associated hepatitis.

Funding Sources: VA Merit BX004694-01, NIH R01 AA012863

13

Lessons learned from COVID-19 pandemic: outcomes after SARS-CoV-2 infection in hematopoietic cell transplant and cell therapy recipients

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Introduction:

Coronavirus disease 2019 (COVID-19), a respiratory illness caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a pandemic in March 2020. hematopoietic cell transplant (HCT) or chimeric antigen receptor-T (CART) cell therapy recipients have a higher risk of mortality with COVID-19. We investigated the outcomes after SARS-CoV-2 infection in HCT/CART recipients.

Methods:

We conducted a single-center prospective study, including all (n=196) adult HCT/CART recipients who were diagnosed with COVID-19 at the University of Kansas Medical Center from March 2020 to March 2022. Bivariate analyses, using the chi-square and t-test, were performed. Kaplan-Meier and cox regression analyses were conducted. COVID-19 severity was defined as mild (absence of hypoxia or abnormal chest imaging), or moderate/severe (evidence of lower respiratory disease/pneumonia on imaging or acute hypoxemic respiratory failure).

Results:

The study included 196 HCT/CART recipients who acquired SARS-CoV-2 infection, including allogeneic HCT recipients as reported in table 1. Clinical findings included pneumonia or abnormal chest imaging (31%), hypoxia (19%), intensive care unit admission (9%), and mechanical ventilation (6%). At least one dose of SARS-CoV-2 vaccine was reported in 70% of patients (45% pre-COVID, 25% post-COVID) while 3% of patients had received pre-exposure prophylaxis. The median duration of viral shedding (positive SARS-CoV-2 PCR) was 6.5 (0.3-23.4) weeks. The mortality rate was 12% with a COVID-specific mortality of 8%. Eighty-four (43%) patients were diagnosed with COVID after Sep 2021 and had the lowest COVID-specific mortality (2% compared to 12.5% in preceding months). Significant predictors of COVID-19 mortality included allogeneic, COVID-19 within 100 days of HCT/CART, COVID-19 diagnosis earlier in the pandemic, prior acute GVHD and active GVHD. In 15 patients with available data, vaccination induced protective anti-spike protein antibody response (>100 U/mL) in 67% of patients with a median titer of 656 (9-688,000) U/mL after completion of the primary vaccination series.

Conclusion:

Hematopoietic stem cell transplant and CART cell therapy recipients have a higher risk of morbidity and mortality with SARS-CoV-2 infection. Strict vigilance, infection prevention measures, vaccination prioritization, close monitoring, and early aggressive treatment interventions are suggested for COVID-19 and future emerging infectious diseases.

Funding Sources: None

Table 1: Baseline/clinical characteristics, COVID-19 severity and outcomes in hematopoietic cell transplant and cell therapy recipients (n=196)

Characteristics	Total (n=196)	COVID-19 severity			P value	Characteristics	Total (n=196)	COVID-19 severity			P value
		Mild (n=136)	Moderate -Severe (n=44)	Deaths (n=16)				Mild (n=136)	Moderate -Severe (n=44)	Deaths (n=16)	
Age Yrs, median (range)	59.8 (21.9-79.5)	59.9 (21.9-79.5)	59.7 (23.6-77.3)	60.6 (24.7-774.6)	0.426	**Male gender, n (%)**	114 (58)	81 (60)	24 (54.5)	9 (56)	0.831
CT type, n (%)						**Ethnicity, n (%)**					
Allogeneic HCT	91 (46)	58 (43)	21 (48)	12 (75)	0.082	Caucasian	150 (76.5)	108 (79)	31 (70.5)	11 (69)	0.070
Autologous HCT	89 (46)	68 (50)	19 (43)	2 (12.5)		Hispanic	21 (11)	15 (11)	6 (14)	0	
CAR-T	16 (8)	10 (7)	4 (9)	2 (12.5)		AA	21 (11)	11 (8)	5 (11)	5 (31)	
COVID-19 diagnosis, n (%)						Others	4 (2)	2 (1.5)	2 (4.5)	0	
04/2020-09/2020	19 (10)	13 (10)	4 (9)	2 (12.5)	0.017	**GVHD ppx, n (%)**					
10/2020-03/2021	59 (30)	35 (26)	15 (34)	9 (56)		Tac/MTX	60 (31)	37 (27)	14 (32)	9 (56)	0.057
04/2021-09/2021	34 (17)	19 (14)	12 (27)	3 (19)		PTCy/CNI/MMF	30 (15)	20 (15)	6 (14)	4 (25)	
10/2021-03/2022	84 (43)	69 (51)	13 (30)	2 (12.5)		None	106 (54)	79 (58)	24 (54.5)	3 (19)	
Primary diagnosis, n (%)						**Prior aGVHD, n (%)**	39 (20)	21 (15)	11 (25)	7 (44)	0.017
Myeloid disorders	67 (34)	43 (31)	15 (34)	9 (56)	0.156	**Prior cGVHD, n (%)**	52 (26.5)	31 (23)	14 (32)	7 (44)	0.133
Lymphoid disorders	54 (28)	35 (26)	13 (30)	6 (37.5)		**Active GVHD, n (%)**	46 (23.5)	24 (18)	14 (32)	8 (50)	0.005
Plasma cell disorders	73 (37)	47 (42)	15 (34)	1 (6)		**Current IST, n (%)**	50 (25.5)	28 (21)	11 (25)	11 (69)	<0.001
Solid organ malignancy	2 (1)	1 (1)	1 (2)	0		**Concurrent infection, n (%)**	23 (12)	11 (8)	9 (20.5)	3 (19)	0.057
Donor type, n (%)						**Subsequent GVHD, n (%)**	16 (8)	6 (4)	9 (20.5)	1 (6)	0.003
Self	104 (53)	78 (57)	23 (52)	3 (19)	0.037	**Vaccine, n (%)**					
Matched unrelated	41 (21)	28 (21)	10 (23)	3 (19)		Vaccinated before COVID-19	89 (45)	68 (50)	18 (41)	3 (19)	<0.001
Matched sibling	23 (12)	13 (10)	5 (11)	5 (31)		After COVID-19	49 (25)	32 (24)	16 (36)	1 (7)	
Haploidentical	28 (14)	17 (12)	6 (14)	5 (31)		Not vaccinated	58 (30)	36 (26)	10 (23)	12 (75)	
Conditioning, n (%)						**Hemoglobin, median (g/dL)**	9.8	9.3	10.9	9.7	<0.001
MAC	126 (64)	90 (66)	29 (66)	7 (44)	0.403	**Ferritin, mcg/L**	1049	508	1022	2666	<0.001
RIC/NMAC	76 (36)	46 (34)	15 (34)	9 (56)		**Neutrophil-lymphocyte ratio, median**	4.3 (0.1-105.4)	3.3 (0.5-29.5)	4.5 (0.1-83.4)	12.4 (2.4-105.4)	0.012
Time to COVID-19 post CT Mo, median (range)	25.4 (0.2-201.9)	28.2 (0.2-201.9)	12.9 (0.2-172.1)	10.5 (1.5-118.4)	0.268	**Viral shedding Wk, median (range)**	6.5 (0.3-23.4)	6.4 (0.3-16.7)	6.1 (3.3-23.4)	7.6 (5.6-10)	0.089
COVID-19 within 100 days, n (%)	23 (12)	11 (8)	6 (14)	6 (37.5)	0.002	**Follow up Mo, median (range)**	5.4 (0.3-24.8)	5.3 (0.3-24.8)	9.4 (0.5-24.2)	1.0 (0.4-12.8)	0.946

Abbreviations: COVID-19, Coronavirus disease 2019; HCT, Hematopoietic stem cell transplant; CT, Cell therapy; CAR-T, Chimeric antigen receptor-T cell therapy; Yr, Year; Mo, Month; Wk, Week; AA, African American; GVHD, Graft-versus-host disease; Ppx, Prophylaxis; Prior aGVHD, Prior acute GVHD (grade II-IV); Prior cGVHD, Prior chronic GVHD (requiring systemic steroids); IST, Immunosuppressive therapy; MAC, Myeloablative conditioning; RIC/NMAC, Reduced intensity-/nonmyeloablative-conditioning; Tac/MTX, Tacrolimus/Methotrexate; PTCy/CNI/MMF, Post-transplant cyclophosphamide, Calcineurin inhibitor (Tacrolimus/Sirolimus), Mycophenolate

14

The Mechanism of Antibody-Mediated Inhibition of ADAMTS13 In Immune Thrombotic Thrombocytopenic Purpura

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Introduction:

Immune thrombotic thrombocytopenic purpura (iTTP) is a potentially life-threatening microangiopathic disorder involving anti-ADAMTS13 antibodies. Understanding how antibodies inhibit ADAMTS13 may improve the diagnosis and treatment of iTTP. To determine whether inhibitory antibodies prevent substrate binding to ADAMTS13, which would increase the substrate concentration at which velocity is half maximal ($K_{0.5}$); decrease the maximal enzyme velocity (V_{max}) of ADAMTS13 by affecting catalytic turnover; or both, we developed an assay using a well-characterized inhibitor of ADAMTS13.

Method:

A single chain fragment of the variable region (scFv4-20) derived from a human monoclonal antibody isolated from an iTTP patient by phage display with potent inhibitory effects on ADAMTS13 (PNAS. 2015; 112:9620) was expressed and purified. Recombinant full length ADAMTS13 and native ADAMTS13 in normal human plasma (NHP) were titrated with a fluorescently labeled surrogate substrate (FRETS-VWF73) in the presence of increasing fixed concentrations of scFv4-20. To evaluate the effects of the inhibitor on V_{max} and $K_{0.5}$, titrations were analyzed individually and applied to a global fit. The relative effect of scFv4-20 on $K_{0.5}$ was inferred from the global fit via the parameter α; values of α within an order of magnitude of unity suggest little to minimal effect of the inhibitor on $K_{0.5}$.

Results:

When ADAMTS13 in NHP was titrated with FRETS-VWF73 in the presence of increasing concentrations of scFv4-20, V_{max} decreased with increasing concentration of scFv4-20, but $K_{0.5}$ did not show a significant change under the standard assay conditions (pH 6.0, 25 ˚C). Similar results were observed under conditions closer to physiological pH and temperature. Titration of recombinant ADAMTS13 with FRETS-VWF73 revealed similar results regarding the effect of scFv4-20 on the V_{max} and $K_{0.5}$. The parameter α was close to 1 when titrations were analyzed by global fit, regardless of reaction conditions or type of ADAMTS13 used, suggesting little to no effect of scFv4-20 on $K_{0.5}$.

Conclusions:
The antibody-mediated inhibition of ADAMTS13 by the inhibitory scFv4-20 likely results primarily from reducing catalytic turnover of the enzyme rather than the binding of ADAMTS13 to VWF. The assay developed can be applicable to explore the way antibodies affect the activity of ADAMTS13 in iTTP.

Funding sources:
Konstantine Halkidis: NIH NHLBI K08 (1K08HL163471-01) (2022-)
Hemostasis and Thrombosis Research Society Mentored Research Award (2020-)
American Heart Association Career Development Award (2022-)

X. Long Zheng: NIH NHLBI R01 (R01HL115187-06) (2019-)
NIH NHLBI R01 (R01HL157975-01A1) (2022-)

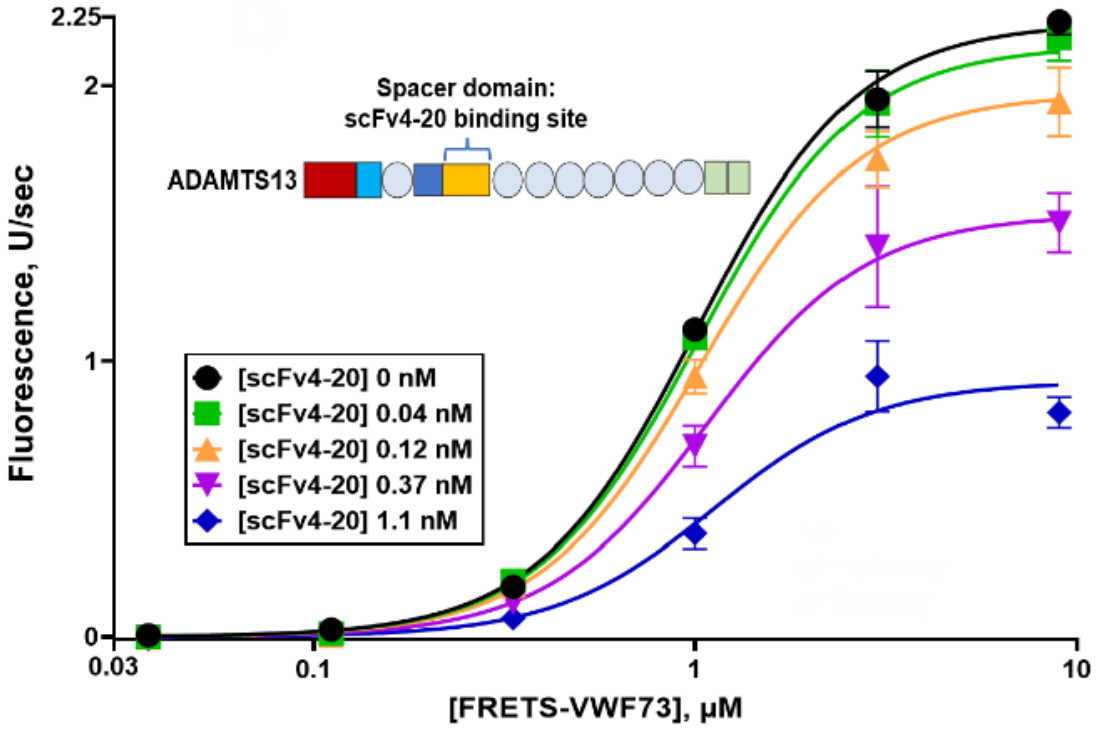

Figure 1. The titration of recombinant full length ADAMTS13 with FRETS-VWF73 in the presence of fixed concentrations of scFv4-20 under conditions of temperature 25˚C and pH 6.0. Cartoon represents the structure of full length ADAMTS13. Rectangles: brown, metalloprotease domain; light blue, disintegrin domain; navy, cysteine-rich domain; yellow, spacer domain; and green, 2 CUB domains. Circles: thrombospondin type-1 domains (T2-8). Spacer domain, the binding side of scFv4-20 to ADAMTS13, is labeled. All the experiments were repeated for at least 3 times. The data in the plots are shown as mean ± SEM. (Abbreviations: ADAMTS-13: a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13; FRETS-VWF73, 5'-maleimide fluorescein-labeled VWF73 fragment; VWF, von Willebrand factor; scFv, single chain variable fragment; CUB: complement C1r/C1s, Uegf, Bmp1; SEM, standard error of the mean).

15

BCMA re-emergence and relapse post-BCMA-CAR-T therapy

Authors: Cui, Wei, MD[1]; Wesson, William, MPH[2]; Mushtaq, Muhammad Umair, MD[3]; Bansal, Rajat, MD[3]; Singh, Anurag, MD[3]; Hoffmann, Marc, MD[3]; Tun, Aung, MD [3]; Balusu, Ramesh, MD[3]; Abdelhakim, Haitham, MD[3]; Abhyankar, Sunil, MD[3]; Shune, Leyla, MD[3]; McGuirk, Joseph, DO[3]; Abdallah, Al-Ola, MD[3]; Ahmed, Nausheen, MD[3]

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Introduction:
The outcomes of patients (pts) with triple and penta-class relapsed refractory multiple myeloma (RRMM) are poor. B- cell maturation antigen (BCMA) chimeric antigen receptor T cell (CAR-T) therapy in RRMM has been approved since March 2021. The overall response rate (ORR) was 73% with median progression-free survival (PFS) and median overall survival (OS) of 8.8 and 19.4 months, respectively. Undetectable soluble sBCMA levels correlated with the depth of responses, though re-emergence of sBCMA level indicates relapse. Our study goal is to determine the correlation of BCMA re-emergence using multiparameter flow cytometry (MFC) from the bone marrow biopsy (BMBx) to predict the outcomes.

Methods:
A total of 19 pts who received BCMA CAR-T therapy recipients for RRMM at the University of Kansas Health System between May 2021 and June 2022. Those with less than 3 months of follow-up were excluded from the analysis. Only patients with established negative BCMA on BMBx at day 30 were included. All patients had standard procedure BMBx at 1 mo., 3 mo., 6 mo, and 1 yr. Eight-color MFC was performed on the BMBx specimens. BCMA antibody was purchased from R & D Systems (Minneapolis, MN). Data analysis was performed using FCS Express 5 software (De Novo Software, Los Angeles, CA). 500,000 to up to 2,000,000 events were acquired in all the cases. Responses were evaluated using the International Myeloma Working Group (IMWG) criteria. Kaplan-Meier analyses were used to estimate PFS. Time to BCMA re-emergence was defined as the time from CAR-T cell infusion to positive BCMA on BM PC.

Results:
Demographic data of all 19 RRMM BCMA CAR-T recipients is shown **(Table 1).** The groups were similar except for higher non-osseous extramedullary disease in the relapsed group. The median follow-up was 9 mo (3-12 mo). Nine patients (47.3%) relapsed and ten (52.6%) did not. The median time to relapse was 5 mo (2 to 12 mo). BCMA re-emergence was demonstrated in a total of 10 patients (52.6%). Of these, 7 (70%) clinically relapsed and 3 (30%) did not. The median time to BCMA re-emergence was 3 mo (2-12 mo.). Amongst the nine patients who relapsed, 7 patients (77.7%) demonstrated BCMA re-emergence, of which 5 patients (55.5%) had BCMA re-emergence prior to clinical relapse (**Figure1**). The median time from BCMA re-emergence to clinical relapse in those 5 patients was 2 mo. (0-7 mo.) Amongst the 10 patients with no relapse, only 3 (30%) demonstrated BCMA re-emergence.

Conclusions:
Re-emergence of BCMA after BCMA-directed CAR-T therapy as detected by MFC on BMBx may be a prognostic marker and correlate with responses. Although there was a higher incidence of BCMA re-emergence in the relapsed group, no significant differences were observed due to the small sample size. This warrants further investigation. Prospective studies are needed to evaluate the correlation between BCMA re-emergence with prognosis and prediction of relapse.

Table 1: Patient and disease characteristics

	Pts with undetected Day 30 BCMA who relapsed (n=9)	Pts with undetected Day 30 BCMA who did not relapse (n=10)	*P* value
Age yrs. (median, range)	65 (42-71)	66 (58-69)	0.31
Mean time from diagnosis to CAR-T infusion yrs., (median, range)	4 (2-14)	7 (2-16)	0.10
High-risk cytogenetics present (n/%)	8 (88%)	7(70%)	0.58
R-ISS Stage at diagnosis (N, %) I II III UNK	 0 (0%) 5 (55%) 3 (33%) 1 (11%)	 4 (40%) 1 (10%) 4 (40%) 1 (10%)	0.08
Extramedullary disease Non osseous (n, %) Osseous (n, %)	9 (100%) 7 (78%) 9 (100%)	6 (60%) 2 (20%) 6 (60%)	0.09 0.02 0.09
Lines of therapy prior to CAR-T (median, range)	5 (4-8)	5 (2-7)	0.35
Triple class RRMM (n, %)	9 (100%)	9 (90%)	1.0
Penta class RRMM (n, %)	6 (67%)	4 (40%)	0.37
Prior Autologous Stem Transplant (n, %)	7 (78%)	10 (100%)	0.21
Number of pts who had re-emergence of BCMA post CART	7 (78%)	4 (40%)	0.17
BCMA re-emergence at 3 months	4 (44.4%)	1 (10%)	
BCMA re-emergence at 6 months	2 (22.2%)	2 (20%)	
BCMA re-emergence at 12 months	1 (11.1%)	0	
No BCMA re-emergence	2 (22.2%)	7 (70%)	

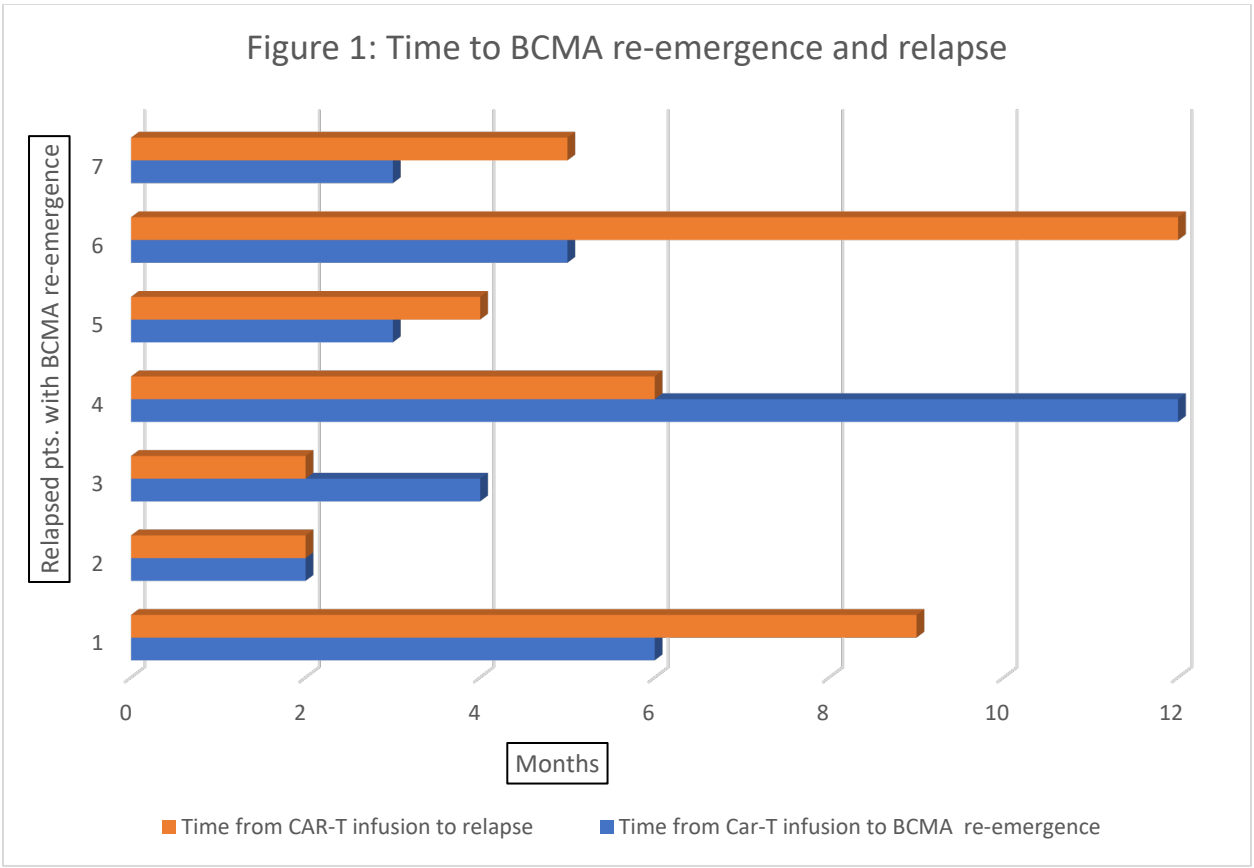
Figure 1: Time to BCMA re-emergence and relapse
Relapsed pts. with BCMA re-emergence
7
6
5
4
3
2
1
0
2
4
6
8
10
12
Months
Time from CAR-T infusion to relapse
Time from Car-T infusion to BCMA re-emergence

16

Eltrombopag Stimulation for Neutrophil and Platelet Recovery Following Axicabtagene Ciloleucel (axi-cel) Therapy in Lymphoma

Authors: Wesson, William, MPH[1,2]; Nelson, Maggie, PharmD, BCOP[1]; Mushtaq, Muhammad, MD[1]; Bansal, Rajat, MD[1]; Kribs, Robert, MD[1]; Singh, Anurag K., MD[1]; Hoffmann, Marc S., MD[1]; Tun, Aung M, MD[1]; Abdallah, Al-Ola, MD[1]; Abdelhakim, Haitham, MD[1]; Abhyankar, Sunil, MD[1]; McGuirk, Joseph P., DO[1]; Shune, Leyla, MD[1]; Ahmed, Nausheen, MD[1]

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Introduction:
Prolonged cytopenia is a potential side effect of CD-19 chimeric antigen receptor T-cell (CAR-T) therapy for lymphoma. ZUMA-1 demonstrated around 20% of axicabtagene ciloleucel (axi-cel) recipients had prolonged cytopenia at 3 months. Grade 3-4 cytopenia was observed in 11% of patients (Pts) at 2 years. While the mechanism behind the prolonged cytopenia is not yet well understood, one management strategy is to stimulate the bone marrow with the thrombopoietin receptor agonist, eltrombopag. This strategy is widely used in diseases like aplastic anemia and immune-mediated thrombocytopenia, but there has been limited evidence surrounding its use with cytopenia following CAR-T. Our practice is to utilize eltrombopag starting at Day 30 following CAR-T administration if either absolute neutrophil count (ANC) < 1000 cells/μL and/or if a patient is requiring growth factor support, and/or if a patient has thrombocytopenia, defined as a platelet count less than 20,000 cells/μL and/or if a patient is dependent on platelet transfusions at Day 30. We compared count recovery, progression-free survival (PFS), and overall survival (OS) of axi-cel recipients who required eltrombopag and those who did not.

Methods:
A retrospective cohort of 50 adult pts treated at the University of Kansas Cancer Center who had previously received axi-cel for B-cell nonHodgkin lymphoma between 2018-2021 were reviewed for clinical endpoints in this study. The patients were stratified into two groups based on whether they had received eltrombopag for count recovery following CAR-T administration. Pts whose disease progressed were censored at the time of progression in the analysis of outcomes. Count recovery was measured based on recovery past the lower limit of normal at our institutional lab, ANC less than 1.8 K/μL, and platelets less than 150 K/μL.

Results:
Twenty (40%) pts received eltrombopag. Demographics were compared between the two groups as shown in Table 1. Patients who received eltrombopag had significantly lower platelet and ANC counts (p= 0.03 and 0.01 respectively). Those who received eltrombopag had a significantly higher incidence of bone marrow involvement at the time of axicel administration (p=0.002). The median duration of eltrombopag was 115 Days (9-524 days). The eltrombopag cohort continued to have significantly lower platelet (120 vs 183 K/μL, p=0.02) and ANC (1.95 vs 3.07 cells/μL, p=0.01) at 1 year. No statistically significant difference was observed in PFS or OS between

patients who had received eltrombopag and those who did not, with a combined PFS of 16.5 months (p=0.54) (Figure 1) and a combined OS of 26 months (p=0.95).

Conclusion:
We conclude that patients on eltrombopag had significantly lower ANC and platelet counts even at 1-year post-CAR-T. The eltrombopag group had similar OS and PFS to those who the group without cytopenia. The role of eltrombopag in the patients with prolonged cytopenia is not entirely clear and warrants further investigation, especially considering the cost of administration and risk of secondary myelodysplasia (MDS). Larger multi-center retrospective studies and prospective data of the role of eltrombopag in improving outcomes are needed.

Table 1. Demographics

Table 1. Demographics		All patients n=50 [%]	Patients who received eltrombopag n=20 [%]	Patients who did not receive eltrombopag n=30 [%]	P value
Median Age in Years (Range)		60.5 (39-86)	61.5 (45-73)	59.5 (39-86)	0.81
Gender					
	Male	26 [52]	9 [45]	17 [57]	0.56
	Female	24 [48]	11 [55]	13 [43]	
Race					
	Caucasian	44 [88]	18 [90]	26 [87]	
	African American	1 [2]	0 [0]	1 [3]	
	Asian American	1 [2]	0 [0]	1 [3]	0.57
	Hispanic	3 [6]	2 [10]	1 [3]	
	Other	1 [2]	0 [0]	1 [3]	
Indication					
	DLBCL	48 [96]	18 [90]	30 [100]	0.15
	FL	2 [4]	2 [10]	0 [0]	
Previous Lines					
	1	9 [18]	2 [10]	7 [23]	
	2	27 [54]	10 [50]	17 [57]	
	3	10 [20]	5 [25]	5 [17]	0.39
	4	1 [2]	1 [5]	0 [0]	
	5+	3 [6]	2 [10]	1 [3]	
Systemic Bridging Therapy					
	Yes	11 [22]	5 [25]	6 [20]	0.73
	No	39 [78]	15 [75]	24 [80]	
Prior Malignancy					
	Yes	6 [12]	3 [15]	3 [10]	0.67
	No	44 [88]	17 [85]	27 [90]	
BM Involvement at Infusion					
	Yes	6 [12]	6 [30]	0 [0]	0.002
	No	44 [88]	14 [70]	30 [100]	
Prior Autologous Transplant		12 [24]	5 [25]	7 [23]	1.0
Prior Allogeneic Transplant		2 [4]	2 [10]	0 [0]	0.15
Platelets (K/µL) Prior to CAR-T (Range)		138.5 (16 -319)	121 (16 -185)	146 (33 - 319)	0.03
ANC (K/µL) Prior to CAR-T (Range)		1.1 (0.37 - 3.8)	0.71 (0.37 - 2.7)	1.2 (0.5 - 3.8)	0.01

17

A Randomized Trial Evaluating Exercise for the Prevention of Weight Regain

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Introduction:

To evaluate the effectiveness of 3 levels of exercise on weight regain subsequent to clinically meaningful weight loss (WL).

Methods:

Adults with overweight/obesity (n=298) initiated a 3-month. behavioral WL intervention which included reduced energy intake, increased exercise, and weekly behavioral counseling. Participants achieving ≥ 5% WL (n=235) began a 12-month behavioral WL maintenance intervention and were randomized to 150 (n= 76), 225 (n= 80), or 300 min/week (n= 79) of partially supervised moderate-to-vigorous intensity exercise.

Results:

Participants randomized to 150, 225 and 300 minutes of exercise completed 129 ± 30, 153 ± 49 and 179 ± 62 minutes of exercise each week (supervised+unsupervised), respectively. Mean WL at 3 months (9.5 ± 3.1 kg) was similar across randomized groups, p= 0.68. Weight change across 12 months was 1.1± 6.5 kg, 3.2 ± 5.7 kg, and 2.8± 6.9 kg in the 150, 225 and 300 min/week groups, respectively. Intent-to-treat analysis revealed no significant overall trend across the 3 treatment groups (p =0.09) or effects for group (p =0.08), or sex (p=0.21).

Conclusions:

We found no evidence for an association between the volume of moderate-to-vigorous intensity exercise and weight regain across 12 months following clinically relevant WL. Further, our results suggest exercise volumes lower than currently recommended for WL maintenance, when completed in conjunction with a behavioral weight maintenance intervention, may minimize weight regain over 12 months.

Funding Sources: NHLBI R01-HL11842 (Donnelly); NIDDK F32-DK103493 (Szabo-Reed); KL2-TR002367 (Szabo-Reed)

18

Exploring cognitive function and relationships with weight loss, intervention adherence and dropout

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Introduction:

To evaluate the association between baseline cognitive function, intervention dropout, adherence and 3-month weight loss (WL) when controlling for confounding demographic variables.

Methods:

107 (*Mage*=40.9 yrs.), BMI in the overweight and obese range (*BMI*=35.6 kg/m^2), men (N=17) and women (N=90) completed a 3-month WL intervention. Participants attended weekly behavioral sessions, comply with a reduced calorie diet, and complete 100 minutes of physical activity (PA)/wk. Cognitive function tasks included Flanker (attention), Stroop (executive control) and working memory, demographics, body weight and cardiovascular fitness were assessed at baseline. Session attendance, adherence to PA and diet were recorded weekly.

Results:

Attention was positively correlated with age ($p<.05$), education ($p<.05$), attendance ($p<.05$), diet ($p<.05$) and PA ($p<.05$). Executive control ($p<.05$), working memory ($p<.05$) were each associated with % WL. Executive control ($p<.01$) and working memory ($p<.001$) were also each associated with education. ANOVA indicated that baseline attention ($p<.01$) was associated with WL, specifically for comparing those who achieved 5-10% WL ($p<.01$) and those who achieved greater than 10% WL ($p<.01$) to those who dropped.

Conclusion:

Results suggest that stronger baseline attention is associated with completion of a 3-mo. WL intervention. Executive control and working memory are associated with amount of WL achieved.

Funding Sources: NHLBI R01-HL11842 (Donnelly); NIDDK F32-DK103493 (Szabo-Reed)

20

Obstructive Sleep Apnea Symptom Subtypes and Hypoxic Burden Independently Predict Distinct Cardiovascular Outcomes

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Introduction:

Studies on heterogeneity of obstructive sleep apnea (OSA) have identified and validated clinically relevant symptom-based subtypes (minimally symptomatic, disturbed sleep, moderately sleepy and excessively sleepy) and novel OSA-specific nocturnal hypoxemia measures. Evidence suggests that excessively sleepy moderate-severe OSA patients have increased risk of incident major adverse cardiovascular events (MACE; composite of coronary heart disease, heart failure, stroke, or cardiovascular mortality) and that OSA-specific hypoxic burden (HB) is associated with increased risk of cardiovascular disease (CVD) mortality. This study provides a systematic assessment of the individual and combined contribution of these factors on incident risk of different CVD outcomes, addressing an important gap in current evidence.

Methods:

Participants from the Sleep Heart Health Study with high-quality oxygen saturation, OSA severity quantified by apnea-hypopnea index (AHI), and symptom data were included. Latent class analysis on 14 symptoms was used to classify participants with moderate-severe OSA (AHI≥15) into subtypes. HB was calculated from respiratory event related hypoxia and total sleep time. Cox proportional hazards models were used to assess associations between OSA severity, symptom subtypes and log-transformed HB with CVD mortality and MACE, adjusted for demographic and CVD risk factors. Analyses were performed in CVD free participants and all participants adjusted for baseline CVD presence. Of particular interest was whether symptom subtypes and/or HB were associated with CVD outcomes independent of each other.

Results:

5,027 participants were analyzed with median follow-up of 11.6 years (CVD mortality) and 11.3 years (MACE). HB was independently associated with CVD mortality in all participants (HR=1.44; 95%CI=1.06-1.97; p=0.021) and CVD free participants (HR=1.62; 95%CI=1.12-2.35, p=0.010) controlling for symptom subtype. On the other hand, symptom subtypes were independently associated with MACE incidence among CVD free participants, controlling for HB, with the excessively sleepy participants having significantly higher risk of MACE (HR=1.98; 95%CI=1.26-3.10, p=0.003) compared to those without OSA.

Conclusion:
OSA symptom subtypes and HB are independently associated with specific CVD-related endpoints. Higher HB was associated with cardiovascular mortality, controlling for symptom subtype. The excessively sleepy subtype was at higher risk of new MACE, controlling for HB. Thus, both of these factors are important for understanding OSA-related CVD risk.

Funding Sources:
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21

PRMT6-dependent arginine methylation of integrin alpha-4 controls alcohol induced fibrosis development

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Introduction:

Alcohol-associated liver disease (ALD) comprises a spectrum of disorders including steatosis, steatohepatitis, fibrosis, and cirrhosis. Alcohol induced fibrosis is a complex disease, and mechanisms contributing to ALD fibrosis are understudied. We aimed to study the role of protein arginine methyltransferase 6 (PRMT6), a new regulator of liver function, in ALD fibrosis.

Methods:

Prmt6 deficient mice and wild type littermates were fed western diet with alcohol in the drinking water for 16 weeks. Mice fed standard chow diet or western diet alone were used as a control. Monocyte infiltration was blocked by CCR2 small molecule inhibitor. Macrophages were ablated using chlodronate liposomes and replaced by injections of 10^6 bone-marrow derived macrophages from wild type or knockout mice. PRMT6 mRNA and protein expression was analyzed in human liver specimens from patients with liver disease for correlation with MELD score and COL1A1 expression.

Results:

We found that *Prmt6* expression in the liver is downregulated in two models of ALD, and negatively correlates with disease severity in human liver specimens. In the liver PRMT6 is primarily expressed in non-parenchymal cells. Using *Prmt6* deficient mice we found that PRMT6 promotes pro-inflammatory signaling and decreases pro-fibrotic signaling in liver macrophages. *Prmt6* deficient mice spontaneously develop liver fibrosis at one year of age and develop more advanced liver fibrosis in several models of liver disease including high fat diet feeding and thioacetamide treatment. In alcohol fed mice *Prmt6* deficiency results in a dramatic increase in fibrosis development.

Mechanistically, we identified that PRMT6 methylates integrin α-4 at R464 residue in infiltrating monocyte derived macrophages, which is necessary for suppression of pro-fibrotic gene expression. Blocking monocyte infiltration into the liver with CCR2 inhibitor or infusion of wild type macrophages in *Prmt6* knockout mice reduced pro-fibrotic signaling and abolished differences between wild type and *Prmt6* knockout mice.

Conclusion:

Taken together our data suggest that alcohol mediated loss of *Prmt6* contributes to alcohol associated fibrosis development through reduced integrin methylation and increased pro-fibrotic signaling in macrophages.

Funding Sources:

This study was supported by grants AA027586 and AA012863 from the National Institute on Alcoholism and Alcohol Abuse, and VA Merit Award I01BX004694.

22

Females May Be at Higher Risk of Severe and Dysplastic Fundic Gland Polyposis: An 844-patient analysis

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Introduction:

The risk of gastric cancer is increasing in the western world for unknown reasons. Fundic gland polyps (FGP) are common. In many cases, the burden of gastric polyps is high making management challenging and causing anxiety among patients. We compared patients with and without FGP to determine potential risk factors associated with severe FGP.

Methods:

In this retrospective, single-center study, all patients with a diagnosis of histologically confirmed fundic gland polyps between January 1, 2021, and December 31, 2021 were included. Controls were defined as patients without FGP during an upper endoscopy, selected randomly in a ratio of 1:1 to cases. Cases and controls were identified by using a specialized text-based search of the pathology and endoscopy reporting software. Upper endoscopies done for suspected or established reflux and/or dyspepsia were included. A structured RedCap electronic database was created to systematically abstract data about demographics, endoscopies, and histology. Severe FGP was defined by the presence of endoscopic descriptors such as “innumerable”, “diffuse”, ”numerous”, “many”, “>50 polyps” etc., and confirmed by endoscopic pictures. Patients with a known inherited gastrointestinal syndrome were excluded. Multivariate logistic regression was performed.

Results:

The prevalence of FGP has increased over the past decade (Figure 1). Eight hundred and forty-four patients (422 with FGP and 422 without FGP) were included (68% female, mean age 56, SD 15.4 years). Increasing age (1.02 (1.01, 1.04)) and >2 years of PPI use [3.01 (1.84, 4.98)] were associated with increased risk of FGP; all P<.05 (Table 1). Of the 422 patients with FGP; 95.5% had mild polyposis and 4.5% had severe polyposis. Most of the patients with moderate to severe polyposis were post-menopausal females (87.5%). Low-grade dysplasia (LGD) within FGP was found in 25 (5.5%) patients (77% were female) and high-grade dysplasia (HGD) within FGP was found in 5 (1.1%) patients (80% were female).

Conclusion:

Longer than 2 years of PPI use is associated with FGP. Post-menopausal females were at the highest risk for severe polyposis. Further research into long-term outcomes is needed to determine which patients could benefit from surveillance.

Funding Sources: none

23

Early Life Stress Drives Obesity and Negatively Impacts the Maintenance of Weight Loss in Mice

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Introduction:

Exposure to early life stress is an underappreciated driver of obesity, however, the impact of early life stress on the ability to maintain weight loss is unclear. We used a mouse model to investigate the role of early life stress on weight loss maintenance.

Methods:

Neonatal maternal separation (NMS) was performed from postnatal day (PD) 1-21. Whole litters were removed from the dam and placed in a warm incubator for 3 hours/day. Naïve mice remained unhandled. All mice were weaned on to a high fat diet on PD22 for obesity development. After 15 weeks, all mice were switched to a low fat diet and calorie restricted to reduce body weight by 20%. In the weight reduced state, half of the mice were given access to a running wheel which was continued for the remainder of the study. Weight regain occurred over 9 weeks in which mice had *ad libitum* access to either a low or high fat diet. Body weight was recorded weekly and body composition was measured every 5 weeks.

Results:

After obesity development, NMS mice weighed more than Naïve control mice ($p<0.003$). This elevated body weight in NMS mice persisted throughout the study. Calorie restriction resulted in a 21.2 ± 0.3 % reduction in body weight. During regain, high fat diet resulted in greater weight ($p<0.001$) and adiposity ($p<0.001$) gains in all groups. Exercise partially mitigated this diet-induced weight gain but in only male mice ($p<0.05$, sex by diet interaction). Overall, NMS and Naïve mice regained a similar amount of body weight and adiposity, however, NMS mice had increased weight gain ($p=0.013$) and adiposity ($p=0.018$) on a low fat diet compared to naïve mice.

Conclusion:

Early life stress clearly increases obesity risk, however, this work importantly demonstrates that exposure to early life stress can also diminish the maintenance of weight loss under certain conditions and highlights the need for future studies.

Funding Sources: F32DK127693, R01 DK099611, R01 DK103872, R01AR071263

24

The prevalence of obesity and lifestyle factors in parents of youth with intellectual and developmental disabilities

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Introduction:
Parents of youth with intellectual and developmental disabilities (IDD) may have a higher prevalence of overweight and obesity compared to the general population, possibly due to the demands of caregiving which limit their time and energy for healthy weight management. Baseline data obtained from parents who served as study partners for their adolescent/young adults participating in an 18-month weight management trial provided an opportunity to describe the prevalence of overweight/obesity and examine lifestyle factors that may influence overweight/obesity such as diet quality, physical activity, and health habits in this high-risk population.

Methods:
We assessed: weight (calibrated scale) and height (stadiometer) for the calculation of BMI (kg/m^2), moderate-to-vigorous physical activity (MVPA) using the International Physical Activity Questionnaire short form, fruit and vegetable intake (FVI) as a proxy for diet quality using the National Cancer Institute's All-Day Fruit and Vegetable screener, and parental habits regarding diet and physical activity using the Healthy Buddies Parent Nutrition and Physical Activity Survey.

Results:
Data was obtained from 110 parents (97.3% female) who were study partners for their adolescents/young adults with IDD. Approximately 81% percent of parents were overweight or obese (25.7% overweight, 55.1% obese), with 46.3% and 20% meeting the recommended U.S. guidelines for MVPA and FVI, respectively. Higher FVI was significantly associated with lower parent BMI (R_s =-0.22, p=0.04). BMI was significantly lower in parents who agreed versus disagreed with the statements "I try to be physically active most days" (30.0 ± 6.5 kg/m^2 vs. 36.1 ± 10.5 kg/m^2, p=0.02) and "I often choose healthy foods for myself" (30.7 ± 7.0 kg/m^2 vs 39.3 ± 8.2 kg/m^2, p=0.001).

Conclusion:
We observed a high prevalence of overweight/obesity, low consumption of fruits and vegetables and low levels of MVPA in parents of adolescents with IDD. These observations suggest that interventions designed to address these factors have the potential to improve the health and wellbeing of both parents and adolescents with IDD.

Funding Sources: This study is funded by the National Institutes of Child Health and Development (HD079642), National Institute of Aging (AG063909) and the National Center for Advancing Translational Science (TL1TR002368).

25

Intravenous immunoglobulin with concurrent platelet transfusion for treatment of thrombocytopenia in patients undergoing allogeneic hematopoietic stem cell transplant

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Introduction:
Severe refractory thrombocytopenia due to alloimmunization is a life-threatening complication in patients with hematologic disorders who are heavily transfused. It is challenging to manage patients with alloimmune thrombocytopenia (AITP) who are undergoing intensive chemotherapy and hematopoietic stem cell transplantation (HSCT) given no response to random donor platelets (PLT) transfusions, limited availability of HLA (human leukocyte antigen)-matched PLT, and high bleeding risk. We reviewed patients. In this study, we investigate the utility of continuous intravenous immunoglobulin (IVIG) and platelet transfusion in patients with AITP after allogeneic HSCT.

Methods:
We conducted a single-center retrospective analysis of seven adult AITP patients who underwent recent allogeneic HSCT. IVIG (2 g/kg) was given as a slow continuous infusion over 48 hours with continuous apheresis PLT infusion (1 apheresis unit over 8 hours). Response was defined as PLT > 50 K/uL within 21 days after IVIG infusion.

Results:
Seven patients with recent allogeneic HSCT were included. Median time since transplant was 12 (7-299) days. Myeloablative and reduced-intensity conditioning were performed in 5 (71%) and 2 (29%) patients, respectively. All patients in this analysis were hospitalized. Reasons for hospitalization included graft-vs-host disease (n=1, 14%), neutropenic fever or infection (n=5, 71%), or active hemorrhage (n=5, 71%). Median PLT count at the time of IVIG/PLT infusion was 4 K/uL. The median maximum PLT count within 21 days of IVIG/PLT infusion was 55 K/uL with a median time to best response of 6 days. Six of the seven patients (86%) were able to achieve a response, and one patient (14%) achieved a maximum PLT count of 27 K/uL.

Conclusion:
Continuous IVIG (2 g/kg) and platelet infusion over 48 hours may be able to overcome life-threatening refractory alloimmune thrombocytopenia in HSCT patients and may provide a bridging measure until platelet engraftment or for life-threatening hemorrhage or invasive procedures with high bleeding risk.

Funding Sources: None

26

Is CART a destination procedure? Lower socioeconomic class patients who live farther from center have less access to CART therapy.

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Introduction:

Axicabtagene ciloleucel (Axi-cel) and tisagenlecleucel (Tisa-gen) are commercially available CD19 chimeric antigen receptor T-cell (CART) therapies for B cell malignancies. It is a requirement for patients to stay within 2 hours of the center for 30 days post CART infusion. Most centers require local lodging for that period if residence is over 30 minutes away. Financial burden may limit access. We therefore hypothesized that those who were likely to receive CART therapies were from higher income neighborhoods or lived closer to the facility.

Methods: /

Since most patients get admitted for CART infusion, we used the Vizient CDB database for CART infusion admissions as well as other admissions. Patients over the age of 18 yrs who got commercially available CART between 2018 to 2020 were included. Distance was calculated in miles from patient zip code to treating center. Using census data, lower income neighborhoods (less than $40,000 median household income) were flagged.

Results:

There were 81 hospitals that had administered CAR-T therapy. We calculated the distance in miles between the patient and the hospital they were treated at for both CART therapy as well as for inpatient admissions for all causes during this period. Most admissions (81.2% all-cause vs 78.6% CART) were from neighborhoods with median income > $40,000. Most of the low-income admissions were from neighborhoods <10 miles (13.3% all admissions vs 15.7% CART). 80.6% of all CART patients came from neighborhoods over 10, with 38.2% living over 60 miles away, while only 15.4% all-cause admissions were from > 60 miles. ($p<.0001$) While 74.9% of higher income CART patients lived beyond 10 miles from center, only 5.7% CART patients lived beyond 10 miles. Results summarized in Table 1

Conclusions:

Lower income patients are more likely to get CART if they live within 10 miles of the center. Less than 10% of patients who live beyond 10 miles got CART therapy. This represents an access issue.

Table 1: Distance to center and neighborhood income of patients admitted for any cause vs for CART therapy			
Distance Range	**All Admissions n (%)**	**CAR-T cases n(%)**	**p value**
Less than 10 miles all neighborhoods	**5,733,410 (46.7%)**	**1,010 (19.4%)**	p<.0001
Neighborhoods with income>$40,000	4,104,484 (33.4%)	196 (3.7%)	p<.0001
Low income neighborhoods *	1,628,926 (13.3%)	814 (15.7%)	p<.0001
10-59 miles all neighborhoods	**4,643,441(38%)**	**2,203 (42.4%)**	p<.0001
Neighborhoods with income>$40,000	4,312,907 (35.3%)	2116 (40.7%)	p<.0001
Low income neighborhoods *	330,534 (2.7%)	87 (1.7%)	p<.0001
60+ miles all neighborhoods	**1,892,270 (15.4%)**	**1,983(38.2%)**	p<.0001
Neighborhoods with income>$40,000	1,531,312 (12.5%)	1,775(34.2%)	p<.0001
Low income neighborhoods *	360,958 (2.9%)	208(4%)	p<.0001
Total admissions	12,269,121 (100%)	5,196(100%)	
* - Patients living in neighborhoods with (based on Zipcode) with median household income below $40,000			

27

Descriptive Study of IgG Protection for PCV13 Serotypes in Immunodeficient Patients on IVIG

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Introduction:
Intravenous immunoglobulin (IVIG) therapy provides IgG antibodies from a donor pool to immunodeficient patients. Since PCV13 vaccine was introduced in 2010, adult donors may not have received the vaccine, thus not having PCV13 specific antibodies to donate. This descriptive analysis will highlight how pneumococcal vaccination affects Streptococcus pneumoniae protection, hospitalization rates, and associated comorbidities in immunodeficient individuals.

Methods:
A retrospective cohort study reviewed 53 primary immunodeficient patients who received IVIG at a single academic infusion center for at least six months from 2016 to 2021. Other measured factors include comorbidities, hospitalization rates, antibiotic prophylaxis, vaccination history. Data were analyzed using Microsoft Excel.

Results:
Prior to IVIG, 81% (30 of 38) of individuals received PPSV23 and 59% (13 of 22) received PCV13 after excluding missing data. 12 individuals received both pneumococcal vaccines prior to starting IVIG and eight individuals received both after starting IVIG.

Among those with PCV 13 vaccination, the average protection against all PCV13 related serotypes was 57% and there was a 45% decrease in hospitalization rates. Those without vaccination only had an average of 45% protection. In addition, among 10 patients with bronchiectasis, only 40% received both pneumonia vaccines.

Conclusion:
While our study is limited due to a small sample size, it highlights the increased protection conferred to PCV-13 specific antibodies in immunodeficient individuals who receive PCV13 while on IVIG therapy. There may be added benefit with decreased hospitalizations in patients who receive PCV13 vaccine. This knowledge may be helpful in determining benefit of PCV13 vaccine for immunodeficient individuals.

Funding Sources: Funding for statistical support was from Division of Allergy, Clinical Immunology and Rheumatology

28

Coexistence of Vasculitides in Patients with Inflammatory Bowel Disease

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Introduction:
The extraintestinal manifestations of Inflammatory Bowel Disease (IBD) are identified in 6%-40% of patients. Systemic vasculitides may present as extraintestinal manifestations of IBD. The purpose of this updated study was to determine the frequency of vasculitides (large, medium, or small vessel) in a cohort of patients with IBD.

Methods:
This is a retrospective chart review of patients from 12/2004 until 08/2021 at a single tertiary medical center using the HERON registry, REDCAP database, and the electronic medical records (EMR). A cohort of patients with ICD-9 and ICD-10 diagnosis codes for inflammatory bowel disease including Crohn's disease (CD), ulcerative colitis (UC), microscopic colitis (MC), and indeterminate colitis (IC) were identified. Patients with vasculitides including giant cell arteritis (GCA), Takayasu's arteritis (TAK), polyarteritis nodosum (PAN), aortitis, ANCA-associated vasculitis, granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA), CNS vasculitis, cryoglobulinemic vasculitis, leukocytoclastic vasculitis (LCV), and rheumatoid vasculitis were identified. One-sided student's t-tests were used for statistical analysis.

Results:
The EMR/HERON query yielded a total of 4100 patients with IBD. There were 844 patients with concomitant ICD-9 or ICD-10 diagnoses codes for vasculitides. A total of 33 patients (0.80%) had concomitant vasculitis and IBD, but 3 patients had to be excluded due to lack of detailed records. Of the 30 patients (0.73%), there were 13 patients (43%) with CD, 12 (40%) with UC, 3 (10%) with MC, and 2 (7%) with IC (Table 1). Sixteen (53%) of patients were female and 14 (47%) were male. The mean age of diagnosis of IBD was 33.6 years old and the mean age of diagnosis of vasculitis was 40.3 years old. The difference in age between the diagnosis of vasculitides and IBD was 6.7 years ($p=0.02$). In 57% of cases IBD was diagnosed before vasculitis. The most common vasculitis diagnoses included LCV (9, 30%) and GPA (5, 17%). ANCA serologies were present in 27% of patients. Of the 30 patients, 3 (10%) developed vasculitis following IBD treatment with adalimumab.

Conclusions:
In this cohort of patients with IBD, a small percentage of patients developed vasculitis (over 0.7%) with an estimated prevalence of 730 per 100,000. In most cases, IBD was diagnosed prior to vasculitides which could indicate that vasculitis may have developed as a secondary process in some patients.

Funding Sources:

1. Data was obtained using HERON, supported by CTSA Award # UL1TR000001 and REDCAP.
2. No Conflict of Interest is reported by the authors of this study.

Patient Number	Gender	IBD	Age at diagnosis of IBD (years)	Biopsy-proven IBD	Vasculitis Diagnosis	Age at diagnosis of vasculitis (years)	Biopsy-proven vasculitis	ANCA Serologies	Imaging evidence of vasculitis	Medications Used for Treatment of IBD and vasculitis
1	Male	UC	58	Yes	GPA	60	No	Negative	None	AZA, SSZ, RTX
2	Male	CD	41	Yes	LCV	44	Yes	Negative	None	ADA, steroids
3	Male	UC	39	Yes	LCV	55	Yes	Negative	None	Steroids
4	Female	CD	Unknown	Unknown	GPA	42	Unknown	Positive	None	CYC
5	Male	UC	60	Yes	GPA	41	No	Positive	None	CYC, MTX, steroids
6	Female	CD	21	Yes	CNS angiitis	16	No	Negative	Yes	MTX, AZA, IFX, steroids
7	Male	UC	21	Yes	UV	22	Yes	None	None	GOM, steroids
8	Male	UC	18	Yes	ANCA vasculitis	67	No	Positive	None	RTX, steroids
9	Male	UC	15	Yes	LCV	44	Yes	Positive	None	Steroids
10	Female	MC	70	Yes	GCA/RA	69	No	Negative	None	LEF, ETN, MRA, steroids
11	Female	CD	21	Yes	LCV	23	Yes	Positive	None	ADA, IFX, UST, steroids
12	Female	UC	25	Yes	PAN	26	Yes	Unknown	None	AZA, IFX
13	Male	IC	24	Yes	TAK	32	No	Negative	Yes	MTX, IFX, AZA
14	Female	UC	24	Yes	Kawasaki	2	Unknown	Unknown	Unknown	GOM, ADA, steroids
15	Female	CD	48	Yes	Behcet	30	No	Negative	Yes	APR, AZA, MTX, steroids
16	Female	IC	33	Yes	EGPA	37	No	Negative	None	AZA, steroids
17	Male	CD	13	Yes	GPA	21	Yes	Positive	None	AZA, steroids
18	Female	CD	17	Yes	LCV	31	Yes	Negative	None	ADA, IFX
19	Male	UC	23	Yes	UV	23	Yes	Negative	None	MTX, IFX
20	Female	CD	Unknown	Unknown	TAK	57	No	Unknown	Yes	MTX
21	Male	UC	20s	Yes	LCV	Unknown	Unknown	Unknown	None	SSZ, steroids
22	Male	CD	30	Yes	LCV	41	Yes	Negative	None	ADA, IFX, steroids
23	Female	MC	Unknown	Unknown	Rheumatoid vasculitis	69	Yes	Negative	None	MTX, SSZ, RTX,
24	Male	UC	28	Yes	PAN	27	Yes	Negative	Negative	AZA, ADA, MTX, steroids
25	Female	CD	47	Unknown	LCV	49	Yes	Negative	None	None
26	Female	MC	81	Unknown	GCA/ Scleroderma	79	Yes	Negative	None	SSZ, HCQ, steroids
27	Female	CD	22	Yes	LCV	36	No	Positive	None	IFX, AZA
28	Female	UC	45	Yes	GPA	51	No	Positive	None	IFX, MTX, RTX
29	Male	CD	Early 20s	Yes	IgAV	64	Yes	Negative	Negative	IFX, ADA, AZA, steroids
30	Female	CD	16	Yes	HUV	12	Yes	Negative	None	MTX, ADA, UPA, HCQ, RTX, UST, steroids

Table 1: Cohort of patients with coexisting IBD and vasculitis: ADA = adalimumab; APR = apremilast; AZA = azathioprine; CD = Crohn's Disease; CYC = cyclophosphamide; EGPA = eosinophilic granulomatosis with polyangiitis; ETN = etanercept; GCA = giant cell arteritis; GOM = golimumab; GPA = granulomatosis with polyangiitis; HCQ = hydroxychloroquine; HUV = hypocomplementemic urticarial vasculitis; IgAV = IgA vasculitis; IC = indeterminate colitis; IFX = infliximab; LCV = leukocytoclastic vasculitis; LEF = leflunomide; MC = microscopic colitis; MRA = tocilizumab; MTX = methotrexate; PAN = polyarteritis nodosum; RA = rheumatoid arthritis; RTX = rituximab; SSZ = sulfasalazine; TAK = Takayasu's arteritis; UC = ulcerative colitis; UPA = upadacitinib; UST = ustekinumab; UV = urticarial vasculitis

29

Recanalize Ureteral Stents with Focused Ultrasound

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[2]Department of Urology, University of Kansas Medical Center

[3]Division of Infectious Diseases, University of Kansas Medical Center

Introduction:

Ureteral stents are small conduits used to ensure urinary flow from the kidney to the bladder and widely used to treat ureteral obstructions and ureteral leaks. Maintaining ureteral patency is key to preventing renal injury and systemic infection. The most problematic and frequent stent-associated complication is stent encrustation. This occurs when mineral crystals (e.g. calcium, oxalate, phosphorus, struvite) are deposited onto the surface and internal lumen of the stent. Encrustation can lead to the obstruction of a stent and increases risk of systemic infection. Ureteral stents need to be replaced typically every 2-3 months. We present a non-invasive, high-intensity focused ultrasound (HIFU) based technique to recanalize obstructed stents.

Methods:

A detailed schematic of the experimental setup in shown in Fig 1. The setup consists of a HIFU system for the treatment of the ureteral stent and ultrasound imaging system to monitor the recanalization of the ureteral stent. The HIFU system produces ultrasound bursts using either a 0.25-MHz or a 1-MHz HIFU transducer. Ureteral stents were acquired from subjects that had that had an indwelling stent for several weeks. Stents were preserved in 0.9% NaCl. The area of maximal encrustation was identified via ultrasound.

Initial experiments were conducted to titrate the needed HIFU parameters, including burst length, burst repetition rate, and duty cycle. During the final experiment, the duty cycle was fixed at 10%, and the ultrasound burst repetition rate was fixed at 1 Hz, while the HIFU amplitude was varied to find the threshold pressure that would displace encrustations. Treatment duration was limited to 2 minutes.

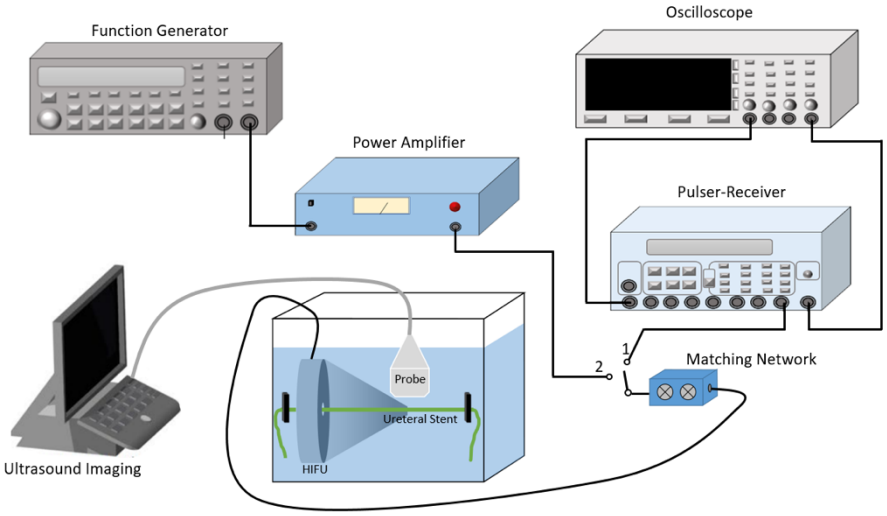
Results:

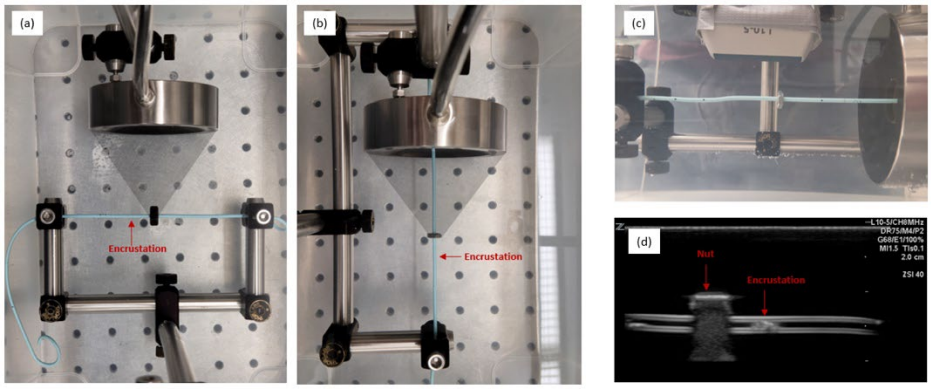
The average negative peak pressure needed to displace an encrustation was similar between perpendicular and parallel transducer orientations, with the same HIFU frequency. When evaluating different HIFU frequencies needed to displace an encrustation, peak negative pressures were higher ($p<0.01$) at 1 MHz vs 0.25 MHz. Treatment of encrusted stents at 0.25 MHz HIFU, with HIFU beam oriented parallel to the stent, resulted recanalization of the ureteral stent.

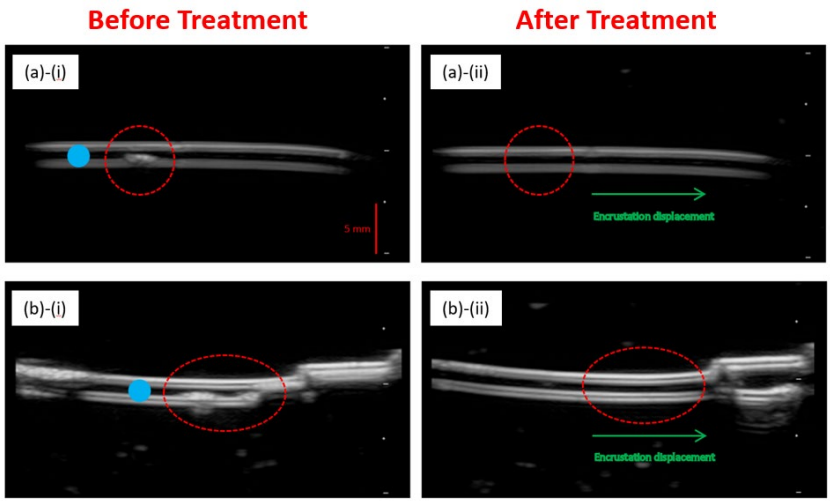
Conclusion:

We presented a noninvasive approach to recanalize obstructed ureteral stent. The approach is to utilize mechanical effect of HIFU to dislodge encrustations from the ureteral stent wall, clearing the stent. Our in-vitro experiments have demonstrated the feasibility of the technology. The approach has a potential to significantly reduce the need for ureteral stent exchange.

Funding Sources: Plans to seek R21 for additional research (porcine study).







30

SARS-CoV-2 wastewater monitoring in Kansas: Correlation with clinical data and variant tracking.

Authors: Hutchison, Justin[1]; Hiripitiyage, Yasawantha[1]; Sturm, Belinda[1]

Author Affiliations: [1] The University of Kansas

Introduction:

The COVID-19 pandemic has highlighted the potential role that wastewater-based epidemiology (WBE) can play in assessing aggregate community health. However, efforts to translate SARS-CoV-2 gene copy numbers obtained from wastewater samples into meaningful community health indicators are ongoing. This work will highlight two efforts to promote the use of WBE: 1) comparison of SARS-CoV-2 wastewater measurements during a low-frequency and a high-frequency clinical testing period and 2) the appearance of variants of interest in Kansas communities over time.

Methods:

These efforts measured the SARS-CoV-2 nucleocapsid (N) genes (N1 and N2) weekly using reverse transcriptase droplet digital PCR. To compare measurements with clinical results, two municipal wastewater treatment plants were monitored for six months. Four biomarkers (human mitochondrial gene NADH dehydrogenase subunit 5 (mit5), creatinine, ammonia, and biological oxygen demand (BOD)) were quantified and used to normalize Sars-CoV-2 gene copy numbers to account for variations in sewershed conditions. The normalized values were correlated to daily new case data and one-, two-, and three-week cumulative case data. Variants were determined by amplifying and sequencing the spike (S) gene using artic primers 75, 76 alt, and 77 followed by with clade assignment performed by Nextclade.

Results:

Mitochondrial and creatinine normalization methods showed the strongest correlations throughout the studying indicating that human-specific biomarkers were better at normalizing wastewater data than ammonia or BOD. During low-frequency clinical testing periods, results were strongly correlated with a six-day case data lag ($\rho = 0.83$), while the high-frequency clinical testing period yielded correlations of 0.81 with a one-day case data lag. Emergence of variants of concern was observed in wastewater at the same time as clinical samples.

Conclusion:

WBE has emerged as an effective public health tool to detect the emergence of disease in a community. As research continues, variant identification has become an additional tool for WBE.

Funding Sources: This work was supported by the Kansas Department of Health and Environment and NIH NIGMS (P20GM113117)

31

Acute exercise dynamically modulates the hepatic mitochondrial proteome

Authors: Franczak, Edziu[1]; McCoin, Colin S.[1,5,6]; Washburn, Michael P.[2]; Sardiu, Mihaela E.[3]; Thyfault, John P.[1,4,5,6]

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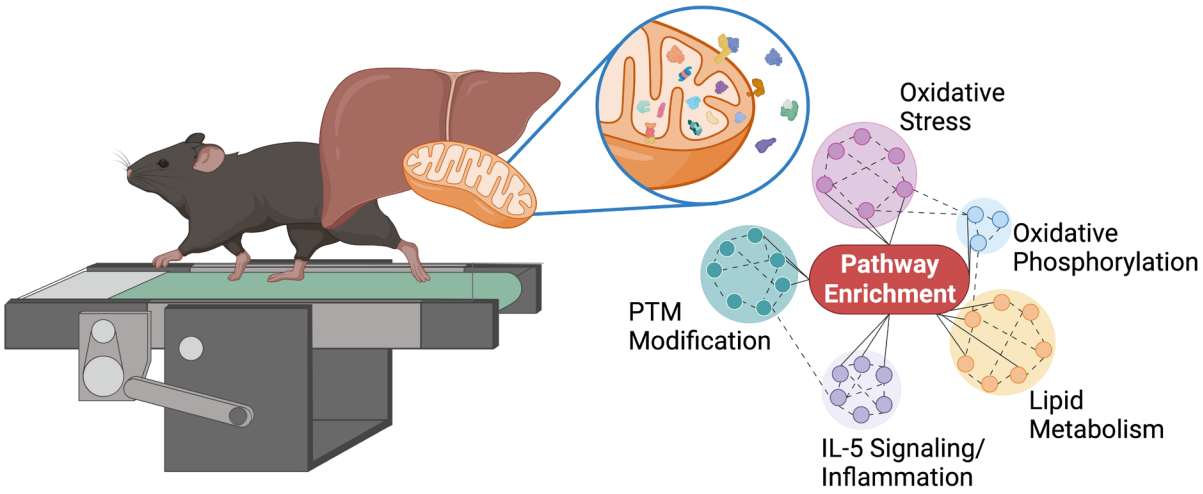
Introduction:
Exercise powerfully increases energy metabolism and substrate flux in tissues, a process reliant on dramatic changes in mitochondrial energetics. Liver mitochondria play a multi-factorial role during exercise to fuel hepatic glucose output. We previously showed acute exercise activates hepatic mitophagy, a pathway to recycle low-functioning/damaged mitochondria, however little is known how individual bouts of exercise alters the hepatic mitochondrial proteome.

Methods:
Here we leveraged proteomics to examine changes in isolated hepatic mitochondria both immediately after and 2 hours post an acute, 1 hour bout of treadmill exercise in female mice. Further, we utilized leupeptin, a lysosomal inhibitor, to capture and measure exercise-induced changes in mitochondrial proteins that would have been unmeasured due to their targeting for lysosomal degradation.

Results:
Proteomic analysis of enriched hepatic mitochondria identified 3241 total proteins. Functional enrichment analysis revealed robust enrichment for proteins critical to the mitochondria including metabolic pathways, tricarboxylic acid cycle, and electron transport system. Compared to the sedentary condition, exercise elevated processes regulating lipid localization, Il-5 signaling, and protein phosphorylation in isolated mitochondria. t-SNE analysis identified 4 unique expressional clusters driven by time-dependent changes in protein expression. Isolation of proteins significantly altered with exercise from each cluster revealed influences of leupeptin and exercise both independently and cooperatively modulating mitochondrial protein expressional profiles.

Conclusion:
Overall, we provide evidence that acute exercise rapidly modulates changes in the proteins/pathways of isolated hepatic mitochondria that include fatty acid metabolism/storage, post-translational protein modification, inflammation, and oxidative stress. In conclusion, the hepatic mitochondrial proteome undergoes extensive remodeling with a bout of exercise.

Funding Sources: This work was supported in part by a VA-Merit Grant 1I01BX002567 (J.P.T.), NIH R01 DK121497 (J.P.T), Center for Children's Healthy Lifestyles and Nutrition Pilot Grant Award (C.S.M.). We would like to acknowledge the IDeA National Resource for Quantitative Proteomics and grants R24GM137786 and P20GM121293 and the Exploris instrument grant S10OD026736.


Oxidative
Stress
Oxidative
Phosphorylation
Pathway
Enrichment
PTM
Modification
Lipid
Metabolism
IL-5 Signaling/
Inflammation

32

Characteristics and prognosis of Differentiated Thyroid Cancer in patients with Graves' Disease

Authors: Gopinath, Chaitra MBBS[1]; Crow, Hannah DO[1]; Panthi, Sujatha MBBS[1]; Bantis, Leonidas PhD[2]; Choudhary, Chitra MD[1]

Author Affiliation: [1]Department of Endocrinology, Diabetes & Clinical Pharmacology, [2]Department of Biostatistics and Data Science. The University of Kansas Medical Center, Kansas City, KS

Introduction:
The incidence of thyroid cancer in the United States and worldwide has increased 300% over the last three decades. Graves' disease (GD) is the most common cause of hyperthyroidism. common cause of hyperthyroidism. Thyroid-stimulating antibodies can result in intrinsic and genetic factors to favor tumor growth process. Recent studies show the incidence of thyroid cancer is higher among patients with GD when compared to toxic multinodular goiter. The current study compares the outcomes of Differentiated Thyroid Cancer (DTC) in patients with GD with non-GD patients.

Methods:
This was a retrospective chart review of 52 patients with a diagnosis of DTC with or without GD. We compared age at diagnosis, type and size of the tumor, radioactive iodine (RAI) use, and DTC recurrence amongst patients with GD with non-GD patients. We used Chi-square to test for independence among the categorical variables at a nominal level of 0.05. The comparison of continuous variables was based on the t-test.

Results:
Patients with GD and DTC had mean age of patients 49 years (range 23 – 78). Out of 52 patients, 29 patients had GD and 23 patients did not have GD. 92% had papillary thyroid cancer and the mean tumor size was 1.03 cm. Patients without GD had mean tumor size of 2.7 cm. 82% of the patients had Stage 1 and 2 DTC. Patients with GD were diagnosed with DTC at a relatively younger age (mean age 46 years) when compared to the patients without GD (mean age 53 years) though statistically not significant (p value 0.098). There was no difference in patients with GD in regard to the type of DTC (p value 0.43) and the stage of DTC (p value 0.048). Both groups of patients had a similar rate of recurrence and RAI use.

Conclusion:
The current study concludes that patients with GD were diagnosed with DTC at an earlier age when compared to patients without GD. Mean tumor size is smaller in GD patients with DTC. The stage of DTC and recurrence rate were similar in the two groups. The study was limited due to small sample size.

Funding sources: None

33

Secondary Acute Lymphoblastic Leukemia in Multiple Myeloma

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Author affiliations: The University of Kansas Hospital, Kansas City, KS [1-6]

Introduction:

Cancer survival and outcomes have consistently over improved over the last decade owing to practice-changing novel modalities of treatment, with multiple myeloma survival improving almost 2-3-fold.[1]The median overall survival for patients with favorable risk disease treated with modern therapies now exceeds 6 years. [2] Lenalidomide constitutes an important part of effective myeloma therapy, though it has been associated with a higher incidence of second primary malignancies, including both hematological and solid malignancies. Therapy related acute myelogenous leukemia (AML) occurs in 10-15% of patients at 10 years after treatment with an alkylating agent and secondary acute lymphoblastic leukemia (sALL) been reported in 1.5% of treated patients. [3] In this single center retrospective analysis, we evaluated the incidence of sALL in our myeloma patients.

Methods and Results:

This was a single center, retrospective chart review of multiple myeloma patients treated between 2009 and 2019. A total of 735 patients with multiple myeloma were evaluated and 6 patients with confirmed diagnosis of sALL were identified. The median age was 68 years; 4 (67%) patients were male, 4 (67%) patients had IgG isotype, 2 (33%) patients had R- ISS stage III disease, and 3 (50%) patients had normal cytogenetics on diagnosis. (See Table 1). All patient's myeloma status was in complete remission at the time of diagnosis of sALL and were on lenalidomide maintenance therapy. Four (67%) of patients were on 10 mg daily. Four (67%) patients received high dose chemotherapy with melphalan 200 mg/m^2 followed by autologous stem cell transplant (ASCT) for MM treatment. The median time from starting lenalidomide therapy until diagnosis of sALL was 62 (35-146) months, while the median time for those who received ASCT until the diagnosis of sALL was 85 (55-135) months. Cytogenetics at the time of diagnosis of sALL was normal in 3 (50%) of the patients, all patients were t(9;22) negative. Five (83%) patients received treatment for sALL while one patient opted to proceed with comfort measures. All five patients achieved a completed response after therapy. One patient passed away from relapsed myeloma. Four (67%) are currently in remission after treatment for both myeloma and sALL.

Conclusion:

Based on these observations, we conclude that the low prevalence of sALL in patient with multiple myeloma and the high efficacy of immunomodulatory agents such as lenalidomide should not alter physician's current practice or preclude their use.

Funding sources: None

Characteristics	Rates
Gender, male: female	4:2
Age, years, median (range)	68 (61-81)
Race, no of patients (%)	
Caucasian	5 (83%)
African American	1 (17%)
MM paraprotein, no. of patients (%)	
IgG	4 (67%)
Light chain	2 (33%)
Baseline R-ISS stage, no of patients (%)	
Stage III	2 (33%)
Stage II	1 (17%)
Stage I	2 (33%)
Unknown	1 (17%)
Patients who received lenalidomide	6 (100%)
No of Patients who received HDCT/ASCT	4 (67%)
Median time from diagnosis of MM till sALL (months)	62 (35-146)

Table 1. Characteristics of patients with secondary ALL in those with Multiple Myeloma (n=6)

R-ISS: Revised multiple myeloma international staging system, MM: multiple myeloma, sALL: secondary Acute Lymphoblastic Leukemia, HDCT/ASCT: High dose chemotherapy/ Autologous stem cell transplant

34

Using Formative Research to Develop a Healthy Lifestyle Program for Recent Kidney Transplant Recipients

Authors: Gibson, Cheryl A[1]; Gupta, Aditi[1]; Naik, Abhijit[2]; Sullivan, Debra K[3]; Doshi, Mona[2]; Lee, Jaehoon[4]; Backes, James[5]; Harvey, Susan[6]; Shaffer, Kelly[2]; Mount, Rebecca R[1]; Valentine, Heather[1]

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Introduction

A significant number of kidney transplant recipients experience weight gain in the first year after transplantation. Post-transplantation weight gain is associated with higher rates of cardiovascular disease, new-onset diabetes, metabolic syndrome and loss of graft function. The objective of this formative research project was to gather data to inform intervention design and implementation of a healthy lifestyle program to counter unnecessary weight gain.

Method

Recent kidney transplant recipients at the University of Kansas Health System and the University of Michigan Transplant Center were invited to participate in an online survey. Survey items included sociodemographic information, current medications, health conditions, weight change post-transplant, diet behaviors, physical activity participation, and desired features of a healthy lifestyle program.

Results

Fifty-three (38 KS; 15 MI) participants, average age 58 ± 12 years, primarily male, completed surveys. Forty percent gained weight post-transplantation with 19% gaining 10+ pounds. Most indicated struggling with their diet after transplantation, with ratings of current eating habits fair to poor (e.g., too few fruits and vegetables, too much sodium, fat and added sugars). Physical activity (PA) stayed the same (17%) or decreased (40%) post-transplantation with most not regularly participating in PA or resistance training. Many participants (41.5%) indicated they would very likely or definitely participate in a healthy lifestyle program of 6 to 12 months in length. Most wanted online PA and nutrition sessions to meet once or twice weekly with several suggestions about what kinds of information and activities to make part of the program, including healthy eating strategies (e.g., how to eat healthfully at restaurants, grocery shopping tips, recipes), resources for at-home physical activities, access to healthy cooking classes and apps to track both physical activity and food intake.

Conclusions

Gathered information will be used to inform and tailor the healthy lifestyle program for recent kidney transplant recipients. Identifying features of a program for the prevention of unnecessary weight gain with patients' input is essential for promoting healthy behaviors.

Funding Sources: None

35

Disruption of the Blood Brain Barrier in ESKD; a novel mechanism underlying cognitive impairment in ESKD

Authors: Gautam, Archana; Lepping, Rebecca J.; Young, Kate J.; Donald, Joseph; Comfort, Branden W.; Brooks, William M.; Montgomery, Robert; Yu, Alan S.; Gupta, Aditi

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Introduction:

Cognitive impairment is common in end stage kidney disease (ESKD). Although disruption of blood brain barrier (BBB) integrity is an early biomarker of cognitive impairment and dementia, BBB has not been assessed in ESKD since gadolinium-based contrast-enhanced MRI used to measure BBB is impractical in ESKD.

Methods:

In this novel single-center cross-sectional pilot study, we used single-photon emission computed tomography (SPECT-CT) with 99mTc labelled DTPA to assess BBB integrity in ESKD. We enrolled 10 ESKD patients and 10 healthy controls (without chronic kidney disease). All participants underwent brain SPECT-CT and cognitive assessments. Cohens D was calculated to compare the SPECT-CT standardized uptake values (SUV) between ESKD and controls.

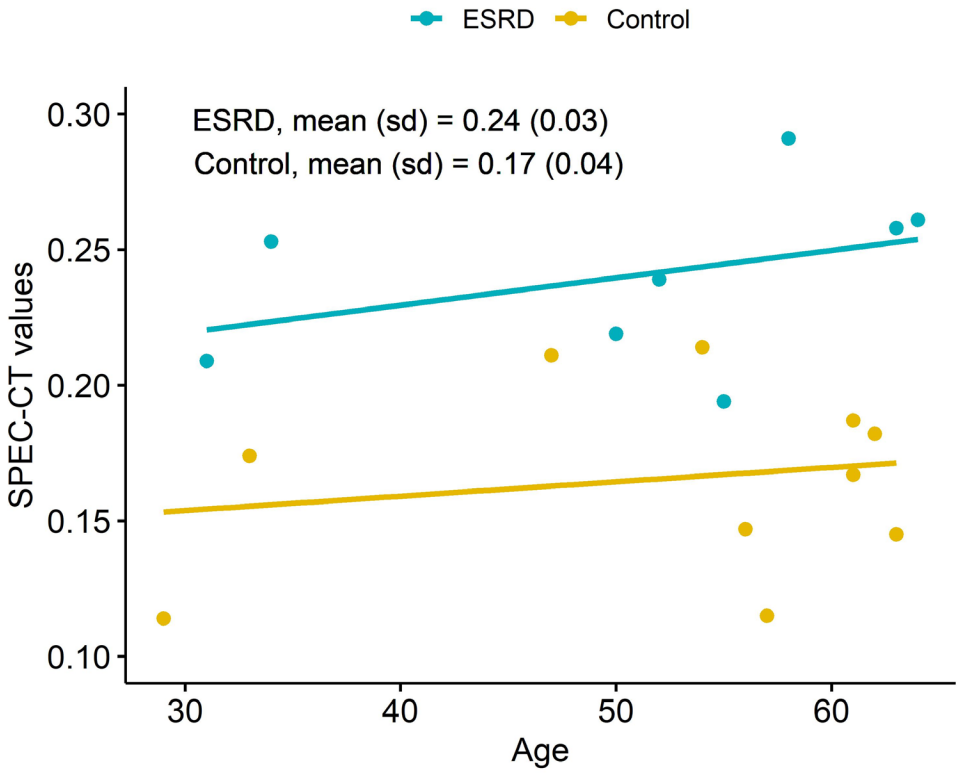
Results:

Despite the ESKD group being younger (51 ± 12 years) than the control group (52 ± 12 years), the ESKD group had a higher SUV (0.24 ± 0.03) indicating a greater disruption of BBB integrity than the control group (0.17 ± 0.04), Cohens D (measure of standard deviations between two means) = 2.35. Figure 1 shows the distribution of SUVs. The ESKD group performed worse on neuropsychological tests, in particular tests of verbal fluency, delayed recall, and Trail making B, than the control group.

Conclusion:

This is the first report demonstrating that BBB integrity is severely disrupted in ESKD patients compared with controls. The association of BBB disruption with cognitive impairment in ESKD suggests that BBB should be further studied as a novel mechanism underlying cognitive impairment in ESKD.

Funding Sources: NIH/ NIA


ESRD
Control
ESRD, mean (sd) = 0.24 (0.03)
Control, mean (sd) = 0.17 (0.04)
SPEC-CT values
0.30
0.25
0.20
0.15
0.10
30
40
50
60
Age

36

Influence of baseline diastolic blood pressure on the effect of lowering systolic blood pressure on mild cognitive impairment and probable dementia

Authors: Gupta, Aditi[1]; Boucher, Robert E.[2]; Wei, Guo[2]; Supiano, Mark A.[2]; Burns, Jeffrey M.[1]; Navaneethan, Sankar D.[3]; Gregg, L Parker[3]; Williamson, Jeff D. [4]; Pajewski, Nicholas M.[5]; Beddhu, Srinivasan[6]

Author Affiliations: 1. University of Kansas Medical Center, Kansas City, KS, United States. 2. University of Utah Health, Salt Lake City, UT, United States. 3. Baylor College of Medicine, Houston, TX, United States. 1114. Wake Forest Baptist Medical Center, Winston-Salem, NC, United States. 5. Wake Forest University School of Medicine, Winston-Salem, NC, United States. 6. The University of Utah School of Medicine, Salt Lake City, UT, United States.

Introduction:

Lowering of systolic blood pressure (SBP) in patients with already low diastolic blood pressure (DBP), can potentially decrease cerebral perfusion and worsen cognitive decline. Therefore, we examined the influence of baseline DBP on the effect of lowering SBP on incident mild cognitive impairment (MCI) and probable dementia (PD).

Methods:

In this post-hoc analysis of the Systolic Blood Pressure Intervention Trial (SPRINT) study (N = 8562), we examined the effects of intensive (< 120 mm Hg) versus standard (< 140 mm Hg) SBP control on a composite, adjudicated outcome of MCI/PD across the range of baseline DBP in a spline Cox regression model. We also tested for interactions of baseline DBP on the effect of SBP intervention on MCI/PD.

Results:

Mean age was 68±9 years, 35% were women and 66% White. There were 640 MCI/PD events over 39,022 participant-years of follow-up. Compared to standard SBP control, intensive SBP control further lowered the DBP in those in the lowest baseline DBP tertile (Figure 1A) but also lowered the risk of MCI/PD (Table 1). While lower baseline DBP was associated with higher risk of MCI/PD (Table 1), there was no evidence that intensive SBP lowering increased the risk of MCI/PD in those with low baseline DBP (Figure 1B) with interaction p = 0.37 for the product term of SBP intervention and baseline DBP.

Conclusion:

Intensive SBP lowering that further lowered DBP did not increase the risk of MCI/PD in those with low baseline DBP. The association of low baseline DBP with greater risk of MCI/PD is unlikely to be causal.

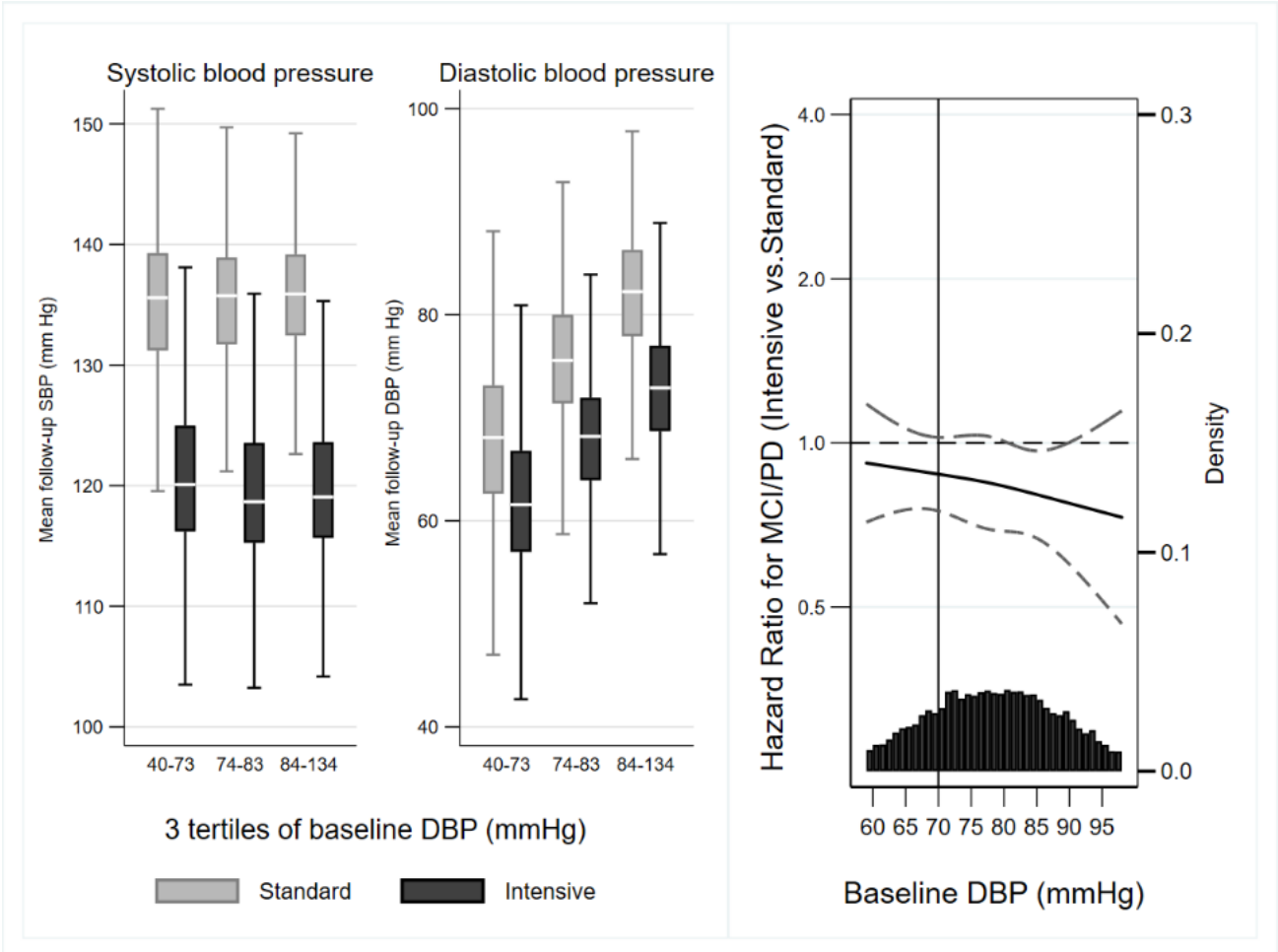
Funding sources: NIH

Table 1: Cox proportional hazard models for hazard ratios for MCI/PD for each 5 mmHg decrease in DBP and intervention.

	SBP intervention alone	DBP alone	Joint model
SBP intervention	0.80 (0.69, 0.94)		0.81 (0.69, 0.95)
Each 5 mmHg decrease in DBP		1.17 (1.13, 1.20)	1.17 (1.13, 1.20)
There was no interaction between baseline DBP and MCI/PD with the SBP intervention p=0.36			

Figure 1

A B



37

Analysis of microRNA cargo in circulating extracellular vesicles from HIV infected individuals with pulmonary arterial hypertension

Authors: Ram, Anil Kumar[1]; Mahajan, Aatish[1]; Gunewardena, Sumedha[2]; Abraham, Ashrita[1]; Krishnamachary, Balaji[1]; Kumar, Ashok[1]; Dhillon, Navneet K.[1]

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Introduction:

The risk of developing pulmonary arterial hypertension (PAH) in HIV–infected individuals is 6- to 8-fold more than the general population and illicit drug use further potentiates the development of HIV-PAH. Relevance of extracellular vesicles (EVs) containing both coding as well as non-coding RNAs in PAH secondary to HIV infection and drug of abuse is yet to be explored.

Methods:

Plasma derived extracellular vesicles were isolated from people living with HIV (PLWH) drug users with PH and without PH by exoEasy kit. Exosomal RNA was extracted using miRNeasy Kit for small RNA sequencing and quantitative RT-PCR analysis. The miRNA gene interaction network and miRNA enrichment analyses were performed using various bioinformatics tools.

Results:

Heat map analysis of small RNA-seq data and volcano plots revealed 13 upregulated and 14 down regulated miRNAs in HIV infected stimulant users with pulmonary hypertension (PLWH+ Stim +PH, n=4)) compared to HIV infected stimulant users without PH (PLWH+ Stim.,n=4). The data was compared with 12 PH datasets available in the GEO database to identify potential candidate gene targets for miRNAs using IPA. The IPA's Molecule Activity Predictor (MAP) predicted the inhibition of BMPR2 by miR-32-5p/92 up-regulated in PLWH+Stim+PH, along with activation of TNF Superfamily Member 10 (TNFSF10) by upregulated miR133b, activation of promoter from human survivin BIRC5 by upregulated miR192-5p and activation of Adenosine A2b receptor (ADORA2B) by downregulated miR-216a-3p/128 cluster. Overrepresentation analysis (ORA) of up-regulated miRNAs in PLWH+Stim+ PH showed significant enrichment of miRNAs (miR-373-3p, miR-9-5p, miR-192-5p, miR-148a-3p, miR-92b-3p, miR-301a-3p and miR-203b-3p) related to the positive regulation of cell proliferation (HIF1α, TP53, BMPR2, TGFβR2, TNF, PRDM1 and STAT3) and negative regulation of intrinsic apoptosis signaling (BCL2, MMP9, BCL2L1, BCL2L2). The ORA of downregulated miRNAs found association with interleukin-2 mediated signaling pathway, transmembrane receptor protein tyrosine kinase signaling pathway and negative regulation of smooth muscle cell proliferation (HMOX1, PPARG, IGFBP3 and BMPR2). Further the significantly differentially expressed miRNAs were validated in an independent set of HIV infected individuals with (n=12) and without PH (n=12) using q-RT-PCR.

This analysis confirmed the upregulation of miR- 32-5p, and 92-b-3p targeting cellular proliferation and downregulation of miR- 216a known to be involved in PH

Conclusion:

Collectively, data suggest association of alterations in the miRNA cargo of circulating EVs with the presence of HIV-PAH.

Funding Sources: NIH Grant RO1DA042715, RO1HL152832

38

Nesolicaftor improves ETI-corrected CFTR function in the presence of TGF-β1 in an *in vitro* model of the cystic fibrosis airway

Authors: Bengtson, Charles; Silswal, Neerupma; Baumlin, Nathalie; Yoshida, Makoto; Dennis, John; Yerrathota, Sireesha; Kim, Michael; and Salathe, Matthias

Author Affiliations: University of Kansas Medical Center, Department of Internal Medicine, Division of Pulmonary Critical Care and Sleep Medicine

Introduction:
A new class of therapies for persons with cystic fibrosis (PwCF), termed CF transmembrane conductance regulator (CFTR) modulators, have led to dramatic improvements in lung function and other clinical outcomes in PwCF. However, individual response is variable and airway inflammation, a key feature of CF pulmonary disease, does not improve. The addition of a therapy to increase available *CFTR* mRNA, termed CFTR amplifiers, was previously investigated and has the potential to improve response to ETI. We examined, in an *in vitro* model of the CF airway, if the addition of the amplifier nesolicaftor (PTI-428) to the CFTR modulator elexacaftor/tezacaftor/ivacaftor (ETI) with and without the presence of the inflammatory mediator transforming growth factor beta 1 (TGF-β1) could improve CFTR function.

Methods:
Homozygous F508del CFBE cells were re-differentiated at the air-liquid interface (ALI). Cells were then treated for 24 hrs a combination of vehicle control, elexacaftor (1 μM)/tezacaftor (5 μM)/ivacaftor (1 μM), nesolicaftor (10 μM) and/or recombinant TGF-β1 (5 ng/mL). Cells were mounted in Ussing chambers (EasyMount Chamber) connected to a VCC MC8 voltage clamp unit (Physiologic Instruments) and CFTR-dependent short-circuit currents (I_{SC}) were recorded upon addition of $CFTR_{inh}$-172 (10 μM) after ivacaftor (1 μM) and forskolin (10 μM) stimulation in the presence of amiloride (10 μM). ASL volume was estimated by meniscus scanning. Ciliary beating (CBF) was measured using high-speed video microscopy. *CFTR* and *miR-145* mRNA expression levels were measured by qPCR and IL-6 and IL-8 protein expression was measured by ELISA.

Results:
ETI-mediated improvement of CFTR function in homozygous F508del CFBE cells was augmented significantly in the presence of nesolicaftor. Nesolicaftor also rescued CFTR function in CFBE cells treated with ETI and TGF-β1. This effect was likely due to stabilization of *CFTR* mRNA, as demonstrated by increased *CFTR* mRNA levels after treatment with nesolicaftor. Nesolicaftor further reversed the TGF-β1-mediated decrease in CBF and increase in inflammatory cytokines IL-6 and IL-8.

Conclusion:
This study demonstrates the benefits of nesolicaftor as an adjunct to the CFTR modulator ETI to improve responses, especially in the inflammatory environment of the CF airway.

Funding Sources: This research was funded by the Cystic Fibrosis Foundation (CFF), SALATH18I0 and 003221G221 (to M.S.); NIH/NHLBI, HL133240 and HL139365 (to M.S.) and HL157942 (to M.S. and M.D.K.).

39

Cerebrospinal Fluid AFB Smear in Adults with Tuberculous Meningitis: A Systematic Review and Diagnostic Test Accuracy Meta-Analysis

Authors: Stadelman, Anna M[1]; Ssebambulidde, Kenneth[2]; Buller, Alexandria[3]; Tugume, Lillian[2]; Yuquimpo, Kyle;[4] Bakker, Caitlin J[5]; Boulware, David R[6]; Bahr, Nathan C[3]

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6. Division of Infectious Diseases and International Medicine, Department of Medicine, University of Minnesota, Minneapolis, MN, USA.

Introduction:

Cerebrospinal fluid (CSF) Ziehl-Neelsen acid-fast bacilli (AFB) smear is a rapid, cheap, widely available test for tuberculous meningitis (TBM). Yet, reported test sensitivity is highly variable. We performed a systematic review and meta-analysis for CSF AFB smear vs. other mycobacterial tests to diagnose TBM.

Methods:

We searched MEDLINE and Embase for studies reporting sensitivity and specificity of AFB smear against mycobacterial tests (reference standard) in adults (≥15 years) with suspected TBM. We used the QUADAS-2 tool to assess risk of bias. We estimated pooled sensitivity and specificity of AFB smear versus the reference standard using random-effects bivariate modeling. We used the I^2 statistic to assess heterogeneity between studies.

Results:

Of 981 articles identified, 11 were eligible for inclusion with a total of 1713 participants. Seven studies were from high-TB burden settings and 4 from low-TB burden settings. The pooled sensitivity and specificity of CSF AFB smear were 8% (95%CI 3-21) and 100% (95%CI 90-100), with substantial heterogeneity in diagnostic performance (I^2 >95% for both) and reference standards.

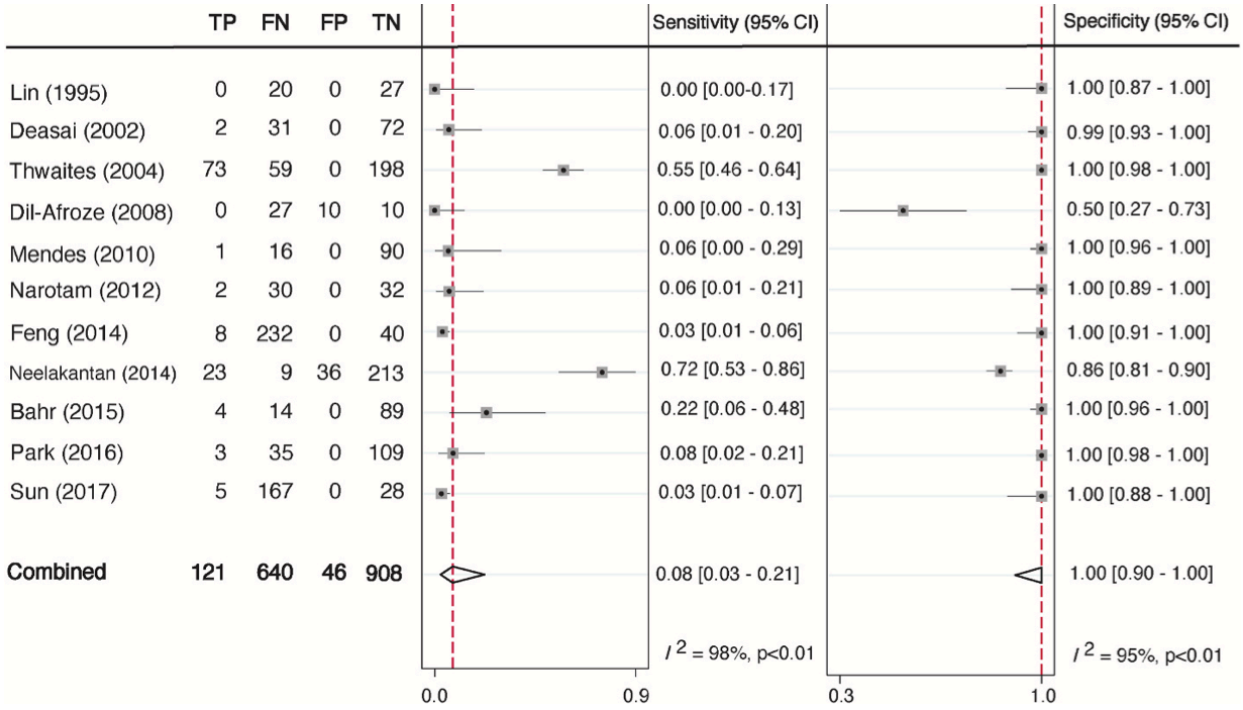
Conclusion:

CSF AFB smear has poor sensitivity in most settings. If other more sensitive tests are available, those should be used preferentially rather than CSF AFB smear.

Funding Sources:

Fogarty International Center, National Institutes of Health, USA (R01NS086312 , D43TW009345). National Institute of Neurological Disorders and Stroke, National Institutes of Health, USA (K23NS110470).

Fig. 2. Diagnostic sensitivity and specificity of AFB Smear versus reference standard



40

Trends in Pricing and Out-of-Pocket Spending on Entecavir Among Commercially Insured Patients, 2014-2018

Authors: Alpern, Jonathan D[1]; Joo, Heesoo[2]; Link, Ben[3]; Ciaccia, Antonio[3]; Stauffer, William M[4]; Bahr, Nathan C[5]; Leventhal, Thomas M[6]

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5 Division of Infectious Diseases, Department of Medicine, University of Kansas Medical Center, Kansas City.
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Introduction:

Chronic hepatitis B (CHB) causes significant liver-related morbidity and mortality. Entecavir, a generic drug that is one of the first-line agents used for treatment of CHB, has had a steep decline in the average price that pharmacies pay for the drug (ie, national average drug acquisition cost [NADAC]) because of manufacturer competition. Yet, the list price—which correlates with out-of-pocket spending—has remained high.

Methods:

Yearly NADAC prices of entecavir 0.5-mg tablets were obtained from Medicaid's publicly available NADAC database for December 2014 through December 2018. We calculated yearly average wholesale price based upon a weighted average calculation of Medicaid expenditures and average wholesale price derived from a criterion standard drug database (ProspectoRx). We used the FDA Orange Book to determine the yearly number of drug manufacturers. We analyzed a commercial database of health claims (IBM Corp). We obtained utilization and fill data for entecavir and calculated mean number of fills per member, mean number of days of supply per member, and mean annual out-of-pocket spending, as well as total spending per member, fill, and 30-day supply stratified by use of a high-deductible health plan.

Results:

With over 1000 annual entecavir fills, as the number of entecavir manufacturers increased from 1 to 11, the NADAC decreased from $30.12 to $1.93 per 0.5-mg tablet. The average wholesale price remained constant at $44.43. Among commercially insured members, mean (SD) out-of-pocket spending per 30-day supply of generic entecavir was $41 ($81) in 2014 and $52 ($97) in 2018. Mean (SD) out-of-pocket spending per 30-day supply of brand name entecavir was $118

($180) in 2014 and $165 ($178) in 2018. Among members with a high-deductible health plan, mean (SD) out-of-pocket spending per 30-day supply of generic entecavir was $103 ($167) in 2014 and $133 ($122) in 2018. Trends in the number of manufacturers, NADAC, average wholesale price, and out-of-pocket spending per 30-day supply of generic entecavir are shown in the Figure.

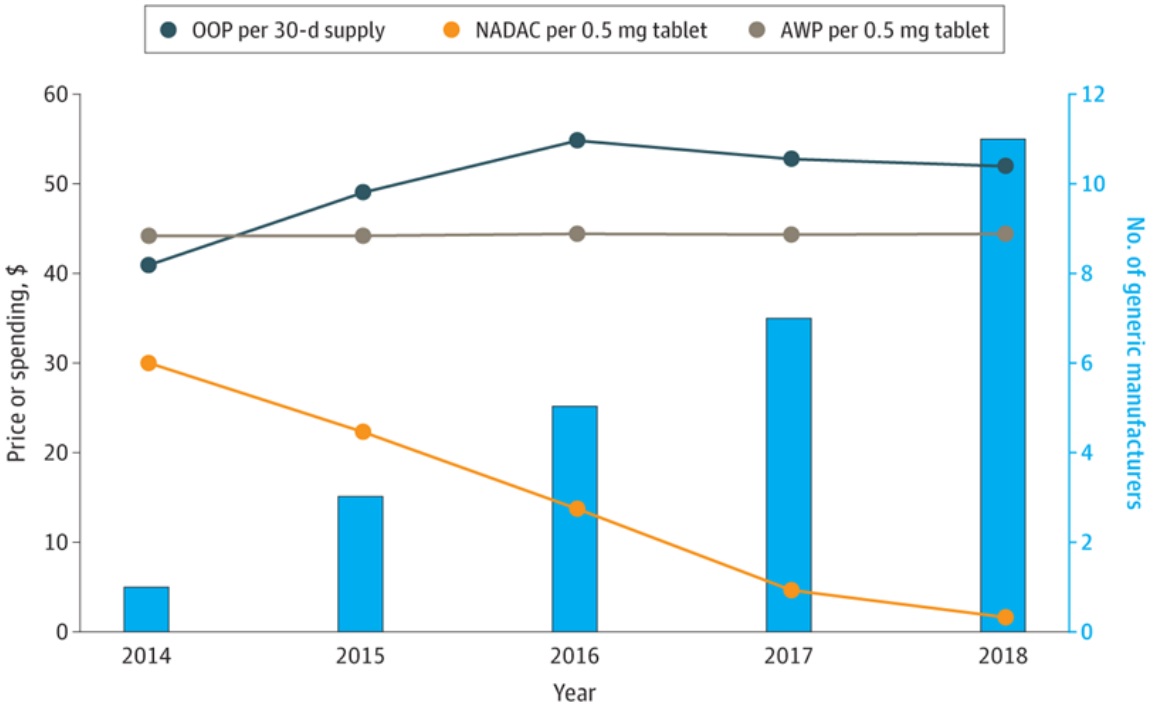
Conclusion:

OOP for entecavir has risen despite an increased number of generic manufacturers and a drop in NADAC

Funding Sources:

Dr Alpern reported receiving funding from Arnold Ventures during the drafting of the manuscript for an unrelated study. Mr Ciaccia reported having clients that include the American Pharmacists Association, Ohio Pharmacists Association, and American Pharmacy Cooperative Incorporated. Dr Stauffer reported receiving an honorarium from Fishawack Health/Emergent BioSolutions and royalties from UpToDate outside the submitted work. Dr Bahr reported receiving research funding from the National Institute of Neurological Disorders and Stroke of the National Institutes of Health (No. K23NS110470) for unrelated work.

Figure: National Average Drug Acquisition Cost (NADAC), Average Wholesale Price (AWP), Out-of-Pocket (OOP) Spending per 30-Day Supply of Generic Entecavir, and Numbers of Generic Entecavir Manufacturers in the US, 2014-2018



41

Quantitative CT and computational respiratory structure-function assessment of air pollution impacts in lung health, asthma, COPD, and IPF

Authors: Choi, Jiwoong[1]; Lee, In Kyu[1]; Kim, Taewon[1]; Abdolijomoor, Asma[1]; Lee, David H[1]; Biswas, Rohit[1]; Lee, Chang-Hoon[2]; Choi, Sunmi[2]; Kang, Hye-Ryun[2]; Kim, Kyoung-Nam[3]; Lee, Kyung-Shin[2]; Kim, Woo Jin[4]; Chae, Kum Ju[5]; Ko, Hongseok[4]; Boomer, Jonathan[1]; Niedbalski, Peter[1]; Hall, Chase[1]; Castro, Mario[1]; Lee, Chang Hyun[2]

Author Affiliations: [1]The University of Kansas, [2]Seoul National University Hospital, [3]Ajou University Hospital, [4]Kangwon National University Hospital, [5]Jeonbuk National University Hospital

Introduction:

We investigated impact of air pollution on multiscale lung structure and function in health, asthma, chronic obstructive pulmonary disease (COPD), and idiopathic pulmonary fibrosis (IPF), using quantitative computed tomography (QCT) and computational fluid dynamics (CFD) analysis.

Methods:

Inspiratory and expiratory CTs, air pollution measurements, and clinical data were collected from 270 participants enrolled in 5 institutions in South Korea, with healthy lungs (age=68±10, M:F=15:51), asthma (age=60±12, M:F=39:56), COPD (age=69±7, M:F=66:10), and IPF (age=72±7, M:F=43:10). Blood RNA sequencing data subset were collected from 64 COPD participants. 185 QCT features and 72 CFD-derived air flow features were computed. ANOVA, post-hoc tests, Pearson's correlation, principal component analysis, and k-means clustering were used for analysis.

Results:

Normalized hydraulic diameter (D_h^*) of the right lower lobe segmental airways (sRLL) was smaller in the high exposure cluster than low exposure cluster by 8.2% ($p=0.017$) in all, and 30.2% in IPF ($p=0.001$). Decrease in D_h^*(sRLL) moderately associated with increase in acinar pressure work rate at the RLL ($r=0.439$, $p<0.05$) and also the right upper and middle lobes (RUL and RML) ($r=0.409$, 0.402, $p<0.05$). In asthma, residential PM2.5 and PM10 exposures associated with pressure drop (ΔP) (whole lung: $r=0.425$, 0.441; left lower lobes (LLL): $r=0.590$, 0.613). And large particles (PM10 and TSP) associated with inspiratory low attenuation area (LAA_{IN}) ($r=0.307$, 0.316; $p<0.05$), indicating regional hyperinflation. In COPD, PM1, PM2.5, PM4, and PM10 were negatively correlated with LAA_{IN} ($r=-0.265$ -0.257, -0.227, -0.258; $p<0.05$), attributable to inflammation-induced hypoinflation, supported by correlation with MMP9 ($r=0.535$, 0.543, 0.521, 0.429, $p<0.001$). PM2.5 associated with transpulmonary pressure (P_{tp}) in COPD ($r=-0.492$) and IPF ($r=-0.536$), with airway resistance (R) ($r=-0.628$), and with ΔP ($r=0.536$) in COPD. Work address-based CO exposure associated with ΔP ($r=0.689$, whole lung; 0.793, RLL), pressure work rate ($r=0.632$), and R ($r=0.554$) in COPD. Work address-based PM2.5 associated with P_{tp} ($r=0.587$) and R ($r=0.604$). Residential exposure to PM2.5 and PM10 associated with P_{tp} in COPD ($r=0.587$) and ΔP in IPF ($r=0.462$, whole lung; 0.672, RLL).

Conclusion:

QCT characterized air pollution exposure impact on regional lung structure-function in asthma, COPD, and IPF. Air pollution exposure associated with mechanical burden of breathing.

Funding Sources: This work was supported in part by Korea Environmental Industry & Technology Institute (KEITI) grant 2018001360001 funded by Ministry of Environment (MOE), Republic of Korea.

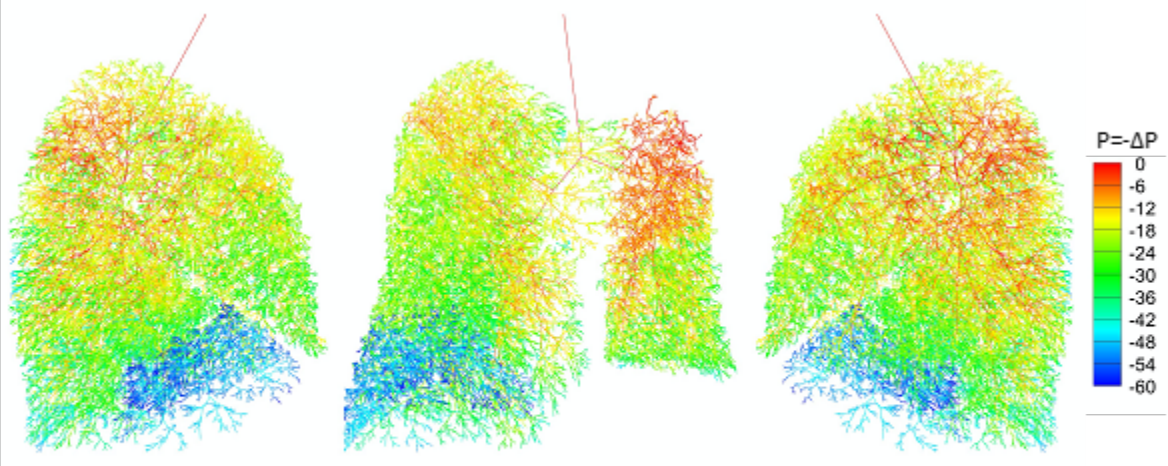


Figure. 1D CFD-derived pressure distribution through the entire conducting airway model from trachea to the terminal bronchioles in a representative COPD patient with high PM and CO exposure, correlated with greater ΔP in the right lower lobe (RLL) (see blue region).

42

Hyperpolarized ^{129}Xe MRI for Evaluating Lung Structure and Function in Post-Acute Sequelae of COVID-19

Authors: Niedbalski, Peter; Frizzell, Bradie; Monge, Cristal; Pelland, Dylan; Choi, Jiwoong; Hall, Chase; Castro, Mario

Author Affiliations: University of Kansas Medical Center

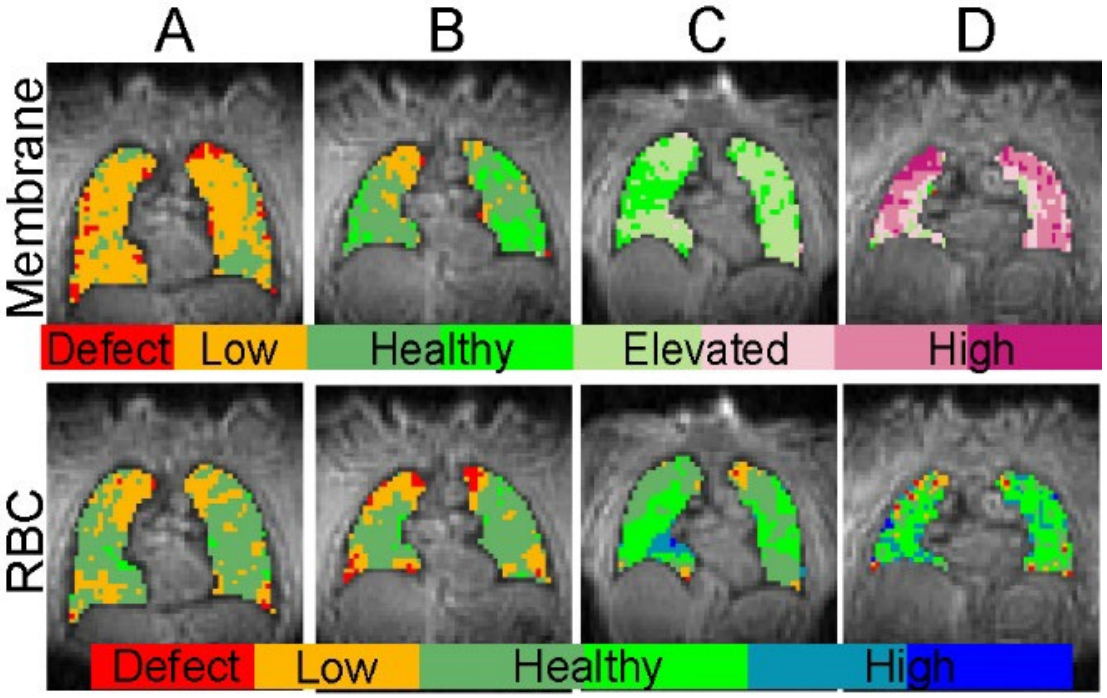
Introduction: A significant subset (10-30%) of patients who recover from COVID-19 experience lingering symptoms that can last over 1 year. While these symptoms are wide ranging, cardio-respiratory symptoms such as dyspnea, cough, and fatigue are among the most common. Challenging the treatment of these patients, respiratory symptoms are not always associated with clinical indicators of impaired lung health such as lung function testing or CT imaging. In this study, we used a novel imaging technique, "hyperpolarized ^{129}Xe MRI" (Xe-MRI) to image lung structure and function in patients with post-acute COVID-19 respiratory symptoms.

Methods: We imaged 39 individuals (25 Female) who have recovered from acute COVID-19, including 27 patients with post-acute COVID-19 respiratory symptoms. We imaged 3 additional healthy never-COVID-19 volunteers (1 Female). Images of ventilation, red blood cells (RBCs), and other pulmonary tissues ("membrane") were acquired and compared to patient-reported respiratory symptoms.

Results: Xe-MRI imaging results in patients with post-acute COVID-19 symptoms showed minimal ventilation defects, widely variable membrane signal, and generally reduced RBC signal (See Figure). Research participants with respiratory symptoms had significantly reduced Xe-MRI RBC/Membrane (0.32 ± 0.09 vs. 0.42 ± 0.13, p = 0.01) than participants without symptoms. Additionally, participants experiencing dyspnea had significantly reduced RBC/Membrane (0.33 ± 0.09 vs. 0.40 ± 0.14, p = 0.048) compared to those without dyspnea. Moreover, patients experiencing fatigue had significantly reduced RBC/Membrane (0.32 ± 0.09 vs. 0.41 ± 0.13, p = 0.02) and RBC/Gas (0.27 ± 0.09 vs. 0.36 ± 0.11, p = 0.01) compared to those without fatigue. Respiratory symptoms including cough and chest tightness were not associated with Xe-MRI markers.

Conclusion: Gas exchange Xe-MRI markers including RBC/Membrane and RBC/Gas ratios were significantly different between participants experiencing respiratory symptoms and those who were symptom free. Xe-MRI ventilation imaging was not significantly different among these groups. These results suggest that post-acute COVID-19 respiratory symptoms are related to gas exchange impairment rather than obstruction. This result is consistent with a vascular origin to lung impairment in post-acute COVID-19. Ultimately, Xe-MRI appears to be an effective tool for elucidating lung injury in this patient population.

Funding Sources: This work was funded by the American Heart Association (Career Development Award 930177) and the Scleroderma Foundation (New Investigator Award).


A
B
C
D
Membrane
Defect
Low
Healthy
Elevated
High
RBC
Defect
Low
Healthy
High

43

A Framework for the Development of Living Practice Guidelines in Health Care

Authors: El Mikati, Ibrahim[1]; Khabsa, Joanne[2]; Akl, Elie A. [2]; Mustafa, Reem A.[1]; and the Living Guidelines Group

Author Affiliations: [1]The University of Kansas Medical Center, [2]The American University of Beirut

Introduction:

Living practice guidelines are increasingly being used to ensure that recommendations are responsive to rapidly emerging evidence. The aim of this paper is to develop a framework that characterizes the processes of development of living practice guidelines in health care.

Methods:

First, 3 background reviews were conducted: a scoping review of methods papers, a review of handbooks of guideline-producing organizations, and an analytic review of selected living practice guidelines. Second, the core team drafted the first version of the framework. Finally, the core team refined the framework through an online survey and online discussions with a multidisciplinary international group of stakeholders

Results:

A major principle of the framework is that the unit of update in a living guideline is the individual recommendation. In addition to providing definitions, the framework addresses several processes. The planning process should address the organization's adoption of the living methodology as well as each specific guideline project. The production process consists of initiation, maintenance, and retirement phases. The reporting should cover the evidence surveillance time stamp, the outcome of reassessment of the body of evidence (when applicable), and the outcome of revisiting a recommendation (when applicable). The dissemination process may necessitate the use of different venues, including one for formal publication.

Conclusion:

The framework will help guideline developers in planning, producing, reporting, and disseminating living guideline projects. It will also help research methodologists study the processes of living guidelines. This study does not provide detailed or practical guidance for how the described concepts would be best implemented.

Funding Sources: None

44

Antigen Testing For COVID-19: Comprehensive Systematic Review and Meta-Analysis

Authors: El Mikati, Ibrahim K.[1]; Mansour, Razan[1]; Al Abed, Farouk[2]; El Alayli, Abdallah[3]; Patel, Payal[4]; Amarin, Justin Z.[5]; Mustafa, Reem A.[1]

Author Affiliations: [1]The University of Kansas Medical Center, [2]The University of Kansas Medical School, [3]SSM Health Saint Louis University Hospital, [4]Emory University, [5]Vanderbilt University

Introduction:

Immunoassays designed to detect SARS-CoV-2 protein antigens are commercially available. We performed a comprehensive systematic review of the literature to evaluate the diagnostic test accuracy of SARS-CoV-2 Antigen (Ag) testing.

Methods:

The review team searched PubMed MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials, from June 2020 to April 2022 for relevant studies. The team statistically pooled estimates using [R software] using random effect model. We conducted subgroup analysis for asymptomatic and symptomatic patients and based on time since symptoms onset. Reviewers assessed the risk of bias using (QUADAS)-2 tool and the quality of evidence using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach.

Results:

The search identified 17,334 references out of which we included 220 studies. All studies compared Ag testing to lab based NAAT. In symptomatic patients the pooled estimates for sensitivity were 0.81 (95% confidence interval (CI): 0.78 to 0.84), in all studies regardless of symptom onset, 0.86 (95% CI: 0.82 to 0.90) in patients within 7-days, and 0.50 (95% CI: 0.37 to 0.63) in patients with more than 7-days of symptom onset. In asymptomatic patients the pooled estimate of sensitivity was 0.63 (95% CI: 0.56 to 0.69). Specificity was 0.99 to 1.00 for all subgroups. The certainty of the evidence was moderate to very low.

Conclusion:

Ag testing showed comparative sensitivity to NAAT reference standard during the first week of symptom onset. Based on that, it is reasonable to consider Ag test as an acceptable alternative test for COVID-19 diagnosis within 7 days of symptom onset.

Funding Sources: None

45

Primary membranous nephropathy flare after COVID-19 vaccination

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Author Affiliations: [1]Division of Nephrology and Hypertension, University of Kansas Medical Center, [2]Renal-Electrolyte Division, University of Pittsburgh Medical Center, [3]Department of Pathology, University of Pittsburgh Medical Center

Introduction:
Primary membranous nephropathy (MN) is most commonly due to phospholipase A2 receptor antibodies (PLA2R Ab). It is unclear whether the COVID-19 vaccine can trigger flares of glomerular diseases such as primary MN. We present a case of a patient with MN and metastatic breast cancer who developed nephrotic syndrome shortly after receiving her second mRNA-1273 COVID-19 vaccine with positive PLA2R Ab by ELISA suggesting MN flare.

Methods:
A 62 year old female with history of Stage IIIB T3N3M0 ER/PR positive HER-2 negative metastatic left breast invasive ductal carcinoma, hypertension, hyperlipidemia, and primary MN presented with bilateral leg edema, dyspnea, and proteinuria 2 weeks after COVID-19 vaccination. She had previous proteinuria of 7029 mg/24hr in August 2018 with PLA2R Ab 128 RU/mL in October 2018. She underwent modified radical mastectomy in September 2018 and adjuvant chemotherapy in November 2018. PLA2R Ab decreased to <2 RU/mL in February 2019 and urine protein/Cr ratio (UPCR) decreased to 1094 mg/g Cr in April 2019. She received mRNA-1273 COVID-19 vaccines in January and February 2021. In March 2021, she presented with bilateral leg edema, dyspnea, and bilateral pleural effusions. Urinalysis had >1000 protein, 24hr urine protein 11.2 g, Cr 1.6 mg/dL, and PLA2R Ab 787 RU/mL. Renal biopsy showed immune complex-mediated glomerulopathy with positive PLA2R and IgG4, consistent with primary MN stage II-III. Electron microscopy showed subepithelial and intramembranous electron-dense deposits. She was treated with lisinopril and furosemide followed by rituximab in May 2021. Prior to rituximab PLA2R Ab was 342 RU/mL and UPCR was 8671 mg/g Cr.

Results:
There is insufficient data on the risk of flares after COVID-19 vaccines in glomerular diseases. Increasingly, both de novo and relapse of pre-existing glomerular disease, including primary MN and minimal change disease, have been reported shortly after administration of the mRNA COVID-19 vaccines. These cases suggest immune-mediated GN flares may be induced by COVID-19 vaccines.

Conclusion:
Our case of primary MN flare after COVID-19 vaccine adds support to a potential association between SARS-CoV-2 antigens and loss of tolerance to the PLA2R antigen. Close follow-up of patients with primary MN and other glomerular diseases after COVID-19 vaccination is warranted.

Funding Sources: None.

46

Are Changes in Clinical Biomarkers Associated with Changes in Lupus Nephritis Pathology on Repeat Biopsy?

Authors: Liang, Kelly[1]; Liang, Kimberly[2]; Li, Yaming[3]; Landsittel, Douglas[4]; Mongelli, Christina[5]; Bastacky, Sheldon[5]

Author Affiliations: [1]Division of Nephrology and Hypertension, University of Kansas, [2]Division of Allergy, Clinical Immunology, and Rheumatology, University of Kansas, [3]Department of Biomedical Informatics, University of Pittsburgh, [4]Department of Epidemiology and Biostatistics, Indiana University School of Public Health-Bloomington,[5]Pitt Biospecimen Core, Department of Pathology, University of Pittsburgh

Introduction:
Renal biopsy is the gold standard for diagnosis of lupus nephritis (LN). Changes in clinical biomarkers of LN are often used to decide whether repeat biopsies are necessary to confirm LN flare. It is unclear whether clinical biomarkers are predictive of changes in LN class or activity on repeat biopsy. The aim of this study was to determine whether clinical biomarkers at initial biopsy, 12 months, and at second biopsy are associated with changes in LN pathology on repeat biopsy.

Methods:
Using the University of Pittsburgh Health Sciences Tissue Bank (HSTB) and Renal Pathology Department stored specimens of LN from 2010-2016, we determined which cases had >1 biopsy. We obtained LN classes and clinical biomarkers within a month of initial biopsy, 12 months, and at repeat biopsy. Descriptive statistics were used to summarize biomarker changes between patients who did and did not undergo repeat biopsy, biomarker changes at second biopsy, and changes in pathology between initial and subsequent biopsy.

Results:
Of 37 LN cases, 31 had baseline creatinine (Cr) values at initial biopsy and 3 had a second renal biopsy. Biomarkers in all patients showed improvement between baseline and 12 months (mean Cr, dsDNA Ab, ESR, and CRP decreased; C3 and C4 increased). At least 3 clinical biomarkers were worse at time of second biopsy in all 3 patients. Two of the 3 had normal Cr at repeat biopsy. All three had initial biopsy showing combined proliferative and membranous (V) LN. In these 3 cases, the LN classes changed from IV+V to III+V at 42 months, remained III+V at 13 months, and remained II+V at 80 months. Mean activity and chronicity indices at repeat biopsy were 2.5/24 and 2/12 respectively.

Conclusion:
Our findings suggest repeat biopsies did not show worse LN class or activity despite worsening of certain biomarkers when renal function was preserved. Further studies are needed to determine which changes in clinical biomarkers are predictive of worse LN class and disease activity on repeat renal biopsy. There is an urgent need for novel noninvasive biomarkers to predict LN flares to guide therapy.

Funding Sources: None.

47

Pituitary Metastasis from Clear Cell Renal Cell Carcinoma

Authors: Pagadala, Prathyusha; Crow, Hanna; Cristiano, Elizabeth

Author Affiliations: The University of Kansas

Introduction:

Pituitary metastasis is a known, but rare cause of a sellar mass seen on imaging. Metastatic lesions to the pituitary usually derive from breast and lung carcinoma while metastasis from renal cell carcinoma is very rare. Here we describe a case of clear cell renal carcinoma which metastasized to the pituitary which also stained positive for a coexisting gonadotroph pituitary adenoma.

Methods/Results:

63-year-old female presented with a two-month history of intermittent diplopia and headaches. Her past medical history was relevant for renal cell carcinoma status post right nephrectomy four years prior, she did not receive any adjuvant therapy.

She underwent an MRI which showed a 2.1 x 2 x 1.6 cm sellar/suprasellar enhancing mass with mass effect on the optic chiasm and extending into the right cavernous sinus consistent with pituitary macroadenoma. Visual field testing was also done which showed mild bitemporal quadrantanopia. Lab evaluation did not show evidence of pituitary hormone excess or deficiency. Sodium was normal, IGF-1 117 ng/ml (reference range 35-201 ng/ml), GH 0.19 ng/ml (0.01 -3.61 ng/ml), alpha subunit 0.4 ng/ml (<1.8 in postmenopausal female), ACTH 15 pg/ml (7-63 pg/ml), prolactin 20.8 ng/ml (3.3 -26.7 ng/ml), TSH 2.36 MCU/ml (0.35-5 MCU/ml) and FT4 0.9 ng/dl (0.6 -1.6 ng/dl).

Neurosurgery was consulted and patient underwent transsphenoidal surgery. Her postoperative period was unremarkable without evidence of diabetes insipidus or secondary adrenal insufficiency. Final pathology revealed clear cell lesion/carcinoma consistent with metastatic renal cell carcinoma. Transcription marker testing was positive for SF1, consistent with a gonadotroph pituitary adenoma.

Conclusion:

This case is representative of pituitary metastasis from renal cell carcinoma presenting many years after initial nephrectomy. Though rare, the possibility of metastatic lesion in a patient with a prior history of malignancy should be considered in all cases of pituitary adenomas.

Funding Sources: None.

48

Impact of menopause on energy metabolism in mice

Authors: Kumari, Roshan[1,2]; Prom, John [1]; Allen, Julie[1]; McCoin, Colin[1,2]; Thyfault, John[1,2] and Morris, Matt[1]

Author Affiliations: [1]University of Kansas Medical Center, [2]VA Medical Center

Introduction:

Perimenopausal to menopausal transition is associated with higher risk of metabolic dysfunction in women likely due to a decline in estrogen levels. These metabolic outcomes include weight gain, insulin resistance, type 2 diabetes, hepatic steatosis, and cardiovascular diseases.

Methods:

Studies from our lab and others suggest that a decline in estrogen levels may influence the development of metabolic dysfunction by affecting metabolic organs including liver, muscle, adipose and brain. Despite the strong evidence that reduced estrogen broadly impacts weight management and metabolism, the underlying mechanisms of metabolic dysfunction during the progressive transition between perimenopause to menopause remains unclear. The VCD (vinyl cyclohexene dioxide) is a proven drug to induce ovarian failure and perimenopause in mice while preserving androgen related function that is similar to human menopause development. For the first time we are leveraging VCD treatment in female mice to determine the effects of perimenopause to menopause transition on changes in body composition (adipose and lean mass), food intake, feeding efficiency, and hepatic steatosis under standard low-fat diet (LFD) conditions. Additionally, we will also investigate the effect of VCD on hepatic mitochondrial quality and bile acid metabolism in response to LFD which are also known to be impacted by estrogen.

Results/Conclusion:

These studies will allow us to understand how estrogen imbalance during perimenopause sets the stage for metabolic dysfunction during menopause.

Funding Sources: This research was supported by NIH 5K01DK112967 & P20GM144269

49

MDSCs, the focus for cancer immunotherapy, are also a target for healthy aging!

Authors: Thiyagarajan, Ramkumar[1]; Zhang, Lixia[2]; Kyuhwan, Kwack[2]; Berman, Reem[2]; Marzullo, Brandon[2]; Seldeen, Kenneth[1]; Kirkwood, Keith[2]; Troen, Bruce[1]

Author Affiliations: [1]The University of Kansas & Veterans Affairs Kansas City Healthcare System, [2]University at Buffalo & Veterans Affairs Western New York Healthcare System

Introduction:
Aging is associated with systemic chronic low-grade inflammation termed Inflammaging, which is recognized as a driver for age-related diseases. During inflammaging, myeloid-derived suppressor cells (MDSCs) expand and exhibit immunosuppressive activity. MDSCs also represent the main immunosuppressive cells present in the tumor microenvironment that sustain cancer progression. MDSCs have been extensively studied in the cancer field, but the role of MDSCs in normal aging and age-related disease has not been explored. Thus, profiling transcriptomic and metabolic changes in MDSCs during normal aging will allow us to delineate their role and lay a foundation and repurpose the immunotherapeutic drugs to alleviate inflammaging and improve healthspan in older adults.

Methods:
Cells were isolated from bone marrow, spleen, and blood from 6- and 24-month-old male C57BL/6J-NIA mice, and flow cytometer analysis was performed to phenotype immune cells. Glucose metabolism of magnetically sorted MDSCs was assessed using a Seahorse XFe24 extracellular flux analyzer. Transcriptomic profiling of MDSCs was performed with NextGen sequencing.

Results
Splenic and circulatory MDSCs of aged mice were increased by 78% ($p=0.049$) and 212% ($p=0.025$) compared to young mice, while bone marrow MDSCs were similar. MDSCs from aged mice bone marrow and spleen also exhibited greater glycolytic capacity (44%; $p=0.005$ and 239%; $p<0.001$, respectively) and increased expression of glucose 6-phosphate dehydrogenase ($p<0.001$) and lactate dehydrogenase ($p<0.001$) than did MDSCs from young mice. NextGen sequencing analysis revealed that there are over 5000 mRNAs that are differentially expressed between young and aged MDSCs. In particular, MDSCs from aged mice expressed 3-fold greater expression of CD38 ($p<0.001$), an immune cell glycoprotein that regulates cytokine release in sites of inflammation.

Conclusion
Aged mice exhibit significantly more MDSCs in both spleen and blood, which displayed greater glycolysis, glycolytic reserve, and glycolytic genes similar to the tumor microenvironment. In aged mice there was also greater expression of the inflammation associated gene, CD38, which is highly expressed in cancer cells and contributes to cancer progression. Future studies will investigate whether the inhibition and/or knockout of CD38 reduces MDSC abundance and activation, curtails the inflammatory milieu and immunosuppressive activity, and ultimately reduces inflammaging and improves healthspan in older mice.

Funding Sources:
National Institutes of Health, Veterans Affairs, and the Indian Trail Foundation.

50

Nicotinamide riboside enhances cognitive function and physical performance in aged mice

Authors: Thiyagarajan, Ramkumar[1]; Seldeen, Kenneth[1]; Shahini, Aref[2]; Redae, Yonas[2]; Leiker, Merced[2]; Andreadis, Stelios[2]; and Troen, Bruce[1]

Author Affiliations: [1]The University of Kansas; VA Kansas City, [2]University at Buffalo; VA Western New York

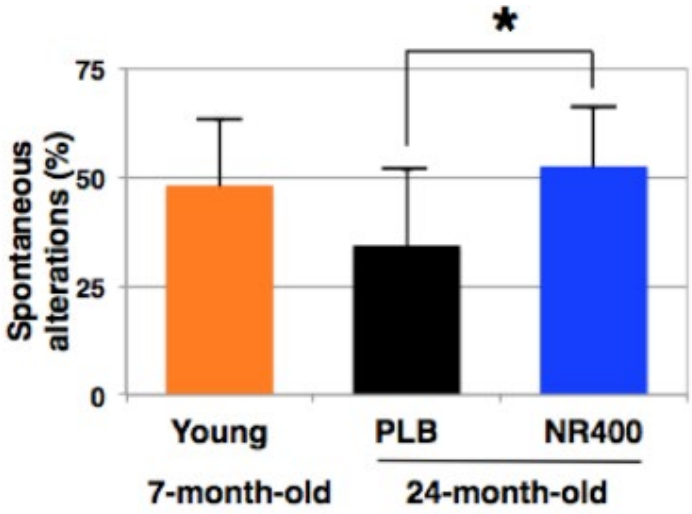
Introduction:
As many as 50% of those aged 85 years or older are frail - a condition of poor physiological reserve that increases susceptibility to falls, disability and mortality. Nicotinamide adenine dinucleotide (NAD+), an essential co enzyme for critical cellular functions, declines with age and may contribute to frailty. Supplementation with nicotinamide riboside (NR), an NAD+ precursor, restores NAD+ levels, and improves cognitive function in an Alzheimer's mouse models. Our goal is to determine if physical and cognitive benefits occur in wild-type aged mice.

Methods:
15-month-old C57BL/6J mice were divided into placebo (PLB, n=8), NR 300 mg/kg (NR3, n=8) and NR 600 mg/kg (NR6, n=8) and received NR over a 4 week period. We also treated 21 month-old with PLB (n=12) and NR 400 mg/kg (NR4, n=10) for a 12 week period. We evaluated treadmill performance, open field test, and grip strength. Furthermore, muscle fibers, NAD+ content, and mitochondrial biomass were assessed in skeletal muscle. We also assessed the impacts of NR on mitochondrial respiration in C2C12 and human myoblasts using a Seahorse extracellular flux analyzer. Finally, cognitive testing including nest building, T-maze, and Barnes maze were assessed in the 21-month-old aged mice.

Results:
NR treatment of the 15-month-old mice for 1 month increased total NAD+ in muscle tissue (NR3 p=0.01; NR6 p=0.004 versus PLB). NR treatment enhanced treadmill endurance and open field activity as well as prevented decline in grip strength. Histologic analysis revealed that the NR treated mice exhibited enlarged slow twitch muscle fibers. NR also boosted cellular respiration in both mouse C2C12 and human myoblasts cells. NR supplementation of old mice significantly enhanced spontaneous alternation (p=0.013) - a measure of memory and exploratory activity, and Barnes maze (p=0.010) - a measure of spatial learning and memory.

Conclusion:
NR supplementation enlarges slow twitch muscle fibers, maintains grip strength, increases aerobic treadmill endurance and open field activity, and improves cognitive function (exploratory behavior, learning and memory) in mice. These findings support the translation of this work into clinical settings to ascertain the benefits of NR supplementation for functional and cognitive impairment during aging.

Funding Sources: Supported by Indian Trail Foundation, Department of Veterans Affairs, and JSMBS Department of Medicine.


*
75
50
25
0
Spontaneous alterations (%)
Young
PLB
NR400
7-month-old
24-month-old

51

Promoting Wellness by Combating Imposter Syndrome in Residents

Authors: Slimmer, Stephanie; and Brubacher, Marie

Author Affiliations: The University of Kansas Medical Center

Introduction:

The Accreditation Council for Graduate Medical Education requires residency programs to include policies and programs that encourage optimal resident well-being. Medical trainees are increasingly at risk for symptoms of burnout, anxiety and depression. Recent studies show imposter syndrome (IS) is linked to psychological distress and burnout. Medical trainees are vulnerable to IS because they are high achievers and susceptible to feelings of self-doubt. Imposter syndrome prevalence varies widely in current studies, but literature has shown as high as an 82% prevalence in medical professionals. While our program has many policies supporting wellness, addressing IS was a novel method to combat burnout symptoms and improve well-being.

Methods:

Our aim was to increase resident awareness of IS, encourage discussion amongst residents regarding IS and provide tools for residents to combat IS to improve wellness and decrease burnout. A mandatory one-hour, small group presentation and discussion was implemented for residents at all training levels. It was facilitated by a chief resident and faculty member. A 10-question survey addressing IS and burnout was given to residents prior to the session. The facilitated discussions began with defining IS, recognizing common situations that trigger IS and individual risk factors for IS. The second half of the session was spent in small peer groups reflecting on IS and strategizing ways to manage IS, which included seeking feedback, avoiding over preparing and procrastination, and practicing self-compassion.

Results:

Our results to date show, on average, residents answer 4 out of 8 questions affirmative for IS and are feeling burned out at least once a month. It does not show a direct correlation between the two but reveals IS is present within the resident cohort. Qualitative feedback from residents regarding this intervention has been positive.

Conclusion/Reflection:

The prevalence of IS in medical professionals and the association with burnout makes it an important topic to address throughout residency. Having open discussions about IS and providing residents tools to manage these feelings will promote wellness and decrease the risk of burnout throughout residency and their career.

Funding Sources: N/A

52

Promoting Wellness by Facilitating New Patient PCP Appointments in the First Six Months of Residency

Authors: Slimmer, Stephanie; Grantham, Connor; Eck, Leigh; Broxterman, Jane

Author Affiliations: University of Kansas Health System

Introduction:

Medical trainees are at increased risk for burnout and depression, yet many residents are not established with a Primary Care Physician (PCP). As stated in the ACGME common program requirements, residents must be given the opportunity to attend medical, mental, and dental appointments, including appointments scheduled during their working hours. Our program offers four dedicated wellness ½ days a year to schedule these appointments. Despite this, our survey data indicated that only 53% of residents (39/73) had an established PCP. Nearly all residents (72/73) responded they were interested in the program facilitating a new patient PCP appointment.

Methods:

To assist incoming residents in establishing with a PCP, program leadership collaborated with outpatient primary care clinics to streamline timely new PCP appointments for resident physicians by providing direct scheduling contact information. Our aim was to significantly increase the percentage of Internal Medicine residents who had an established PCP. Pre-intervention surveys highlight that time constraint was the largest barrier to establishing with a PCP (65/72). To mitigate this barrier, all facilitated appointments were scheduled in lieu of a half day of clinical assignment without need to make-up the clinical assignment.

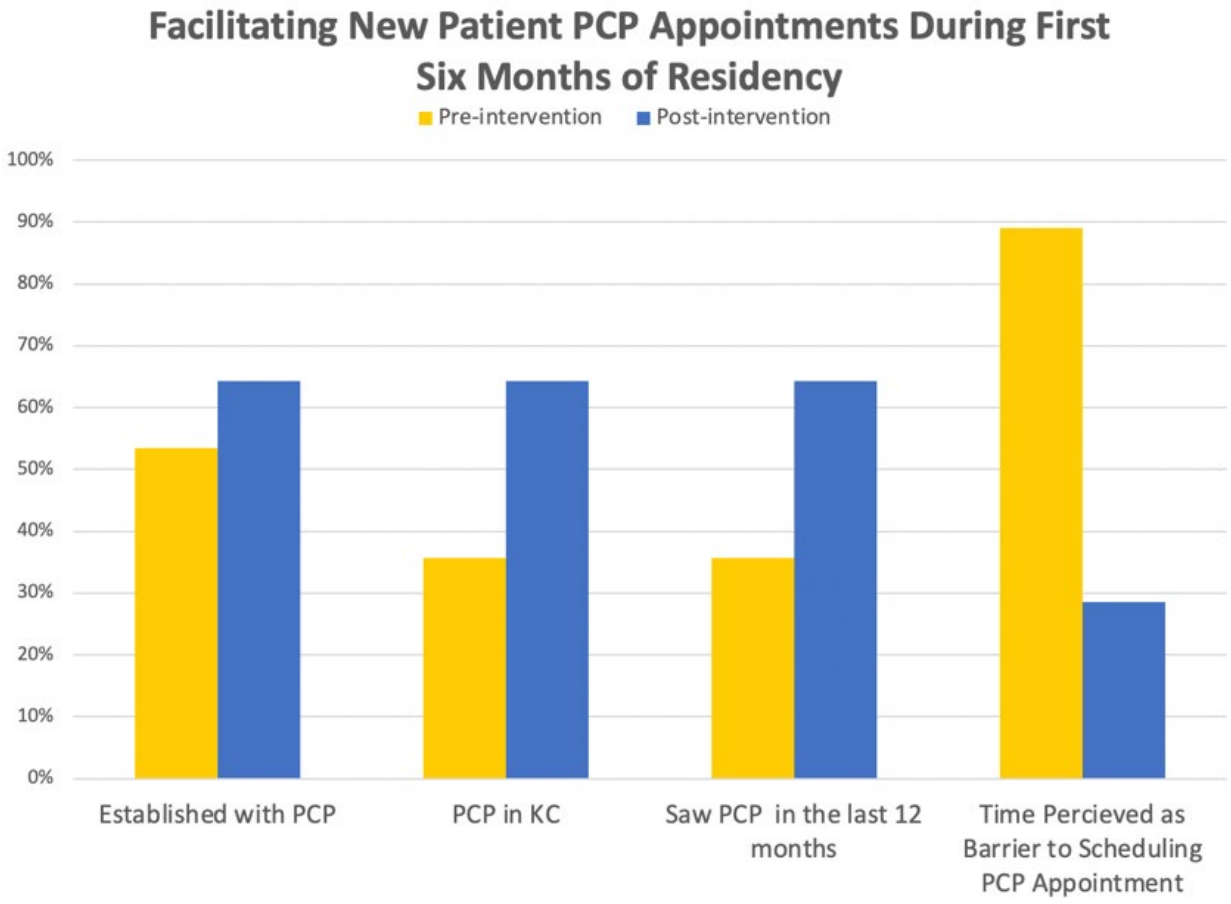
Results:

Only 35% (26/72) of residents had a PCP located in the Kansas City area prior to this intervention. 64% (9/14) of PGY1s had a PCP in the Kansas City metropolitan after intervention. Only 36% (4/11) reported time being a barrier to scheduling a PCP appointment, as opposed to 90% (65/72) prior to intervention. Pre-intervention and post-intervention data was similar in residents reporting feeling burned out at least once a year and becoming more calloused towards people since starting medical training. This study was not powered in a way to assess the effects of burnout.

Conclusion:

The amount of residents without a PCP highlighted a critical wellbeing need. This is important given the increased risk of physician burnout and depression during training. A busy resident schedule is the most common barrier to scheduling, and the majority of residents are open to their program streamlining this scheduling process. Having a primary care physician throughout residency will promote wellness, and therefore assist in decreasing burnout and depression.

Funding Sources: NA



53

Development of a Well-Being Dashboard to Drive Programmatic Accountability and Change

Authors: Lowry, Becky; Brubacher, Marie; Thomas, Laura; Eck, Leigh

Author Affiliations: The University of Kansas Medical Center, Department of Internal Medicine, Division of General & Hospital Medicine

Introduction:

Physician well-being is essential for safe, high-quality patient care. Residency training in the United States negatively influences the health and well-being of resident physicians. In a large study of internal medicine residents by West CP, et al, overall burnout was identified in 51.5% of responding residents. In 2017, the ACGME revised its Common Program Requirements for all accredited residency and fellowship programs to address well-being more directly and comprehensively. The requirements emphasize that *psychological, emotional, and physical well-being are critical in the development of the competent, caring, and resilient physician*. Beyond this, inclusiveness and a sense of belongingness in the GME learning environments is critical to ensure that we are supporting and expanding our diverse physician cohort.

Methods:

We developed a Well-Being Dashboard to capture metrics on interventions developed and implemented to support our resident physicians' psychological, emotional and physical wellbeing. Additionally, this dashboard tracks data specific to recruitment and retention of female internal medicine residents as well as underrepresented in medicine (URiM) resident physicians. This Well-Being Dashboard is reviewed by the Clinical Competency Committee and Program Evaluation Committee at least on a semi-annual basis to assist our team in accountability and to drive further change and programing.

Results:

By tracking data, we have identified a high level of engagement in "wellbeing consult" appointments with our psychologic support team when residents are asked to opt out of a scheduled appointment as opposed to opt in to scheduling an appointment; this has informed our process as we expand engagement in wellbeing consults. Because of metrics informed by dashboard data, it was evident that our preliminary residents were not utilizing our programmatic wellbeing consults, and we were able to quickly pivot to "opt out" scheduling for our preliminary cohort to improve normalization of seeking counseling and support service appointments and minimize stigma.

With detailed review of recruitment data specific to URiM and female students, we have been successful in inviting, interviewing and ranking more students from each of these cohorts in each recruitment cycle.

Conclusion:

Creating a specific Well-Being Dashboard has been an integral innovation for our program for insuring accountability and improvement in well-being and diversity. Our tool is highly applicable in the clinical learning environment and can be easily disseminated and implemented by all programs seeking to prioritize resident well-being and diversity.

Creating this dashboard has given our program a framework to capture metrics to ensure that our implemented strategies are allowing us to achieve our end state goals. With this framework in place, we can expand on our dashboard beyond personal resilience factors to include efficiency of practice metrics. Specific examples of metrics that our program plans to capture and track include practice-specific system measures including EMR utilization during non-clinical work hours as well as outpatient inbox messaging volume.

Intentionally tracking and monitoring specific wellbeing metrics will continue to drive programmatic accountability and growth.

54

Investigation of the Immunization Information System and Electronic Health Record interface in two Primary Care Clinics

Authors: McGreevy, Sheila[1]; Murray, Megan[2]; Montero, Leny[2]; Gibson, Cheryl[1]; Comfort, Branden[1]; Barry, Michael[3]; Kirmer-Voss, Kaylee[2]; Coy, Allison[2]; Zufer, Tahira[2]; Rampon, Kathryn[2]; Jennifer Woodward[2]

Author Affiliations: [1]University of Kansas Medical Center, Department of Internal Medicine, [2]University of Kansas Medical Center, Department of Family Medicine and Community Health, [3]University of Kansas Medical School

Introduction:

Our objective is to assess the accuracy of the COVID vaccination status within the Electronic Health Record for a panel of patients in a primary care practice.

Methods:

This study evaluated COVID-19 vaccination status of primary care patients within a university-based health system. Data was derived from Kansas and Missouri Immunization Information Systems and the Electronic Health Record.

Results:

Our study showed the immunization data for a panel of primary care patients is not accurate when significant numbers of vaccines are given outside the health system and the interface with the Immunization Information System is dependent on a case-by-case, manual query of the local Immunization Information Systems.

Conclusion:

Manual queries of Immunization Information Systems are not adequate for accurate assessment of immunization status for a panel of patients.

Funding Sources: None

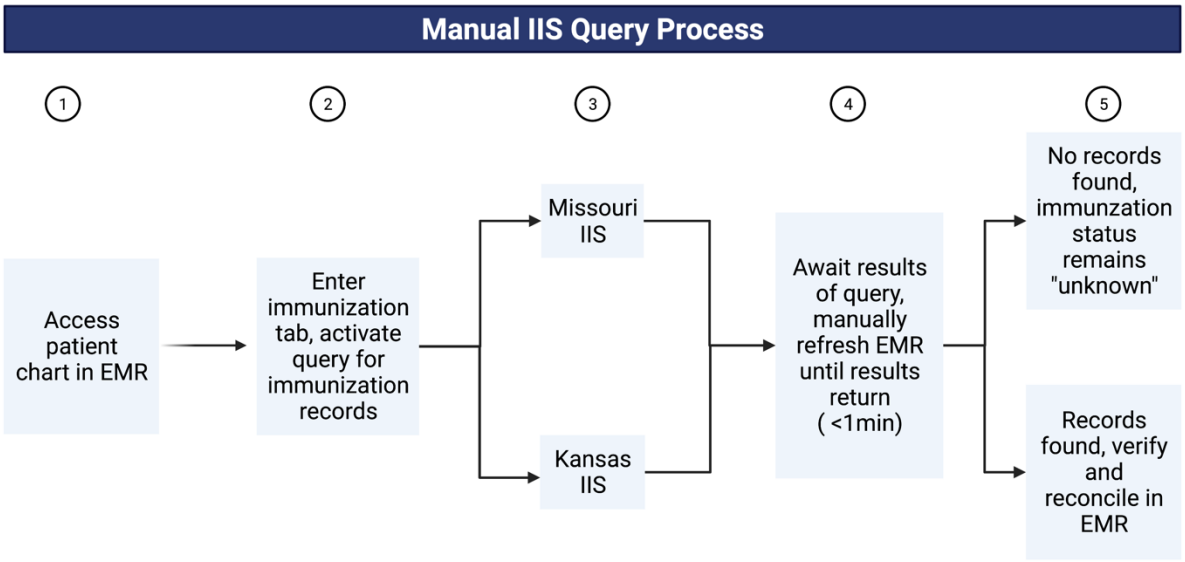


Table 1 Vaccine status breakdown before and after manual query of IIS

	Initial vaccination status n (%)	Results of manual query of IIS for patients with “unknown” vaccination n (%)	Post query vaccination status n (%)
Vaccinated Total	5,065 (55.1)	1,807(43.9)	6,872 (74.8)
Fully Vaccinated	4,613 (50.2)	1,491 (36.2)	6,104 (66.4)
Partially Vaccinated	452 (4.9)	316 (7.7)	768 (8.4)
“Unknown” Status	4,114 (44.8)	2,292 (55.7)	2,292 (25.0)
“Postponed”	7 (0.1)	4 (0.1)	11 (0.1)
Patient Deceased	0 (0.0)	11 (0.3)	11 (0.1)
Total	9,186	4,114	9,186

55

High intensity interval training (HIIT) boosted physical performance and reduced frailty in older Veterans – however, benefits were lost during the pandemic

Authors: Seldeen, Kenneth[1]; Rahman, Ayesha[2]; Satchidanand, Nikhil[2]; Bowen, Taylor[2]; Mador, Jeff[2]; and Troen, Bruce[1]

Author Affiliations: [1]The University of Kansas; VA Kansas City, [2]University at Buffalo; VA Western New York

Introduction: The Veteran Interval Training (VET-IT) trial was designed to evaluate the feasibility and safety of administering a short session (<10 minute) 3-times-a-week high intensity interval training (HIIT) exercise session in Veterans between the ages of 60 and 85 years. The trial successfully administered a 3-month HIIT regimen to 23, identifying increased muscle strength, 6-minute walk endurance, cognition, and quality of life – before being abruptly discontinued due to the COVID pandemic. The goal of this study is to assess the impacts of the pandemic on key geriatric parameters assessed in the VET-IT Trial.

Methods: A total of 18 of the original 23 participants returned for a single follow-up visit. Most original parameters were reevaluated including: frailty (exhibiting 3 or more of unexpected weight loss, low activity, poor endurance, weak grip strength, and slow gait speed), 6-minute walk for endurance, the short physical performance battery (SPPB: balance, chair rise, and gait speed), quadriceps strength, cognition via the VA-St. Louis University Mental Survey (VA-SLUMS), and the Quality of Life, Enjoyment, and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF). New assessments to the follow-up include body composition assessment (InBODY), sleep assessment surveys, and activity monitoring via FitBit Charge 4 devices. Statistical comparisons were performed using paired student's T-Test.

Results: Of the returning participants, 44.4% remain physical active although only 16.7% participate in some form of HIIT. 2 of the 18 participants reported having COVID. After approximately 2-years following their final assessments, participants exhibited greater frailty ($p=0.0079$), and trends towards decreased leg muscle strength ($p = 0.10$) and quality of life ($p=0.07$). Other VET-IT study parameters remain similar (cognition, 6-minute walk, SPPB, and grip strength), while gait speed and chair rise times improved (potential due to test-retest methodological differences). New assessments revealed older Veterans exhibit frequent sleep disturbances and are potentially at risk for sarcopenia (body composition data).

Conclusion: Although many gains from HIIT training remained robust, increases in frailty and inactivity are of concern, as is poor sleep quality. Our newly funded VA RR&D study, "HIIT@Home" will examine new strategies to sustain HIIT exercise involvement following periods of training.

Funding Sources: Supported by the Department of Veterans Affairs, NY SUNY Seed Grant, NIH, and the JSMBS Department of Medicine, University at Buffalo.

56

Vitamin D supplementation and HIIT separately increase vitamin D receptor expression in the muscles of old mice: a role for vitamin D in muscle satellite cells?

Authors: Seldeen, Kenneth[1]; Leiker, Merced[2]; Thiyagarajan, Ramkumar[1]; Weiss, Carleara[2]; Rajabian, Nika[2]; Shahini, Aref[2]; Andreadis, Stelios[2]; and Troen, Bruce[1]

Author Affiliations: [1]The University of Kansas; VA Kansas City, [2]University at Buffalo; VA Western New York

Introduction:
Vitamin D (VitD) insufficiency (25-OH VitD levels < 30 ng/ml) is highly prevalent (~70% estimated nationally), and our published data suggest long term VitD insufficiency leads to physical performance deficits in mice (Seldeen et al., Aging 2018). The underlying nature of such decline is not understood. The vitamin D receptor (VDR) is a transcription factor that has recently been found to exist in muscle fibers and satellite cells that are important for muscle quality. The goal of this study is to identify the role of VitD and exercise in mediating VDR expression and satellite cell activity.

Methods:
Young (6 months) and old (24 months) VitD sufficient mice fed chow with 1000 IU/day of vitamin D were studied as controls. Old mice were supplemented with either 0 or 8000 IU VitD/kg chow for four months. In a separate trial a 10-minute high intensity interval training (HIIT) exercise was administered 3x a week for 6 weeks. Hindlimb muscles were harvested and then examined for VDR, the satellite cell marker Pax7, and four myosin heavy chain fiber types by immunohistochemistry. Western blots were also used to evaluate VDR expression in nuclear extracts of muscle 1 hour following a session of HIIT.

Results:
Muscles from old mice exhibited decreased VDR expression compared to young mice. However, VDR expression is greater in aged mice supplemented with 8000 IU versus 0 IU as well as in the muscles from mice administered 6-weeks of HIIT versus mice that were sedentary. Nuclear extracts of the tibialis anterior muscle from mice 1 hour after a bout of exercise exhibited markedly more VDR than from non-exercised mice. Satellite cell population was lower in the muscles of old mice, but greater in mice supplemented with 8000 IU VitD/kg compared to mice of the same age given a VitD deficient diet.

Conclusion:
Exercise increased VDR expression in skeletal muscle. Furthermore, VitD supplementation alone may increase the expression of VDR and the number of satellite cells. These findings suggest that VitD enhances the capacity for muscle regeneration in older individuals – and thus supplementation may be an important consideration to promote healthy aging.

Funding Sources: Supported by the Department of Veterans Affairs, NIH, and the Indian Trail Foundation.

57

HIIT increases myonuclear accretion and progenitor cell proliferation in aged mice

Authors: Chaves, Lee[1]; Berman, Reem[2]; Redae, Yonas[2]; Thiyagarajan, Ramkumar[1]; Seldeen, Kenneth[1]; Troen, Bruce[1]

Author Affiliations: [1]The University of Kansas & Veterans Affairs Kansas City Healthcare System, [2]University at Buffalo & Veterans Affairs Western New York Healthcare System

Introduction: Age associated sarcopenia that increases the risk of falls and disability presents a large challenge to the healthcare systems. Exercise plays an important role in activating muscle progenitor cells, regeneration, and muscle mass, which lead to improved physical performance. Yet the time commitment for traditional exercise regimens seems to be a barrier leading to poor participation among older individuals. Short session high intensity interval training (HIIT) holds promise for delivering equivalent or even better outcomes relative to standard exercise regimens. However, the underlying biology and the impact of HIIT on myonuclear accretion, muscle regeneration, and progenitor cell proliferation in young and old mice remains poorly elucidated.

Methods: We compared 6-month and 24-month NIA C57BL/6 mice that were either sedentary or administered 6 weeks of a 10-minute HIIT program. Following the treatment phase, mice were euthanized to harvest the extensor digitalis longus (EDL), a predominately fast twitch muscle. The EDL was digested with collagenase A to allow separation of individual fibers. Fixed fibers were stained with DAPI to allow determination of myonuclear accretion, while other fibers were cultured to assess progenitor cell proliferation. Hindlimb muscles were collected from young and old mice for single cell quantification with flow cytometry examining alpha-7-integrin as a marker of muscle progenitor cells.

Results: Time-lapse brightfield microscopy demonstrated the progressive proliferation of progenitor cells derived from single muscle fibers. Dramatic declines in progenitor cell number were observed in the old versus young mice, which were reversed in the fibers harvested from the old mice who received the 6 weeks of HIIT. Myonuclear number increased within single fibers harvested from mice administered HIIT.

Conclusions: HIIT increases satellite cell and myonuclear accretion in 24-month-old mice equivalent to 70 -year-old humans. Myonuclear accretion is associated with the ability of a muscle to regenerate in response to exercise. Further work will examine differences in progenitor cell proliferation in relationship to physical performance gains in response to HIIT. These studies will also permit characterization of the mechanisms underlying age-related sarcopenia and lay the foundation to develop interventions in older adults to enhance functional capacity and promote healthy aging.

Funding Sources: National Institutes of Health, Veterans Affairs, and the Indian Trail Foundation.

58

Vitamin D deficiency increases, while supplementation decreases, risk of COVID-19 linked hospitalization, ICU transfer, and mortality in a Veterans Affairs cohort

Authors: Seldeen, Kenneth[1]; Mullin, Sarah[2]; Mammen, Manoj[2], Mccray, Wilmon[2]; Asa, Benjamin[2]; Elkin, Peter[2]; Troen, Bruce[1]

Author Affiliations: [1]The University of Kansas & Veterans Affairs Kansas City Healthcare System, [2]University at Buffalo & Veterans Affairs Western New York Healthcare System

Introduction:
The coronavirus-19 (COVID-19) pandemic is a global crisis with a significant mortality risk for all individuals, especially with concomitant comorbidities. Studies examining vitamin D status and supplementation have shown mixed benefits for reducing COVID-19 severity, suggesting the need for further investigation.

Objective:
To determine if patients who were found to be vitamin D deficient were at higher risk for infection, hospitalization, ICU admission, and death. Secondarily, to determine the impacts of vitamin D supplementation on these outcomes.

Methods:
Retrospective case-cohort study of the Department of Veterans Affairs Corporate Data Warehouse. We employed regression analysis to control for age and the two-year Elixhauser morbidity score. Vitamin D status was defined as sufficient (>30 ng/ml), insufficient (20-29 ng/ml), or deficient (<20 ng/ml).

Results:
A total of 51,492 COVID-19 negative and 4,549 positive patients had vitamin D levels within 90 days of the COVID-19 test date. Individuals with a vitamin D deficiency were more likely to be hospitalized (OR: 1.37, CI: 1.14-1.64, p=0.001), transferred to the ICU (OR: 1.34, CI: 1.03-1.74), p=0.028), and to die (OR: 1.56, CI: 1.13-2.14, p=0.006). However, deficient patients with prescriptions for vitamin D supplementation were less likely to become infected with COVID-19 (21%, p=0.014) and, across all vitamin D groups, supplementation reduced the risk of hospitalization (OR: 0.8, CI: 0.69-0.93, p=0.003), ICU transfer (OR: 0.6, CI: 0.47-0.75, p<0.001), and mortality (OR: 0.55, CI: 0.41-0.73, p<0.001).

Conclusions:
Therefore, serum vitamin D levels are important prognostic indicators of COVID-19 severity, and supplementation prior to illness and/or hospitalization reduces risk of infection and severity. Further research should include a prospective randomized controlled trial of vitamin D supplementation initiated prior to COVID-19 exposure.

Funding Sources: National Institutes of Health, Veterans Affairs, and the Indian Trail Foundation.

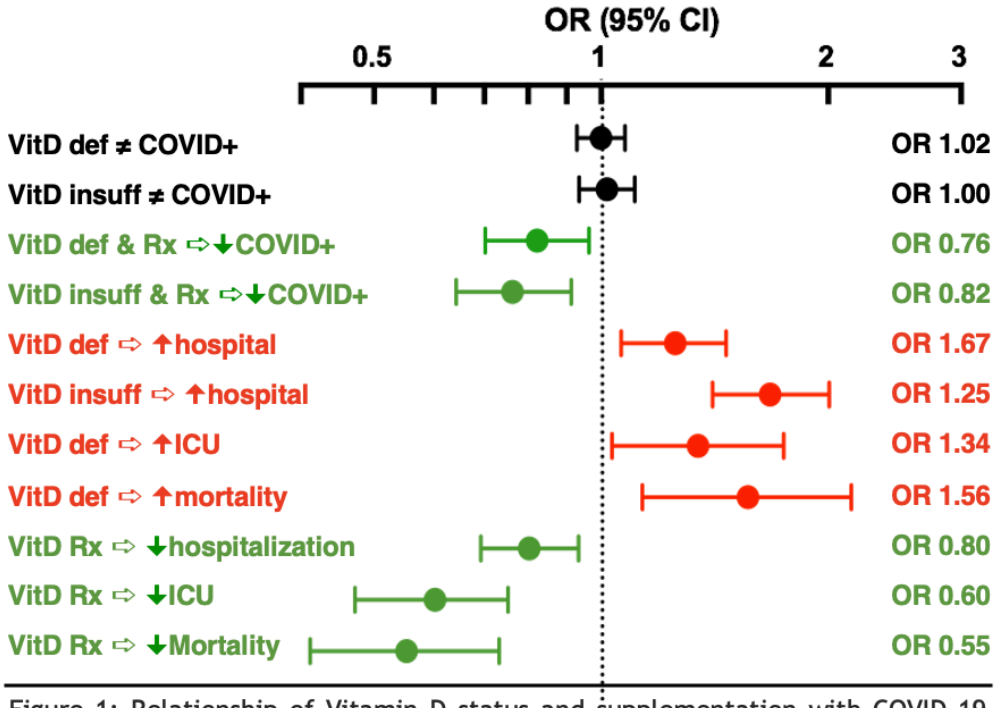


Figure 1: Relationship of Vitamin D status and supplementation with COVID 19 infectivity rates and outcomes displayed as odds ratios with 95% confidence intervals.

59

Parent Health Beliefs and Habits and Weight Change in Adolescents with Intellectual Disabilities

Authors: Hastert, Mary; Ptomey, Lauren T

Author Affiliations: University of Kansas Medical Center, Department of Internal Medicine, Division of Physical Activity and Weight Management

Background: Little is known about effective weight management strategies for adolescents with intellectual disabilities (ID). Parental engagement in weight management counseling is shown to improve weight loss in neurotypical peers, but there is limited literature in the ID population. The purpose of this analysis is to evaluate if parents engaged in a 6-month weight loss intervention improved their health habits, activity, and modeling behaviors, as well as if these changes were correlated with weight loss in adolescents with ID.

Methods: This is a secondary analysis from a 6-month randomized weight loss trial in adolescents with mild-to-moderate ID and overweight/obesity. Adolescents and a parent received 6 months of bi-weekly, one-on-one health education sessions with instructions for adolescents to reduce energy intake and increase physical activity. Parents completed the Healthy Buddies Parent Nutrition and Physical Activity Survey, which assess the 3 subscales of family health habits, parent activity, and parent modeling behaviors. An average score was calculated for each subscale and change scores were calculated from baseline to 6 mos. Additionally adolescent weight, body mass index, and waist circumference were collected at baseline and 6 mos. Correlations between changes in family health habits, parent activity, and parent modeling behavior subscales and adolescent weight, body mass index, and waist circumference were evaluated using a spearman correlation analysis using SAS 9.4 at significance level 0.05.

Results. Data was collected from fifty-one adolescents (~17 years of age, 53% female) and a parent at baseline and 6 months. Parents saw a significant increase across time in family health habits (p = 0.003) and parent activity (p = 0.009) and a non-significant increase in modeling behaviors (p > 0.05) at 6 months. Improvements in family health habits, parent activity, and modeling behaviors were not correlated with changes in adolescent weight, body mass index, or waist circumference across time (all p > 0.05). No significant correlation was found after controlling for age and sex.

Conclusions. Parents of adolescents with ID significantly improved their family health habits and parent activity after their child participated in a 6-month weight loss intervention. Further research is needed to determine the role of parents in promoting successful weight loss in adolescents with ID.

Funding Sources: National Institutes of Child Health and Development (R01HD079642).

60

No Difference in Cardiometabolic Risk Factors Between Energy Expenditures: The MET-2 Trial

Authors: Hastert, Mary; Ptomey, Lauren T; Herrmann, Steve; Donnelly, Joseph E

Author Affiliations: University of Kansas Medical Center, Department of Internal Medicine, Division of Physical Activity and Weight Management

Introduction:

Exercise is suggested for the reduction of cardiometabolic risk factors in adults independent of changes in diet. However, the volume of exercise needed in healthy young adults with overweight/obesity is unknown and has not been evaluated in a randomized efficacy trial.

Methods:

This secondary analysis examined changes in fasted lipid panels and body composition (DXA) in young adults (18-30 years, BMI 25-40 kg/m^2) who completed the 10-month Midwest Exercise Trial-2. This efficacy trial randomized participants (2:2:1 ratio) to supervised exercise 5 sessions/week at an energy expenditure of either 400 or 600 kcal/session or non-exercise control and asked to maintain usual ad libitum diets. Changes in outcomes from baseline to 10 months ($p<0.05$) were evaluated using paired and independent t-tests.

Results:

Young adults (n = 69, age ~ 24 yrs., ~ 46% female) complied with the study protocol and completed all outcome assessments: 400 kcal/session (*n*=28), 600 kcal/session (*n*=27), control (*n*=14). The control group had no significant outcome changes from baseline to 10 months. The 400-kcal group had decreases in percent fat mass (-3.3 ± 4.2%, $p < 0.001$), waist circumference (-1.4 ± 1.9 in., $p < 0.001$) and increases in percent fat-free mass (3.3 ± 3.3%, $p < 0.001$). The 600-kcal group had decreases in percent fat mass (-3.9 ± 3.8%, $p < 0.0001$), waist circumference (-1.7 ± 2.4 in., $p < 0.001$), glucose (-2.9 ± 6.9 mg/dL, $p = 0.04$), and increases in percent fat-free mass (3.9 ± 3.8%, $p < 0.0001$). Across all outcomes, there were no differences between the 400-kcal and 600-kcal groups ($p > 0.05$).

Conclusion:

In a sample of young adults with overweight/obesity, a prescribed 600 kcal versus 400 kcal energy expenditure during a 10-month exercise intervention and ad libitum diet did not provide additional impact on cardiometabolic risk factors.

Funding: The National Institutes of Health (DK49181).

61

The Development and Rasch Analysis of the 18-item Health Resilience Profile (HRP)

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Author Affiliations: [1]Department of Dietetics and Nutrition, University of Kansas Medical Center, [2]Department of Health Sciences, Northern Arizona University, [3]Department of Health, Exercise Science and Recreation Management, The University of Mississippi, [4]Department of Internal Medicine, Center for Physical Activity and Weight Management, University of Kansas Medical Center

Introduction:

Previous research has identified limitations in the efficacy of the 25-item Connor-Davidson Resilience Scale (CD-RISC) in assessing resilience of individuals enrolled in a weight management program. The purpose of this study was to develop and evaluate a resilience measurement instrument, focused on health behavior change, in adults enrolled in a health coach delivered weight management program.

Methods:

A two-part study was conducted to: 1) develop a resilience instrument (Health Resilience Profile; HRP) specific to adults with overweight/obesity attempting health behavior change (Sample 1: *n* = 427; female = 83.8%; age = 44.5 ± 11.9 years) and 2) optimize the instrument performance using Rasch analysis in adults enrolled in a health coaching program (Sample 2: *n* = 493; female = 62.1%; age = 49.8±12.5 years).

Results:

Two issues were identified by the first study: 1) four unacceptable misfit items with high Infit/Outfit statistics (i.e., <0.5 or >1.5), and 2) inappropriate rating scale functioning indicated that a five-category rating scale did not accurately reflect resilience levels in participants (i.e., category boundaries not arranged in sequence). The second study revised and re-examined the instrument after removing the four misfit items from study one and using a four-category rating scale in place of the previous five-category scale. Results from the second study indicated that the four-category rating scale functioned more effectively, item difficulty (-3.57 to 3.40 logits) and distribution was well matched to participants' resilience level (mean 1.47 ± 1.8; range = -2.20 to 8.77 logits) based on item-person mapping, and there was adequate distribution of HRP items free from measurement error as shown by item separation index (15.87) and separation reliability (1.00) measures. Finally, items did not show differential functioning across subgroups based on group affiliation (i.e., age, sex, alcohol use, and obesity status; $p<0.001$).

Conclusion:

These findings indicate that the 18-item HRP is optimized for use in measuring resilience levels in adults enrolled in a health coach delivered weight management program. Given the high rates of attrition often observed in weight management programs, accurately assessing, and providing health coaching to improve resilience may contribute to reduce attrition and improve outcomes.

Funding Sources: N/A

62

Nutrition Counseling for Weight Management During the COVID-19 Pandemic

Authors: Mary Hastert, MS, RD; Annie Eller, RD.

Author Affiliation: University of Kansas Medical Center, Department of Internal Medicine

Background:

The COVID-19 pandemic proved challenging for Registered Dietitians (RDs) working in a weight management setting. Fortunately, technology allowed RDs to safely deliver weight management services remotely; however, it is unclear if patients are achieving similar weight loss. The purpose of this study was to compare weight change of patients enrolled in a clinical weight management program who attended in-person vs remotely delivered nutrition counseling sessions.

Methods:

Participants were enrolled in a clinical weight management program and completed individual nutrition counseling with an RD. Weight loss (kg) was obtained retrospectively from medical records over a 3-year period. Individuals were included in the in-person delivery arm if they completed sessions prior to April 2020, versus included in the remote delivery-arm if they started sessions after April 2020.

Results:

182 medical records were analyzed (24 male, 158 female; mean baseline Body Mass Index 40.9 kg/m2). Patients in the in-person arm (n=115) attended an average of 4.9 sessions across 24.4 weeks. Patients in the remote delivery (n=67) arm attended an average of 4.1 sessions across 11.6 weeks. There was no significant different in weight loss for in-person (3.6±6.4 kg, 3.21% body weight) compared to remote delivery (3.5±5.3 kg, 3.07% body weight; p=0.89). Regardless of delivery method, patients who completed $\geq$10 visits with an RD lost a mean 11.8±4.2 kg, versus only 7.26±6.4 kg with 6-9 visits and 1.78±8.7 kg with 2-5 visits ($p<0.001$).

Conclusion:

Weight loss did not differ between delivery method. However, patients achieved significantly greater weight loss with increased RD contact provided through telehealth services.

Funding Sources: None.

63

Autonomic Dysfunction in Sjogren's Disease

Authors: Fenando, Ardy[1]; Estes, Jordan[1]; Mohamad, Maha[1]; Shah, Sareena[2]; Lee, John K[2], Baker, Joshua[3]; Noaiseh, Ghaith[1]

Author Affiliations: [1]University of Kansas Health System, Kansas City, KS, [2] University of Missouri-Kansas City, Kansas City, KS, [3]University of Pennsylvania, Philadelphia, PA

Introduction:

Sjogren's Disease (SjD) is a heterogeneous autoimmune disease associated with debilitating symptoms. Autonomic dysfunction (AD) is common in SjD and may contribute to symptom burden. We sought to compare AD symptom severity in SjD patients to those with FMS and healthy controls and implemented a patient-based stratification method to assess if AD is more prominent in certain subsets.

Methods:

This is a cross-sectional study of SjD and FMS patients recruited in our Sjogren's center between December 2021 and March 2022. Patients fulfilled 2016 ACR-EULAR criteria and FMS Survey Diagnostic Criteria and Severity Scale, respectively. Demographic, clinical, and laboratory variables were collected.

A symptom-based stratification method was used to categorize SjD patients into 4 subgroups, based on the severity of pain, fatigue, dryness, anxiety, and depression, using Newcastle Sjogren's Stratification software (available online at https://github.com/SJOGRENS/Symptom-Based-Subgroups), in which fatigue, dryness, and sicca symptoms were evaluated using EULAR's Sjogren's Syndrome Patient Reported Index (ESSPRI), while Hospital Anxiety and Depression Scoring (HADS) was used to assess anxiety and depression. Mean COMPASS-31 scores were compared between SjD, fibromyalgia groups and historical controls (n=30) using previously published data. We also assessed COMPASS-31 scores in SjD subgroups and studied the association with clinical and laboratory variables, particularly in relation to the anti-SSA and SSB status.

Results:

Sixty-two consecutive SjD and 20 FMS patients were recruited. The mean age for SjD patients was 55 years, with a mean disease duration of 8.3 years. Fifty-two (84%) were female. The mean COMPASS-31 score was significantly higher in SjD patients, compared to healthy controls (30.8±16.7 *vs* 8.9±8.7, $p<0.0001$), but lower compared to FMS patients (30.8±16.7 *vs* 41.9±20.3, $p=0.0169$). Of 62 SjD patients, Eight were classified as high symptom burden (HSB), 16 as low symptom burden (LSB), 20 as pain dominant with fatigue (PDF), and 18 as dryness dominant with fatigue (DDF). COMPASS-31 score inversely correlated with Sjogren's serotype and was the highest in the seronegative group (Table 1). COMPASS-31 score was highest in the high symptom burden subgroup (Figure 1).

Conclusion:

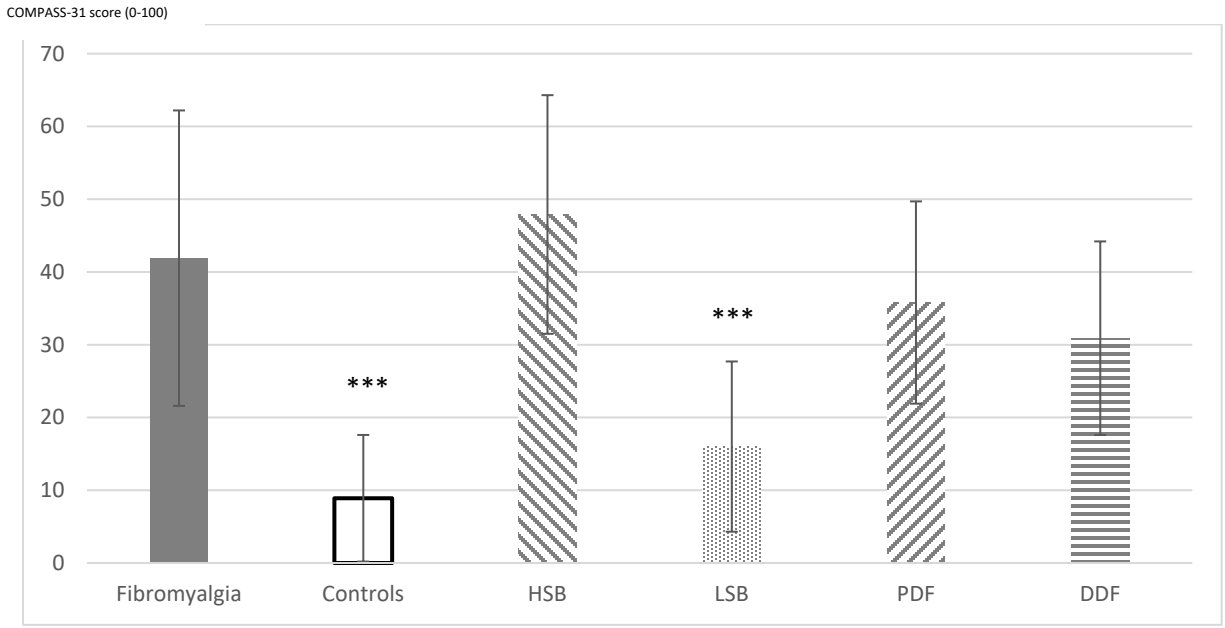
To our knowledge, this is the first study that assesses AD in SjD using COMPASS-31 in comparison to FMS patients and a healthy population. Higher COMPASS-31 was observed in seronegative patients and those with the highest symptom burden, highlighting that AD may be implicated in symptom burden beyond the common symptoms of fatigue, dryness, and pain.

Funding Sources: none

Table 1. COMPASS-31 scores in SjD patients according to Anti-SSA and Anti-SSB status. Data are presented as mean (standard deviation)

	Anti-SSA *and* SSB positive	Anti-SSA - only positive	Anti-SSA *and* SSB negative	*P*-value
Mean COMPASS-31 score (SD)	23 (13.7)	28.9 (16.8)	40.7 (15.8)	0.0057

Figure 1. Total COMPASS-31 scores in FMS, healthy controls, and SjD Subgroups.



*** Represents P<0.001 for comparison to fibromyalgia

64

Evaluation of the Safety of Vedolizumab in Combination with Other Immunosuppression Biological Therapy in Patients with Inflammatory Bowel Disease

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Author Affiliations: University of Kansas Medical Center

Introduction:
Inflammatory bowel disease (IBD) causes a wide range of symptomology frequently leading to co-management of disease activity between gastroenterologist and rheumatologists. Recently in efforts to optimize treatment, there has been interest in using combination biological therapy with vedolizumab.

Methods:
A retrospective single center study was performed on individual patients, between the ages 18 to 80, treated with combination therapy with vedolizumab and any other biological (etanercept, adalimumab, golimumab, certolizumab, infliximab, ustekinumab, JAK inhibitors) between 2014 and May 2021. Patients were identified through a database search via diagnosis code and medication list review with subspecialty clinics. Individual patient charts were then reviewed to confirm IBD diagnosis and use of combination therapy during their time of follow-up at this institution. Additional data was abstracted regarding baseline characteristics, infections, cancer diagnoses, and mortality.

Results:
Sixteen patients meeting the study criteria for a complete retrospective chart review were identified. The mean age at initiation of combination therapy was 39.8 years of age. 56% of the patients were male. 81.2% of the patients were diagnosed with Crohn's disease and 18.8% with ulcerative colitis. 56.25% had complaints of joint pain and 37.5% were evaluated by rheumatology. Dual biological therapy was initiated for IBD control in 75% of patients and for joint pain in 25% of patients. 69% received adalimumab, 44% received ustekinumab, and 6% received certolizumab. One of the patients received adalimumab then transitioned to ustekinumab. The mean duration of dual biological therapy was 11.9 months. 14 of 16 patients remained on dual therapy during the duration of the study. One patient developed antibodies against adalimumab which lead to discontinuation. One patient had to discontinue dual therapy due to insurance authorization. The minimum duration of combination therapy was 1 month and the maximum duration was 22 months. Seven total infections occurred in 4 patients (25%). Serious infections requiring hospitalization or IV antibiotics occurred in two patients (12.5%). None of the patients developed a new diagnosis of cancer or experienced a reoccurrence of cancer. No deaths occurred during the time of follow-up.

Conclusion:
This retrospective study reviewing 16 cases of patients treated with vedolizumab and dual biological combination therapy demonstrates additional data regarding infection, cancer, and mortality rates. Further studies are needed to better characterize and evaluate the safety profile of vedolizumab combination therapy in IBD patients for intestinal and extra-intestinal manifestations.

Funding Sources: CTSA Award # UL1TR002366

65

Nuclear receptor REV-ERBα regulates TGFβ1-induced fibroblast to myofibroblast transition *in vitro* in human lung fibroblasts

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Background:
Transforming growth factor-β1 (TGFβ1) is a multifunctional cytokine that is known to induce fibroblast-to-myofibroblast transition (FMT). FMT is a key indicator of pro-fibrotic markers, such as αSMA and COL1A1, and the release of pro-fibrotic mediators (e.g., IL-1, IL-6, IL-33, etc.) is evident in pulmonary fibrosis (PF). Current literature strongly suggests that the circadian clock disruption in the lung may be a key player contributing to the pathogenesis of chronic airway disease. Nuclear receptor REV-ERBα is a key transcription factor that regulates the circadian clock and stabilizing this receptor using small molecules may have a great potential to devise novel therapies to treat chronic lung diseases. In this study, we hypothesize that circadian clock-based therapeutics Rev-erbα agonist (GSK4112) can attenuate TGFβ1-induced FMT in human lung fibroblasts.

Methods:
To explore this hypothesis, we cultured human lung fibroblasts (WI-38 cells and primary human lung fibroblasts) followed by TGFβ1 (5 or 10 ng/ml) treatment with or without GSK4112 (20 μM) for 48 h. We examined FMT markers and pro-fibrotic factors using molecular techniques such as slot-blot analysis, immunofluorescence staining, confocal microscopy, Western blotting, and ELISA.

Results:
Secretory COL1A1 in conditioned medium was significantly reduced in GSK4112 and GSK+TGFβ1 treated groups compared to the TGFβ1 treated group. Immunostaining by confocal microscopy showed significantly reduced αSMA expression, and Western blotting confirmed significantly reduced αSMA expression in GSK4112 and GSK+TGFβ1 treated groups compared to the TGFβ1 treated group. Pro-fibrotic mediator IL-6 release in the conditioned medium measured by ELISA revealed significantly increased TGFβ1-induced IL-6 which was blocked in GSK4112 and GSK+TGFβ1 treated groups.

Conclusion:
Rev-erbα agonist GSK4112 significantly reduced TGFβ1-induced pro-fibrotic markers and pro-fibrotic mediator IL-6 in WI-38 and human primary lung fibroblasts. Understanding how the circadian clock regulates TGFβ1-mediated canonical signaling pathways will enable us to develop novel clock-based therapeutics to inhibit pro-fibrotic responses thereby attenuating the progression of chronic lung diseases in the future.

Funding Sources: This work was funded by the NIH R01 HL14253 and KUMC, School of Medicine, Internal Medicine Start-Up Funds.

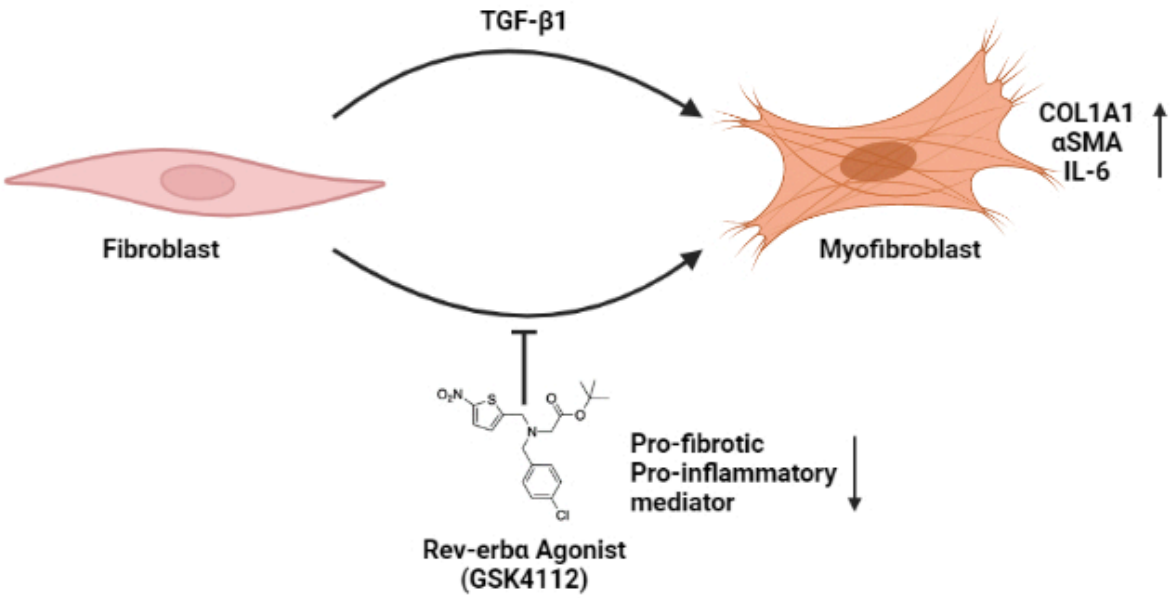

Fig 1. Rev-erbα agonist (GSK4112) inhibits fibroblast to myofibroblast transition in human lung fibroblast.

66

Blocking NOTCH3 prevents cigarette smoke-induced mucociliary dysfunction in airway epithelial cells of COPD donors

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Introduction:
COPD is the third leading cause of death worldwide, and its prevalence is expected to increase with an aging population. Tobacco smoking and pollutant exposure are the major driving forces of COPD. Mucus hypersecretion and decreased mucociliary clearance (MCC) are two important features of the disease. NOTCH3 signaling has been reported to induce goblet cells differentiation. In this study, we assessed whether blocking NOTCH signaling could prevent mucociliary dysfunction in COPD *in vitro*.

Methods:
Primary human bronchial epithelial cells (HBEC) from healthy smoker (HS) and from smoker with COPD (COPD), were differentiated at the air-liquid interface before exposure to whole cigarette smoke (WCS) and analyzed at 1h, 4h, 24h and 7 days later. We investigated ciliary beat frequency (CBF), mucus concentrations and viscosity, ion channel functions, and mucociliary transport (MCT). Signaling by NOTCH2 and NOTCH3 was assessed by Western blot and blocked using specific, functionally antagonistic antibodies. Markers of cilia (p73, FOXJ1 and acetylated tubulin) and a gel-forming mucin (MUC5AC) were evaluated by quantitative PCR and/or immunostaining.

Results:
Baseline mucociliary parameters such as CBF, FOXJ1 and P73 mRNA levels were downregulated in cells from COPD compared to HS. On the other hand, mucus concentrations, mucus viscosity, and MUC5AC protein expression were increased. CBF was decreased 4h after WCS exposure in cells from HS and COPD correlating with a decrease in FOXJ1 and p73 mRNA expression; seven days later, cells from HS recovered to baseline levels respectively, but cells from COPD did not. NOTCH2 and NOTCH3 protein levels were increased 1h after WCS exposure in cells from smokers with COPD but not in cells from HS. Pre-treatment with NOTCH3 blocking antibody (but not NOTCH2) prevented smoke-induced decreases of CBF and MCT in cells from smokers with COPD.

Conclusion:
NOTCH3 signaling maintains the balance of ciliated and secretory cells necessary for proper mucociliary clearance. Downregulating secretory cells entirely did not prevent MCC dysfunction. NOTCH3 reveals to be a good target in preventing further decline in MCC *in vitro*, by maintaining an equilibrated cell composition in the airway epithelium.

Funding Sources: Flight Attendant Medical Research Institute, CIA #160011; James and Esther King Florida Biomedical Research Program, Grant #5JK02; NIH R01 HL139365, HL133240, and HL157942.

67

Safety and Cost Effectiveness of Chimeric Antigen Receptor T Cell Therapy in the Outpatient Setting

Authors: Shahzad, Moazzam; Shippey, Ernie; Mushtaq, Muhammad MD; Bansal, Rajat MD; Abhyankar, Sunil MD; Shune, Leyla MD; McGuirk, Joseph DO; Ahmed, Nausheen MD

Introduction:

Since the commercial approval of chimeric antigen receptor T cell (CAR-T) therapies, administration and toxicity monitoring have largely been in an inpatient setting due to the risk of significant toxicities such as cytokine release syndrome (CRS) and neurotoxicity in the first 30 days. Administration in the outpatient setting can be safe and cost-effective. Here we report the cost savings and adverse events of CAR-T in an outpatient setting as compared to the inpatient setting.

Methods:

Cost differences of the commercial CD19 CAR-T axicabtagene ciloleucel (axi-cel) and tisangenlecleucel (tisa-cel) among inpatient and outpatient settings in 2020 were investigated using the Vizient Database®. Cost analysis for both settings was done for the initial 30 days post-CAR-T infusion. There were no billing codes for CRS and neurotoxicity till 2021. Clinical surrogates such as fever, hypotension, hypoxia, sepsis were used for CRS while febrile convulsion not otherwise specified (NOS), febrile seizure NOS, altered mental status, somnolence, stupor, and coma were used for neurotoxicity. ICD 10 codes for adverse effects were also used.

Results:

In 2017-2020, there were 81 organizations in the database that performed CAR-T procedures. In 2020, there were 1369 inpatient and 71 outpatient encounters, which were analyzed for cost and adverse events. (Table 1) The incidence of CRS was 43.2% (n=592) and 40.8% (n=29) in inpatient and outpatient groups, while that of neurotoxicity was 37.3% (n=511) and 29.6% (n=21) respectively. For cost analysis, we included the 16 centers (22% of all centers) that offered both inpatient and outpatient administration in 2020. Median inpatient cost was $397,610 ($346,550-$650,749) and median outpatient group cost was $243,050 ($204,344-$408,467). An analysis of variance (ANOVA) was run between inpatient and outpatient cases was found to be significant ($P<0.0001$). (Table 2) (Figure 1) (Figure 2)

Conclusion:

As the field of CAR-T therapy continues to grow, outpatient programs are likely to increase. Incidence of adverse effects was lower in the outpatient group, likely patient selection effect. This data suggests that outpatient CAR-T therapy is feasible cost-effective and has the potential to grow and improve value. While it appears to be an attractive option, there is a need for more studies on patient selection and creating a robust outpatient infrastructure is needed.

Table 1: Inpatients and outpatient group cost per episode in the 16 facilities offering both programs in 2020

Outcome Variable	Inpatient CART infusion encounters (n= 1369)	Outpatient CART infusion encounters (n=71)
CART therapy Tisa-cel Axi-cel	 335 (24%) 1,034 (76%)	 19 (27%) 52 (73%)
Average number of hospital admission days during CART initial admission	18.14	Not applicable
Total ED visit encounters in first 30 days	1821	108
Average cost of each ED visit	$ 1821.57	$ 1924.91
Percentage of outpatients needing admission	Not Applicable	19.3%
For outpatient group with any admission in 30 days (n=13), median number of days of admission	Not Applicable	11.23
Additional cost of initial and additional hospitalization (if applicable) *CART administration cost not included.	$ 276,174	$ 117,203
Incidence of CRS within 30 days (defined as febrile neutropenia, fever, sepsis)	592 (43.2%)	29 (40.8%)
Incidence of neurotoxicity	511 (37.3%)	21 (29.6%)

Figure 1: Median Inpatient CART Cost

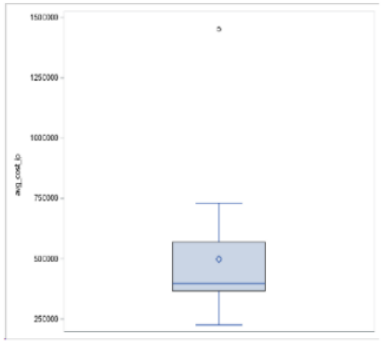
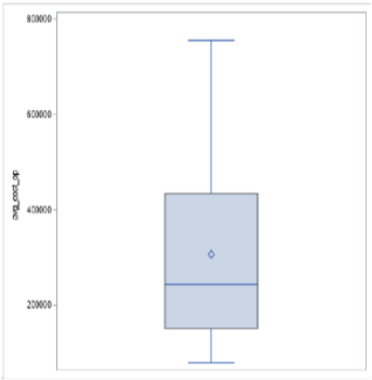


Table 2: Median inpatient and outpatient CART cost per case in the 16 facilities offering both programs in 2020

Variable	n=number of programs	Median	Lower 95% CL for Mean	Upper 95% CL for Mean	t value	P value
Inpatient Median Cost	16	$ 397,610	$ 346,550	$650,749	6.99	<0.0001
Outpatient Median Cost	16	$ 243,050	$ 204,344	$408,467	6.4	<0.0001

Figure 2: Median Outpatient CART Cost



68

Telehealth increases access to transplant survivorship care for allogeneic stem cell recipients regardless of patient age, distance to transplant center or neighborhood income.

Authors: Fitzmaurice, Sarah; Morey, Cherie; Bansal, Rajat MD; Mushtaq, Muhammad MD; Abdelhakim, Haitham MD; Singh, Anurag MD; Shune, Leyla MD; Abhyankar, Sunil MD; McGuirk, Joseph DO; Ahmed, Nausheen MD

Background:
Transplant Survivorship Clinic at our institution serves to improve outcomes and overall health of allogeneic transplant survivors. The COVID19 pandemic allowed for growth of telemedicine to help serve our patients. By July 2020, many of our transplant recipients and survivors had access to telehealth. We examine the patterns of use of telehealth and hypothesize that the use of telemedicine allowed continued access to care compared to the era prior to availability. We compared our transplant survivorship clinic data from July- December 2020, when telehealth was well established and compared to July-December 2019.

Methods:
All patients who were seen by the survivorship team for end of treatment visits, graft versus host disease assessments and survivorship visits annually between July-December 2019 and July-December 2020 were included. Their zip codes were used to get direct distance to survivorship clinic, average drive time, driving distance and average household income as in zip-codes.com database.

Results:
Total number of office visits in July-Dec 2019 was 163 visits (0% telehealth) and in July-Dec 2020 was 228 (66.2% telehealth). All encounters (telehealth and office visits) were lower in July and August 2020 compared to July and August 2019 but was higher later in 2020 from 9/2020-12/2020 compared to 9/2019- 12/2019. Comparing all encounters during 7/2019-12/2019 to 7/2020-12/2020, there was no statistically significant difference in median age (58 vs 60 yr), gender (males: 58% vs 59%), white vs nonwhite (11% vs 8.7%), median years from transplant (4yr vs 3 yrs), median income of patient neighborhood ($63,735 vs $60,465) and average drive time to center from zip code (40min vs 51min).

Comparison of patients who chose telehealth vs. office visit is summarized in table 1. There was no significant difference in demographic variables listed except for age.

Conclusion:
Despite the pandemic, total number of patient encounters in July-December 2020 was higher than 2019. Most of the visits were telehealth visits, demonstrating increased access and patient preferences. Distance to center and neighborhood income did not appear to influence utilization of telehealth. Patients who chose telehealth were younger, but it served patients up to age 85 yrs, showing wide acceptability and utilization.

Table: Comparison of telehealth vs office visit for July-December 2019 and 2020

	Telehealth visits (n=151)	Office visits (n=240)	P value
Age (yrs), median (range)	55 (22-77)	60 (21-85)	0.003
Males, n (%)	91 (60)	137 (57)	0.599
Time since transplant (yrs), median (range)	4 (0.5-28)	3 (0.5-22)	0.156
No shows, n (%)	14 (6)	13 (9)	0.311
Neighborhood income ($), median (range)	644489 (24100-159021)	60465 (25472-158857)	0.314
Average drive time to clinic (minutes), median (range)	44 (6-1061)	49 (0-1200)	0.760

69

Sudden-Onset Achalasia After COVID-19 Infection: PCR Analysis of Esophageal Muscle Tissue

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Author Affiliations: [1] Division of Gastroenterology, Hepatology, and Motility-University of Kansas School of Medicine, Kansas City, KS
[2]Department of Pathology-University of Kansas School of Medicine, Kansas City, KS
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Introduction:

Achalasia has been linked to viral infections. We have observed cases of sudden-onset achalasia after COVID-19. We aimed to evaluate and compare esophageal muscle tissue for SARS-CoV-2 from patients with and without post-COVID-19 onset of achalasia.

Methods:

A prospective study at a single medical center and included 3 groups: 1-Sudden-onset achalasia type 2 (A2) post SARS-CoV-2 infection; 2-Longstanding A2 prior to SARS-CoV-2 infection (achalasia onset pre-dated SARS-CoV-2 infection); 3-Longstanding A2 and no known SARS-CoV-2 infection (multiple tests were negative at different time periods). Circular muscle biopsies were obtained from the lower esophageal sphincter area during peroral endoscopic myotomy (POEM) procedure. Total mRNA was purified from FFPE samples. The presence of SARS-CoV-2 nucleocapsid (N) and spike (S) proteins as well as inflammatory markers (NLRP3, IL-18, TNF) was assessed by RT-PCR. The study was IRB approved at the University of Kansas. Independent-Samples Kruskal-Wallis Test was used to compare groups. Values are reported as mean ± standard deviation. A two-tailed p value < 0.05 was considered significant. mRNA level is reported as relative expression and normalized to 18S.

Results:

Table 1 shows the characteristics of study subjects. Figure 1 demonstrates comparisons between groups for mRNA level for N protein, S protein and the inflammatory markers NLRP3, IL18, and TNF. The Sudden-onset achalasia post SARS-CoV-2 infection group had the highest levels of the N protein in all 4 cases (confirmed and suspected, 625-fold that of group 2) and higher levels of the S protein in the 2 confirmed COVID-19 cases. While the S protein was 5-fold higher in the sudden-onset type 2 achalasia post SARS-CoV-2 infection, it did not reach statistical significance. The presence of SARS-CoV-2 correlated with an increase in the inflammatory markers NLRP3 and TNF (Figure 1C-E). No inflammatory markers were detected in group 3 (achalasia type 2 with no known SARS-CoV-2 infection).

Conclusion:

Our data implicate a connection between SARS-CoV-2 infection and achalasia development and possibly identify a previously unknown consequence of COVID-19

Funding Sources:

None

Table 1. Subjects characteristics

Group	**Group 1*** (A2 post SARS-CoV-2)	**Group 2** (A2 pre-dating SARS-CoV-2)	**Group 3** (A2 no SARS-CoV-2)	***p* value**
# of Subjects	4 (75% M)	6 (67% M)	2 (50% M)	
Median age (range)	34 (26-51)	71.5 (39-86)	70 (60-80)	
SARS-CoV-2 N Protein mRNA	9148.58 (17730.14)	9.79 (10.99)	0.00	**0.0026**
SARS-CoV-2 S Protein mRNA	54.21 (58.20)	6.76 (11.94)	0.00	NS

*In group 1: 2 subjects had confirmed SARS-CoV-2 infection and 2 subjects, though not tested, were suspected to have had SARS-CoV-2 given exposure history.

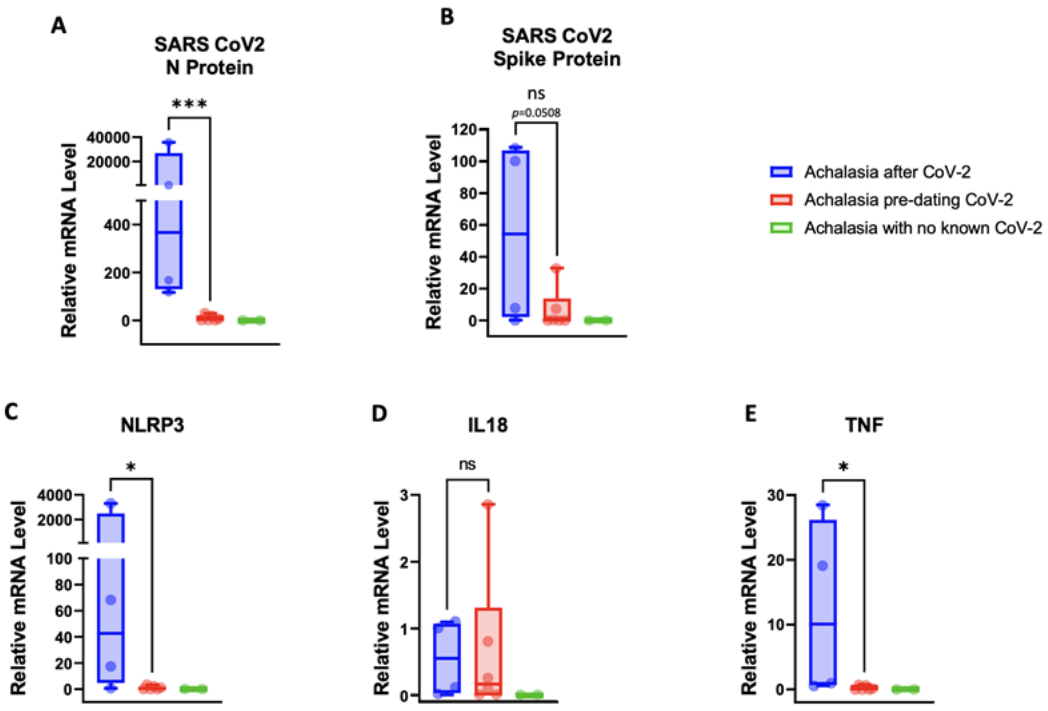

Figure 1. PCR analysis results. A-Levels of nucleocapsid (N) protein RNA. B-Levels of spike (S) protein RNA. C-Levels of NOD-like receptor family pyrin domain-containing 3 (NLRP3) RNA. D-Levels of interleukin 18 (IL-18) RNA. E-Levels of tumor necrosis factor (TNF) RNA.

70

Machine Learning Accurately Risk Stratifies HCV Cirrhosis Patients According to Their Incidence of Hepatocellular Carcinoma

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Introduction:
After sustained virological response (SVR), the incidence of hepatocellular carcinoma (HCC) remains higher in patients with hepatitis C virus (HCV) and cirrhosis, than in patients without cirrhosis (0.5% per year). Surveillance for HCC is considered cost-effective if the incidence of HCC is > 1.5% per year in cirrhosis. We used machine learning to stratify the risk of HCC in HCV cirrhosis patients based on pre-treatment and post-SVR characteristics.

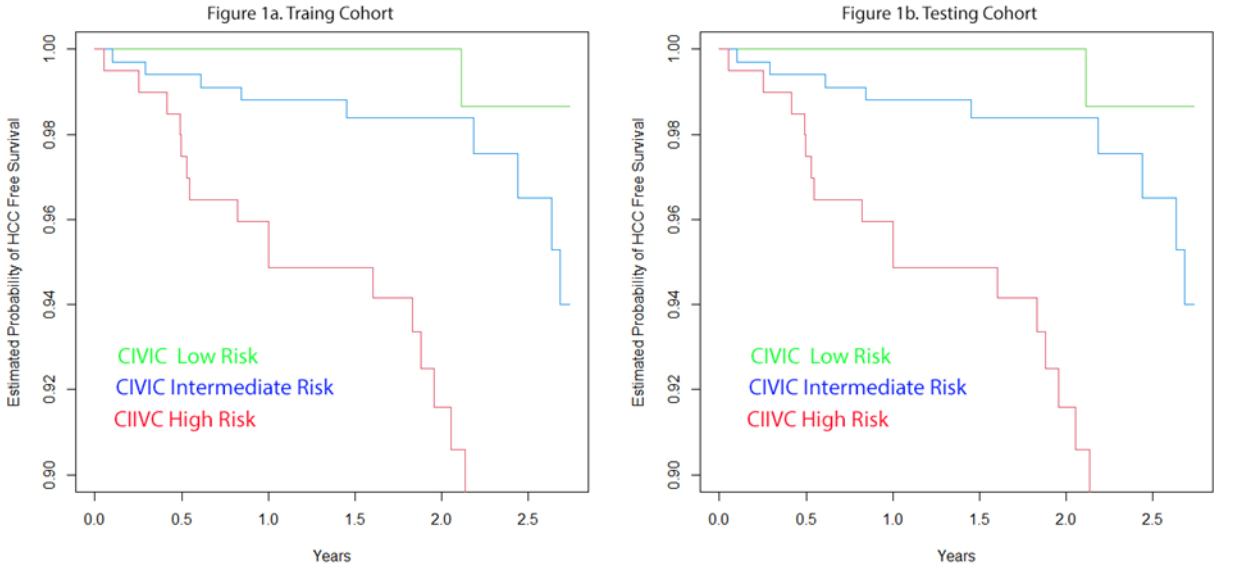
Methods:
Ten centers across five countries participated in this retrospective cohort study of patients with HCV cirrhosis and SVR. Patients underwent post-SVR Vibration-controlled Transient Elastography (VCTE), as well as HCC surveillance by ultrasound. We excluded patients with less than one year of follow-up. Lasso Cox regression analysis used a λ regularization index to prevent overfitting without sacrificing accuracy.

Results:
A total of 50 HCC occurred among 1278 patients during 2493 person-years follow-up after the first post-SVR VCTE. Patients were evenly divided into a training and testing cohort (n= 639 each). HCC occurred at an incidence rate of 2.0% within the first year in both training and testing cohorts. In the training cohort, an index of λ=0.0087 results in the most balanced cross-validation (CV) C-Index of 0.684 (95% CI 0.627 – 0.741). In the testing cohort, the C-Index of the CIVIC Score was 0.729 (95% CI 0.691 - 0.767). The model for the maChine learnIng hcV cIrrhosis hCc (CIVIC) Score comprises gender, pre-treatment ALT, platelet, albumin, and post- SVR VCTE LS. Two CIVIC Score cut points were established to stratify patients according to an incidence rate of < 0.5%, 0.5 – 1.5%, and >1.5% in the training cohort. Figures 1a and 1b show that the risk stratifies patients in the training and testing cohort. The low, intermediate, and high-risk groups account for 18.7%, 45.5%, and 35.8% of the entire cohort.

Conclusion:
The CIVIC Score can accurately risk-stratify patients with HCV cirrhosis after SVR for their risk of HCC. A fifth of patients are at very low risk of HCC, similar to non-cirrhotic patients, while another one-third are below the cost-effective threshold for screening. Our findings can be used to personalize HCC risk and surveillance.

Funding Sources: 1K23DK10929401A1

Figure 1. The maChine learnIng hcV cIrrhosis hCc (CIVIC) Score Risk Stratifies HCV Cirrhosis Patients According to Their Incidence of Hepatocellular Carcinoma



71

Myofibroblast Depletion Reduces Renal Cyst Growth and Fibrosis in Autosomal Dominant Polycystic Kidney Disease

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Introduction:
Autosomal dominant polycystic kidney disease (ADPKD) involves the development and persistent growth of fluid filled renal cysts. In a recent study, we showed that ADPKD renal cyst epithelial cells can stimulate the proliferation and differentiation of peri-cystic myofibroblasts (MFs). Although dense MF populations are often found surrounding renal cysts, their role in cyst enlargement or fibrosis in ADPKD is unclear. Here we examined the effect of MF depletion in the *Pkd1*$^{RC/RC}$ (RC/RC) mouse model of ADPKD.

Methods:
We generated an in RC/RC;αSMA^{tk} mouse that uses the ganciclovir-thymidine kinase system to selectively deplete α-smooth muscle actin (αSMA) expressing MFs.

Results:
Ganciclovir treatment for 4 weeks depleted MFs, reduced renal fibrosis and preserved renal function in RC/RC; αSMA^{tk} mice. Importantly, MF depletion significantly reduced cyst growth and cyst epithelial cell proliferation in RC/RC; αSMA^{tk} mouse kidneys. Similar ganciclovir treatment did not alter cyst growth or fibrosis in wild type or RC/RC littermates. In vitro, co-culture with ADPKD MFs increased 3D microcyst growth of human ADPKD cyst epithelial cells. Furthermore, conditioned cell culture media from ADPKD renal MFs increased microcyst growth and cell proliferation of ADPKD cyst epithelial cells. Further examination of ADPKD MF conditioned media showed high levels of protease inhibitors including PAI1, TIMP1,2, NGAL and TFPI-2, and treatment with recombinant PAI1 and TIMP1 increased ADPKD cyst epithelial cell proliferation *in vitro.*

Conclusion:
These findings show for the first time that MFs directly promote cyst epithelial cell proliferation, cyst growth and fibrosis in ADPKD kidneys, and targeting MFs could be a novel therapeutic strategy to treat PKD.

Funding Sources: This study was supported by NIH R01-DK083525 and KUMC institutional support grants to RR. ND and AJ were supported by postdoctoral fellowship grants from American Heart Association and Kansas Institutional Development Award respectively (P20 GM103418).

72

Notch3 inhibition ameliorates systemic inflammation in HIV-associated Nephropathy

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Introduction: Anti-retroviral therapy (ART) suppresses HIV-associated Nephropathy (HIVAN) but does not protect from continuous generation of viral proteins and inflammation. We need therapies that inhibit viral replication and inflammation simultaneously to avoid progression into chronic kidney disease. We have previously shown that Notch signaling is activated in HIVAN and Pan Notch inhibition ameliorated disease progression in the Tg26 mouse model of HIVAN. Here, we determined specifically the role of Notch3 pathway in HIVAN pathogenesis.

Methods: To determine the role of Notch3, we labelled renal sections from HIVAN patients and mouse model (Tg26) for Notch3 via immunohistochemistry. We determined if HIV-1 induces Notch3 activation. We generated Tg26 mice with global Notch3 knockout (Tg-N3KO) and characterized the kidneys, followed by RNA sequencing. Macrophage- podocyte interactions were then studied. Soluble TNF alpha levels were evaluated using ELISA.

Results: Notch3 was activated in glomerular, tubular and interstitial cells of HIVAN biopsies and Tg26 mice. Notch3 expression was induced when podocytes were transfected with HIV-1 construct. Genetic knockout of Notch3 (N3KO) in Tg26 (Tg-N3KO) mice resulted in a significant increase in the life span. This was associated with marked improvement in glomerular and tubular injury and renal function. A striking reduction in infiltrating immune cells was observed. RNA sequencing and validation data indicated a marked reduction of macrophage markers in Tg-N3KO mice verses Tg26 mice. We then isolated and cultured bone marrow derived macrophages from Tg26 and Tg-N3KO mice and found that Notch3 and Notch ligands, Jagged 1 and Delta like 4 (Dll4) were markedly upregulated in Tg26 mice. N3KO normalized them. Conditioned macrophage media from BMDM derived from Tg26 mice resulted in Notch activation of podocytes. Finally, we found that Notch3 deletion not only affected the kidneys but reduced the systemic expression of soluble inflammatory factor tumor necrosis factor alpha.

Conclusion: Notch 3 deletion in HIVAN model reduced kidney injury, improved renal function, reduced macrophage infiltration and reduced systemic TNF alpha levels which may collectively be responsible for the increase life span of the Tg26 mice. Thus, inhibition of Notch3 may constitute an attractive therapeutic strategy in HIV related CKDs.

Funding Sources: NIH R01DK108433, KINBRE bridging NIH P20 GM103418.

73

Neutrophil extracellular trap formation in bronchoalveolar lavage fluid is associated with worse baseline lung function and worse survival in patients with idiopathic pulmonary fibrosis

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Introduction:

Idiopathic pulmonary fibrosis (IPF) has an average survival from diagnosis of three to five years. Despite the importance of IPF, treatments currently offer minimal clinical benefit. It is urgent to develop better prognostic tools and mechanisms of lung injury in IPF. Previously, bronchoalveolar lavage fluid (BALF) neutrophilia was found to be associated with worse survival in IPF. Herein, we explore a possible link between BALF neutrophilia in IPF and poor outcomes; lung injury induced by the activity of neutrophil extracellular traps (NETs). NETs are degranulated neutrophilic nucleolar material rich in citrullinated proteins have been associated with a worse clinical phenotype in chronic lung diseases such as asthma. The goal of this study was to explore the relationship between markers of NET formation in the human lung and outcomes in IPF.

Methods:

156 patients with IPF with stored bronchoalveolar lavage fluid (BALF) were tested for markers of NETs (neutrophil elastase (NE) and double stranded DNA (dsDNA), (measured by in triplicate and averaged via ELISA and fluorometric assay respectively). Each NET marker level was normalized to BALF protein level. Date of death was extracted from the medical record and confirmed by the Center of Disease Control's National Death Index (Table 1).

Correlations were calculated via Spearman and models were built to adjust for sex, age, and pack-years smoking and disease severity. Survival analyses were performed using Cox-proportional hazards-model including adjustments for confounding variables.

Results:

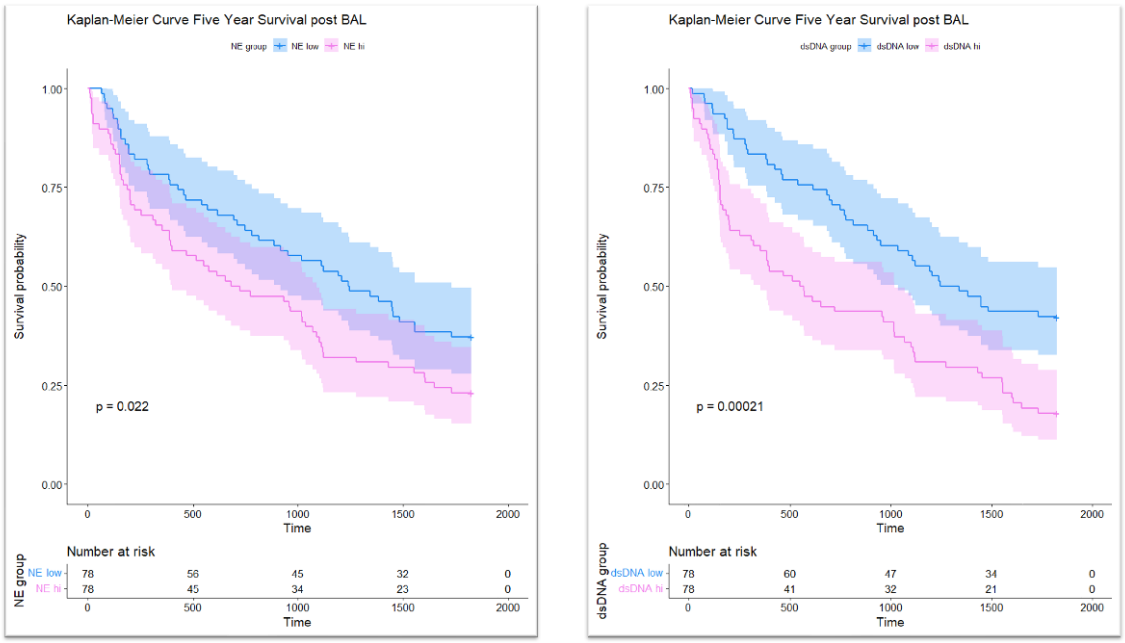
NE and dsDNA were both significantly associated with worse survival in our adjusted analysis (HR: 1.83, p = 0.0016 and HR 2.02. p = 0.00061 respectively). We performed a dichotomized analysis of each NET marker based on median values in the cohort and found that the “high” NET groups (NE and dsDNA) each had significantly worse survival than the “low” NET groups in a time-to-death analysis (p = 0.022 and p=0.00021 respectively) (Figure 1).

Conclusion:

NETosis is associated with worse prognosis in IPF and may be a novel target for future therapeutic research.

Funding Sources: Scott Matson is supported by NIH funding via: 1P20GM130423-01 through the KIPM COBRE mechanism.

Figure 1.



BAL: Bronchoalveolar lavage, NE: Neutrophil elastase, dsDNA: double stranded DNA

Table 1.

	(N=156)
Age at Time of BAL	
Mean (SD)	66.1 (7.56)
Median [Min, Max]	67.0 [46.0, 82.0]
Sex	
Male	100 (64.1%)
Female	55 (35.3%)
Smoking status	
Current	27 (17.3%)
Prior	77 (49.4%)
Never	52 (33.3%)
Pack years of Smoking	
Mean (SD)	40.6 (24.6)
Median [Min, Max]	38.0 [0, 118]
Baseline FVC% predicted	
Mean (SD)	66.3 (17.5)
Median [Min, Max]	68.0 [26.0, 106]
Baseline DLCO% predicted	
Mean (SD)	79.2 (22.6)
Median [Min, Max]	81.0 [29.0, 127]
Died within 5 years N (%)	109 (69.9%)
Days to Death 5 yrs: Mean (SD)	993 (696)
Died before 11/3/2019: N (%)	150 (96.2%)
Days to Death 11/3/2019: Mean (SD)	1600 (2000)

74

Treatment Outcomes for Rheumatoid Arthritis Interstitial Lung Disease; a Real-world, Multisite Study of Immunosuppression Impact on Pulmonary Function

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Introduction:

Rheumatoid arthritis (RA) interstitial lung disease (ILD) is common in patients with RA and leads to poor outcomes. There are no randomized, placebo-controlled data to support the role of immunosuppression in RA-ILD despite wide clinical use. We created a retrospective cohort of RA-ILD patients from five separate ILD centers in the United States to understand the impact of immunosuppression on pulmonary function trajectory in RA-ILD.

Methods:

Patients with RA who started ILD treatment with mycophenolate, azathioprine, or rituximab were retrospectively identified. Change in lung function before and after treatment initiation was analyzed using random-effects linear modeling. Prespecified secondary analyses included an interaction analysis for baseline radiologic pattern (i.e., usual interstitial pneumonia (UIP) vs non-UIP). Models were adjusted via propensity weighting for: age at ILD treatment initiation, ethnicity, pulmonary hypertension, prednisone use and sex.

Results:

212 patients were included in the analysis: 92 (43.4%) were treated with azathioprine, 77 (36.3%) with mycophenolate and 43 (20.3%) with rituximab (Table 1). In our analysis of the collective impact of immunosuppression, forced vital capacity % predicted (FVC) improved after 12 months of treatment compared to the potential 12-month response without treatment [+3.90%, $p < 0.0001$; 95% CI, (1.95, 5.84)]. Diffusing capacity for carbon monoxide % predicted (DLCO) also improved at 12 months [+4.53%, p=0.0002; (2.12, 6.94)] (Figure 1). The presence of RA-UIP did not significantly impact the response to immunosuppression (p=0.506).

Conclusion:

Our data supports the current paradigm of primary, initial immunosuppression for treatment of RA-ILD. There are concerns about the use of immunosuppression in fibrotic patterns of ILD such as UIP given results of randomized trials in idiopathic pulmonary fibrosis, however in our pre-specified secondary analysis, UIP did not significantly impact treatment response when added to our model. Limitations of observational and retrospective study design highlight the urgency for randomized, placebo-controlled trials in RA-ILD.

Funding Sources: Scott Matson is supported by NIH funding via: 1P20GM130423-01 through the KIPM COBRE mechanism.

Table 1.

Characteristics	**N=212**
Mean Age at treatment initiation (SD)	63.5 (14.6)
Mean Age at RA diagnosis (SD)	56.5 (13.7)
Male, n (%)	80 (37.7)
Non-white race, n (%)[a]	34 (16.3)
Non-Hispanic, n (%)[b]	140 (67.6)
Ever smoker, n (%)[c]	126 (59.7)
Seropositive, n (%)[d]	187 (90.3)
Anti-CCP positive, n (%)[e]	136 (72.3)
RF positive, n (%)[f]	159 (80.3)
RA-UIP, n (%)[g]	80 (40.4)
GERD, n (%)[h]	146 (69.5)
Pulmonary hypertension, n (%)[i]	67 (32.7)
OSA, n (%)[j]	86 (42.2)
Pulmonary function at treatment initiation	
Mean FVC % (SD)	66.9 (18.2)

Characteristics	N=212
Mean DLCO % (SD)	50.5 (18.1)
Baseline treatment when ILD specific treatment initiated	
Prednisone, n (%)	144 (67.9)
Mean Prednisone dose mg (SD)	13.2 (15.8)
Hydroxychloroquine, n (%)	56 (26.4)
Leflunomide, n (%)	29 (13.7)
Methotrexate, n (%)	25 (11.8)
Infliximab, n (%)	15 (7.1)
Sulfasalazine, n (%)	13 (6.1)
Etanercept, n (%)	12 (5.7)
Abatacept, n (%)	10 (4.7)
Adalimumab, n (%)	8 (3.8)
Golimumab, n (%)	4 (1.9)
Tofacitinib, n (%)	4 (1.9)
Certolizumab, n (%)	2 (0.9)
ILD treatment initiated	
Azathioprine, n (%)	92 (43.4)
Azathioprine Daily dose range, Mean (mg)	50-300 (120.1)
Mycophenolate, n (%)	77 (36.3)
Mycophenolate Daily dose range, Mean (mg)	500-3000 (1964.3)
Rituximab, n (%)*	43 (20.3)

RA = rheumatoid arthritis, Anti-CCP = antibodies to cyclic citrullinated peptides, RF = rheumatoid factor.
RA-UIP = consensus determination of definite or probable usual interstitial pneumonia. FVC = forced vital capacity, DLCO = diffusing capacity for carbon monoxide, ILD = interstitial lung disease.
**Rituximab universal starting dose was 1000 mg on day 1 infusion.*

Figure 1.

(1A/B) FVC and DLCO trends. Time 0 = treatment initiation. The pre-treatment trend (blue dotted line) is projected forward from time 0 to +24 months and compared to the observed trend after treatment. Gray shading indicates 95% confidence intervals

75

Pulmonary Research Team – Quality Improvement in Clinical Research

Authors: Kothari, Mayank[1]; Hellwig, Heidi[1]; Manyara, Mary[1]; Scott, Larry[1]; Bruce, Amanda[1]; Schmid, Andreas[1]; Bengtson, Charles[1]; Salathe, Matthias[1]; Harrison, Megan[1]; Mermis, Joel[1]

Author Affiliations: [1]The University of Kansas

Introduction:

The value of quality improvement (QI) to advance clinical care through process improvement has been established. Successful QI is achieved by evaluating, modifying, and measuring processes over time to improve outcomes. We hypothesize that establishment of a clinical research QI team will have similar impact and aim to demonstrate that clinical research focused QI can ultimately improve the quality of life of patients with different pulmonary diseases through more effective clinical research.

Methods:

The QI process begins with analysis of the 5P's (Professionals, Process, Patterns, Purpose, and Patients). Following analysis of the 5P's, a global aim and related process specific aims were identified. Through the exploration of specific aims and change ideas, processes were identified to be further studied and subsequently measured.

Results:

A clinical research quality improvement team has been created and process review has been completed. The 5P's identified these patient groups of focus:

- Smokers, and vape users – > 16 to 45 years old (college students, VAMC, ENT referrals) in the KC metro area but expanding with the help of a mobile research unit.
- NCFB/NTM – >18 years old (often >65 years old), KUMC and KC metro referrals.
- CF – > referrals from CF registry and clinics categorized by patients on modulators vs not on modulators.
- COPD / AATD – > Frontiers, outside clinic referrals, VAMC, and KU Pulmonary clinic.

Study start-up and patient recruitment have been identified as initial process to target for improvement. Based on the review of current processes we have started notifying clinicians prior to clinic of eligible study participants. Additionally, we have identified startup stakeholders and increased the frequency of communication regarding action items. By working on this process, we expect to streamline and standardize key aspects of study start-up communication as depicted in the figure below.

Conclusions:

Similar to clinical care, QI can be used to change processes in clinical research. Through the implementation of these QI efforts, we improve enrollment and are able to offer as many patients as possible the benefit of innovative therapies.

Funding Sources:

This research was supported by the Internal Medicine department at University of Kansas Medical Center.

76

IL-13 Regulated Airway Epithelial Genes Correlate to Lung Function and Markers of T2 Asthma in SARPIII Participants

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Introduction:
Asthma is a chronic airway disease with reversible airway obstruction, airway inflammation with heterogenous underlying disease pathology. Genetic studies indicate *Muc5AC* and *IL13* gene expression are increased in T2 severe asthma contributing to measures of airway remodeling. **We hypothesized IL-13 regulated airway epithelial genes associate with clinical measures of T2 inflammation in asthma.**

Methods:
Airway epithelial cells procured from SARPIII participants (7 centers N=201: Healthy [42], non-severe [52], severe [62]) at baseline had RNA-sequencing performed. A subset of participants had endobronchial tissue immunostained for inflammatory cells. Measures of lung function, questionnaires and T2 asthma were used for correlation analyses. Statistical analysis performed using a mixed model with random intercept and Pearson correlation.

Results:
In SARPIII, *Muc5AC* (by 0.91±0.41 from 16.04±0.36) and *IL-13* (by 0.08±0.12 from 0.16±0.11) increased in severe asthma ($p<0.0001$, $p=0.09$). IL-13 regulated airway epithelial genes 1) increased *IL13Ra2* ($p=0.009$), *BPIFB1* ($p=0.02$), and *mKI67* ($p=0.003$) versus 2) decreased *OCLN* ($p=0.01$), *Muc5B* ($p=0.03$), *SCGB1A1* ($p<0.0001$), and *BPIFA1* ($p=0.08$) in severe asthma. Increased genes associated to clinical variables including exacerbations in past year: *IL-13* (0.35, $p=0.0001$), *IL13Ra2* (0.22, $p=0.01$), *mKI67* (0.30, $p=0.001$), *Muc5AC* (0.20, $p=0.03$); Blood Eos%: *IL-13* (0.18, $p=0.03$), *Muc5AC* (0.37, $p<0.0001$); serum IgE (kU/L): *Muc5AC* (0.17, $p=0.03$); sputum Eos%: *Muc5AC* (0.35, $p=0.0002$); FeNO (ppb): *IL-13* (0.38, $p<0.0001$), *Muc5AC* (0.37, $p<0.0001$), and inversely preBD FEV%pred: *IL-13* (-0.19, $p=0.02$), *BPIFB1* (-0.21, $p=0.007$), *Muc5AC* (-0.37, $p<0.0001$); ACT: *IL13Ra2* (-0.02, $p=0.03$), *mKI67* (-0.36, $p<0.0001$). Decreased genes associated with clinical variables including preBD FEV%pred: *OCLN* (0.16, $p=0.05$), *SCGB1A1* (0.44, $p<0.0001$), *Muc5B* (0.23, $p=0.004$); ACT: *SCGB1A1* (0.33, $p=0.0003$), *Muc5B* (0.24, $p=0.01$), and inversely to Blood Eos%: *OCLN* (-0.24, $p=0.003$), *SCGB1A1* (-0.47, $p<0.0001$), *Muc5B* (-0.26, $p=0.001$); sputum Eos%: *OCLN* (-0.39, $p<0.0001$), *SCGB1A1* (-0.45, $p<0.0001$), *Muc5B* (-0.28, $p=0.002$); FeNO: *SCGB1A1* (-0.37, $p<0.0001$), *BPIFA1* (-0.26, $p=0.001$), *Muc5B* (-0.48, $p<0.0001$); exacerbations: *SCGB1A1* (-0.29, $p=0.001$), *Muc5B* (-0.23, $p=0.01$). IL-13 regulated genes correlated to eosinophils (counts/mm^2) in endobronchial tissue: *SCGB1A1*, *BPIFA1* and *Muc5B* inversely correlated (-0.77, $p<0.0001$; -0.51, $p=0.02$; -0.57, $p=0.009$) while *Muc5AC* directly correlated (0.67, $p=0.001$).

Conclusion:
IL-13 regulated epithelial genes are involved in airway remodeling by altering the transcription profile of mucin and secretory genes in a T2-eosinophilic asthma endotype.

Funding Sources: NIH grant NHLBI U01HL146002, U10 HL109257, UL1 TR002366 and Parker B. Francis Foundation

RNA Transcript	**Asthma Status**	**Estimate±SD** (log2 expression)	**P value**
IL-13:			
IL13	Healthy (intercept)	0.17±0.04	
	Non-severe	0.16±0.05	**0.002**
	Severe	0.08±0.05	0.09
IL13RA1	Healthy (intercept)	11.80±0.03	
	Non-severe	-0.06±0.04	0.08
	Severe	-0.006±0.04	0.86
IL13RA2	Healthy (intercept)	1.43±0.04	
	Non-severe	0.05±0.05	0.30
	Severe	0.13±0.05	**0.009**
OCLN	Healthy (intercept)	11.0±0.04	
	Non-severe	-0.04±0.05	0.37
	Severe	-0.12±0.05	**0.01**
Secretory:			
MUC5B	Healthy (intercept)	14.63±0.13	
	Non-severe	-0.58±0.17	**0.001**
	Severe	-0.36±0.17	**0.03**
MUC5AC	Healthy (intercept)	15.90±0.13	
	Non-severe	0.77±0.18	**<0.0001**
	Severe	0.91±0.17	**<0.0001**
SCGB1A1	Healthy (intercept)	16.3±0.14	
	Non-severe	-0.69±0.18	**0.0002**
	Severe	-1.16±0.18	**<0.0001**
BPIFA1	Healthy (intercept)	12.26±0.25	
	Non-severe	-1.01±0.34	**0.004**
	Severe	-0.58±0.33	0.08
BPIFB1	Healthy (intercept)	17.25±0.08	
	Non-severe	0.12±0.11	0.26
	Severe	0.25±0.10	**0.02**
Proliferation:			
MKI67	Healthy (intercept)	7.58±0.08	
	Non-severe	0.01±0.11	0.92
	Severe	0.40±0.11	**0.0003**
KRT5	Healthy (intercept)	13.02±0.07	
	Non-severe	-0.11±0.10	0.26
	Severe	-0.005±0.10	0.96
KRT14	Healthy (intercept)	3.64±0.12	
	Non-severe	-0.19±0.16	0.24
	Severe	-0.02±0.16	0.91

77

Tight junction protein claudin-5 protects the podocytes after injury in proteinuric renal diseases.

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Author Affiliations: [1]Jared Grantham Kidney Institute, Department of Internal Medicine, University of Kansas Medical Center, Kansas City, KS, United States

Introduction:

*Focal and segmental glomerulosclerosis (FSGS) i*s characterized by podocyte injury and impairment of the glomerular filtration barrier causing proteinuria, nephrotic syndrome, and kidney failure. Podocytes respond to injury by foot process effacement and "fusion", with loss of slit diaphragms and replacement by tight junctions (TJ) between neighboring podocytes. Why TJs appear, and their role is unknown. Claudins are membrane proteins which are necessary to form TJs, and claudin-5 (Cldn5) is specifically expressed at the plasma membrane in adult podocytes and migrates to TJs upon injury.

Methods:

To study the role of Cldn5, we generated Cldn5 homozygous Floxed (fl/fl) mice and crossed them to NPHS2-Cre mice to achieve podocyte-specific deletion of Cldn5 (Cre+). Glomeruli were isolated for Western blotting and immunofluorescence staining. Urine was collected from Cre+ mice and Cre- control littermates (N= 17-18 per group) at 5, 8, 15, 25, 35 and 45-weeks for measurement of albumin, by ELISA, and creatinine. Data was analyzed by linear mixed models with repeated measures over time.

Results:

Podocyte-specific Cldn5 knockout mice (Cre+) were born at normal Mendelian ratios. Cldn5 was detected in podocytes of control mice by immunofluorescence and Western blotting and was absent from Cre+ mice indicating complete Cre excision. Cre+ mice developed increasing urine albumin/creatinine ratio (UACR) with age, compared to Cre- ($P = 0.011$), and male mice had increasing UACR with age compared to females ($P = 0.015$).

Conclusion:

Cldn5 has a protective role in the glomerular filtration barrier at baseline. Since podocyte foot process effacement and TJ formation is common to all nephrotic disorders, Cldn5 may be critical in the adaptive response to FSGS and other podocytopathies. Ongoing studies are testing the role of Cldn5 in Adriamycin-induced podocyte injury.

Funding sources: This research is partially funded by NIH R01 DK115727

78

Examining the role of urinary phosphate in kidney cyst formation, tubular injury, and inflammation

Authors: Jansson, Kyle[1]; Zhang, Shiqin[1]; Fields, Timothy[1]; Swenson-Fields, Katherine[1]; Rowe, Peter[1]; Stubbs, Jason[1]

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Introduction: Chronic kidney disease (CKD) is characterized by the progressive loss of kidney function associated with increased inflammation and fibrosis in the kidneys. High dietary phosphate intake increases urinary phosphate excretion and has been associated with an increased risk for CKD progression. Additionally, increased urinary phosphate excretion leads to phosphate-based nanocrystal deposition in kidneys which may promote kidney injury. The effect of increased urinary phosphate on mechanisms of kidney cyst growth and injury is not well defined currently.

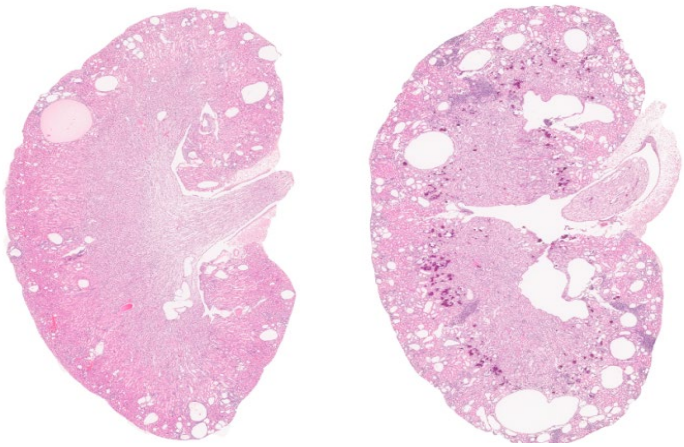
Methods: A mouse model of cystic kidney disease, the *Pkd1*$^{RC/RC}$ mouse, was placed on a high versus low phosphate diet and analyzed for changes in cyst growth. Further analyses determined the effect of increased dietary phosphate on mineral deposition and changes in markers of kidney injury, inflammation and fibrosis. Additional studies analyzed the NaPi2a-/- mouse, a model with high levels of urinary phosphate wasting, to determine the effect of urinary phosphate on mechanisms of kidney injury.

Results: *Pkd1*$^{RC/RC}$ mice on a high phosphate diet had increased cyst growth and deposition of phosphate-based minerals in their kidneys compared to mice on a low phosphate diet. Mineral deposits in these kidneys were spatially colocalized with macrophages. Gene expression for markers of kidney injury, inflammation, and fibrosis were increased in *Pkd1*$^{RC/RC}$ mice on a high phosphate diet. To determine the specific effect of urinary phosphate on kidney injury, kidneys from NaPi2a-/- mice were analyzed and showed reduced kidney function as well as increased gene expression for markers of kidney injury, inflammation, and fibrosis compared to wild type mice.

Conclusion: Increased urinary phosphate excretion exacerbates cyst growth in a mouse model of cystic kidney disease and promotes declines in kidney function. This may be due to deposition of phosphate-based crystals stimulating kidney injury leading to inflammation and fibrosis in the kidneys.

Funding Sources: RO1 DK122212 (NIDDK, NIGMS)

Low Phosphate **High Phosphate**



***Pkd1*$^{RC/RC}$**

79

Application of Endoscopic Powered Resection (EPR) in Pancreatic Necrosectomy Post-Cystogastrostomy

Authors: Reddy, Pranay, MD, MPH[1]; Valadez, David, MD[2]; Sutton, Richard, DO[2]; Olyaee, Mojtaba, MD[2]

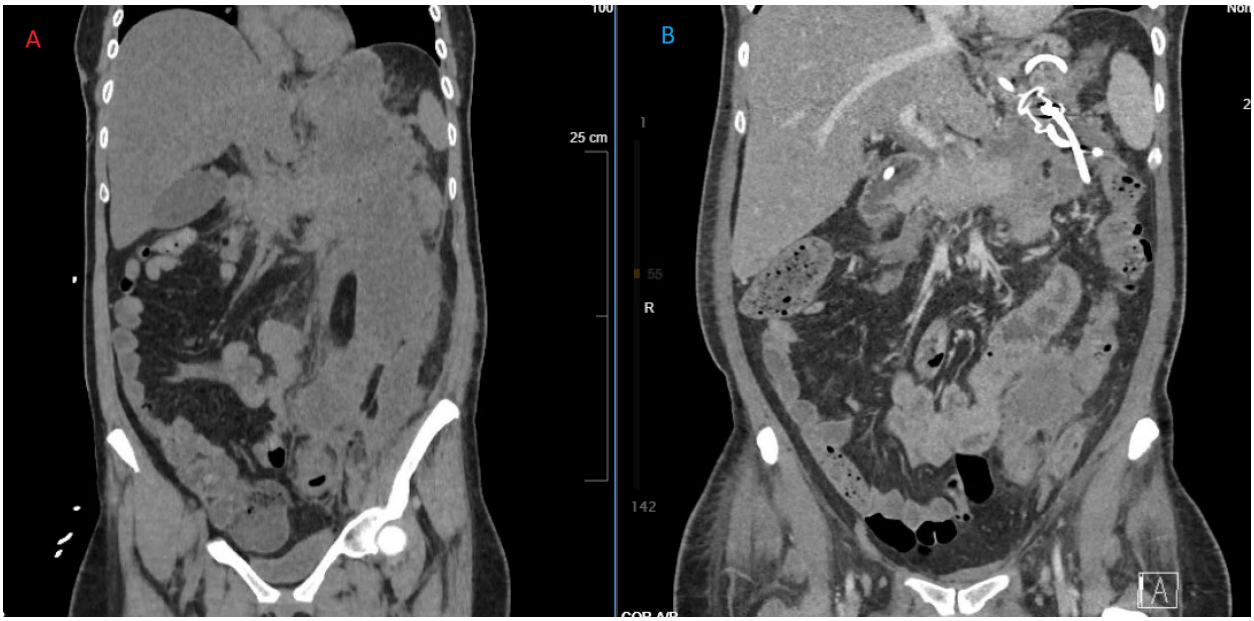
Author Affiliations: 1. Jefferson Health Northeast Department of Internal Medicine, 2. KUMC Department of Gastroenterology

Introduction:
Patients with severe pancreatitis routinely develop walled off necrotic collections that require a procedure known as a Cystogastrostomy. This procedure creates an opening between the necrotic collection and the stomach to help facilitate removal of necrotic tissue. Serial endoscopic necrosectomies are often required to remove all the necrotic debris. Endoscopic powered resection (EPR) is a procedure used to perform mechanical mucosectomies of polyps within the gastrointestinal tract. This method of mechanical resection has recently been applied to endoscopic pancreatic necrosectomy and debridement. The following case highlights a novel application of EPR in performing pancreatic necrosectomies following cystogastrostomy to help decrease the number of repeat procedures.

Methods/Case:
A 47-year-old patient with past medical history of asthma, hyperlipidemia, breast cancer, recent hypertriglyceridemia-induced acute pancreatitis who initially presented with fevers, chills and abdominal pain. Initial labs remarkable for leukocytosis WBC 19.7 K/UL. CT scan showed concern for new infected peripancreatic necrotic fluid collection measuring 9.5 x 6.0 cm extending inferiorly along the left paracolic gutter. An EUS with cystogastrostomy and endoluminal stent placement was performed to facilitate drainage of the necrotic collection. Repeat EGD with both EPR and snare necrosectomy was performed the following week. CT scan completed two days later showed marked interval decrease in the multiloculated peripherally enhancing peripancreatic air and fluid collection now measuring 7.3 x 4.0 cm. The patient underwent second necrosectomy one week later with EPR and snare mechanical debridement which revealed an 18 cm cyst cavity. Significant amount of necrotic tissue removed at that time and patient scheduled for repeat EGD in 3 weeks with endoluminal stent retreatment.

Results/Conclusion:
Endoscopic pancreatic necrosectomy is often performed 4 weeks after the initial episode of pancreatitis to allow formation of a true, walled off necrotic collection. When performing endoscopic necrosecromy of large collections, at least 5 procedures are often required to completely removal all necrotic tissue. As shown in this case, implementation of EPR with traditional endoscopic snare necrosectomy can facilitate efficient removal of debris and help decrease the number of repeat necrosectomies. This could ultimately improve resource utilization and have major implications on overall patient morbidity and mortality.

Funding Sources: None



A. **Coronal CT Pre-Necrosectomy**

B. **Coronal CT Post-cystogastrostomy, stent placement and necrosectomy**

80

A Rare Hybrid gNET: The Neoplastic Jack of All "Grades"

Authors: Reddy, Pranay, MD, MPH[1]; Valadez, David, MD[2]; Olyaee, Mojtaba, MD[2]

Author Affiliations: 1. Jefferson Health Northeast Department of Internal Medicine, 2. KUMC Department of Gastroenterology

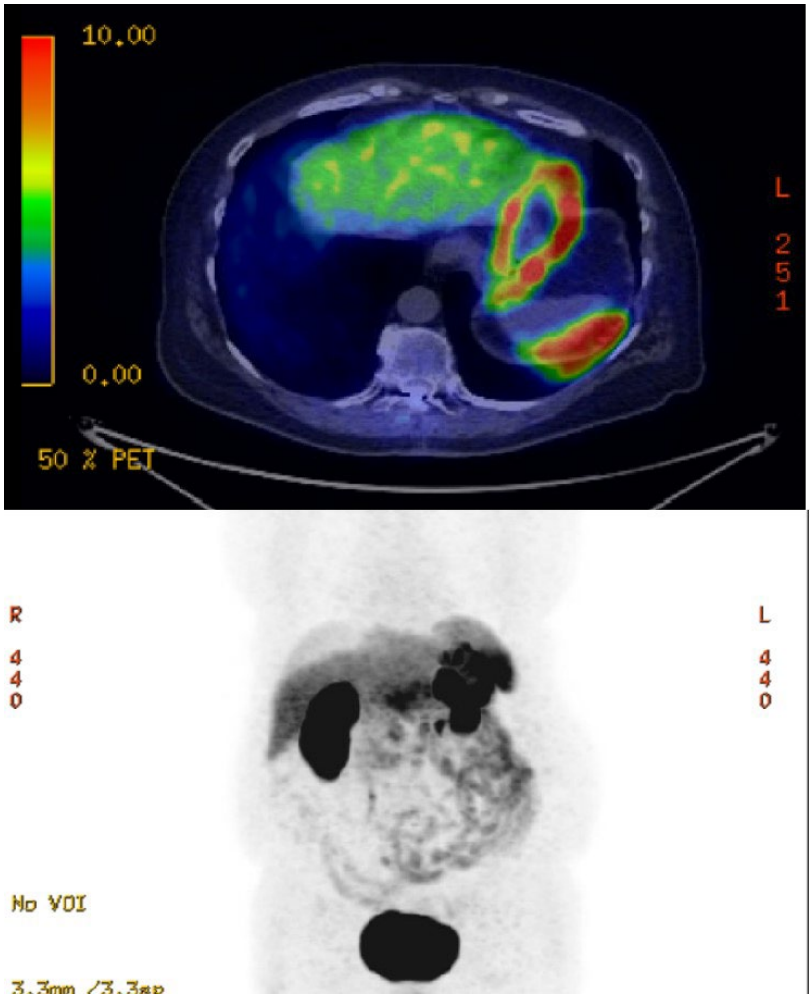
Introduction:
Gastric neuroendocrine tumors (gNETs) are rare malignancies which arise from enterochromaffin-like cell (ECL) precursors within the gastric mucosa. There are 4 classifications of gNETs primarily based on size, number of lesions, serum gastrin level, tissue invasion, proliferation index and immunohistochemistry. Applying a combination of factors, gNETs are typically classified into one of these four categories with relative ease. The following case highlights an exceedingly rare hybrid presentation of gNET containing features of all four classification subtypes.

Methods/Case:
A 78-year-old female with a past medical history of hypertension, diabetes mellitus, chronic kidney disease and gastroesophageal reflux disease (GERD) initially presented with worsening symptoms of GERD. The patient denied any alarm symptoms but did endorse persistence of reflux symptoms despite proton pump inhibitor use. Screening EGD with EUS showed polyps which were removed with mucosal resection. Initial pathology illustrated well differentiated gNET. She underwent a DOTA-TATE PET/CT scan which showed heterogenous uptake involving the gastric body reflecting focal gNET without evidence of metastasis. The patient underwent total gastrectomy and esophagojejunostomy with upper GI series revealing no evidence of anastomotic leak.

Results:
On subsequent pathology, at least 46 semi pedunculated gastric polyps were identified of which the greatest tumor dimension was 0.6 cm with a mitotic rate less than 2 mitoses/2mm2. Pathology and immunohistochemistry revealed well differentiated gNET, grade 1 and 2, staining positivity for Chromogranin A (CgA), synaptophysin, CD56, and CAM 5.2 with a Ki67 proliferation index > 6%. Patient's serum gastrin was within normal limits at 51pg/ml and 24-hour urine 5-HIAA revealed a normal level of 5.7 mg/24hr. She was referred to a geneticist for massive parallel sequencing.

Conclusion:
This case displays a rare, hybrid presentation of gNET with features of all four classification subtypes. The positive synaptophysin, normal serum gastrin and increased Ki67 index are characteristic of gNET Type 3 and 4 which carry a poor prognosis. Type 3 and 4 however, are typically large (>2cm), single tumors. This patient had many, smaller tumors with positive CgA staining commonly seen in Type 1 and 2. Hybrid gNETs are extremely uncommon neoplasms which create a diagnostic and therapeutic challenge requiring a truly multidisciplinary effort.

Funding Sources: None



DOTA-TATE PET/CT scan showing heterogenous uptake in the gastric body concerning for focal gNET.

81

A Rare Pancreatic Tail Schwannoma in an Asymptomatic 58-Year-Old Female

Authors: Reddy, Pranay, MD, MPH[1]; Valadez, David, MD[2]; Olyaee, Mojtaba, MD[2]

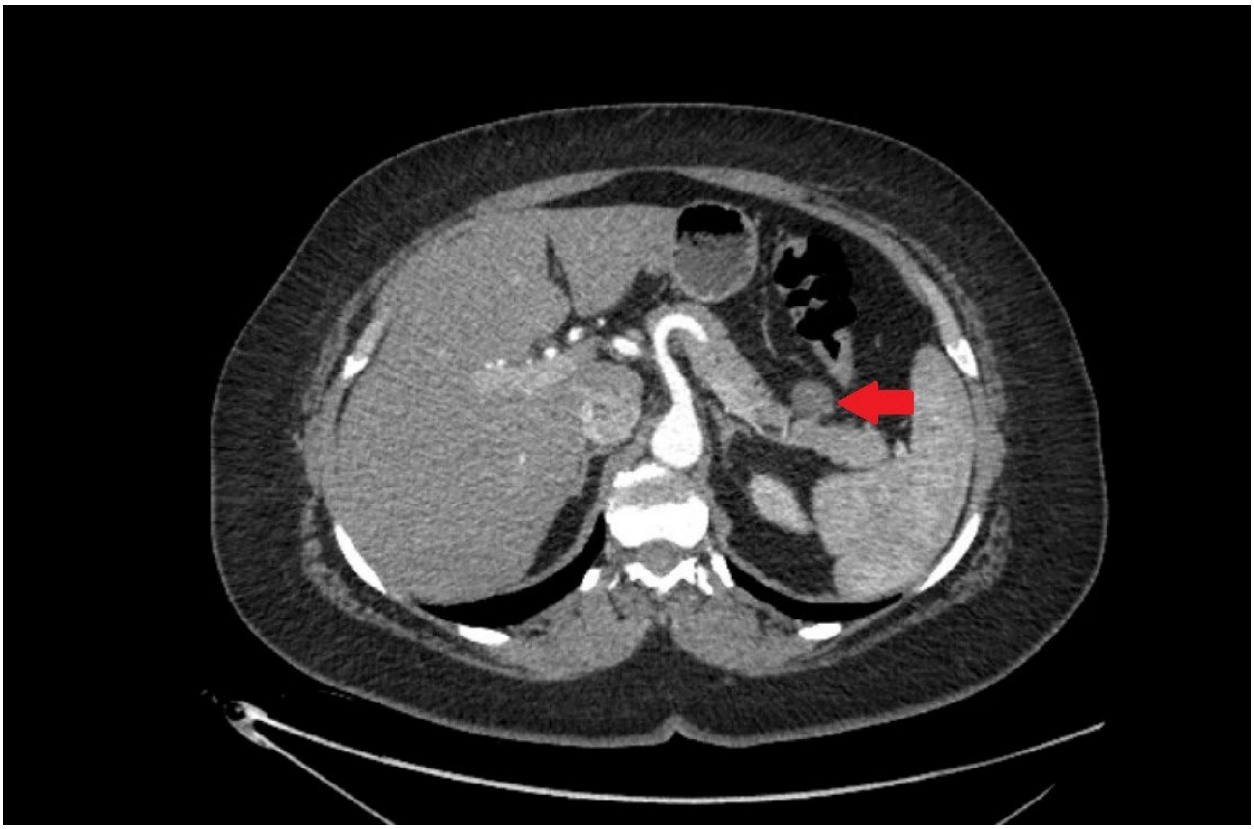
Author Affiliations: 1. Jefferson Health Northeast Department of Internal Medicine, 2. KUMC Department of Gastroenterology

Introduction:
Schwannomas are tumors which originate from Schwann cells responsible for fabricating myelin. Although Schwannomas are the most common benign peripheral nerve tumor in adults, there are several variants which are remarkably less common. Pancreatic schwannomas are an exceedingly rare type of nerve sheath tumor which arise from either sympathetic or parasympathetic vagal nerve fibers within the pancreas. In 2017, only 68 cases of pancreatic schwannoma had been reported in the preceding forty years with most occurring in the pancreatic head and body. In this case, we discuss an extraordinarily uncommon presentation of a pancreatic tail schwannoma in an asymptomatic 58-year-old female.

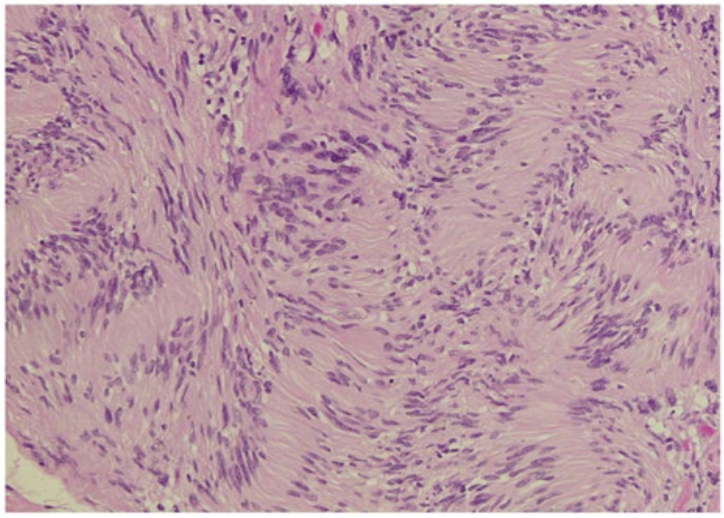
Methods/Case: A 58-year-old female with a past medical history of hypertension and hypothyroidism presented with findings of a 2 cm exophytic pancreatic tail lesion seen on prior CT imaging. The patient reportedly had a strong family history of aortic aneurysms and was found to have a right renal lesion on screening CT. She subsequently underwent CT abdomen and pelvis which revealed a lesion concerning for pancreatic tail malignancy. Endoscopic ultrasound (EUS) was performed which showed a 17 x 20 mm isoechoic peripheral pancreatic tail lesion. Fine needle aspiration (FNA) was performed which revealed spindle cells concerning for malignancy. Pathology and immunohistochemistry were inconclusive due to scant FNA aspirate obtained during EUS. Patient was taken to the operating room for exploratory laparotomy with distal pancreatectomy and splenectomy. Pathology of resected pancreatic mass showed typical histology with nuclear palisading and thick-walled vessels. Immunohistochemical staining supported the diagnosis of Schwannoma with diffuse, strong positivity for S-100 and SOX10 as well as negative staining for desmin, smooth muscle actin, CD34, pancytokeratin, CD117 and DOG1.

Results/Conclusion: Pancreatic schwannoma most commonly presents with abdominal pain although 30% of cases are found in asymptomatic patients with lesions discovered incidentally on screening CT scans. Although these lesions rarely display malignant transformation, they pose a significant diagnostic dilemma despite advances in radiographic imaging modalities. Endoscopic ultrasound is often limited by insufficient specimen collection and the preoperative diagnosis often becomes quite difficult. Enucleation of tumor is typically a sufficient therapeutic modality however radical resection is often required to establish the definitive diagnosis.

Funding Sources: None



2 cm exophytic pancreatic tail lesion



Histopathology showing spindle cells and nuclear palisading

82

Internal Medicine Residency Training: Is It Time to Focus on POCUS?

Authors: Rouse, Michael[1]; Pandya, Sahil[2]; Thomas, Laura[3]

Author Affiliations: [123]University of Kansas Health System, Department of Internal Medicine

Introduction:

Point-of-care ultrasound (POCUS) is rapidly gaining an evidence-based support to compliment traditional management techniques for common diagnoses treated by Internal Medicine (IM). In evaluation of programs, most residents feel POCUS is a crucial skill to acquire during residency, yet most feel that training is insufficient. While University of Kansas Internal Medicine residency program currently does provide POCUS sessions instill confidence in skill acquisition, they are not consistent. For POCUS training, a longitudinal ultrasound curriculum should be considered for increased knowledge retention however many barriers exist including adequately trained faculty for ongoing supervision and feedback.

Methods:

Surveys were sent to PGY1-3 categorical Internal Medicine residents during the end of the 2021-22 academic year. Questions gauged interest in POCUS, current frequency and satisfaction of POCUS in didactics and rounding, and importance for POCUS training for residency and for post-graduate practice.

Results:

43 of 69 IM categorical residents completed the survey (62%). Most residents were either very interested (53%) or somewhat interested (26%) in POCUS. Most reported POCUS was used rarely (53%) or only occasionally (40%) in didactics or rounding with most either not at all satisfied (44%) or slightly satisfied (35%) with the level of exposure. Most felt POCUS it was important for residency training (75%) and in their future role as an attending physician (68%) (Figure 1).

Conclusion:

IM categorical medicine overall have a strong interest in POCUS and feel it is important to their current training and post graduate practice, yet current exposures for didactic and rounding are not consistent. This information is being used to enhance POCUS training for IM residents through increased didactic and clinical rounding applications. These educational enhancements will focus on a longitudinal approach to increase likelihood of knowledge retention and improve consistency. Additional efforts to increase attending physician proficiency in POCUS will be required. Follow up surveys will be needed to evaluate the success of these implementations.

Funding Sources: none

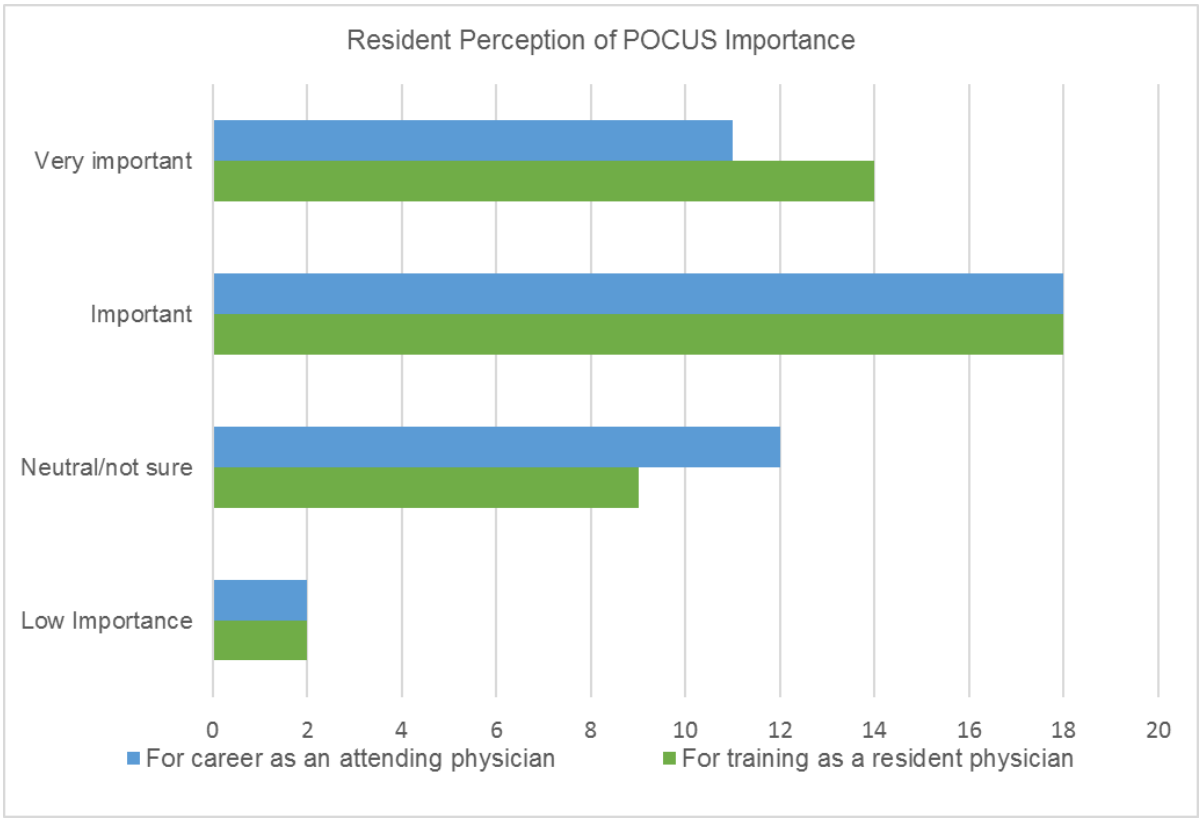


Figure 1. Importance in POCUS training for resident and post-graduate practice (n=43)

83

The Impact of Caregiver Physical Activity on Physical Activity Levels of Adults with Alzheimer's Disease and Related Dementia

Authors: Chang, Joy [a,b]; Helsel, Brian[c]; Sherman, Joseph[a]; Ptomey, Lauren[a]

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[b] Division of Physical Activity and Weight Management, Department of Internal Medicine, University of Kansas Medical Center

[c] Department of Neurology, University of Kansas Medical Center

Introduction:

The purpose of this project is to examine the association between daily minutes of moderate to vigorous physical activity (MVPA) and sedentary time between adults with Alzheimer's disease and related dementia (ADRD) and their caregiver.

Methods:

Adults with ADRD and their caregiver wore accelerometers (ActiGraph GT3X) over a 7-day period to monitor physical activity. Accelerometer data was considered valid if participants had at least 4 days with 8 hours of wear time. Spearman correlations were calculated, and linear regression was used to examine the relationship of MVPA and sedentary time between adults with ADRD and their caregiver after controlling for age, sex, and race

Results:

Valid data was obtained from 65 adults with ADRD (~73 years of age, 36.9% female, 93.8% non-Hispanic white) and their caregiver (~69 years of age, 69.2% female, 89.2% non-Hispanic white). Adults with ADRD sedentary time (rho = 0.54, $p < 0.001$) and MVPA (rho = 0.34, $p = 0.006$) were positively correlated with their caregiver's sedentary time and MVPA, respectively. When controlling for age, sex, and race, there was evidence that caregiver sedentary time ($b=0.74$, $p< 0.001$) and MVPA ($b=0.20$, $p=0.047$) predicted adults with ADRD sedentary time and MVPA.

Conclusion:

There is evidence that caregiver sedentary time and MVPA are positively associated with sedentary time and MVPA in adults with ADRD. For every 5 minutes of MVPA that caregivers obtain, adults with ADRD will participate in an additional minute of MVPA. Future research should investigate if interventions targeting increased caregiver MVPA can effectively increase MVPA of adults with ADRD.

Funding Sources: National Institute of Aging (AG061187)

84

Effect of Telehealth Delivery of Weight Management by (Allied) Health Professionals in Rural Areas

Authors: Gorczyca, Anna[1]; Washburn, Richard[1]; Ptomey, Lauren[1]; Mayo, Matthew[2]; Krebill, Ron[2]; Sullivan, Debra[3]; Gibson, Cheryl[1]; Lee, Robert[4]; Stolte, Sarah[1]; Donnelly, Joseph[1]

Author Affiliations:

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[2] Department of Biostatistics and Data Science

[3] Department of Dietetics and Nutrition

[4] Department of Population Health

Introduction:
Weight management delivered by university affiliated interventionists has shown clinically relevant weight loss in rural adults; however, this approach is unsustainable. Thus, we evaluated a telehealth weight loss intervention delivered by personnel associated with rural health clinics, e.g., nurses, registered dietitians, or allied health professionals trained by members of our weight management research team to adults with overweight/obesity.

Methods:
Personnel (n=6) were trained to deliver weight management (6-mos. weight loss, 12 mos. maintenance) that included education/behavioral counseling, reduced energy diet and increased physical activity. Interventionists were provided training with a detailed intervention notebook, a 1-day on-site session at each clinic and 4 one-hour sessions delivered via Zoom®. Rural adults (BMI= 35 kg/m^2, 82% female) were randomized (2:2:1) to 1 of 3 intervention arms: group phone (GP, n=71), individual phone (IP, n=80) or enhanced usual care (EUC, n=36). Identical interventions were delivered weekly by GP (~45 min, 12-15 participants) or IP (~15 min) across 6 mos. Participants in the EUC arm attended 1- 45 min. in-person session at baseline and were provided with printed materials on healthy eating, portion size and physical activity. An intent-to-treat analysis with multiple imputation for missing data (1-way ANOVA followed by 2 pairwise t-tests) was used evaluate our primary aim, weight change across 6 mos. (GP vs. IP and IP vs. EUC).

Results:
Clinically relevant weight loss was observed in the GP (-11.4 ± 6.7 kg, 11.7%) and the IP arms (-9.1 ± 6.8 kg, 9.2%) but not in the EUC arm (-2.6 ± 4.8 kg, 2.5%), with statistically significant differences between arms ($p < 0.0001$). Specifically, 6 mo. weight loss was significantly greater in the IP vs. EUC arms (6.5 kg, 97.5% CI [-9.8 to -3.2] but did not differ between the GP and IP arms (2.4 kg, 97.5% CI [-5.2 to 0.48]. Participant per session intervention delivery costs were ~ $7, $14, and $42 for the GP, IP and EUC arms, respectively.

Conclusion:
Weight management delivered by personnel associated with rural health clinics via telehealth represents a low-burden, affordable option that if implemented has the potential to provide weight management to underserved residents of rural areas with overweight/obesity.

Funding Sources: DK108372

85

OSCE with a twist of RIME: Objectively differentiating students in a clinical setting

Authors: Fink, Jennifer MD; Rouse, Michael DO; Newman, Jessica DO

Author Affiliations: University of Kansas Medical Center

Introduction/Background:
The implementation of the ACE (Active, Competency-Based, Excellence-Driven) curriculum at the University of Kansas School of Medicine required an objective assessment of clinical knowledge. For the internal medicine (IM) clerkship, prior to the 2021-22 academic year, this evaluation included the National Board of Medical Examiners subject exam and a two-station standardized patient encounter. In a comprehensive analysis we determined that the assessment was limited to evaluation of students' competency in the 'reporter' level of the RIME (reporter-interpreter-manager-educator) framework. Our clerkship aimed to create an observed standardized clinical encounter (OSCE) to allow for improved differentiation of the students' level of proficiency in more advanced clinical reasoning representative of their clinical experiences. At the start of the 2021-2022 AY, we implemented a tri-campus 5-station OSCE which included assessment of skills deemed vital to IM: an oral presentation, progress note documentation, clinical reasoning, data interpretation, and management. One specific goal of this change was to assess student perception of the OSCE as realistic and at the appropriate level of difficulty.

Methods:
Following the creation of the 2021-2022 OSCE, a five-question Likert item satisfaction survey was administered to the students.

Results:

Stations 1 and 2 (Dale Miller) portrayed a realistic patient encounter for reporting/presenting a patient's history and physical exam	Stations 3 and 4 (Karen Bjerke) portrayed a realistic patient encounter for interpreting new patient information and developing a problem list	Station 5 (Regina Watson) portrayed a realistic patient encounter for providing medical decision making based on emerging information	Adequate time was provided to complete the OSCE stations	Overall difficulty of the OSCE
4.39	4.48	4.29	3.86	2.46
Q1-Q4		Q5		
Strongly Disagree	1	Very difficult	1	
Somewhat Disagree	2	Somewhat difficult	2	
Neutral	3	Neutral	3	
Somewhat Agree	4	Somewhat difficult	4	
Strongly Agree	5	Very easy	5	

The qualitative five-point Likert survey data analysis showed each station provided a realistic patient encounter while evaluating different clinical elements through the lens of the RIME framework. The average score was 4.29, 4.39, 4.48 on each station with ‘4’ being somewhat agree and ‘5’ being strongly agree. Additionally, the average score for difficultly of the OSCE was 2.46/5 with ‘2’ being somewhat difficult and ‘3’ neutral.

Conclusion:
The RIME framework has been shown to be an effective tool to evaluate levels of student learners in a clerkship. Use of the new five-station comprehensive IM OSCE better incorporated multiple clinical skills that are required for comprehensive history and physical examination performance, effective communication, data analysis and clinical reasoning. Students completing the OSCE felt that that the level of difficulty was appropriate and was reflective of skills they were required to demonstrate during their clerkship. Further analysis is underway to analyze the impact on score distributions.

Funding Sources: Academy of Medical Educators Grant 2021

86

Recognizing and Responding to Microaggressions: A case-based discussion session to promote a culture of inclusivity

Authors: Meyers, Kyle; Broxterman, Jane; Long, Larry; Lowry, Becky; Sparkman-Barnes, Lynette; Thomas, Laura; and Brubacher, Marie

Introduction:

The ACGME requires residency programs to include policies and programs that encourage optimal resident well-being. Incidences of bias and microaggressions in the clinical setting are prevalent, experienced disproportionately by trainees from underrepresented minorities and are associated with symptoms of burn-out and psychologic distress.

Methods:

Our aim was to increase resident recognition of microaggressions and to provide strategies to respond with when these offenses to occur. Objectives included, identify how verbal assaults take form via explicit bias and microaggressions, appreciate how patient-driven verbal assaults create a conflict of interest for clinicians and negatively impact provider wellbeing and review strategies to support ourselves and our peers. Prior to the session, residents participated in the online Harvard Implicit Association Test. A power point presentation was followed by 90 minutes of discussion on 6 case examples involving patient or physician driven microaggressions targeting race, religion, gender and sexual orientation and gender identity. The session was moderated by a chief resident, faculty member and behavioral health psychologists.

Results:

After the program, residents received a 4 question post-survey. One individual suggested every other year training, “so that people wouldn’t get burnt out having such deep discussion”. In response to the question “How beneficial was this training on a scale of 1-10 (+)?”, the median response was 7. Interestingly, 2 responders selected 1 with an associated comment, “This should not be a part of our training as physicians. Please do not force us to sit through it again”.

Discussion

Promoting a culture of inclusion to foster resident wellness is a priority at our training program. We developed a structured program with reflection and discussion aimed at understanding the prevalence of bias and microaggressions and providing strategies to support ourselves and peers. In general, the session was well received but concerns regarding the utility and intensity of the session were raised. We feel this reinforces the importance of addressing microaggressions and bias but underscores that this is deeply personal and emotionally charged subject for some. We better appreciate the challenges faced by our trainees from under-represented groups and the importance of addressing bias and incidences of microaggressions.

Funding Sources: None

87

Title: A PSMA Dilemma in the Setting of Co-occurring Malignancies

Authors: Rooney, Anthony; Nagji, Alykhan; Chen, Ronald; Parikh, Rahul

Author Affiliations: University of Kansas Medical Center

Case Description:

The availability of prostate-specific membrane antigen (PSMA) targeted imaging has dramatically changed the landscape for localization and staging of prostate cancer. In the OSPREY study (which in conjunction with the CONDOR study led to the approval of the first commercially available PSMA PET imaging agent, 18F-DCFPyL) the specificity of this agent for identifying pelvic nodal involvement in high-risk prostate cancer patients undergoing radical prostatectomy and pelvic lymphadenectomy was 94.5-99.4% and the positive predictive value for patients with suspected recurrent/metastatic prostate cancer was estimated at 73.7 – 90.2%. However, in the time that this agent has been available for clinical use, numerous case reports have highlighted a growing number of entities, both benign and malignant, which have been associated with radiotracer uptake on PSMA-directed imaging. Additionally, PSMA expression has been identified in cancer types other than prostate cancer including conventional renal cell carcinoma, colon, breast, transitional cell carcinoma (bladder), testicular-embryonal, and neuroendocrine tumors. Accordingly, the specificity of PSMA based testing for identifying metastatic prostate cancer in patients with more than one malignancy is likely reduced. Herein we report the case of a 74-year-old man with a remote history of localized renal cell carcinoma s/p nephrectomy who presented with biochemical recurrence of prostate cancer after radical prostatectomy for locally advanced disease. PSMA PET (18F-DCFPyl) at the time of biochemical recurrence demonstrated a hypermetabolic left upper lobe lung nodule concerning for metastatic disease. Pathology from a wedge resection of his left upper lobe lesion revealed metastatic renal cell carcinoma. This case highlights the importance of obtaining tissue for histopathologic confirmation of metastatic disease to guide anti-neoplastic therapy in patients for whom PSMA-directed imaging may have reduced specificity.

Funding Sources: N/A

88

Trends of Access to Early Phase Clinical Trials in Underrepresented Populations During the COVID-19 Pandemic

Authors: Balmaceda, Julia[1]; Mudaranthakam, Dinesh Pal[4]; Krebill, Hope[2]; Doolittle, Gary[3]; Sun, Weijing[4]; Lin, Tara[2]; Jewell, Andrea[2]; Parikh, Rahul[3]; Saeed, Anwaar[3]; Abbasi, Saqib[2]; Jensen, Roy[4]; Baranda, Joaquina[2]

Author Affiliations: 1University of Kansas, School of Medicine, Kansas City, KS; 2University of Kansas Cancer Center-Clinical Research Center, Fairway, KS; 3University of Kansas Cancer Center, Westwood, KS 4University of Kansas Cancer Center, Kansas City, KS

Introduction:
As the only NCI designated cancer center in the region, it is the mission of University of Kansas Cancer Center (KUCC) to lead efforts to reduce the cancer burden affecting our catchment area. KUCC serves a total population of 4.5 million; 96 counties (78%) and 25% of the population are rural based upon Rural-Urban Continuum Codes (RUCC). Notably, Kansas is a non-Medicaid expansion state and many rural individuals live at or below the poverty level. All but 12 of the 123 counties in KUCC catchment area are primary care Health Professional Shortage Areas by geographic and/or population standards. Paradigm-changing clinical trials (CT) are critical for high quality cancer care, and access to early phase trials should not be contingent on geographic location. Here we report early phase clinical trial participation for rural and underrepresented populations at our cancer center.

Methods:
At the KUCC, all the clinical trials and their accrual information are centrally tracked in a clinical trial management system (CTMS, powered by WCG Velos). All data elements are standardized across every clinical trial that the KUCC executes. For this research study, we have extracted data from the CTMS system across every early phase study that had an enrollment from 2016 to 2021.

Results:
Between 2016 and 2021, the KUCC recruited 98, 82, 145, 220, 178, and 175 patients respectively by year to early phase clinical trials. In 2016, 3% of participants were from a minority racial group, 6% were Hispanic, and 19% were from a rural community. In 2021, 9% of participants were from a minority racial group, 1.7% were Hispanic and 14% were from a rural community.

Conclusion:
Despite the impact COVID-19 had on healthcare systems, the University of Kansas Cancer Center has maintained clinical trial accrual of rural and racial minority patients. Sustaining these efforts for expansion of early-phase will give more patients access to potentially life-saving treatments. Further expanding access to these populations will cast a wider net for screening potential patients in an era of precision medicine.

Funding Sources: NIH: 3P30CA168524-09S2, George and Floriene Lieberman Endowment

89

Definitions for Acute Hepatic Porphyria: an International Delphi Consensus

Authors: Mansour, Razan[1]; El-Mikati, Ibrahim; Sandberg, Sverre[2]; Stein, Penny[3]; Edel, Yoni[4]; Mustafa, A. Reem[1]

Author Affiliations: [1]The University of Kansas, [2]Norwegian Porphyria Centre, [3]King's College Hospital, [4]Samson Assuta Ashdod University Hospital

Introduction:
Despite the extensive published literature on acute hepatic porphyrias (AHPs); some terms regarding acute hepatic porphyria remain ambiguous and are frequently used when diagnosing and managing patients with AHP. This study aims to establish clear definitions for nine AHP related terms.

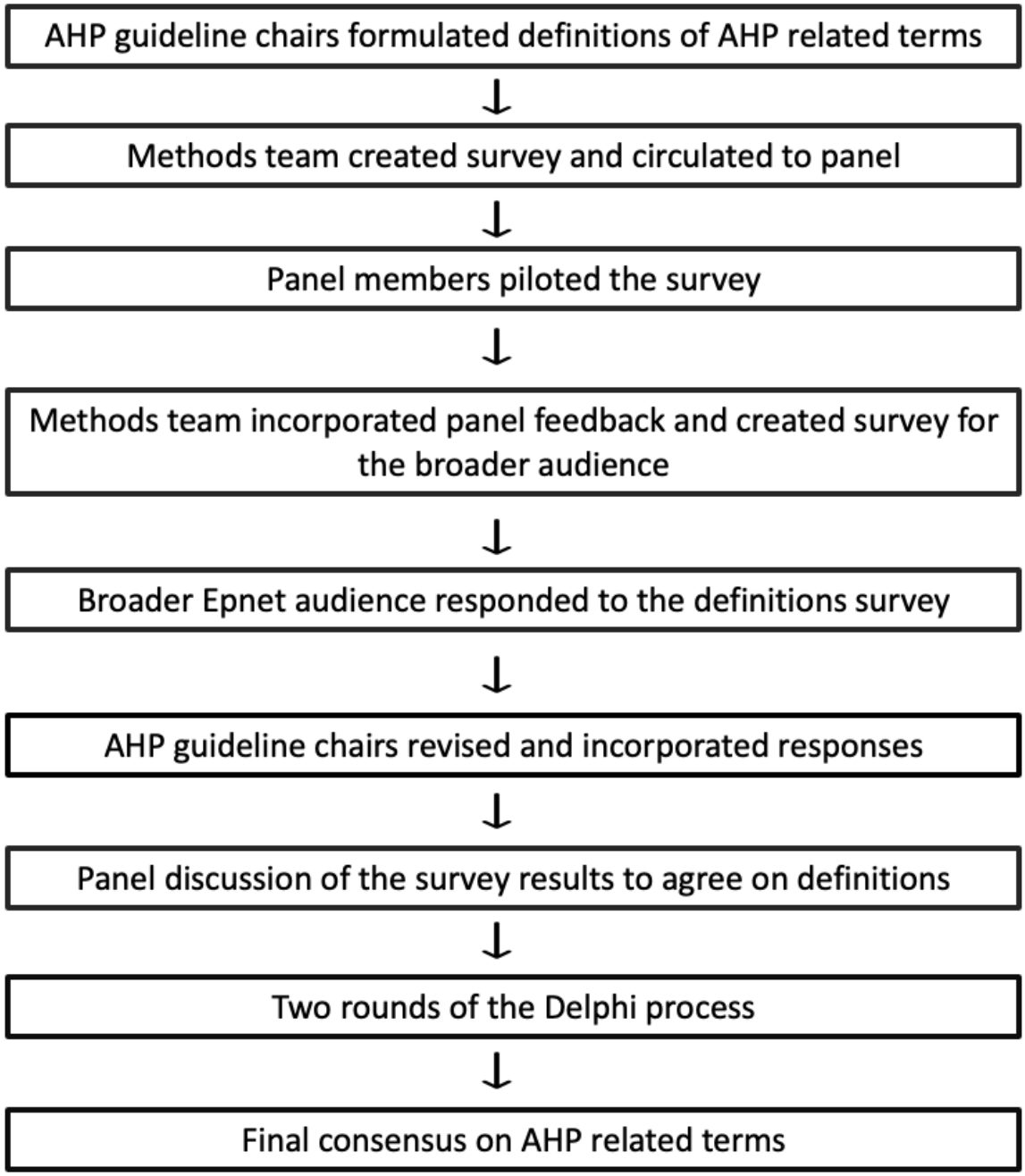
Methods:
The study implemented a Delphi method and took place in two phases to establish definitions for AHP related terms: the brainstorming phase, and the Delphi rounds phase. Figure-1 illustrates the steps that the authors followed to reach consensus for AHP related definitions. An panel group of 35 experts contributed to both phases of the Delphi rounds which consisted of narrowing down and quantifying the definitions in a formal consensus process.

Results:
A total of nine definitions entered the first Delphi round. Response rates in the first survey were 85% (30/35). Seven acute hepatic porphyria terms had > 70% agreement on definitions, and two terms had < 70% agreement. The clinical chairs incorporated the comments of the expert panel group, and three new proposed definitions then entered the second round of Delphi. There were 31 responses to the definitions in the second survey. The response rate in the second round was 88% (31/35). all definitions in the second survey achieved a percentage agreement of >70%, divided as follows: Acute porphyria attack: 74%, Latent (inactive) acute hepatic porphyria: 74%, and Asymptomatic acute porphyria (in remission): 77.8%. Table-1 summarizes the final consensus of definitions on acute hepatic porphyria terms.

Conclusion:
The Delphi process have been used in the medical literature to establish definitions on various medical issues, with the intention to better the understanding on these topics and address gaps in the clinical setting. Consensus now exists on a framework for the definition of AHP terms. This should aid development of practice guidelines, clinical trial design, and clinical management.

Funding Sources: This research was supported by the European Porphyria Network

Figure-1: Summary of the methods utilizing a Delphi consensus process on the definitions of acute hepatic porphyrias.



90

Interventions to Enhance Communication Between Providers and Patients with Limited English Proficiency: A Systematic Review of Randomized Controlled Trials

Authors: Mansour, Razan[1], Brown, David[2], Mustafa, A. Reem[1], LeMaster W. Joseph[1]

Author Affiliations: [1]The University of Kansas Medical Center, [2]The University of Kansas School of Medicine

Introduction:
In the United States, there is substantial ethnic and linguistic diversity that may contribute to significant communication barriers between patients and providers. Available literature does not assess the impact of interventions on patient-provider communication. Our aim was to review current interventions to enhance communications between health care providers and patients with limited English proficiency (LEP).

Methods:
Data sources: We retrieved studies from Embase, Wiley Cochrane, and MEDLINE published up until February 2022. Additional relevant studies were utilized from listed references in other systematic reviews related to our topic. In this systematic review, e sought to identify existing randomized controlled trials that demonstrated successful interventions that improved communication between providers and patients with limited English proficiency. We included studies that had published results that reported intervention effects in a distinct language discordant population; or in which ≥ 80% of the study population reported limited

Results:
The search identified a total of 2,497 articles, of which 136 were used in full text synthesis. After full text review, we included 84 articles for data extraction. Most studies were conducted in the United States (n = 74; 88.09%). Few studies were conducted before the year 2000. Seventy-five (89.28%) studies listed a funding source whereas 10 (11.9%) studies did not. The median sample size was 218 (interquartile range 100-447). Seventy-two (85.71%) studies explicitly reported an eligibility criterion. Eighty-three of the RCTs (98.8%) had a parallel RCT design. We defined a logical framework by a typology of outcomes, as well as types of interventions in each study. In terms of intervention, most studies utilized interventions related to individual patient behaviors or measured changes in healthcare systems/processes.

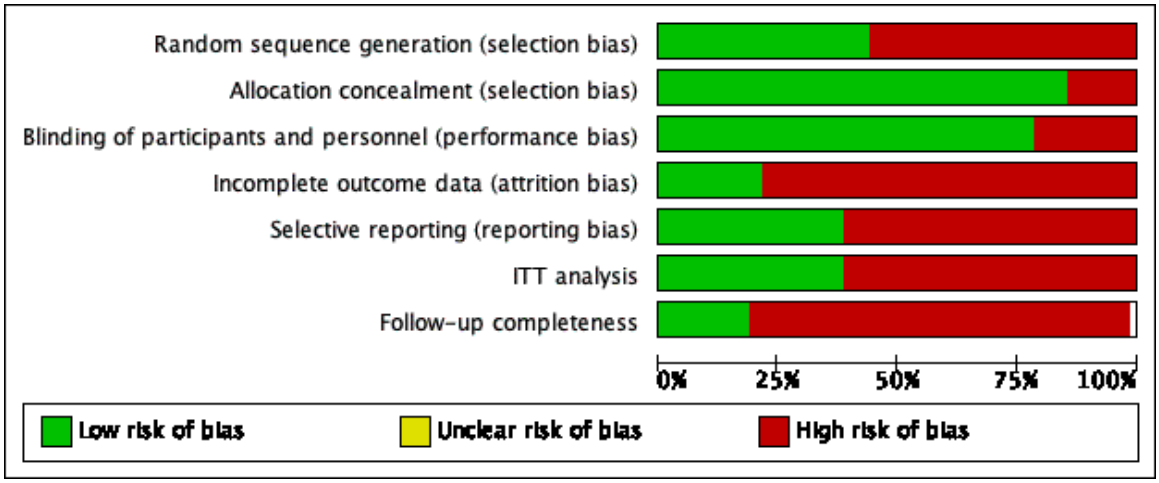
Conclusion:
Use of interventions that included forms of counseling or patient education had the most success in improving patient-provider communication. Additionally, studies which utilized one-on-one interaction with patients had more successful outcomes. Assessed interventions did not address their impact on patient-provider communication.

Funding Sources: None

Table 1: Summary of the outcome and intervention categories among the included studies

Outcome categories	Development or change of condition Biomarkers Knowledge Attitude Skills/behaviors Healthcare system process outcomes
Intervention categories	Language services Counseling (In-person interviews) Counseling (Phone) Counseling (Web/virtual) Education (Providers) Education (Patients-written materials) Education (Patient-AV) Education (Patient-classes) CHW Ed (Materials) CHW Ed (Interactive classes) Care Coordination Complex interventions (Multiple interventions)

Figure 1. Risk of Bias for the included studies



91

A Chilling Diagnosis

Authors: Hegde, Vishwajit[1]; Royer, Gavin[2]; Spikes, Leslie[3]

Author Affiliations: The University of Kansas

Case Description:

Hypothermia is defined as a core body temperature below 35°C and can have multiple etiologies including environmental, infectious, metabolic, and neurologic processes. Due to the multifactorial nature of temperature regulation, when a patient presents with hypothermia it is important to consider a broad differential. We present an interesting case of a patient with hypothermia, pancytopenia, and bradycardia who was initially felt to be septic. However, upon further review of the patient's entire clinical picture, a neurological process was felt to be more likely, and the patient was ultimately found to have hypothalamic dysplasia driving his symptomatology.

Funding Sources: None

93

Impact Of Changing Tacrolimus Formulation On Cerebral Blood Flow And Cognitive Function

Authors: Mahaparn, I.; Lepping, R.; Montgomery, R. N.; Mukherjee, R.; Billinger, S.; Brooks, W. M.; Gupta, A.

Author Affiliations: University of Kansas Medical Center (KUMC), Kansas City, KS

Introduction:

Cognitive impairment is common among kidney transplant (KT) recipients. Most KT recipients are on calcineurin inhibitor therapy to prevent rejection. Calcineurin inhibitors such as tacrolimus are inherent vasoconstrictors. Vasoconstriction can reduce cerebral blood flow (CBF), and negatively impact cognitive function, and cerebrovascular response to exercise. The once-daily extended-release (LCP) tacrolimus has fewer side effects than immediate release (IR) tacrolimus. The role of calcineurin inhibitors and the impact of specific formulation of tacrolimus on CBF, cognitive function, and cerebrovascular response to exercise is unknown. In this pilot study we assessed whether changing from IR tacrolimus to LCP tacrolimus modulates CBF, cognitive function, or cerebrovascular response to exercise in KT recipients.

Methods:

In this proof-of-concept pilot study we enrolled 30 stable KT recipients on IR tacrolimus and randomized them to intervention (switch to LCP tacrolimus) and control (continue IR tacrolimus) in a 2:1 ratio. We measured CBF, cognitive function, and cerebrovascular response to exercise at baseline and at 12 weeks. We used ANCOVA to evaluate changes in outcome variables, with baseline values and study arm as covariates. We used descriptive statistics with mean changes in outcome variables and spaghetti plots to compare the two groups.

Results:

Participants were 52±13 years old. There was no difference in plasma tacrolimus levels at baseline and at 12 weeks in the two arms. CBF was higher in the LCP tacrolimus arm than the control arm. Similarly, the change in cognitive function was more favorable in the LCP tacrolimus arm. The resting middle cerebral artery velocity decreased in both arms, but the decrease in the LCP tacrolimus arm was less than the control arm.

Conclusion:

Changing IR tacrolimus to LCP tacrolimus may improve CBF and cognitive function in KT recipients. Larger studies are needed for conclusive results.

Funding Sources: Veloxis Pharmaceuticals, NIH K23 (to A. Gupta), S10 RR29577, P30 AG072973, P30 DK106912

94

Early cyst formation leads to the development of an inflammatory microenvironment and tissue remodeling in polycystic kidney disease

Authors: Chakraborty, Anubhav[1,4]; Parnell, Stephen C.[2,4]; Zhang, Yan[3,4]; Daniel, Emily A.[3.4]; Raman[3.4], Archana; Reif, Gail[3.4]; Wallace, Darren P.[1,3.4]

Author Affiliations: [1]Department of Cell Biology and Physiology, University of Kansas Medical Center, Kansas City, KS, USA
[2]Department of Biochemistry and Molecular Biology, University of Kansas Medical Center, Kansas City, KS, USA
[3]Internal Medicine, University of Kansas Medical Center, Kansas City, KS, USA
[4]Jared Grantham Kidney Institute, University of Kansas Medical Center, Kansas City, KS, USA

Introduction:

Polycystic kidney disease (PKD) is a genetic disorder characterized by the formation and growth of numerous fluid-filled cysts. BRAF, a kinase that activates MEK-ERK signaling, is a central intermediate for cAMP-induced cell proliferation and cyst growth in PKD. Recently, we showed that collecting duct (CD)-specific expression of active $BRAF^{V600E}$, a common activating mutation ($BRaf^{CD}$), was sufficient to induce renal cyst formation in an otherwise normal mouse. A key pathological feature of PKD is the development of interstitial inflammation and fibrosis, leading to a decline in renal function. Our hypothesis is that cyst formation induces an inflammatory microenvironment early in the renal cystic disease.

Methods:

To examine changes in gene expression due to cyst formation, we performed RNA sequencing on 3-week-old cystic kidneys from $BRaf^{CD}$ mice and $Pkd^{RC/RC}$ mice, an orthologous, slowly progressive model of PKD. Kidneys from 3-week-old wild-type mice were used as controls. Pathway analysis was used to identify common pathways affected during initial cyst formation due to active BRAF-MEK-ERK signaling and mutated *Pkd1*.

Results:

We found that 566 out of 641 differentially expressed genes (DEGs) in the BrafCD kidneys were also changed in the $Pkd1^{RC/RC}$ kidneys (out of 840). Enrichment analysis indicated that inflammation, cytokine response, tissue fibrosis, and remodeling were some of the top activated pathways and cellular functions (FDR<0.05; Z-score>2). 88 of the 566 common DEFGs were identified as inflammatory genes (Fold Change ≥1.5; FDR<0.05), including elevated expression of tumor necrosis factor-alpha (TNFα), toll-like receptor 8, and interleukin-34. The renal tubule injury marker neutrophil gelatinase-associated lipocalin (NGAL, LCN2) and tissue remodeling factors such as MMP-8, mucins (MUC5B, MUC15), lipase family member K, glutathione peroxidase 5, and protease inhibitors (cystatin-11 and -12, serine peptidase inhibitor) were also upregulated.

Conclusion:

Renal cyst initiation due to active BRAF or mutated *Pkd1* was associated with elevated gene expression of markers for inflammation and tissue remodeling prior to the overt cystic disease, suggesting that cystic cells contribute to the early development of an inflammatory microenvironment.

Funding Sources: This work was supported by a grant from the National Institute of Diabetes and Digestive and Kidney Disease (R01DK081579; DPW).

95

Hypogammaglobulinemia Following Anti-CD20 Therapy: Retrospective Analysis of Patient Risk Factors

Authors: Wesson, William, MPH[1]; Ng Stephanie[1]; Love, Marissa, MD[2]; Gierer, Selina, DO[2]

Author Affiliations:

1) University of Kansas School of Medicine, Kansas City, KS
2) Division of Allergy, Clinical Immunology & Rheumatology, University of Kansas Medical Center, Kansas City, KS

Introduction:
Rituximab, an anti-CD20 biologic depletes peripheral B-cells, preventing production of antibodies. Some patients subsequently develop persistent hypogammaglobulinemia resulting in serious infections requiring the use of prophylactic antibiotics or immune globulin supplementation. We suspect this patient subset may have unmasked primary immunodeficiencies presenting after rituximab exposure. In our retrospective review, we characterized risk factors used to identify patients at risk of rituximab induced immunodeficiency who may benefit from monitoring surrounding rituximab therapy.

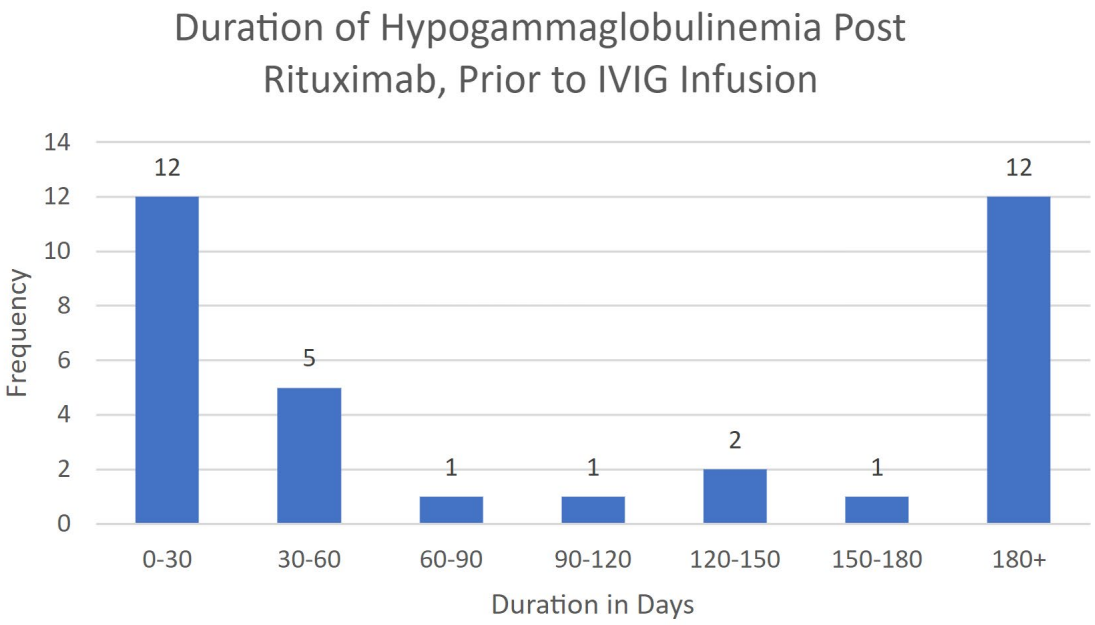
Methods:
A retrospective case review of fifty adult patients from an allergy and immunology outpatient clinic was conducted. Patients included had previously received rituximab and immune globulin supplementation. Patient charts were reviewed for immune evaluation prior to rituximab treatment and to determine if they met criteria for Common Variable Immunodeficiency (CVID) prior to versus post rituximab therapy.

Results:
A retrospective case review of fifty adult patients from an allergy and immunology outpatient clinic was conducted. Patients included had previously received rituximab and immune globulin supplementation. Patient charts were reviewed for immune evaluation prior to rituximab treatment and to determine if they met criteria for Common Variable Immunodeficiency (CVID) prior to versus post rituximab therapy.

Conclusion:
A retrospective case review of fifty adult patients from an allergy and immunology outpatient clinic was conducted. Patients included had previously received rituximab and immune globulin supplementation. Patient charts were reviewed for immune evaluation prior to rituximab treatment and to determine if they met criteria for Common Variable Immunodeficiency (CVID) prior to versus post rituximab therapy.

Funding Sources: None

	No. (%) of Patients
Characteristic	**Total (N = 50)**
Gender	
Male	20 (40)
Female	30 (60)
Race/Ethnicity	
White	43 (86)
Black	4 (8)
Non-White Hispanic	2 (4)
Pacific Islander	1 (2)
Immunoglobulin Screening	
Prior to Rituximab	22 (44)
Only Post Rituximab	28 (56)



96

A Sticky Situation: Case Series of Successful treatment of Glue Ear with Dupilumab

Authors: D'Mello, Andrea F.[1]; Kaur, Snimar[2]; Everist, Brynn E.[3]; Gierer, Selina A.[1]; Ator, Gregory A.[4]

Author Affiliations: [1]Division of Allergy, Clinical Immunology and Rheumatology, University of Kansas Medical Center, Kansas City, KS, [2]Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India, [3]Kansas City Allergy & Asthma Associates PA [4]Department of Otolaryngology, Head and Neck Surgery, University of Kansas Medical Center, Kansas City, KS

Introduction:

Dupilumab, a monoclonal antibody that binds and inhibits the interleukin-4 receptor alpha subunit, is FDA approved for use in atopic dermatitis, asthma, and chronic rhinosinusitis with nasal polyposis. Currently, it is being investigated for treatment of conditions associated with eosinophilic inflammation. We present a case series of three patients with allergic rhinoconjunctivitis and recurrent episodes of glue ear otitis who had promising therapeutic relief with use of dupilumab. Patients had a multi-year history of chronic glue ear otitis with numerous medical and surgical interventions without resolution, including near systemic steroid dependence. While presence of eosinophilic inflammation was not diagnostically proven in these cases, treatment with dupilumab demonstrated positive outcome.

Methods:
A retrospective study assessed data from three patients, including comorbidities, duration of recurrent chronic glue ear otitis, relevant diagnostic studies, medical and surgical interventions.

Results:
After a minimum of three doses of dupilumab, all patients reported subjective improvement with decreased ear drainage and improved hearing. Fewer episodes of glue ear otitis were reported and none of the patient's required treatment with systemic steroids. Moreover, repeat audiogram demonstrated improvement in previously noted hearing loss after initiation of dupilumab.

Conclusion:
Dupilumab may be a novel, effective, and non-surgical treatment option for patients with chronic otitis media with effusion (glue ear otitis) and underlying atopic conditions. This case series is the first to highlight the positive clinical impact of dupilumab when used in patients with glue otitis media. The role of dupilumab for treatment of glue ear otitis needs further investigation.

Funding Sources: None

97

Cryptochrome stabilizer KL001 attenutes house dust mite allergen-induced epithelial barrier function in human bronchial epithelial cells

Authors: Duraisamy, Santhosh Kumar; Srinivasan, Ashok Kumar; Sundar, Isaac K.

Author Affiliations: Department of Internal Medicine, Division of Pulmonary, Critical Care and Sleep Medicine, University of Kansas Medical Center, Kansas City, KS, USA

Introduction:
House dust mite (HDM) is a common allergen known to disrupt the airway epithelial barrier leading to dysregulated immune response, resulting in allergic lung diseases such as asthma. Circadian clocks are known to regulate several physiological processes such as epithelial barrier function and inflammatory response. Prior study shows circadian clock gene cryptochrome (CRY), interacts with the immune system to regulate inflammatory disorders such as rheumatoid arthritis. Currently, it remains unclear whether HDM-induced epithelial barrier dysfunction can be attenuated by stabilizing CRY using the small molecule KL001 in human bronchial epithelial cells.

Methods:
We measured epithelial barrier function by monitoring transepithelial electrical resistance (TEER) using an xCELLigence real-time cell analyzer in 16-HBE cells. Cells were grown in 96-well e-plates to measure TEER 0-48 hrs post-treatment in Control (untreated), HDM (50 µg/ml), KL001 (20µM) alone, and KL001+HDM (pretreated with CRY stabilizer for 4 hrs) groups. Additionally, we employ immunostaining followed by confocal microscopy to determine HDM-induced delocalization of tight junction (TJ: Occludin and Zonula occludens 1) and adherence junction complex (AJC: E-cadherin and β-catenin) proteins in 16-HBE cells 24 hrs post-treatment. Finally, we measured mRNA and protein levels of core circadian clock targets and epithelial barrier function markers by quantitative real-time PCR (qRT-PCR) and Western blot analyses.

Results:
HDM-induced epithelial barrier dysfunction was confirmed by significantly reduced TEER at 12-24 hrs. However, KL001 pre-treatment attenuates HDM-induced epithelial barrier function (TEER) until 12-24 hrs. Confocal microscopy revealed that HDM-induced delocalization of TJ and AJC proteins was attenuated in the KL001+HDM group. Similarly, qRT-PCR and Western blotting analyses in the KL001+HDM group showed modulation of specific TJ (Occludin and ZO-1) and AJC proteins (E-cadherin) and core circadian clock genes (Bmal1, Cry1/2, and Rev-erbα) at the mRNA and protein levels.

Conclusion:
Small molecule KL001 shows protection against HDM-induced epithelial barrier dysfunction (**Fig. 1**). The exact molecular mechanism by which KL001 mediates protection either directly by stabilizing CRY or indirectly via other clock-independent mechanisms remains unclear. Studies like this will further enable us to determine whether clock-based therapeutics can be used to treat inflammatory lung diseases such as asthma and allergic rhinitis.

Funding Sources: This work was funded by the NIH R01 HL14253 and KUMC, School of Medicine, Internal Medicine Start-Up Funds.

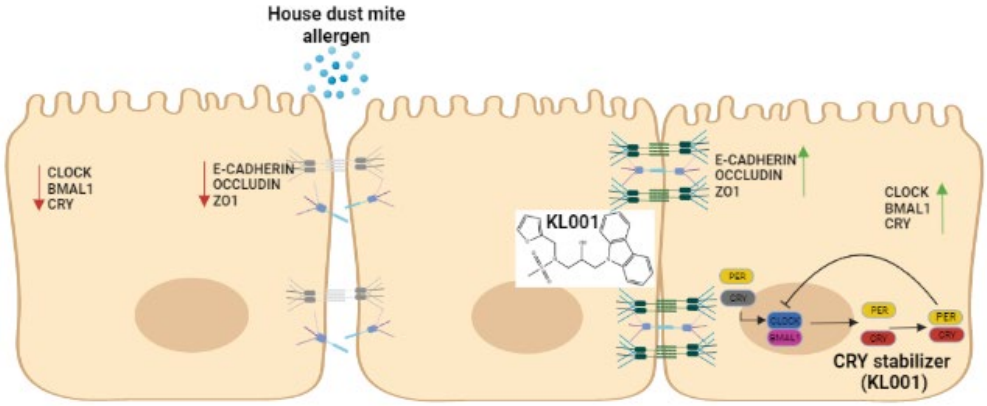


Fig. 1. Small molecule KL001 treatment attenuates HDM-induced barrier function in human lung epithelial cells.

98

Rev-erbα agonist attenuates house dust mite and Th2 cytokine-mediated epithelial barrier dysfunction in human bronchial epithelial cells

Authors: Duraisamy, Santhosh Kumar; Srinivasan, Ashok Kumar; Castro, Mario; Sundar, Isaac K.

Author Affiliations:
Department of Internal Medicine, Division of Pulmonary, Critical Care and Sleep Medicine, University of Kansas Medical Center, Kansas City, KS, USA

Introduction:
House dust mite (HDM) and Th2 cytokines (IL-4 and IL-13) drive allergic lung diseases such as asthma and allergic rhinitis resulting in altered epithelial barrier function and dysregulated immune response. Prior reports demonstrate the intricate role of circadian clock molecules that regulate epithelial barrier function and immune response. Rev-erbα is a key circadian molecule that regulates physiological processes such as inflammation, metabolism, and immune response. There are no studies that demonstrate whether activation of Rev-erbα/β using specific synthetic ligands (Rev-erb agonists) can protect against HDM and Th2 cytokine-mediated epithelial barrier dysfunction in human bronchial epithelial cells.

Methods:
We utilized the xCELLigence real-time cell analysis-based electrical impedance measurement to monitor HDM and Th2 cytokine-mediated change in transepithelial electrical resistance (TEER) in 16-HBE cells. Cells were grown in 96-well e-plates to confluency to measure TEER in Control (untreated), HDM (50µg/ml), Rev-erb agonists (GSK4112/SR9009/SR9011; 20µM) or antagonist (SR8278 20µM) alone and Rev-erb agonist/antagonist+HDM (pretreated for 4 hrs) groups. Finally, we measured markers of epithelial barrier function tight junction protein (TJ: Zonula occludens 1) and adherence junction complexes (AJC: E-cadherin and β-catenin) by immunostaining followed by confocal microscopy 24 hrs post-treatment.

Results:
HDM and Th2 cytokines caused a significant change in the TEER at 24- and 48-hrs post-treatment in 16-HBE cells (**Fig. 1**). However, pre-treatment with Rev-erb agonists (GSK4112, SR9009, SR9011) for 4 hrs along with HDM or Th2 cytokines showed a differential response in attenuation of epithelial barrier dysfunction via augmented expression of AJC and TJ proteins confirmed by confocal microscopy. Pre-treatment with Rev-erb agonists+HDM showed attenuation of epithelial barrier function markers, and SR8278+HDM showed a synergistic response in modulating TJ and AJC protein expression.

Conclusion:
We for the first-time report that Rev-erb agonists that activate Rev-erb(s) protect against HDM and Th2 cytokine-induced epithelial barrier dysfunction. The exact molecular mechanism for Rev-erb agonist-mediated protection still needs to be investigated which may have implications for the treatment of allergic lung diseases.

Funding Sources: This work was funded by the NIH R01 HL14253 and KUMC, School of Medicine, Internal Medicine Start-Up Funds.

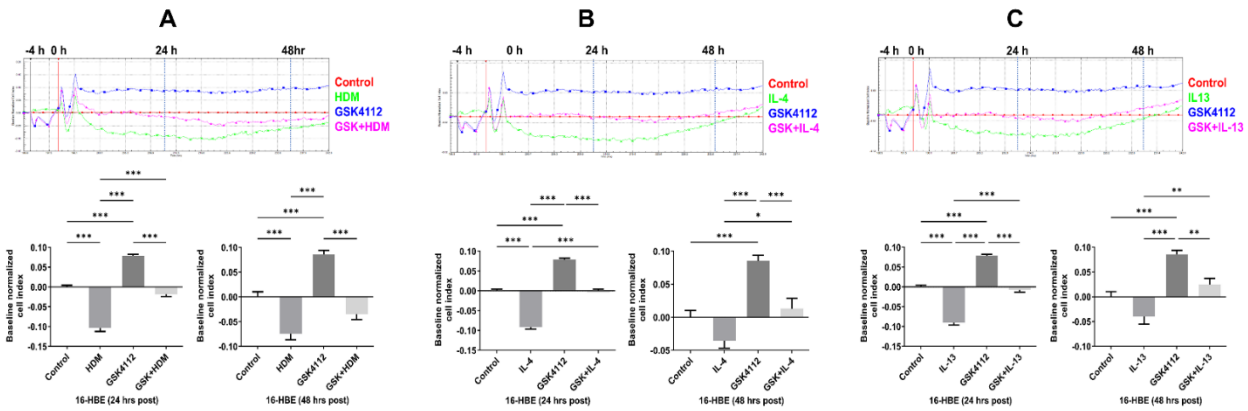


Fig. 1. Rev-erb agonist GSK4112 attenuates HDM and Th2 cytokine-induced epithelial barrier function in human bronchial epithelial cells.

99

A Comparison of Nutrient Intake between Weight Loss Diets for Adolescents with IDD

Authors: Rachel N.S. Foster, Lauren T. Ptomey, & Joseph E. Donnelly

Author Affiliations: University of Kansas Medical Center - Division for Physical Activity and Weight Management

Introduction:
Adolescents with intellectual and developmental disabilities (IDD) are more likely than neurotypical youth to be obese. Researchers evaluated the impact of two weight loss diets on energy intake, consumption of fruits/vegetables (F/V), added sugars, and whole grains in adolescents with IDD participating in a 6-mo. weight loss intervention.

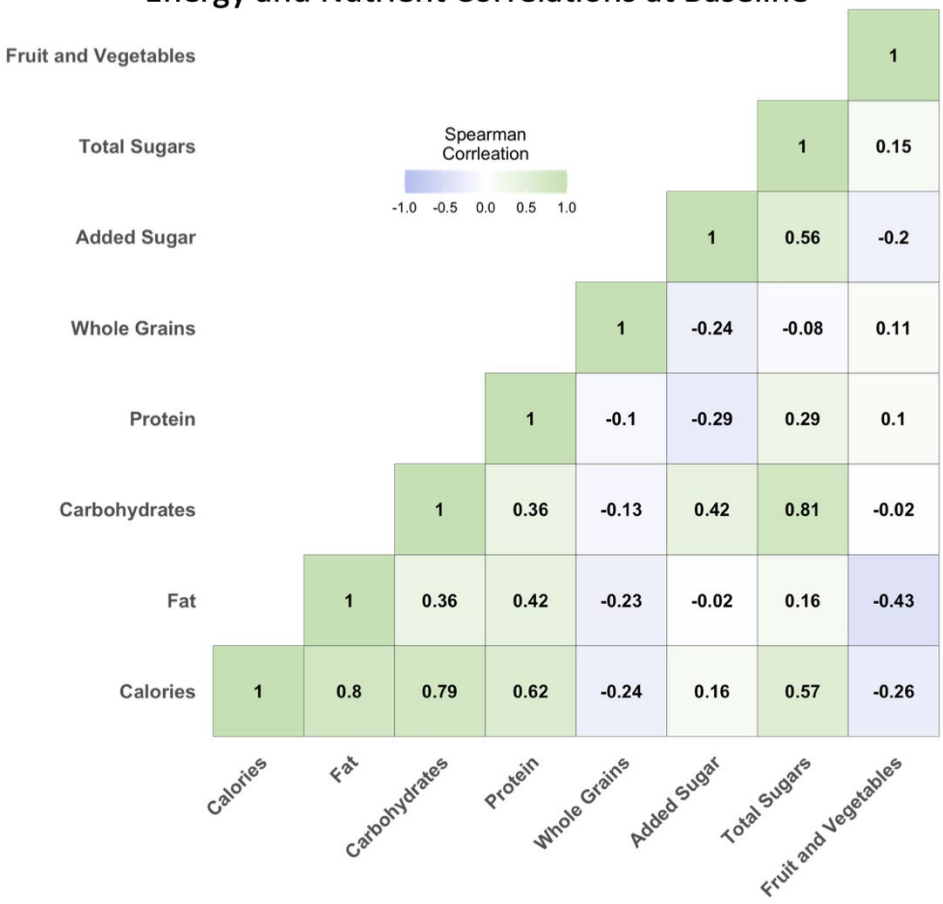
Methods:
This is a secondary analysis of data from a 6-mo. trial in adolescents with IDD randomized to a reduced energy (500-700 kcal below estimated daily energy expenditure) enhanced stop light (eSLD) or a conventional meal plan diet (CD). The eSLD categorized foods by energy density and was enhanced with portion-controlled entrées, shakes, and ≥5 servings of F/V per day. The CD followed the US dietary guidelines and recommended consumption of ≥5 servings of F/V per day. Dietary data obtained from 3-day food records collected at baseline and 6 mos. were entered into NDSR 2017 for analysis.

Results:
Adolescents (N=74, 57% female, *M*age=15.90) were randomized to the eSLD (n=35) or CD (n=39) groups. Food records were obtained from 44 participants at baseline (eSLD=20, CD=24) and 6 mo. (eSLD=14, CD=15). Baseline consumption: 1887 kcals, 4.49 servings of F/V, 58.5g of added sugar, and 1.17 servings of whole grains/day in the eSLD group and 1787 kcals, 3.75 servings of F/V, 52.95g of added sugar, and 1.31 servings of whole grains in the CD group. There were no differences in energy, F/V, or added sugar at baseline or 6 mo. (all $p>0.05$). Consumption of whole grains was higher in the eSLD group compared with the CD group at 6 mo. ($p=0.04$). Mann-Whitney U tests showed energy and added sugar intake decreased 16% ($p=0.08$), and 36% ($p=0.02$) in the eSLD group, and 21% ($p=0.007$) and 66% ($p=0.03$) in the CD group from baseline to 6 months, respectively. Whole grains increased for the eSLD group ($p=0.19$) and decreased in the CD group ($p=0.16$) from baseline to 6 mo. F/V intake increased in the eSLD group ($p=0.86$) and in the CD group from baseline to 6 mo. ($p=0.007$).

Conclusions:
Both diets are efficacious in reducing energy intake and improve aspects of diet quality in adolescents with IDD.

Funding Sources: NIH R01 HD079643

Energy and Nutrient Correlations at Baseline



Diet Change from Baseline to Six Months

	Enhanced Stoplight Diet		Conventional Diet	
Variables	Baseline n = 15[1]	6 months n =15[1]	Baseline n = 17[1]	6 months n = 17[1]
Energy (kcals)	1,803.29 ± 445.85	1,636.11 ± 347.29	2,023.33 ± 437.14	1,512.17** ± 306.53
Total Fat (g)	71.97 ± 28.50	55.24* ± 17.72	82.08 ± 21.89	63.14 ± 23.26
Total Carbs (g)	228.15 ± 58.06	220.89 ± 57.23	225.37 ± 60.43	174.59** ± 51.50
Total Protein (g)	67.02 ± 32.71	74.65 ± 26.03	74.00 ± 19.61	66.73 ± 14.44
Whole Grains (oz)	0.63 ± 0.69	1.09 ± 1.00	0.56 ± 0.50	0.44 ± 0.41
Added Sugar	0.13 ± 0.06	0.10 ± 0.06	0.12 ± 0.06	0.08* ± 0.04
Total Sugar	103.06 ± 37.63	102.43 ± 48.53	105.30 ± 38.85	68.64** ± 30.39
Fruits & Vegetables	1.24 ± 0.79	1.80* ± 1.25	1.24 ± 0.79	1.36 ± 0.79

[1]Mean ± SD; *p<0.05; **p<0.01

100

Associations between Obesity and Alzheimer's Disease Risk Factors in Adults with Down Syndrome

Authors: McGrevey, Danica[a,b]; Helsel, Brian[c]; Danon, Jessica[a]; Sherman, Joseph[a]; Donnelly, Joseph[a]; Ptomey, Lauren[a]

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Introduction:

Most adults with Down Syndrome (DS) will develop pathology associated with Alzheimer's disease (AD). Evidence in adults without DS suggest that obesity is a significant risk factor for AD, however, this has not been explored in adults with DS. The purpose of this study was to examine the association of obesity, assessed by BMI, on factors related to AD risk including cognitive function, moderate to vigorous physical activity (MVPA), and cardiorespiratory fitness in adults with DS.

Methods:

This is a secondary analysis using baseline data from a physical activity trial in adults with DS. Participants attended a single laboratory visit where BMI, cardiorespiratory fitness ($V0_2Max$), and cognitive function (CANTAB® DS Battery) were obtained. Physical activity, assessed by accelerometer, was collected for the 7 days following the laboratory visit. The cognitive function outcomes included the first attempt memory score (higher score indicates better cognitive function) and multitasking cost, simple reaction time, and five-choice reaction time scores (lower scores indicate better cognitive function). Spearman correlations and linear regression were used to measure the associations between BMI, cardiorespiratory fitness, MVPA, and cognition.

Results:

Data was collected for 57 adults with DS (27.9 ± 9.1 years of age, 54% female, 56% with obesity). Cardiorespiratory fitness (rho = -0.74, $p<0.001$), MVPA (rho = -0.33, p=0.024), and multitasking cost (β = -22.3; p=0.004) were negatively correlated with BMI. Additionally, cardiorespiratory fitness was negatively associated with multitasking cost (β = -20.2, p=0.03) and MVPA had a significant positive association with first attempt memory score (β = 0.2, p=0.02).

Conclusion:

Results of the study suggest that a higher BMI is associated with decreased cardiorespiratory fitness and MVPA and increased cognitive function in adults with DS. Additionally, higher cardiorespiratory fitness and MVPA were associated with better cognitive function. Further research is needed to better examine the direct relationship between BMI and cognitive function; however, the results of this study point to an indirect relationship between BMI and cognitive function.

Funding Sources: National Institute of Aging (AG036909)

101

Community based virtual group exercise program for the promotion of physical activity in adults and adolescents with intellectual and developmental disabilities

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Introduction:

Adults and adolescents with intellectual and developmental disabilities (IDD) participate in less physical activity (PA) than typical developing peers. Several barriers including transportation and trained exercise staff prohibit regular PA for this population. The purpose of this program was to assess the feasibility of a weekly fee for service live virtual group exercise class to adults (>18 years of age) and adolescents (13-17 years of age) with IDD in the community to promote PA and social interaction in a group setting.

Methods:

PA classes were delivered remotely over Zoom by trained staff and 5 health profession students 2 days/wk for 12-months. Classes consisted of a warmup and cool down and ~25-30 minutes of aerobic based PA. Class satisfaction and self-reported improvements related to PA and socialization were measured at 3-month intervals by both the participant and caregiver.

Results:

Thirteen participants (1 adolescent, 12 adults) enrolled in the program with an average of 9 active participants a month. Participants who enrolled in the program for at least 3 months attended ~78% of classes offered. Participants reported an average class satisfaction score of 92% and an average self-improvement score of 87%. Caregivers reported an average class satisfaction score of 88% and an average participant improvement score of 74%.

Conclusion:

Attendance at the group class and participant/caregiver satisfaction and self-improvement scores demonstrate that a community based virtual group PA program may be a feasible approach for the promotion of PA and social interaction for adults and adolescents with IDD.

Funding Sources: None

102

Preliminary Analysis of a Ring-Fit Adventure Session among Adults with Down Syndrome

Authors: Suire, Kameron; Sherman, Joseph; Helsel, Brian; Rice, Annie; Ptomey, Lauren

Author Affiliation: University of Kansas Medical Center, Division of Physical Activity

Introduction:

Participation in physical activity among adults with Down syndrome (DS) is extremely low. Adults with DS face unique barriers to participation in physical activity including disinterest or inability in participating in typical exercise modes due to gait challenges, self-confidence to exercise with typically developed peers, and affordable/accessible transportation to facilities to participate in MVPA. Exergaming, which integrate MVPA into video game play, represent an affordable, accessible, non-traditional home-based exercise mode that has been shown to increase physical activity in typically developed populations. The purpose of this study was to determine the feasibility using a novel exergaming platform, Ring-Fit Adventure™ in adults with DS.

Methods:

Adults with DS were asked to play Ring-Fit Adventure for ~15 minutes while wearing a portable accelerometer and being observed by research staff. Approximately ~7 minutes were spent learning how to use the game and ~8 minutes were spent in active play. Immediately after gameplay, participants completed a survey asking about their experiences and satisfaction with the game. The exercise physiologist who observed each session was also asked to complete a survey about each participant asking about safety concerns and potential feasibility.

Results:

15 adults with DS (*M* age = 23, 33% female) completed the feasibility study. The accelerometer data indicated participants obtained 4.74 ± 2.43 minutes of light physical activity and 3.32 ± 1.85 minutes of MVPA, during the 8 minutes of active play. No participant fell or became unstable during the gameplay. Participant surveys indicated that 13 (87%) participants reported “highly enjoying” the gameplay and 14 participants (93%) felt they could play the game at home without getting hurt. The observing exercise physiologist felt all 15 participants (100%) could play the game safely at home with varying levels of support.

Conclusion:

Ring-Fit Adventure™ appears to be a safe and enjoyable form of physical activity adults with DS. Future, research is warranted to assess the effectiveness of Ring-Fit Adventure in adults with DS to increase MVPA across time.

Funding Source: N/A

103

Does Sildenafil Improve Endothelial Dysfunction in Rheumatoid Arthritis? – A Pilot Clinical Trial

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Introduction:

Rheumatoid arthritis (RA) is independently associated with an increased cardiovascular disease (CVD) risk. One of the early stages of atherosclerosis is endothelial dysfunction. Using drugs like sildenafil to target endothelial dysfunction is a promising novel CVD prevention strategy in RA. Our objective was to determine if sildenafil use in RA improves endothelial dysfunction (as measured by brachial artery flow-mediated dilation [FMD] and peripheral arterial tone [PAT]), as well as serum vascular biomarkers.

Methods:

This was a phase II, randomized double-blind placebo-controlled crossover trial of 25 RA patients, with no known CVD, but at least one traditional CVD risk factor. Patients were randomized 1:1 to receive either sildenafil or placebo for 3 months, then after a 2-week washout, crossed over to each respective group for 3 months. Vascular studies (FMD and PAT) and serum vascular biomarkers (e-Selectin, ICAM-1, VCAM-1) were performed at baseline, 3 months pre- and post-washout, and 6 months. Adverse events were collected. Given the cross-over design, analyses included a random effects model for within-subject comparisons of sildenafil versus placebo periods, adjusting for the baseline variable within that period and a term for treatment order. All tests were 2-sided with $\alpha=0.05$.

Results:

233 subjects were screened; 25 subjects were randomized. 13 subjects were randomized to placebo first; 12 to sildenafil first. Baseline characteristics were similar between groups. Mean

age was 62.0+/-10.9 years; 84% female; and 92% white. Six adverse events occurred. The primary endpoint (increase in %FMD in Sildenafil vs. Placebo periods) was not significant (p=0.19). However, sildenafil use was associated with a significant increase by 0.200 units of PAT ratio (p=0.003), adjusted by treatment order and baseline PAT ratio. Exploratory linear mixed models comparing vascular biomarkers between Sildenafil vs. Placebo periods, adjusted for treatment order and the baseline biomarker level, did not show significant differences except for ICAM-1 (55.3 units higher in Sildenafil vs. Placebo periods, p=0.011).

Conclusion:

Sildenafil was associated with a significant improvement in endothelial function as measured by PAT. The study is limited due to small sample size. Future larger studies are required to assess whether PDE5 inhibitors may improve endothelial dysfunction in RA.

Funding Sources: NIH/NIAMS grant number R21AR069174-03

104

The Diagnostic Value and Clinical Significance of Myositis-Specific Antibodies in Patients Suspected to Have Autoimmune Myopathies and/or Autoimmune Rheumatic Diseases

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Introduction:
Myositis-specific antibodies (MSA) are thought to be highly specific in patients with idiopathic inflammatory myopathies.[1] However, in clinical practice these antibodies are frequently found in the absence of autoimmune myopathy which may lead at times to unnecessary interventions and treatments. We sought to determine the frequency of final clinical diagnoses, including autoimmune myopathy, in patients tested positive for one or more MSA.

Methods:
We conducted a retrospective chart review on patients with documentation of MSA testing from November 1, 2007 to December 31, 2019 in our academic center.

Data extracted included clinical variables (myalgias, muscle weakness, interstitial lung disease (ILD) and history of malignancy within 3 years of positive antibody test) and laboratory tests including anti-nuclear antibodies and creatine kinase. Electromyographic testing and skeletal muscle biopsy studies were reviewed. Patients with a neuromuscular or autoimmune rheumatologic diagnosis were identified. A neuromuscular specialist determined the presence or absence of an autoimmune myopathy based on CK level, weakness, EMG and muscle biopsy findings when available. Frequency of associated clinical diagnoses in patients with positive MSA were calculated. In addition, we reviewed the frequency of certain clinical diagnoses specifically with anti-synthetase antibodies.

Results:
We identified 47 subjects with positive MSA. Thirty-three (70%) were females. Thirty-four (72%) were Caucasian. Only 16 out of 47 subjects (34%) with positive MSA had an autoimmune myopathy. Among subjects with positive MSA but no autoimmune myopathy (n=31), 26 (83.8%) had ILD and/or a rheumatologic diagnosis and 5 (16.1%) had neither. In patients with autoimmune myopathy (n=16), there was an overlap with ILD and/or rheumatologic diagnosis in 5 patients (31.25%). Of all subjects with positive MSA (n=47), 31 (65.9%) had a rheumatologic diagnosis and/or ILD. Five (10.6%) did not have a rheumatologic diagnosis, autoimmune myopathy or ILD. Anti-synthetase antibodies were found in 19 subjects. These antibodies were associated with autoimmune myopathy in 7 subjects (36.8%). Anti-synthetase syndrome was diagnosed in only 5 (26.3%) with positive anti-synthetase antibodies while a rheumatologic diagnosis was present in 12 (63.1%). Among patients with positive anti-synthetase antibodies and autoimmune myopathy (n=7), perimysial pathology on muscle biopsy was found in 4 (57.1%).

Conclusion: Despite the reported specificity of MSA for the diagnosis of autoimmune myopathy, we observed that most MSA positive subjects in our cohort did not have this diagnosis. We also found that rheumatologic diagnoses and ILD were frequently found in patients with positive MSA with or without autoimmune myopathy. Similarly, anti-synthetase antibodies did not necessarily indicate the presence of anti-synthetase syndrome or autoimmune myopathy.

Funding Source: NA

Positive myositis specific antibody	Number of patients (n = 47)
With autoimmune myopathy n= 16	
Autoimmune myopathy alone	11 (68.75)
Autoimmune myopathy + ILD	2 (12.5%)
Autoimmune myopathy + Rheumatologic diagnosis	1 (6.25%)
Autoimmune myopathy + both ILD and rheumatologic diagnosis	2 (12.5%)
Without autoimmune myopathy n= 31	
ILD alone	5 (16.1%)
Rheumatologic diagnosis alone	7 (22.5%)
Both ILD and Rheumatologic diagnosis	14 (45.1%)
Patient with no ILD or rheumatologic diagnosis	5 (16.1%)

Positive myositis-specific antibodies in comparison to clinical diagnoses

105

Evolution in Resource Utilization for Unique Toxicities Related to Chimeric Antigen Receptor T Cell Therapy from 2017 to 2020: A Database Review

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Introduction:

CD-19 CAR-T therapy was FDA approved in 2017 for relapsed/refractory diffuse large B-cell lymphoma and acute lymphoblastic leukemia ≤ 26yr old. One of the hallmark toxicities associated with CAR-T therapy is cytokine release syndrome (CRS). Treatment involves tocilizumab, an interleukin-6 antagonist for CRS and steroids for ICANS. Management of higher-grade CRS and ICANS typically involves intensive care unit (ICU) admission and management.

We completed a retrospective review using the Vizient database® to investigate toxicity incidence and resource utilization in patients who received CAR-T therapy between 2018 and 2020.

Methods:

The Vizient® CDB database was used to analyze CAR-T recipient for patients over 18 years of age receiving commercial CD19 CAR-T axicabtagene ciloleucel (axi-cel) and tisangenlecleucel (tisa-cel) between 2018 to 2020. We compared patients who received CAR-T therapy between October 2017 to March 2018 (group 1) to the patients who received CAR-T therapy between October 2019 and March 2020 (group 2). With no available diagnosis code for CRS or ICANS till 2021, billing codes of clinical surrogates such as fever, sepsis, dyspnea, febrile seizure, febrile convulsions, altered mental status, somnolence, stupor and coma were used. Other adverse events such as weakness and nausea were also captured.

Results:

There were 81 institutions that had performed CAR-T therapy in the period 2018 through 2020. The 2017-2018 period (group 1) included 215 patients, with median age of 59 (49-68) years while the CAR-T recipients in 2019-2020 (group 2) had 655 patients with median age of 62 (52-69) years. Most patients received Axi-cel in both groups. Fever and dyspnea were the most common presentations of CRS in both groups. The incidence of fever was improved in group 2 (36%) as compared to group 1(44%)(p=-.0263) . Similarly, the incidence of dyspnea was also improved in group 2 (21%) versus group 1 (49%)(p=<0.0001). The incidence of sepsis was also significantly lower in group 2 (13%) compared to group 1(18%) with an absolute difference of 5.8% (P

value=0.04). There was no other statistically significant difference in other signs and symptoms, except nausea, which was improved in group 2 compared to group 1. As for ICANS, while there was a trend of reduced incidence of neurotoxicity in group 2 as compared to group 1, it was not statistically significant (P= 0.2723). Overall, the ICU utilization was similar, 24.7 vs 24.6% in both groups (p=0.9). The 30 days mortality was similar in both groups, at 6% vs 3.7%. The dosing of tocilizumab decreased by 20% and dexamethasone or equivalent steroid decreased by 70% in group 2 as compared to group 1 (Table 1).

Conclusions:

The incidence of CRS and ICANS in patients receiving CAR-T therapy remains high with up to one-fourth of patients needing ICU care at some point during their hospitalization which has not changed. Interestingly, we note that the utilization of tocilizumab and steroids has decreased by 20% and 70% respectively, which implies better understanding of supportive care and improvement in the implementation of standardized operation protocols for use of these medications. Further study on factors and timing of these medications leading to observed shift in practice are needed.

Funding Sources: None

Table 1: Comparison of Cytokine Release Syndrome presentation between Group 1 (2017-2018) and Group 2(2019-2020)

Variable	Group 1 (October 1st 2017 to March 31st 2018), n= 215, n (%)	Group 1 (October 1st 2019 to March 31st 2020), n= 699, n (%)	Absolute Change, (%)	OR	z-stat	P-value
Median Age (range)	59 (49-68) years	62 (52-69) years				
Type of CAR-T						
Tisa-cel	67 (31%)	182 (26%)				
Axi-cel	148 (69%)	517 (74%)				
Fever	95 (44)	250 (36)	-8.2	0.71	2.222	**P = 0.0263**
Sepsis	39 (18)	88 (13)	-5.6	0.65	2.046	**P= 0.0407**
Hypotension	69 (32)	236 (34)	1.7	1.08	0.454	P = 0.6499
Hypoxia	53 (53)	143 (21)	-4.3	0.78	1.308	P = 0.1908
Dyspnea	105 (49)	150 (21)	-27.3	0.29	7.599	**P < 0.0001**
Nausea	211 (98)	580 (83)	-15.3	0.08	4.628	**P < 0.0001**
Weakness	51 (24)	201 (29)	4.9	1.29	1.442	P = 0.1493
Chills	4 (2)	8 (1)	-0.9	0.54	0.799	P = 0.4245
Neurotoxicity	50 (23)	139 (20)	-3.3	0.81	1.098	P= 0.2723
ICU admission	53 (25)	172 (25)	-0.1	0.98	0.117	P = 0.9067
30 day Mortality	13 (6)	26 (4)	-2.3	0.60	1.462	P = 0.1437
Tocilizumab Units Charged (SU 8mg/Kg)	990	794	-20			
Steroids Units Charged (SU 4mg)	352	107	-70			

Abbreviations: CAR-T; Chimeric Antigen Receptor T cell therapy, CRS; Cytokine Release Syndrome, ICU; Intensive Care Unit, SU; Standard Unit

106

Comparison of Efficacy and Safety Profile of Allogeneic Versus Autologous CD19 Chimeric Antigen Receptor T Cell Therapy in Hematological Malignancies: A Systematic Review and Meta-Analysis

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Introduction:

Chimeric antigen receptor T cell (CAR-T) therapy is an adoptive immunotherapy employing genetically modified T cells. Autologous CD19 CAR-T cell therapy is currently approved B cell malignancies. "Off the shelf" allogeneic CAR-T cells derived from the third party, healthy donors may overcome several barriers to autologous CAR-T cells. We performed a systematic review and meta-analysis to assess and compare the safety and efficacy of allogeneic versus autologous CAR-T cell therapy.

Methods:

Web of Science/MEDLINE/PubMed, Embase, and Cochrane Registry of Controlled Trials were searched following the PRISMA guidelines using MeSH terms and keywords for "Receptors, Chimeric antigen" OR "Artificial-T-cell receptor" OR "immunotherapy, adoptive" OR "CD-19". Our search produced 3506 articles, and after removing duplicates, 2243 records were screened. We included 98 prospective trials of CD-19 CAR-T enrolling two or more patients from Jan 1, 2013 to Nov 1, 2020. Pooled analysis was done using the 'meta' package (R Studio software), and a random-effects model was used to estimate the pooled prevalence with 95% confidence intervals (CI).

Results:

We looked at 98 articles in total including 8 articles for allogenic, 86 for autologous, 4 for donor CAR-T cell. Due to considerable heterogeneity in study populations among these three groups, a comparative analysis was not feasible. (Table 1)

Universal "off the shelf" CART

A total of 68 patients from 8 studies were evaluated. Median age was 22.5 (4.8-64) years and 64% were males (n= 9/14). The median follow-up time was 10 (2-18) months. Underlying diagnosis was ALL 72% (n= 49), chronic lymphocytic leukemia (CLL) 9% (n= 6), and NHL 19% (n= 13). The pooled overall response rate (ORR) was 77% (95%CI 0.63-0.89, I^2 =22%, p=0.25, n=68) with complete response (CR) of 75% (95%CI 0.57-0.90, I^2 =48%, p=0.07, n=65). The pooled incidence of cytokine reactivity syndrome (CRS) grade I/II and grade III/IV was 53% (95%CI 0.16-0.89, I^2 =89%, p<0.01, n=65) and 10% (95%CI 0.01-0.25, I^2 =50%, p=0.06, n=65)

respectively. Neurotoxicity (NT) grade I/II was 12% (95%CI 0.01-0.30, I^2 =47%, p=0.09, n=47) and GvHD grade I/II was 8% (95%CI 0.01-0.19, I^2 =0%, p=0.57 n=53).

Donor CAR-T

A total of 43 patients from 4 studies were evaluated. The median age was 44.5 (3-68) years and 57% were males (n=16/28). Underlying diagnosis was ALL 56% (n=24), NHL 24% (n=10), and CLL 21% (n= 9), The pooled ORR was 47% (95%CI 0.30-0.64, I^2 =0%, p=0.58 n=36), CR was 40% (95%CI 0.26-0.55, I^2 =0%, p=0.48 n=49), PR was 6% (95%CI 0.00-0.16, I^2 =0%, p=0.47 n=49). CRS and NT were not observed except in one study, where 28.5% of the patients experienced grade I/II CRS.

Autologous CAR-T

A total of 2553 patients from 86 studies were evaluated. Median age was 37.5 (9-72) years with the median follow-up time of 8.8 (1.12-57.9) months. The pooled ORR was 80% (95%CI 0.75-0.84, I^2 =79%, p<0.01 n=2000), CR was 68% (95%CI 0.63-0.74, I^2 =85%, p<0.01 n=2441), PR was 15% (95%CI 0.11-0.20, I^2 =70%, p<0.01 n=1337). The pooled incidence of CRS grade I/II and grade III/IV was 47% (95%CI 0.39-0.56, I^2 =91%, p<0.01 n=1965) and 11% (95%CI 0.07-0.14, I^2 =79%, p<0.01 n=2136) respectively. The pooled incidence of NT grade I/II was 11% (95%CI 0.07-0.17, I^2 =83%, p<0.01 n=1347) and NT grade III/IV was 13% (95%CI 0.10-0.18, I^2 =75%, p<0.01 n=1730).

Conclusion:

CAR-T Allogeneic third-party "off the shelf" constructs are currently in phase I and dose escalation trials, and early reported data so far shows promising efficacy signals with similar rates of CRS and NT. While there is a risk of GvHD with the allogeneic constructs (universal and donor-derived) the GvHD was mostly low grade (grade I-II). Given these promising features, readily available "off-the-shelf" third-party constructs, which are still early in development, therefore offer an attractive potential option to overcome manufacturing and access barriers with present-day autologous CAR-T therapy.

Funding Sources: None

Table 1: Combined Table for Autologous/ Allogeneic /Donor T cell CAR-T(n=2664)

Characteristics		Autologous CAR-T	Allogeneic CAR-T	Donor T Cell CAR-T
No. of studies		86	08	04
Total no. of patients (n)		2553	68	43
Median Age years (Range)		37.5(9-72)	22.5 (4.8-64)	44.5 (3-68)
Median Follow Up (Months)		8.8 (1.12-57.9)	10 (2-18)	Not Available
Pooled Overall Response		80% (95%CI 0.75-0.84, I^2 =79%, p<0.01 n=2000)	77% (95%CI 0.63-0.89, I^2 =22%, p=0.25, n=68)	47% (95%CI 0.30-0.64, I^2 =0%, p=0.58 n=36)
Pooled Complete Response		68% (95%CI 0.63-0.74, I^2 =85%, p<0.01 n=2441)	75% (95%CI 0.57-0.90, I^2 =48%, p=0.07, n=65)	40% (95%CI 0.26-0.55, I^2 =0%, p=0.48 n=49)
Pooled partial Response		15% (95%CI 0.11-0.20, I^2 =70%, p<0.01 n=1337)	7% (95%CI 0.00-.025, I^2 =42%, p=0.48, n=38)	6% (95%CI 0.00-0.16, I^2 =0%, p=0.47 n=49)
Pooled Acute GVHD		None	8% (95%CI 0.01-0.19, I^2 =0%, p=0.57 n=53) Grade I/II	10% Grade III/IV (as reported by one study)
Pooled Neurotoxicity	*Grade I/II*	11% (95%CI 0.07-0.17, I^2 =83%, p<0.01 n=1347)	12% (95%CI 0.01-0.30, I^2 =47%, p=0.09, n=47)	None
	Grade III/IV	13% (95%CI 0.10-0.18, I^2 =75%, p<0.01 n=1730)	Not Available	None
Pooled Cytokine Release Syndrome (CRS)	*Grade I/II*	47% (95%CI 0.39-0.56, I^2 =91%, p<0.01 n=1965)	53% (95%CI 0.16-0.89, I^2 =89%, p<0.01, n=65)	28.5% of grade I/II (as reported by one study)
	Grade III/IV	11% (95%CI 0.07-0.14, I^2 =79%, p<0.01 n=2136).	10% (95%CI 0.01-0.25, I^2 =50%, p=0.06, n=65)	None

107

Plasma derived extracellular vesicles from SARS-CoV -2 infected patients induce pulmonary vascular dysfunction in HIV-transgenic rats

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Introduction:
People living with HIV-1 are known to have increased risk of hospitalization and mortality due to COVID-19 compared to the general population. Further it remains unexplored how HIV patients will respond to Long-term effect of COVID. COVID-19 is known to cause endothelial injury, vascular re-modelling, and coagulopathy and we recently reported increased apoptosis of pulmonary microvascular endothelial cells in response to the in-vitro treatment with the circulating extracellular vesicles (EVs) from the COVID-19 patients. Here now we compared the in-vivo effect of these EVs on the pulmonary vascular disease in HIV-Transgenic (HIV-Tg) and wild-type (WT) rats.

Methods:
Plasma derived small extracellular vesicles (10µg) from healthy never-infected volunteers (UI-EVs) and from the hospitalized critically ill COVID-19 patients (Cov-EVs) were injected (i.v) into 8 months old HIV-Tg or WT Fischer male rats every alternative day for 3 weeks. Echocardiography and hemodynamics were performed, followed by harvesting of lung and heart tissues for the analysis of pulmonary vascular remodeling and right ventricle hypertrophy, respectively.

Results:
Comparison of transthoracic echocardiography analysis at the baseline and after 3 weeks of EV treatment showed an increase in the Δ RV/LV end-diastolic area ($p<0.001$) and a decrease in Δ RV/LV ejection fraction($p<0.001$) in the Cov-EV treated HIV-Tg rats whereas no significant change was observed in HIV-Tg rats treated with UI-EVs. However, in case of WT rats the increase in Δ RV/LV EDA($p=0.432$) and decrease in Δ RV/LV EF($p=0.100$) were not significant even when administered with Cov-EVs. In addition, Cov-Ev treated HIV-Tg rats showed significantly increased RVSP ($p<0.001$) and Fulton Index ($p<0.05$), whereas WT rats administered Cov-EVs did not show increased RVSP ($p=0.081$) and Fulton Index ($p=0.7823$) compared to UI-EV treated rats. Correspondingly, medial hypertrophy in small(0-50µm) and medium sized (50-100 µm) pulmonary vessels along with the hypertrophy of cardiomyocyte were observed in the HIV-Tg rats from Cov-EV group. Interleukin-6 and transforming growth factor -Beta (TGF-β) levels were also found to be significantly higher in HIV-Tg rats treated with Cov-EVs vs UI-EV group.

Conclusion:
Overall our findings showing the development of pulmonary vascular dysfunction in HIV-Tg rats treated with plasma derived EVs from COVID-19 patients suggest that co-infections may adversely contribute and increase the risk of developing long-covid.

Funding Sources: NIH Grant RO1DA042715,RO1HL152832

108

Metformin improves HMGB1-induced mucociliary dysfunction in CF airway epithelial cells

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Introduction:
CF-related diabetes mellitus (CFRD) is a major predictor of worse lung function in CF. Hyperglycemia triggers a pro-inflammatory response by inducing expression of damage-associated molecular patterns (DAMP). High mobility group box protein 1 (HMGB1) functions as a DAMP and promotes inflammation. HMGB1 levels are inversely correlated with lung function in CFRD patients. However, how elevated levels of HMGB1 impact mucociliary function remains unclear. We therefore sought to investigate the role of HMGB1 in CF bronchial epithelial (CFBE) cells and test whether metformin could reverse the effects of HMGB1 on mucociliary function.

Methods:
F508del CFBE cells were re-differentiated at the air-liquid interface and cultured in normal glucose (5.5 mM) media. Cells were treated with elexacaftor (1 μM)/tezacaftor (5 μM)/ivacaftor (1 μM) (ETI) with or without metformin (1 μM) for 24h. Recombinant HMGB1 (10 ng/mL) was added basolaterally. CFTR currents were measured in Ussing chambers. ASL volume estimated by meniscus scanning. Ciliary beat frequency (CBF) measured using SAVA. HMGB1 expression measured by ELISA. Gene expression quantified by ddPCR.

Results:
CFBE cells exposed to high glucose (12.5 mM) and treated with ETI for 24h showed a significant increase in CFTR conductance but no improvement in ASL volumes compared to controls. Metformin further increased CFTR activity leading to significant improvements in ASL volumes in ETI-treated CFBE cells under high glucose. Metformin also reduced HMGB1 levels in the basolateral media. Treatment of CFBE cells cultured under normal glucose with HMGB1 caused ASL volume depletion, reduced CBF, and increases in mRNA expressions of *IL1B*, *TGFB1*, and *TNFA* after 24h even in the presence of ETI. Metformin rescued the effects of HMGB1 on ASL volumes, CBF, and the expressions of *IL1B*, *TGFB1*, and *TNFA.*

Conclusion: Our data show that physiological concentrations of HMGB1 can induce inflammation and mucociliary dysfunction even in the presence of ETI. Metformin reverses the effects of HMGB1 on mucociliary dysfunction and inflammation *in vitro*. These data set the stage for clinical trials to test the efficacy of metformin as an anti-inflammatory agent to improve ion channel and mucociliary function in CFRD.

Funding Sources: NIH (R01 HL157942 and R01 HL133240) and CFF (SALATH18I0).

109

Improving Scheduling Efficiency Across Sleep Medicine Clinical Stakeholders: A Preliminary Quality Improvement Study

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Introduction:

Sleep disorders are highly prevalent conditions with relevant public health burden. The Sleep Clinic at the Division of Pulmonary Critical Care and Sleep Medicine is a busy clinical operation with an ever-growing demand to provide care for new patients. Despite the addition of new providers, there is still a shortcoming in access to appointments for patients. Preliminary assessments suggest that that the scheduling processes may be highly heterogeneous, contributing to the lack of access. Consequently, registered nurses (RNs) may be spending additional time on scheduling tasks, removing them away from relevant patient care tasks and contributing to job dissatisfaction. We aimed at establishing a quality improvement process to quantify the proportion of time nurses spend on specific tasks.

Methods:

In partnership with the KUMC Improvement in Research and Clinical Studies program, we mapped our current scheduling workflows for the different types of appointments, sleep studies and care management pathways. Next, we deployed a self-reported task recording instrument to RNs (N=3) and asked them to annotate specific tasks they were conducting at the Sleep Clinic for one week (8/15/2022-8/19/2022). We used descriptive statistics to quantify the number and proportion of different tasks among the selected RNs during the study period, focusing on non-nursing tasks. Non-nursing tasks were identified as tasks that could be delegated to unlicensed staff.

Results:

RNs spent, on average, 51% of their non-nursing task time on scheduling, 20% on telehealth-related tasks, 12% on durable medical equipment downloads, 9% on prior authorizations, 7% on administrative phone calls and 1% on patient reminders during the analyzed week.

Conclusion:

This preliminary quality improvement study identified that RNs spend approximately half of their non-nursing task time on patient scheduling. While the complexities of the scheduling processes in the Sleep Clinic may not allow a large reduction on time spent with scheduling, this study helped identify workflow intervention targets that could partially mitigate this issue, such as the potential

development of clinical algorithms across all sleep medicine stakeholders. Other issues related to access to care and appointment availability were also highlighted through this investigation and will be addressed in future studies.

Funding Sources: University of Kansas Health System, Division of Pulmonary, Critical Care and Sleep Medicine at the University of Kansas Medical Center

110

An mRNA amplifier rescues cigarette smoke-induced mucociliary dysfunction in an *in vitro* COPD model

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Author Affiliations: Department of Internal Medicine, University of Kansas Medical Center, Kansas City, KS, USA

Introduction:
Cigarette smoke (CS) causes impairments in mucociliary clearance and is a leading cause of chronic obstructive pulmonary disease (COPD). COPD is characterized by progressive airway obstruction due to mucus hypersecretion and inflammation of airway epithelial cells. CS increases expression of transforming growth factor beta-1 (TGF-β1), which induces mucociliary dysfunction by negatively regulating the expression of ion channels important for mucus hydration, including the cystic fibrosis transmembrane conductance regulator (CFTR) and large-conductance, Ca^{2+}-activated, and voltage-dependent K^+ (BK) channel. Amplifiers are a class of CFTR modulator that increase CFTR expression by stabilizing *CFTR* mRNA. The current study aimed to examine whether the amplifier nesolicaftor could rescue the effects of TGF-β1 on parameters of mucociliary function in primary human bronchial epithelial cells (HBEC). The study further tested whether nesolicaftor could prevent mucociliary dysfunction induced by CS exposure in an *in vitro* COPD model.

Methods:
We used Ussing chamber experiments for studying ion channel functions, SAVA software for quantifying ciliary beat frequency (CBF), RNA immunoprecipitation (RIP) assay for binding site studies and Fluorescence Recovery After Photobleaching (FRAP) for measuring mucus viscosity.

Results:
Nesolicaftor reversed TGF-β1-induced reductions in CBF and CFTR conductance in primary HBEC. The effects of nesolicaftor were not specific to CFTR as it also rescued TGF-β1-mediated impairments in BK function. Mechanistically, nesolicaftor increased binding of poly(rC)-binding protein 1 (PCBP1) to a consensus sequence in the 3'-UTR of leucine-rich repeat-containing 26 (*LRRC26)* mRNA, which encodes the BK subunit critical for its function, to increase LRRC26 expression. HBEC from smoker COPD donors (COPD-HBEC) were exposed to whole CS of two cigarettes for a total of 12 puffs or to room air. CS exposure of COPD-HBEC caused CFTR and BK dysfunction, resulting in reduced CBF and increased mucus viscosity. Pretreatment of COPD-HBEC with nesolicaftor prevented CFTR, BK, and mucociliary dysfunction caused by CS.

Conclusion:
Collectively, these data demonstrate that nesolicaftor may have beneficial effects in chronic airway disease by improving ion channel function important for mucociliary clearance.

Funding Sources: Flight Attendant Medical Research Institute, CIA #160011; James and Esther King Florida Biomedical Research Program, Grant #5JK02; NIH R01 HL139365, HL133240, and HL157942.

111

Short-term mortality is high in refractory multiple myeloma patients waiting for idecabtagene vicleucel access.

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Introduction:
The survival of relapsed refractory multiple myeloma (RRMM) myeloma is dismal. Idecabtagene vicleucel (ide-cel) is a B cell maturation antigen (BCMA) directed chimeric antigen receptor T cell therapy (CAR-T) therapy, approved on March 26th, 2021, for RRMM patients who failed 4 lines of therapy based on the pivotal phase 2 KarMMa trial. Since its approval, limited access due to limited manufacturing slots has been a universal challenge. At our institution, due to limited manufacturing slots, there were patients who qualified but could not receive ide-cel. We compared the characteristics and survival of eligible patients who could not receive CAR-T due to limited access to those who could receive it.

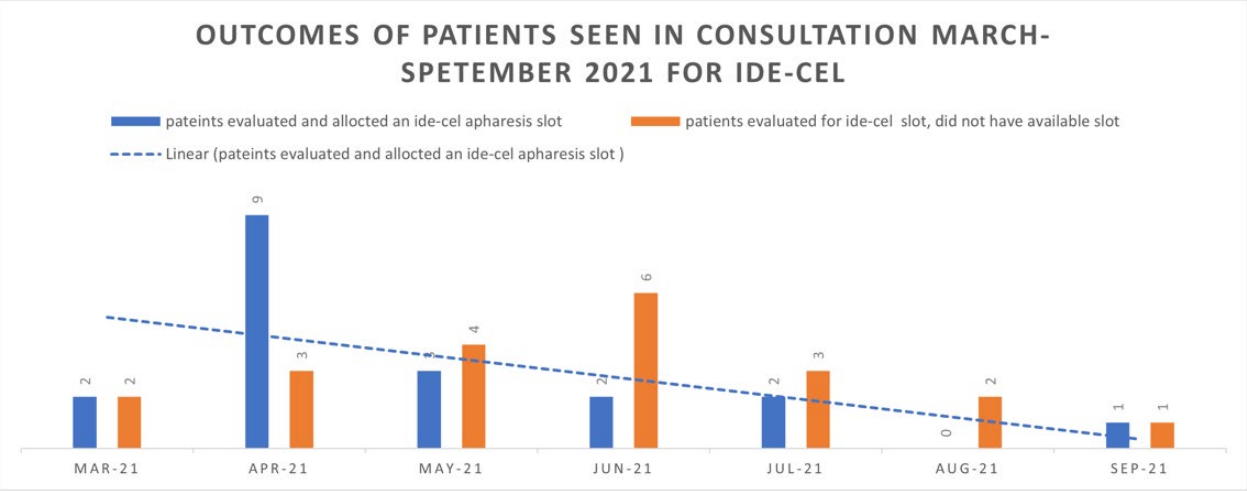
Methods:
All patients evaluated at our center as a consult for ide-cel from 3/30/21 to 9/29/21 were included. Patients who did not qualify based on FDA approval, who did not meet KarMMa enrollment criteria or who chose alternative therapies, were excluded. Patients who qualified were included and divided into two groups based on whether they were able to get an apheresis slot for ide-cel. Survival was calculated from the date of the first consult.

Results:
Between 3/30/2121 and 9/29/21, 54 pts were evaluated for commercially available ide-cel. Of these, 40 patients were eligible for ide-cel. 19 of these eligible patients got an apheresis slot, while 21 patients did not **(Figure 1, 2).** Demographics are shown in **table 1.**
The Median follow-up was 4 months (0-7mo). The median days from the date of consult to the collection was 27 days (8-114). The median days from collection to infusion was 41.5 days (34-91). The most common alternative therapy was belantamab mafodotin (n=8) Median follow-up was 4 mo (0-7mo). Overall survival following CAR-T therapy consult was higher among CAR-T recipients *vs*. those who could not receive it(p=0.03). One death (5.3%) occurred in the ide-cel treatment group with progressive disease and inability to get ide-cel infusion after apheresis due to ongoing respiratory viral infection. Five deaths (23.8%) in the group that did not receive CAR-T, all related to progressive disease and complications of therapy.

Conclusion:
Despite inherent limitations of our single-center experience, the survival advantage seen in the ide-cel group, compared to standard therapies, emphasizes the urgent need for efforts to increase access to ide-cel and other CAR-T constructs for multiple myeloma.

Funding Sources: None

Table 1. Demographics	Idecabtagene vicleucel recipients (n=19)	Patients who did not receive idecabtagene vicleucel (n=21)	*P* value
Gender			
Male	11 (57.8%)	15 (71.4%)	
Female	8 (42.2%)	6 (28.6%)	
Race			
Caucasian	15 (78.9%)	13 (61.9%)	
African American	4 (21.1%)	6 (28.6%)	
Other	0	2 (9.5%)	
Median Age in Years (Range)	61 (43-71)	61 (46-82)	0.87 (NS)
Median Years Since Diagnosis (Range)	7 (1-16)	4 (1-10)	0.14 (NS)
Median Number of Lines of Therapy (Range)	7 (4-13)	5 (4-9)	0.04 (S)
Myeloma Subtype			
IgG Kappa	5 (26.3%)	3 (14.1%)	
IgG Lambda	3 (15.7%)	4 (19.1%)	
Light Chain (Lambda or Kappa)	5 (26.3%)	7 (33.3%)	
Other	6 (31.7%)	7 (33.3%)	
High Risk Cytogenetics per IMWG criteria	6 (31.6%)	9 (42.8%)	
Pentarefractoy	17 (89.5%)	15 (71.5%)	
Prior BCMA Exposure	6 (31.6%)	3 (14.3%)	
Prior Autologous Transplant	16 (84.3%)	14 (66.7%)	
Prior Allogeneic Transplant	3 (15.7%)	0	



112

Precision Therapy for Anaplastic Large Cell Lymphoma: A Bench to Bedside Study

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Introduction:
More than 80% of anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL) patients harbor the (nucleophosmin) NPM1-ALK fusion gene t(2;5) chromosomal translocation. We evaluated the preclinical and clinical efficacy of ceritinib treatment of this aggressive lymphoma.

Methods:
We studied the effects of ceritinib treatment in NPM1-ALK+ T-cell lymphoma cell lines in vitro and examined the effects of ceritinib treatment on tumor size and survival advantage in vivo utilizing tumor xenografts in mouse models. Moreover, we evaluated the clinical response of a NPM1-ALK+ ALCL patient treated with ceritinib in a phase II clinical trial (NCT02186821). We reviewed all hematologic malignancies profiled by a large hybrid-capture NGS based comprehensive genomic profiling assay of 406 genes plus introns from 31 genes commonly rearranged in cancer, as well as RNA for 265 genes for a portion of these cases for ALK alterations.

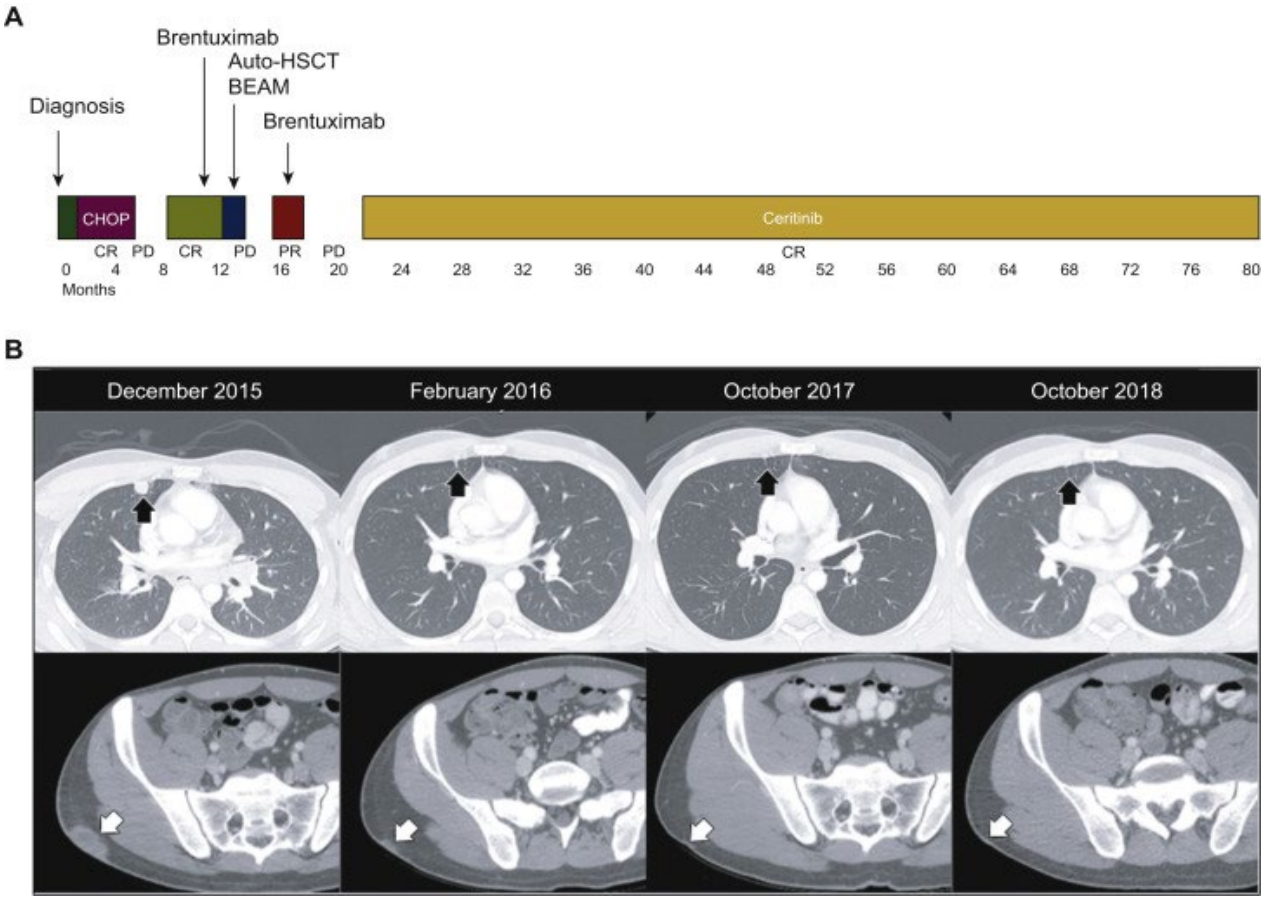
Results:
In our in vitro experiments, ceritinib inhibited constitutive activation of the fusion kinase NPM1-ALK and downstream effector molecules STAT3, AKT, ERK1/2, and induced apoptosis of these lymphoma cell lines. Cell cycle analysis following ceritinib treatment showed G0/G1 arrest with a concomitant decrease in the percentage of cells in S and G2/M phases. Fusion kinase inhibition also resulted in reduced clonogenic potential and CD30 expression. Further, treatment with ceritinib in the NPM1-ALK+ ALCL xenograft model resulted in tumor regression and improved

survival. Of 19,272 patients with hematopoietic diseases sequenced, 58 patients (0.30%) harbored ALK fusions, including tumors beyond ALK+ lymphomas such as histiocytic disorders and multiple myeloma, B-cell neoplasms, Castleman's disease, and juvenile xanthogranuloma. Most importantly, one refractory NPM1-ALK+ ALCL patient treated with ceritinib achieved complete remission with ongoing clinical benefits to date, five years after initiation of therapy.

Conclusion:
The data presented from preclinical studies and the report of durable complete response with ceritinib therapy in NPM1-ALK+ ALCL provides a strong rationale for a prospective study of ceritinib in ALK+ T-cell lymphomas and other ALK+ hematologic malignancies.

Funding Sources:
This work was supported in part by The Cancer Prevention and Research Institute of Texas [grant number RP1100584]; the Sheikh Khalifa Bin Zayed Al Nahyan Institute for Personalized Cancer Therapy [grant number 1U01 CA180964]; NCATS [grant number UL1 TR000371] (Center for Clinical and Translational Sciences); and The MD Anderson Cancer Center support grant [grant number P30 CA016672]. VS is supported by NIH / NCI [grant number 1R01CA242845-01A1]. DRW thanks support from the Hall Family Foundation endowed Chair in Molecular Medicine and the National Foundation for Cancer Research . RAJ is a recipient of [grant number P30-CA168524] from NCI . Parts of this work have been funded by grant to HMA [grant number R01 CA151533]. RB acknowledges the Sosland Family Foundation Research Award; Hale Family Foundation Research Award; Frontiers Clinical and Translational Pilot Award UL1 TR000001; and American Cancer Society-Institutional Research Grant [grant number ACS-IRG-16-194-07]. We would like to thank Luke Juckett for the initial analysis of the Foundation Medicine Database.

Figure: Ceritinib induces a deeper molecular response in NPM1-ALK+ ALCL patient



A. Timeline and clinical history of a patient. B. PET CT images describing therapeutic response of NPM1-ALK+ ALCL patient to ceritinib. The patient had multiple lung and several soft tissue lesions. Representative lesions in the right upper lobe (black arrow) and right gluteal subcutaneous fat (white arrow) are shown (December 2015 scan). There was a response to ceritinib therapy on the first follow-up scan in February 2016, with residual scarring at the site of the right upper lobe metastasis and residual right gluteal skin thickening. There is a persistent positive response as of the most recent scan in October 2018.

113

TOQQ-RCC: using Tele-mentoring to Optimize Quality of care and Quality of life for patients with Renal Cell Carcinoma

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Introduction:
Overall survival from metastatic renal cell carcinoma (RCC) has risen in recent years due in part to therapies such as immune checkpoint inhibitors (ICI) and tyrosine kinase inhibitors (TKI). TKI and ICI have unique, high-impact side effect profiles and deficits persist in clinicians' understanding of patient tolerance of and response to treatment, particularly in rural and community practices. We developed a tele-mentoring series to improve knowledge and clinical care gaps in ICI and TKI toxicity assessment and management for persons treated for RCC.

Methods:
Rural and community cancer care teams were invited by the Masonic Cancer Alliance, the outreach network of The University of Kansas Cancer Center, to participate in a five session Project ECHO® (Extension for Community Health Outcomes) didactic and case-based educational series. Topics included distress screening, shared decision-making for RCC treatment, ICI and TKI toxicity assessment and management, at-home ICI administration, and implementing toxicity monitoring protocols. Using a mixed-methods approach, pre/post ECHO surveys assessed participant engagement and satisfaction. Clinician interviews, transcribed and analyzed thematically, assessed current practice protocols. Organizational Readiness for Implementing Change (ORIC) was administered pre/post-ECHO; mean scores were calculated to determine readiness for change in toxicity monitoring and management protocols.

Results:
Fifty-two attendees from 11 cancer care institutions across Kansas and Missouri registered for the ECHO sessions. An average of 15 participants attended each session including physicians, advanced practice providers, nurses, and other disciplines. Session evaluations rated content/delivery as good or outstanding. Themes from qualitative analysis revealed patient education as a primary barrier to effective toxicity identification and management. One-third of participants completed the post-ECHO ORIC; mean scores dropped by 0.4 (10%) indicating decreased readiness to implement changes to toxicity monitoring and management protocols.

Conclusions:
Rural and community oncology clinicians are willing to engage in tele-mentoring to improve knowledge and clinical care gaps regarding ICI and TKI toxicity assessment and management. A decrease in ORIC scores post-ECHO may indicate increased understanding of the complex processes and resources required to institute meaningful improvement to toxicity monitoring and management protocols for patients treated in rural and community settings. Future directions will include formal organizational needs assessments.

Funding Source: This project was supported by a Pfizer Global Medical Education Grant.

114

Project BRA: Breast cancer Risk Assessment

Authors: Nye, Lauren E.[1]; Smith, Sharla[2]; Knight, Catherine J.[1]; Klemp, Jennifer R.[1]

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Introduction:

In Kansas, breast cancer (BC) incidence is similar in Black and white women, yet Black women are 42% more likely to die from BC. In models where screening is equal, there is no difference in survival from early-stage BC. Barriers to BC early detection in Black women include provider lack of knowledge in cancer risk, performing risk assessments and providing culturally sensitive education to patients. Our team developed a didactic and case-based intervention using Project ECHO® (Extension for Community Health Outcomes) to improve knowledge on performing BC risk assessment and enhance risk stratified screening in Community Health Clinics (CHCs). A Community Advisory Board (CAB) was established to address barriers to early detection.

Methods:

In 2021, CHCs participated in five ECHO sessions focused on calculating BC risk and cultural sensitivity and led by breast oncology, genetics, screening, and health care equity experts. Pre/post surveys assessed knowledge and satisfaction. A CAB member survey described organizational characteristics and community reach. Asset mapping identified barriers, resources, and opportunities to promote BC screening. Descriptive statistical analyses and the RE-AIM framework assessed reach and scalability.

Results:

Seventy-seven individuals from 16 CHCs registered to participate; an average of 26 attendees at each session; 34% attending two or more. Participants included physicians (19%), advanced practice providers (18%), nurses (29%), and allied health professionals (34%). Sixty-three (82%) completed the baseline survey; 10 (13%) completed the post-ECHO survey. At baseline, 32% of participants reported lack of training and time as barriers to performing risk assessment. While post-ECHO survey responses were low, 60% reported knowledge improvement. Participants reported practice changes in collecting family history beyond first degree relatives. CAB members reported expertise in community engagement and development (44%), patient care (15%), healthcare access (15%) and advocacy (26%). CAB collaboration led to support for offering tomosynthesis imaging in the state-funded program, Early Detection Works (EDW). Asset mapping identified gaps in access to EDW for Black women.

Conclusions:

Project BRA demonstrated successful ECHO participation and achieved perceived knowledge changes in performing BC risk assessment. Next steps include incorporating CAB informed opportunities to expand and advocate for improved access to risk-stratified screening across Kansas.

Funding Source: This project was supported by a Susan G. Komen and Western Missouri Affiliates Community Grant.

115

Kansurvive: Testing a Model for Improving Cancer Survivorship Care in Rural Practice

Authors: Klemp, Jennifer R.[1]; Knight, Catherine J.[1]; Ellerbeck, Edward[2]; Befort, Christie[2]; Nelson, Eve-Lynn[3]; O'Dea, Anne[1]; Nelson-Brantley, Heather[4]; Hughes, Dorothy[2]; Greiner, Allen[5]

Author Affiliations: The University of Kansas Cancer Center, Division of Medical Oncology[1]; The University of Kansas Medical Center, Department of Population Health[2], Department of Pediatrics[3], School of Nursing[4], Department of Family Medicine and Community Health[5]

Introduction:

Despite evidence-based practice (EBP) guidelines existing for cancer survivorship care, implementation in rural primary care practice has fallen short. Approximately 72.5% of Kansas cancer survivors who have completed treatment receive most of their health care from primary care providers (PCPs), increasing the importance of their engagement in the acute and extended phases of survivorship care. PCPs describe a lack of basic awareness of risk-based surveillance, effects of cancer treatment and their management, inadequate resources and growing administrative demands as reasons for not working to improve survivorship care. Pilot data established need, feasibility, and acceptability within our network to evaluate the effectiveness of the Kansurvive ECHO® (Extension for Community Health Outcomes) tele-mentoring intervention to enhance EBP care for rural cancer survivors in primary care practice.

Methods:

In 2021, PCPs and their teams caring for rural cancer survivors were invited to participate in four case-based Kansurvive ECHO® sessions focused on EBP survivorship guidelines for breast, colorectal, lung, and prostate cancer. Pre/post ECHO evaluations assessed content, delivery, and perceived readiness to implement practice change. Semi-structured interviews gained input on practice-level variables impacting implementation of EBP. Baseline practice-level data collected from electronic health records (EHRs) included preventive health and survivorship quality measures. Virtual practice facilitation (PF) meetings using the iPARIHS framework, provide a supportive service to engage in quality improvement. Post-intervention data from EHRs will assess concordance with survivorship care guidelines.

Results:

COVID delayed recruitment, prevented in-person clinics visits, and caused project pauses during case surges, however, 15 primary care practices from Kansas and Nebraska were recruited to participate in the project. Sixty healthcare professionals from recruited clinics registered for the ECHO sessions. To-date, 138 baseline chart abstractions have been completed and quality measure scorecards compiled to assist clinics with goal setting. Ongoing virtual PF meetings offer clinic support with quality improvement initiatives and an EHR optimization working group was established to guide survivorship care through alerts, order sets, and health maintenance modules.

Conclusions:

Project efforts continue and include engaging clinics with PF, support to enhance EHRs to better align with EBP survivorship guidelines, post-intervention data collection, and qualitative and quantitative data analysis results and dissemination.

Funding Source: This project is supported by the NCI/NIH under Award Number 5R01CA240103-03.

116

Bringing experimental therapeutics clinical trials network (ETCTN) to underrepresented population

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Introduction:

Access to health care including clinical trials (CT) leading to paradigm-changing cancer treatments are critical for high quality cancer care and equity in society. In this report, we highlight methods in accruing to ETCTN wherein underrepresented rural, low-income, and racial minorities comprise >50% of enrollment.

Methods:

University of Kansas Cancer Center (KUCC) is one of eight National Cancer Institute (NCI) designated cancer centers awarded CATCH-UP.2020 (CATCH-UP), a congressionally mandated P30 supplement to enhance access for minority/underserved populations to ETCTN precision medicine CT. KUCC catchment area is 23% rural by Rural Urban Continuum Codes (RUCC); almost 90 % of counties are designated primary care HPSA's (Health Professional Shortage Areas). KUCC Early Phase and Masonic Cancer Alliance (rural outreach network) partnered to operationalize CATCH-UP. We engaged disease-focused champion investigators in disease working groups and MCA physicians who selected scientifically sound CT that fit catchment area needs. Patient and Investigator Voices Organizing Together, a patient research advocacy group provided practical feedback. MCA navigator coordinated recruitment. Telehealth was used for rural patients that would have a significant distance to travel just to be screened.

Results:

CATCH-UP was initiated in September 2020. Twenty-eight CT were activated, many in community sites. Average activation time was 81 days. Delays were mainly from CT amendments. KUCC enrolled the first patient in the CATCH-UP program. In 6 months, we met accrual requirements (24/year, 50% minorities). During first year, we enrolled 47 (>50% minorities), an

increase of 680% from our average accrual of 6/year (>50% minorities) in ETCTN through Early Drug Development Opportunity Program (2016-2020). To date, we have enrolled 61, 54% from rural, HPSA, race and other minorities. Although the proportion of minorities did not change but remained high, this funding allowed us to substantially increase the number of patients from a catchment area with high proportion of geographically and socioeconomically underserved minorities given access to early phase CT through ETCTN.

Conclusion:

Amid COVID-19 pandemic, the NCI CATCH-UP program and methods we used allowed access to novel therapies for rural, medically underserved, and other minority groups.

Funding Sources: NIH: 3P30CA168524-09S2.

117

A strategy to optimize clinical trial recruitment: Utilization of the electronic health record in a clinic-based approach

Authors: Leavens, Eleanor[1,2]; Comfort, Branden[2]; Woodward, Jennifer[3]; Ellerbeck, Edward[1,2]; McRae, Jennifer[2]; Hiles, Megan[2]; Brim, Tara[2]; Scharf, Shivani[2]; Nollen, Nicole[1]

Author Affiliations:
[1]University of Kansas School of Medicine, Department of Population Health
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[3]University of Kansas School of Medicine, Department of Family Medicine

Introduction:
Sufficient participant recruitment is critical to the success of clinical trials and without it, study completion is delayed or jeopardized. Utilization of registries that query the electronic health record (EHR), in collaboration with clinical departments, would allow researchers to directly engage with patients, likely resulting in enhanced study recruitment, improved patient access to clinical trials, and reduced study costs. We describe a novel recruitment strategy using one such registry.

Methods:
The study team collaborated with the university's Departments of Internal Medicine and Family Medicine. The study aims to reduce tobacco-related harm among patients with COPD who were unwilling to quit smoking by helping them switch to a reduced harm e-cigarette (projected sample size = 45). Study inclusion/exclusion criteria were input into the Curated Cancer Clinical Outcomes Database which queried the EHR to identify potential patients. Researchers, in collaboration with clinician partners, contacted patients via a letter describing the research and notifying patients that research staff would contact them by phone to offer study screening. Letters were approved and signed by the clinical department. Recruitment is ongoing.

Results:
In total, 1508 patients who meet basic inclusion criteria have been identified. Thus far, an ad hoc group of 613 have been mailed a letter to ensure timely phone follow up; all patients have received a follow-up phone call. Of those that received a letter, we have been unable to contact 346 (e.g., left a voicemail, number disconnected) and an additional 155 were not interested in screening. Nineteen asked to be called back and 42 were ineligible, resulting in 51 patients that met initial inclusion criteria. All patients have been or will be scheduled for final screening.

Conclusion:
This recruitment strategy was successful in identifying research participants with a high likelihood of being eligible. Recruitment success was accomplished while maintaining reduced clinic burden and financial cost to the study. This recruitment strategy likely increased patient access to research aiming to improve patient health while also advancing research priorities in public health. This recruitment strategy can be replicated in health systems nationwide and will improve recruitment and retention to enhance clinical trial success.

Funding Sources: This research was supported by a University of Kansas Cancer Center Cancer Prevention and Control Pilot Award (PI: Leavens).

118

Plasmacytomas and Polyps – a Perplexing Presentation

Authors: Mathews, Thomas[1]; Cunningham, Mark[1]; Bonino, John[1]; Jackson, Mollie[1]

Author Affiliations: [1]University of Kansas Medical Center

Introduction:

Solitary extramedullary plasmacytoma (SEP) affecting soft tissue is extremely rare. These tumors are most commonly discovered in the respiratory tract. However, there are very few case reports of these tumors being identified in the gastrointestinal (GI) tract. Further, there are no known documented cases of multiple plasmacytomas in the GI tract.

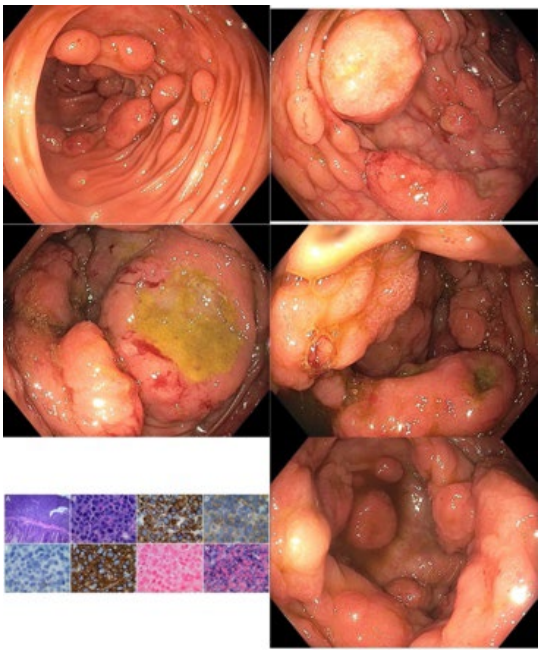
Case Description:

An 80-year-old male with history of acute lymphoid leukemia, multiple myeloma (MM), and pancytopenia (secondary to chemotherapy) was admitted for acute renal failure. He had noted intermittent diarrhea and fatigue over the previous several weeks. He had a normal colonoscopy 5 years previously. Labs demonstrated significantly increased fLLC of 974 (fKLC 0.08), as well as decreased IgG, IgA, and IgM; SPEP showed IgG lambda paraprotein spike, indicative of relapse of MM. His liver enzymes and bilirubin were normal. CT scan of the abdomen and pelvis showed moderate and irregular thickening of the cecum and ascending colon. Gastroenterology was consulted for colonoscopy. This revealed innumerable small and large polypoid masses up to 4 cm diameter throughout the colon. Many had ulcerations up to 2 cm diameter. Most were in the cecum and ascending colon. Biopsies were obtained. Histopathology confirmed plasma cell neoplasia.

Conclusion:

Plasmacytoma is a tumor of plasma cells that arises from bone or from mucosal surfaces throughout the body. Mucosal plasma cell neoplasms are known as extramedullary plasmacytoma. We can further delineate plasmacytomas as either solitary bone plasmacytoma (SBP) – a single bone lesion, solitary extramedullary plasmacytoma (SEP) – a solitary soft tissue lesion, or multiple solitary plasmacytoma (MSP) – multiple sites of disease in soft tissue, bone, or both. While exceedingly rare, plasmacytomas usually present as a solitary lesion (typically involving bone). About 4% of plasmacytomas are extramedullary. However, there has been no known documented report of MSP with multiple sites in the colon, especially to the degree found in this case. Though there have been rare case reports of single SEP lesions of the colon, to our knowledge no case reports have been published reporting the diffuse nature of the colonic SEPs like in our patient. Clinicians should consider plasmacytomas in patients with MM presenting with changes in bowel habits.

Funding Sources: None.



A – B, Atypical large cell proliferation involving the mucosa and submucosa of the right colon. The malignant cells are positive for CD3 (C), CD4 (D), CD138 (F), and lambda light chain (H). The malignant cells are negative for CD20 (E), and kappa light chains (G). (A: H&E stain 100x magnification; B: H&E stain 1000x magnification; C – F; immunohistochemical stains 1000x magnification; G – H: chromogenic in-situ hybridization stains 1000x magnification).

119

Compacted Periampullary Diverticulum Masquerading as Pancreatic Head Mass on Endoscopic Ultrasound

Authors: Reddy, Pranay, MD, MPH[1]; Valadez, David, MD[2]; Sutton, Richard, DO[2]; Altfillisch, Charlie, MD[3]; Olyaee, Mojtaba, MD[2]

Author Affiliations: 1. Jefferson Health Northeast Department of Internal Medicine, 2. KUMC Department of Gastroenterology, 3. KUMC Department of Internal Medicine

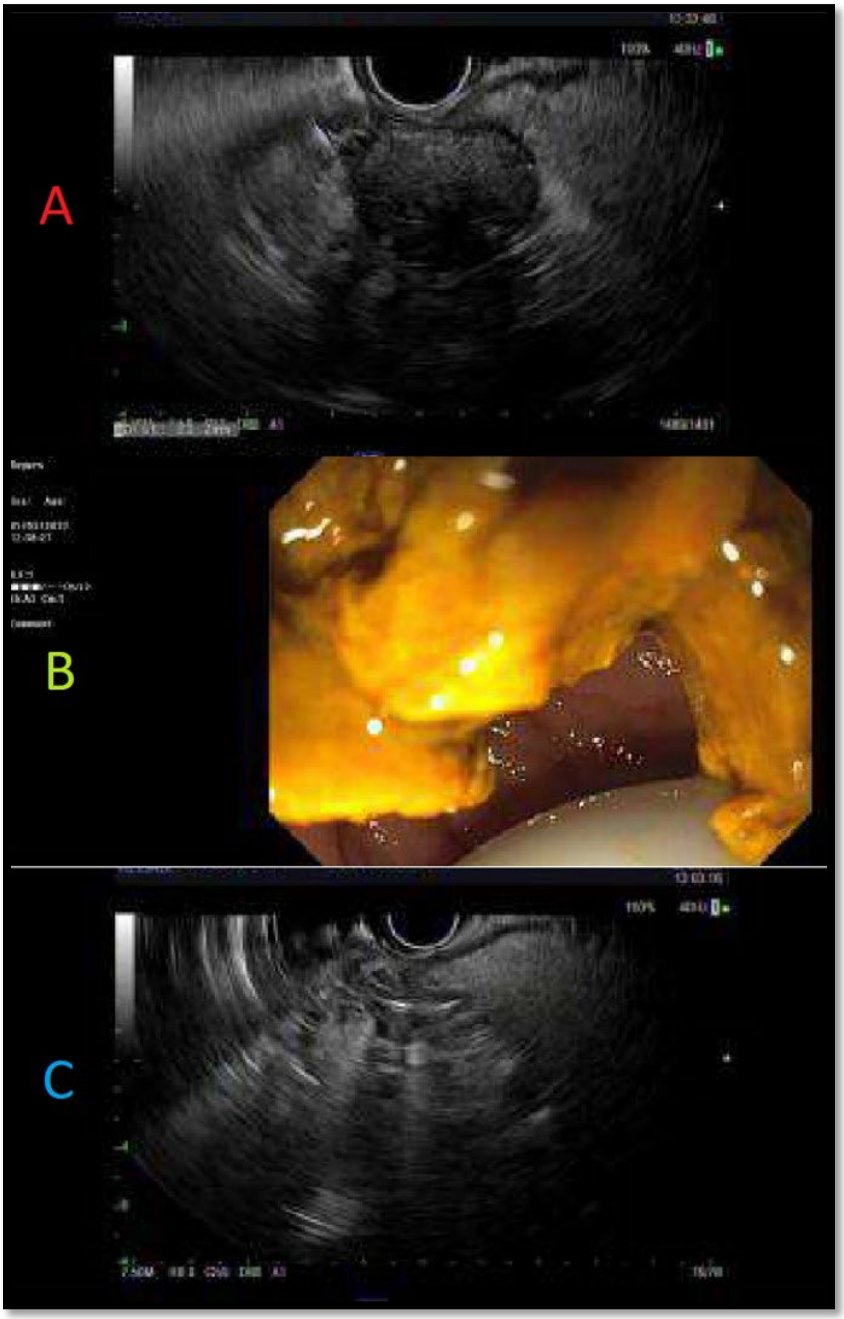
Introduction:
Endoscopic ultrasound (EUS) has become an increasingly important modality in the diagnosis and treatment of gastrointestinal malignancy as well as both pancreatic and biliary disease. It provides high-resolution, real-time imaging of the GI tract and surrounding structures. EUS is classically operator dependent and can often display suboptimal sensitivity and specificity. Numerous techniques such as Endoscopic guided fine-needle aspiration (EUS-FNA), EUS fine needle biopsy (EUS-FNB), rapid on-site cytological evaluation (ROSE) and contrast harmonic-enhanced EUS (CH-EUS) help to increase the sensitivity and specificity of this diagnostic modality. The following case describes a patient with initial EUS findings concerning for pancreatic head malignancy which was ultimately identified as a periampullary diverticulum compacted with sludge.

Methods/Case:
A 70-year-old patient with a past medical history of prostate cancer and cholelithiasis status post recent cholecystectomy presented with CT imaging findings concerning for pancreatic head mass. The patient underwent initial EGD with EUS which illustrated a well circumscribed, heterogeneously echoic 26.8 x 24 mm uncinate process mass concerning for neuroendocrine tumor (NET). FNB was performed and cytology ultimately showed no evidence of malignancy. Due to continued concern for pancreatic NET, patient underwent repeat EGD and EUS. EUS redemonstrated the large heterogeneously echoic pancreatic head lesion concerning for mass.

Results:
Attempts were made to visualize the ampulla with linear EUS scope, however there was significant debris in the second portion of the duodenum. Duodenoscope was then passed and a large caliber but narrow opening periampullary diverticulum was visualized and appeared to be filled with compacted sludge. A combination of biopsy forceps and water lavage was used to clean out the compacted sludge. The EUS scope was then readvanced into the second part of the duodenum and the suspected mass which was previously visualized was no longer visible.

Conclusion: EUS is a an important minimally invasive diagnostic procedure that has both high clinical success rate with minimal adverse events. EUS, like many other diagnostic modalities, has limitations when identifying and ruling out malignancy. This case highlights one such limitation showing that although initial findings were concerning for malignancy, further investigation revealed a duodenal diverticulum with compacted debris masquerading as an uncinate mass.

Funding Sources: None



A. EUS showing well circumscribed, heterogeneously echoic uncinate process mass.

B. Duodenoscopy showing periampullary diverticulum compacted with sludge.

C. After lavage of sludge, EUS showing absence of suspected mass which was previously visualized.

120

Diffuse Intestinal Amyloidosis Complicated by Pancreatic NET, Splenic Vein Thrombosis with Gastrosplenic Shunt Formation and Bleeding Angioectasias Requiring Total Colectomy

Authors: Reddy, Pranay, MD, MPH[1]; Khurana, Shruti, MD[2]; Esfandyari, Tuba, MD, MSc[2]; Madan, Rashna, MBBS[3]

Author Affiliations: 1. Jefferson Health Northeast, 2. KUMC Department of Gastroenterology, 3. KUMC Department of Pathology

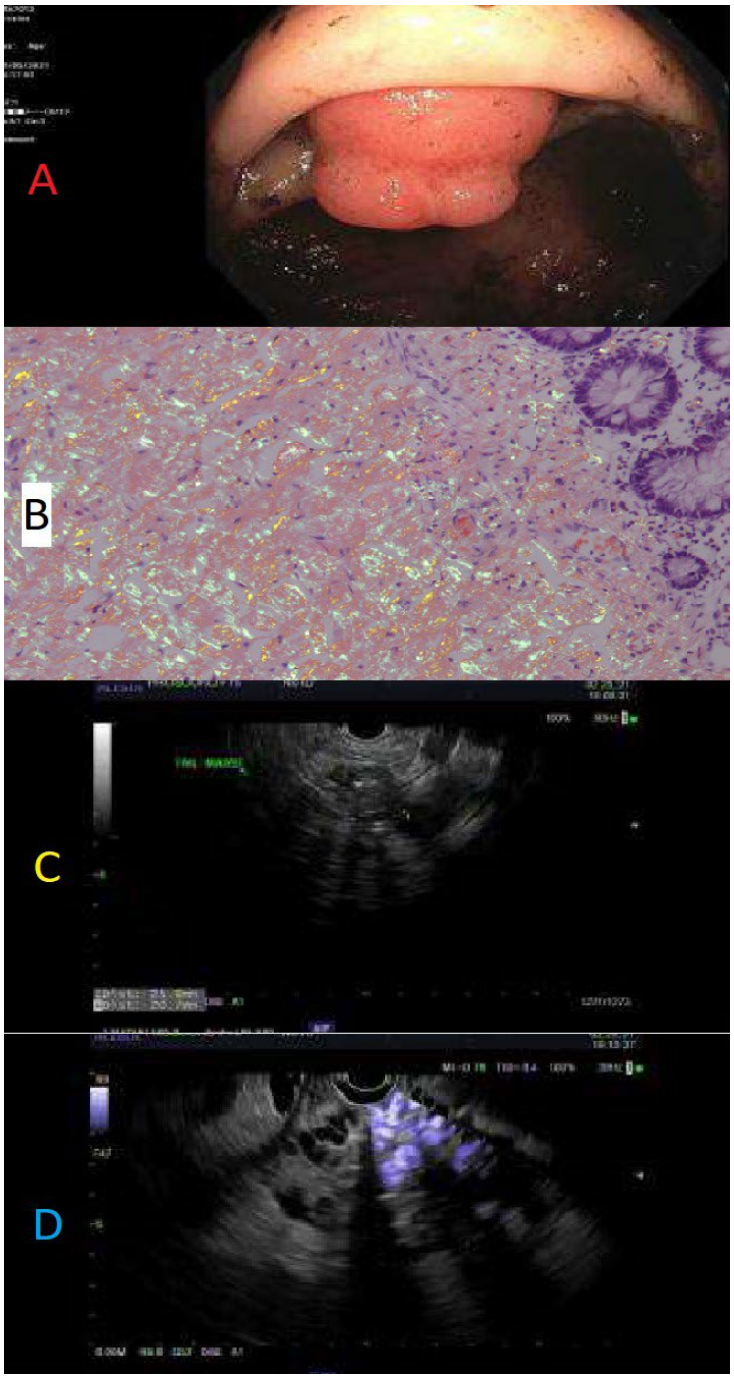
Introduction: Pancreatic Neuroendocrine tumors (pNETs) are endocrine tumors arising from the pancreas and are one of the most common NETs. Splenic vein thrombosis with resulting sinistral hypertension is a rare complication of pNETs causing isolated gastric varices and less commonly portal hypertensive colopathy if portal vein becomes involved. In this case, we present a 78-year-old male with intestinal amyloidosis complicated by pancreatic neuroendocrine tumor (NET), splenic vein occlusion with gastrosplenic shunt formation and gastrointestinal hemorrhage secondary to diffuse colonic angioectasias.

Methods: A 78-year-old male with history of ADPKD, CAD, and HTN was initially found to have colonic mass on screening colonoscopy. Biopsies at that time illustrated congo red staining positivity for light chain (AL) amyloidosis. He was maintained on daratumumab in the outpatient setting and remained complication free for nearly two decades. Following a cardiac catheterization with stent placement, patient was started on dual antiplatelet therapy and had resulting hematochezia requiring admission. Colonoscopy showed friable mucosa with ulceration from rectum to cecum as well as ulcerated polypoid lesions. The following year patient was found to have pancreatic tail mass on CT and subsequently underwent EUS with FNA revealing pNET. Clinical course was further complicated by splenic vein thrombosis, large gastrosplenic shunt formation and type II isolated bleeding varices. He ultimately underwent coil embolization with IR and was started on lanreotide injections for pNET.

Results: The patient now presented with melenic stools of two days duration. EGD redemonstrated nonbleeding type I isolated gastric varices and colonoscopy revealed numerous actively bleeding colonic angioectasias treated with ablation. Due to persistent hematochezia, CT venogram was performed which demonstrated pneumoperitoneum concerning for perforated viscus. He was seen by colorectal surgery, underwent total colectomy with ileostomy and was eventually discharged to rehab in stable condition.

Conclusion: Splenic vein thrombosis is a rare complication of pNETs which can cause isolated gastric varices and is recognized as an important cause of upper GI bleeding. This case highlights a rare complication of pNET whereby a splenic vein occlusion and large gastrosplenic shunt eventually involved the portal vein causing true right sided portal hypertension with development of portal hypertensive colopathy characterized by bleeding angioectasias.

Funding Sources: None



A) Large amyloidoma extruding from terminal ileum B) Cecum histopathology: Positive congo red stain with apple-green birefringence under polarized light C) EUS showing 25mm x 21mm hypoechoic lesion in pancreatic tail with few calcifications D) Hypoechoic pancreatic tail lesion with intervening fundal varices preventing biopsy.

Abstract by Poster Number

Poster #	Presenting Author (Last, First)	Division of Presenting Author	Type of Abstract
1	Bansal, Ajay	Gastroenterology, Hepatology & Motility	Basic/Biomedical Mechanisms
2	Ghosh, Priyanka	Gastroenterology, Hepatology & Motility	Basic/Biomedical Mechanisms
3	Price, Michael	Pulmonary, Critical Care & Sleep Medicine	Basic/Biomedical Mechanisms
4	Shafiq, Muhammad	General & Hospital Medicine	Clinical Research
5	Holden, Rachel	Physical Activity & Weight Management	Clinical Research
7	Preet, Ranjan	Medical Oncology	Basic/Biomedical Mechanisms
8	Sun, Weijing	Medical Oncology	Clinical Research
9	Gratton, Matthew	Medical Informatics	Basic/Biomedical Mechanisms
10	Mazzotti, Diego	Medical Informatics	Clinical Research
11	Bansal, Ajay	Gastroenterology, Hepatology & Motility	Clinical Research
12	Rooge, Sheetal	Gastroenterology, Hepatology & Motility	Basic/Biomedical Mechanisms
13	AL-Ramahi, Joe	Hematologic Malignancies & Cellular Therapeutics	Clinical Research
14	Halkidis, Konstantine	Hematologic Malignancies & Cellular Therapeutics	Basic/Biomedical Mechanisms
15	Wesson, William	Hematologic Malignancies & Cellular Therapeutics	Clinical Research
16	Wesson, William	Hematologic Malignancies & Cellular Therapeutics	Clinical Research
17	Szabo-Reed, Amanda	Physical Activity & Weight Management	Clinical Research
18	Szabo-Reed, Amanda	Physical Activity & Weight Management	Clinical Research
20	Mazzotti, Diego	Medical Informatics	Clinical Research
21	Tikhanovich, Irina	Gastroenterology, Hepatology & Motility	Basic/Biomedical Mechanisms

Poster #	Presenting Author (Last, First)	Division of Presenting Author	Type of Abstract
22	Altfillisch, Charles	Gastroenterology, Hepatology & Motility	Clinical Research
23	Foright, Rebecca	Physical Activity & Weight Management	Basic/Biomedical Mechanisms
24	Bodde, Amy	Physical Activity & Weight Management	Clinical Research
25	Mushtaq, Umair	Hematologic Malignancies & Cellular Therapeutics	Clinical Research
26	Mushtaq, Umair	Hematologic Malignancies & Cellular Therapeutics	Clinical Research
27	Love, Marissa	Allergy, Clinical Immunology & Rheumatology	Clinical Research
28	Maz, Mehrdad	Allergy, Clinical Immunology & Rheumatology	Clinical Research
29	Waller, Stephen	Infectious Diseases	Basic/Biomedical Mechanisms
30	Hutchison, Justin	Infectious Diseases	Basic/Biomedical Mechanisms
31	Franczak, Edziu	Endocrinology, Diabetes & Clinical Pharmacology	Basic/Biomedical Mechanisms
32	Gopinath, Chaitra	Endocrinology, Diabetes & Clinical Pharmacology	Clinical Research
33	Venkatesh, Priyanka	General & Hospital Medicine	Clinical Research
34	Mount, Rebecca	General & Hospital Medicine	Clinical Research
35	Gupta, Aditi	Nephrology & Hypertension	Clinical Research
36	Gupta, Aditi	Nephrology & Hypertension	Clinical Research
37	Ram, Anil Kumar	Pulmonary, Critical Care & Sleep Medicine	Basic/Biomedical Mechanisms
38	Bengtson, Charles	Pulmonary, Critical Care & Sleep Medicine	Basic/Biomedical Mechanisms
39	Bahr, Nathan	Infectious Diseases	Clinical Research
40	Bahr, Nathan	Infectious Diseases	Clinical Research

Poster #	Presenting Author (Last, First)	Division of Presenting Author	Type of Abstract
41	Choi, Jiwoong	Pulmonary, Critical Care & Sleep Medicine	Basic/Biomedical Mechanisms
42	Niedbalski, Peter	Pulmonary, Critical Care & Sleep Medicine	Clinical Research
43	El Mikati, Ibrahim	Nephrology & Hypertension	Clinical Research
44	El Mikati, Ibrahim	Nephrology & Hypertension	Clinical Research
45	Liang, Kelly	Nephrology & Hypertension	Case Report/Clinical Vignette
46	Liang, Kelly	Nephrology & Hypertension	Clinical Research
47	Pagadala, Prathyusha	Endocrinology, Diabetes & Clinical Pharmacology	Case Report/Clinical Vignette
48	Kumari, Roshan	Endocrinology, Diabetes & Clinical Pharmacology	Basic/Biomedical Mechanisms
49	Thiyagarajan, Ramkumar	Geriatric Medicine	Basic/Biomedical Mechanisms
50	Thiyagarajan, Ramkumar	Geriatric Medicine	Basic/Biomedical Mechanisms
51	Slimmer, Stephanie	General & Hospital Medicine	Education
52	Slimmer, Stephanie	General & Hospital Medicine	Education
53	Broxterman, Jane	General & Hospital Medicine	Education
54	McGreevy, Sheila	General & Hospital Medicine	Patient Safety/Quality Improvement Research
55	Seldeen, Kenneth	Geriatric Medicine	Clinical Research
56	Treanor, Owen	Geriatric Medicine	Basic/Biomedical Mechanisms
57	Chaves, Lee	Geriatric Medicine	Basic/Biomedical Mechanisms
58	Troen, Bruce	Geriatric Medicine	Clinical Research
59	Hastert, Mary	Physical Activity & Weight Management	Clinical Research

Poster #	Presenting Author (Last, First)	Division of Presenting Author	Type of Abstract
60	Hastert, Mary	Physical Activity & Weight Management	Clinical Research
61	Prevallet, Ashley	Physical Activity & Weight Management	Education
62	Eller, Annie	Physical Activity & Weight Management	Clinical Research
63	Fenando, Ardy	Allergy, Clinical Immunology & Rheumatology	Clinical Research
64	Krause, Megan	Allergy, Clinical Immunology & Rheumatology	Clinical Research
65	Prasad, Chandrashekhar	Pulmonary, Critical Care & Sleep Medicine	Basic/Biomedical Mechanisms
66	Baumlin, Nathalie	Pulmonary, Critical Care & Sleep Medicine	Basic/Biomedical Mechanisms
67	Shune, Leyla	Hematologic Malignancies & Cellular Therapeutics	Clinical Research
68	Shune, Leyla	Hematologic Malignancies & Cellular Therapeutics	Clinical Research
69	Samo, Salih	Gastroenterology, Hepatology & Motility	Basic/Biomedical Mechanisms
70	Dunn, Winston	Gastroenterology, Hepatology & Motility	Clinical Research
71	Jamadar, Abeda	Nephrology & Hypertension	Basic/Biomedical Mechanisms
72	Sharma, Madhulika	Nephrology & Hypertension	Basic/Biomedical Mechanisms
73	Matson, Scott	Pulmonary, Critical Care & Sleep Medicine	Basic/Biomedical Mechanisms
74	Matson, Scott	Pulmonary, Critical Care & Sleep Medicine	Clinical Research
75	Kothari, Mayank	Pulmonary, Critical Care & Sleep Medicine	Patient Safety/Quality Improvement Research
76	Boomer, Jonathan	Pulmonary, Critical Care & Sleep Medicine	Clinical Research
77	Choudhury, Sonali	Nephrology & Hypertension	Basic/Biomedical Mechanisms
78	Jansson, Kyle	Nephrology & Hypertension	Basic/Biomedical Mechanisms

Poster #	Presenting Author (Last, First)	Division of Presenting Author	Type of Abstract
79	Reddy, Pranay	Gastroenterology, Hepatology & Motility	Case Report/Clinical Vignette
80	Reddy, Pranay	Gastroenterology, Hepatology & Motility	Case Report/Clinical Vignette
81	Reddy, Pranay	Gastroenterology, Hepatology & Motility	Case Report/Clinical Vignette
82	Rouse, Michael	General & Hospital Medicine	Education
83	Chang, Joy	Physical Activity & Weight Management	Clinical Research
84	Gorczyca, Anna	Physical Activity & Weight Management	Clinical Research
85	Fink, Jennifer	General & Hospital Medicine	Education
86	Brubacher, Marie	General & Hospital Medicine	Education
87	Rooney, Anthony	Medical Oncology	Case Report/Clinical Vignette
88	Balmaceda, Julia	Medical Oncology	Clinical Research
89	Mansour, Razan	Nephrology & Hypertension	Clinical Research
90	Mansour, Razan	General & Hospital Medicine	Clinical Research
91	Hegde, Vishwajit	General & Hospital Medicine	Case Report/Clinical Vignette
93	Mahaparn, Irisa	Nephrology & Hypertension	Clinical Research
94	Chakraborty, Anubhav	Nephrology & Hypertension	Basic/Biomedical Mechanisms
95	Gierer, Selina	Allergy, Clinical Immunology & Rheumatology	Clinical Research
96	D'Mello, Andrea	Allergy, Clinical Immunology & Rheumatology	Case Report/Clinical Vignette
97	Duraisamy, Santhosh Kumar	Pulmonary, Critical Care & Sleep Medicine	Basic/Biomedical Mechanisms
98	Duraisamy, Santhosh Kumar	Pulmonary, Critical Care & Sleep Medicine	Basic/Biomedical Mechanisms

Poster #	Presenting Author (Last, First)	Division of Presenting Author	Type of Abstract
99	Foster, Rachel	Physical Activity & Weight Management	Clinical Research
100	McGrevey, Danica	Physical Activity & Weight Management	Clinical Research
101	Danon, Jessica	Physical Activity & Weight Management	Clinical Research
102	Suire, Kameron	Physical Activity & Weight Management	Basic/Biomedical Mechanisms
103	Liang, Kimberly	Allergy, Clinical Immunology & Rheumatology	Clinical Research
104	Williams, Christopher	Allergy, Clinical Immunology & Rheumatology	Clinical Research
105	Ahmed, Nausheen	Hematologic Malignancies & Cellular Therapeutics	Case Report/Clinical Vignette
106	Ahmed, Nausheen	Hematologic Malignancies & Cellular Therapeutics	Clinical Research
107	Kumar, Ashok	Pulmonary, Critical Care & Sleep Medicine	Basic/Biomedical Mechanisms
108	Kim, Michael	Pulmonary, Critical Care & Sleep Medicine	Basic/Biomedical Mechanisms
109	Nazir, Usman	Pulmonary, Critical Care & Sleep Medicine	Patient Safety/Quality Improvement Research
110	Silswal, Neerupma	Pulmonary, Critical Care & Sleep Medicine	Basic/Biomedical Mechanisms
111	Appenfeller, Allison	Hematologic Malignancies & Cellular Therapeutics	Clinical Research
112	Balusu, Ramesh	Hematologic Malignancies & Cellular Therapeutics	Clinical Research
113	Knight, Catie	Medical Oncology	Patient Safety/Quality Improvement Research
114	Knight, Catie	Medical Oncology	Patient Safety/Quality Improvement Research
115	O'Dea, Anne	Medical Oncology	Patient Safety/Quality Improvement Research
116	Abbasi, Saqib	Medical Oncology	Clinical Research
117	Leavens, Eleanor	General & Hospital Medicine	Clinical Research

Poster #	Presenting Author (Last, First)	Division of Presenting Author	Type of Abstract
118	Mathews, Thomas	General & Hospital Medicine	Case Report/Clinical Vignette
119	Reddy, Pranay	Gastroenterology, Hepatology & Motility	Case Report/Clinical Vignette
120	Reddy, Pranay	Gastroenterology, Hepatology & Motility	Case Report/Clinical Vignette

Abstract by Presenting Author Last Name

Presenting Author (Last, First)	Poster #	Division of Presenting Author	Type of Abstract
Abbasi, Saqib	116	Medical Oncology	Clinical Research
Ahmed, Nausheen	105	Hematologic Malignancies & Cellular Therapeutics	Case Report/Clinical Vignette
Ahmed, Nausheen	106	Hematologic Malignancies & Cellular Therapeutics	Clinical Research
AL-Ramahi, Joe	13	Hematologic Malignancies & Cellular Therapeutics	Clinical Research
Altfillisch, Charles	22	Gastroenterology, Hepatology & Motility	Clinical Research
Appenfeller, Allison	111	Hematologic Malignancies & Cellular Therapeutics	Clinical Research
Bahr, Nathan	39	Infectious Diseases	Clinical Research
Bahr, Nathan	40	Infectious Diseases	Clinical Research
Balmaceda, Julia	88	Medical Oncology	Clinical Research
Balusu, Ramesh	112	Hematologic Malignancies & Cellular Therapeutics	Clinical Research
Bansal, Ajay	1	Gastroenterology, Hepatology & Motility	Basic/Biomedical Mechanisms
Bansal, Ajay	11	Gastroenterology, Hepatology & Motility	Clinical Research
Baumlin, Nathalie	66	Pulmonary, Critical Care & Sleep Medicine	Basic/Biomedical Mechanisms
Bengtson, Charles	38	Pulmonary, Critical Care & Sleep Medicine	Basic/Biomedical Mechanisms
Bodde, Amy	24	Physical Activity & Weight Management	Clinical Research
Boomer, Jonathan	76	Pulmonary, Critical Care & Sleep Medicine	Clinical Research
Broxterman, Jane	53	General & Hospital Medicine	Education
Brubacher, Marie	86	General & Hospital Medicine	Education
Chakraborty, Anubhav	94	Nephrology & Hypertension	Basic/Biomedical Mechanisms

Presenting Author (Last, First)	Poster #	Division of Presenting Author	Type of Abstract
Chang, Joy	83	Physical Activity & Weight Management	Clinical Research
Chaves, Lee	57	Geriatric Medicine	Basic/Biomedical Mechanisms
Choi, Jiwoong	41	Pulmonary, Critical Care & Sleep Medicine	Basic/Biomedical Mechanisms
Choudhury, Sonali	77	Nephrology & Hypertension	Basic/Biomedical Mechanisms
Danon, Jessica	101	Physical Activity & Weight Management	Clinical Research
D'Mello, Andrea	96	Allergy, Clinical Immunology & Rheumatology	Case Report/Clinical Vignette
Dunn, Winston	70	Gastroenterology, Hepatology & Motility	Clinical Research
Duraisamy, Santhosh Kumar	97	Pulmonary, Critical Care & Sleep Medicine	Basic/Biomedical Mechanisms
Duraisamy, Santhosh Kumar	98	Pulmonary, Critical Care & Sleep Medicine	Basic/Biomedical Mechanisms
El Mikati, Ibrahim	43	Nephrology & Hypertension	Clinical Research
El Mikati, Ibrahim	44	Nephrology & Hypertension	Clinical Research
Eller, Annie	62	Physical Activity & Weight Management	Clinical Research
Fenando, Ardy	63	Allergy, Clinical Immunology & Rheumatology	Clinical Research
Fink, Jennifer	85	General & Hospital Medicine	Education
Foright, Rebecca	23	Physical Activity & Weight Management	Basic/Biomedical Mechanisms
Foster, Rachel	99	Physical Activity & Weight Management	Clinical Research
Franczak, Edziu	31	Endocrinology, Diabetes & Clinical Pharmacology	Basic/Biomedical Mechanisms
Ghosh, Priyanka	2	Gastroenterology, Hepatology & Motility	Basic/Biomedical Mechanisms
Gierer, Selina	95	Allergy, Clinical Immunology & Rheumatology	Clinical Research

Presenting Author (Last, First)	Poster #	Division of Presenting Author	Type of Abstract
Gopinath, Chaitra	32	Endocrinology, Diabetes & Clinical Pharmacology	Clinical Research
Gorczyca, Anna	84	Physical Activity & Weight Management	Clinical Research
Gratton, Matthew	9	Medical Informatics	Basic/Biomedical Mechanisms
Gupta, Aditi	35	Nephrology & Hypertension	Clinical Research
Gupta, Aditi	36	Nephrology & Hypertension	Clinical Research
Halkidis, Konstantine	14	Hematologic Malignancies & Cellular Therapeutics	Basic/Biomedical Mechanisms
Hastert, Mary	59	Physical Activity & Weight Management	Clinical Research
Hastert, Mary	60	Physical Activity & Weight Management	Clinical Research
Hegde, Vishwajit	91	General & Hospital Medicine	Case Report/Clinical Vignette
Holden, Rachel	5	Physical Activity & Weight Management	Clinical Research
Hutchison, Justin	30	Infectious Diseases	Basic/Biomedical Mechanisms
Jamadar, Abeda	71	Nephrology & Hypertension	Basic/Biomedical Mechanisms
Jansson, Kyle	78	Nephrology & Hypertension	Basic/Biomedical Mechanisms
Kim, Michael	108	Pulmonary, Critical Care & Sleep Medicine	Basic/Biomedical Mechanisms
Knight, Catie	113	Medical Oncology	Patient Safety/Quality Improvement Research
Knight, Catie	114	Medical Oncology	Patient Safety/Quality Improvement Research
Kothari, Mayank	75	Pulmonary, Critical Care & Sleep Medicine	Patient Safety/Quality Improvement Research

Presenting Author (Last, First)	Poster #	Division of Presenting Author	Type of Abstract
Krause, Megan	64	Allergy, Clinical Immunology & Rheumatology	Clinical Research
Kumar, Ashok	107	Pulmonary, Critical Care & Sleep Medicine	Basic/Biomedical Mechanisms
Kumari, Roshan	48	Endocrinology, Diabetes & Clinical Pharmacology	Basic/Biomedical Mechanisms
Leavens, Eleanor	117	General & Hospital Medicine	Clinical Research
Liang, Kelly	45	Nephrology & Hypertension	Case Report/Clinical Vignette
Liang, Kelly	46	Nephrology & Hypertension	Clinical Research
Liang, Kimberly	103	Allergy, Clinical Immunology & Rheumatology	Clinical Research
Love, Marissa	27	Allergy, Clinical Immunology & Rheumatology	Clinical Research
Mahaparn, Irisa	93	Nephrology & Hypertension	Clinical Research
Mansour, Razan	89	Nephrology & Hypertension	Clinical Research
Mansour, Razan	90	General & Hospital Medicine	Clinical Research
Mathews, Thomas	118	General & Hospital Medicine	Case Report/Clinical Vignette
Matson, Scott	73	Pulmonary, Critical Care & Sleep Medicine	Basic/Biomedical Mechanisms
Matson, Scott	74	Pulmonary, Critical Care & Sleep Medicine	Clinical Research
Maz, Mehrdad	28	Allergy, Clinical Immunology & Rheumatology	Clinical Research
Mazzotti, Diego	10	Medical Informatics	Clinical Research
Mazzotti, Diego	20	Medical Informatics	Clinical Research
McGreevy, Sheila	54	General & Hospital Medicine	Patient Safety/Quality Improvement Research
McGrevey, Danica	100	Physical Activity & Weight Management	Clinical Research

Presenting Author (Last, First)	Poster #	Division of Presenting Author	Type of Abstract
Mount, Rebecca	34	General & Hospital Medicine	Clinical Research
Mushtaq, Umair	25	Hematologic Malignancies & Cellular Therapeutics	Clinical Research
Mushtaq, Umair	26	Hematologic Malignancies & Cellular Therapeutics	Clinical Research
Nazir, Usman	109	Pulmonary, Critical Care & Sleep Medicine	Patient Safety/Quality Improvement Research
Niedbalski, Peter	42	Pulmonary, Critical Care & Sleep Medicine	Clinical Research
O'Dea, Anne	115	Medical Oncology	Patient Safety/Quality Improvement Research
Pagadala, Prathyusha	47	Endocrinology, Diabetes & Clinical Pharmacology	Case Report/Clinical Vignette
Prasad, Chandrashekhar	65	Pulmonary, Critical Care & Sleep Medicine	Basic/Biomedical Mechanisms
Preet, Ranjan	7	Medical Oncology	Basic/Biomedical Mechanisms
Prevallet, Ashley	61	Physical Activity & Weight Management	Education
Price, Michael	3	Pulmonary, Critical Care & Sleep Medicine	Basic/Biomedical Mechanisms
Ram, Anil Kumar	37	Pulmonary, Critical Care & Sleep Medicine	Basic/Biomedical Mechanisms
Reddy, Pranay	119	Gastroenterology, Hepatology & Motility	Case Report/Clinical Vignette
Reddy, Pranay	120	Gastroenterology, Hepatology & Motility	Case Report/Clinical Vignette
Reddy, Pranay	79	Gastroenterology, Hepatology & Motility	Case Report/Clinical Vignette
Reddy, Pranay	80	Gastroenterology, Hepatology & Motility	Case Report/Clinical Vignette
Reddy, Pranay	81	Gastroenterology, Hepatology & Motility	Case Report/Clinical Vignette

Presenting Author (Last, First)	Poster #	Division of Presenting Author	Type of Abstract
Rooge, Sheetal	12	Gastroenterology, Hepatology & Motility	Basic/Biomedical Mechanisms
Rooney, Anthony	87	Medical Oncology	Case Report/Clinical Vignette
Rouse, Michael	82	General & Hospital Medicine	Education
Samo, Salih	69	Gastroenterology, Hepatology & Motility	Basic/Biomedical Mechanisms
Seldeen, Kenneth	55	Geriatric Medicine	Clinical Research
Shafiq, Muhammad	4	General & Hospital Medicine	Clinical Research
Sharma, Madhulika	72	Nephrology & Hypertension	Basic/Biomedical Mechanisms
Shune, Leyla	67	Hematologic Malignancies & Cellular Therapeutics	Clinical Research
Shune, Leyla	68	Hematologic Malignancies & Cellular Therapeutics	Clinical Research
Silswal, Neerupma	110	Pulmonary, Critical Care & Sleep Medicine	Basic/Biomedical Mechanisms
Slimmer, Stephanie	51	General & Hospital Medicine	Education
Slimmer, Stephanie	52	General & Hospital Medicine	Education
Suire, Kameron	102	Physical Activity & Weight Management	Basic/Biomedical Mechanisms
Sun, Weijing	8	Medical Oncology	Clinical Research
Szabo-Reed, Amanda	17	Physical Activity & Weight Management	Clinical Research
Szabo-Reed, Amanda	18	Physical Activity & Weight Management	Clinical Research
Thiyagarajan, Ramkumar	49	Geriatric Medicine	Basic/Biomedical Mechanisms
Thiyagarajan, Ramkumar	50	Geriatric Medicine	Basic/Biomedical Mechanisms
Tikhanovich, Irina	21	Gastroenterology, Hepatology & Motility	Basic/Biomedical Mechanisms

Presenting Author (Last, First)	Poster #	Division of Presenting Author	Type of Abstract
Treanor, Owen	56	Geriatric Medicine	Basic/Biomedical Mechanisms
Troen, Bruce	58	Geriatric Medicine	Clinical Research
Venkatesh, Priyanka	33	General & Hospital Medicine	Clinical Research
Waller, Stephen	29	Infectious Diseases	Basic/Biomedical Mechanisms
Wesson, William	15	Hematologic Malignancies & Cellular Therapeutics	Clinical Research
Wesson, William	16	Hematologic Malignancies & Cellular Therapeutics	Clinical Research
Williams, Christopher	104	Allergy, Clinical Immunology & Rheumatology	Clinical Research