American Thoracic Society

EDUCATION

Minority Trainee Development Scholarship

AWARD WINNING ABSTRACTS 2020

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PROGRAM OVERVIEW

The American Thoracic Society (ATS) would like to congratulate the 40 Minority Trainee Development Scholarship (MTDS) recipients for their outstanding abstracts and excellent contribution to the Society!!

The MTDS program provides an opportunity for individuals of minority status in science and medicine to travel to the ATS International Conference yearly. A unique aspect of the MTDS is that a trainee at any level (high school and beyond) who submits an abstract is eligible to be considered for this award. On average each year, the ATS receives 60+ applications and a sub-committee chaired by Dr. Yolanda Mageto, ranks applications to select the top applicants. From 2002 to 2013 this program was supported by Merck; however, in the past few years that ATS has funded this program because the Society values advancing the careers of early career professionals.

History and Results:

The MTDS program aims to address the lack of underrepresented minorities in respiratory medicine. The program was created in 2002 under the leadership of Membership and Training Committees spearheaded by Dr. Estelle Gauda in an effort to recruit the best and brightest underrepresented minorities to the field of pulmonary, critical care and sleep medicine.

- Of the **407** past awardees **155 participants** are pursuing a career in Pulmonary, Critical Care and /or Sleep Medicine and **192 participants** have remained members of the ATS.
- MTDS Awardees have stated in surveys done from 2011 – 2020 that they would not have attended the ATS International Conference if it were not for the MTDS scholarship.

Criteria:

Each MTDS recipient is an author of an abstract accepted for presentation at the ATS 2020 International Conference. The awards are based on the quality of science, the contribution of the trainee to the project and the potential impact of the award on the trainee's career development. Additional award criteria includes:

- Must be a member of an underrepresented minority group as defined by the NIH (African American, Hispanic, Native American, Alaskan Native or Pacific Islander)
- Must not be a recipient of another abstract award to the 2020 ATS International Conference
- Must be a trainee (high school through post-doctoral fellow) at a US Institution.
- Must be an author (preferably first author) of an abstract accepted for presentation at the ATS IC.

The Minority Trainee Development Scholarship (MTDS) would like to thank the American Thoracic Society for their generosity in supporting this program!

For more information about this program, please click the button below or contact Liz Guzman at lguzman@thoracic.org

Click here to learn more about MTDS

CONGRATULATIONS to all Minority Trainee Development Scholarship (MTDS) AWARDEES

Abstract Title: High IL-6 asthma is associated with lower FEV1 and greater likelihood of metabolic dysfunction

Authors: Dionne Adair MBBS, Njira Lugogo MD, Matheos Yosef, Shokoufeh Khalatbari

University of Michigan

INTRODUCTION: The incidence of asthma has increased dramatically over the last several decades, in tandem with a rise in obesity. Studies suggest that IL-6 may play a key role in disease pathogenesis in obesity-associated asthma. We sought to examine the relationship between IL-6 levels and lung function in asthmatics, and the impact of obesity and metabolic dysfunction.

METHODS: We utilized the Coronary Artery Risk Development in Young Adults (CARDIA) cohort to confirm associations between IL-6, asthma and metabolic dysfunction. In this cohort, a history of asthma, metabolic disease, lung function measurements, CRP and serum IL-6 were collected. We performed a cross sectional analysis of the cohort at year 20, as this was the timepoint for IL-6 measurements. In addition, we compared median IL-6 in the black vs the white population overall irrespective of asthma status. Univariable and multivariable stepwise regression analyses of (log)IL-6 were performed on demographic and clinical variables (see table). Metabolic syndrome, as defined by NIH criteria was included in the model. The 95th percentile of IL-6 was used as the cutoff to determine high (vs low) IL-6. Wilcoxon rank sum test was used to compare clinical data between groups.

	Univariable		Multivariable	
Characteristic	Estimate	P value	Estimate	P value
C-Reactive Protein (CRP) (ug/mL)	0.069	<.0001	0.0496	<.0001
Race (Black)	.368	<.0001	0.138	<.0001
Sex (Female)	0.138	<.0001		
FEV1 (L)	-.241	<.0001	-.0765	<.0001
FVC (L)	-.191	<.0001		
FEV1/FVC ratio	0.524	0.0147		
Body Mass Index (kg/m^2)	0.050	<.0001	0.028	<.0001
Metabolic Dysfunction* (Y/N)	0.432	<.0001	0.112	0.0013
Hemoglobin A1c (%)	0.148	<.0001		
Fasting Glucose (mg/dL)	0.003	<.0001		
Two or more asthma attacks in your lifetime	0.166	0.0004		
Currently taking meds for asthma (Y/N)	0.232	<.0001		
Asthma in past year (Y/N)?	0.220	<.0001		
Average Systolic Blood Pressure (mmHg)	0.007	<.0001		
Average Diastolic Blood Pressure (mmHg)	0.014	<.0001		

*Metabolic Dysfunction defined as three or more of the following measurements:

- Abdominal obesity (Waist circumference of greater than 40 inches {101.6cm} in men and greater than 35 inches {88.9 cm} in women)
- Triglyceride level of 150 mg/dL or greater
- HDL cholesterol of less than 40 mg/dL in men or less than 50 mg/dL in women
- Systolic blood pressure of 130 mmHg or greater or diastolic blood pressure of 85 mmHg or greater
- Fasting glucose of 100 mg/dL or greater

RESULTS: Our analysis included 858 healthy (without co-morbid diseases or asthma) and 448 individuals with asthma. Our cohort included a large number of healthy subjects and a high proportion of blacks. While the univariable analyses showed all the variables were significantly associated with (log)IL6, only race (Black), CRP, FEV1, BMI and metabolic dysfunction were significant in the multivariable model as shown in the table below. The black population had higher IL6 levels (median=1.64, p<.0001) than whites (median=1.18). The individuals who met criteria for metabolic syndrome also had higher (log)IL-6 levels (median=0.90 vs median=0.43, p<.0001). We found a positive association of (log)IL-6 with CRP (r=0.51, p<.0001) & BMI (r=0.41, p<.0001). Increasing (log)IL-6 negatively correlated with FEV1(r=-0.25, p<.0001). IL-6 appears to be an independent factor affecting lung function with lean asthmatics with high IL-6 levels demonstrating a significant reduction in the FEV1 (median=2.35, IQR=2.06-2.69; p=0.003) compared to those with low IL-6 levels (median=2.88, IQR=2.41-3.37). Obese subjects with asthma and high IL-6 demonstrate the most significant reduction in lung function.

CONCLUSION: High IL-6 asthma is associated with the greatest reduction in lung function and a greater likelihood of metabolic dysfunction. The black population had higher mean IL-6 levels indicating that a race specific reference range may be appropriate.

Dionne Adair is a fellow at the University of Michigan. Her research efforts seek to examine the association between IL-6, asthma and metabolic dysfunction. Her passion for refining the management of severe asthma has motivated her to contribute to the ever-growing body of literature on this subject, with the aim of becoming an expert in this field. In the long term, she hopes to return to Jamaica to give back. When not occupied with pulmonary medicine, she enjoys traveling and watching sports (especially a basketball game with LeBron James).

Abstract Title: Education And Graft Survival In Lung Transplantation

Authors: Dr. Olawale Amubieya, S. Sam Weigt

UCLA

RATIONALE: Lung transplantation is an effective tool for the treatment of select patients with a range of end stage lung diseases, but life expectancy post-transplant remains modest with median survival of 5.5 years and donor organs are a scarce resource. The identification of potentially modifiable patient factors to improve transplant survival is of great clinical interest. We hypothesize that higher health literacy as estimated by highest education level attained will be associated with decreased one year composite mortality and allograft failure.

METHODS: We conducted a retrospective analysis of panel data provided by the United Network of Organ Sharing. Data for 21,916 lung transplants conducted between May 2005 and June 2018 were included. Logistic regression accounting for regional clustering using a random effects model was used to estimate the effect of health literacy on transplant outcomes.

RESULTS: Having attended some college was associated with a 6.5% decrease in the odds of 1 year composite mortality or graft failure as compared to recipients with a high school degree or lower, p=0.04.

CONCLUSION: The presence of some college education was associated with a modest decrease in the odds of mortality or graft failure at one year post-transplant. Further study is required to better characterize this relationship and determine whether it is truly the result of differences in health literacy or if education level is a surrogate for a confounder. It would be of particular interest to determine if the difference in mortality between less and more educated transplant recipients could be mitigated through a patient education intervention.

Dr. Olawale Amubieya is a first-generation Nigerian-American born and raised in Houston, TX. He graduated from Yale University with a B.S. in Molecular Biophysics & Biochemistry. He completed his MD at Columbia College of Physicians and Surgeon prior to becoming a resident and chief resident in Internal Medicine at UCLA. He is currently a third-year clinical fellow in Pulmonary and Critical Care Medicine at UCLA. He is also a scholar of the UCLA Specialty Training and Advanced Research (STAR) program where he is undertaking research training and working towards a PhD in Health Policy and Management at the UCLA Fielding School of Public Health. He will spend the next two years completing his PhD while undergoing specialty training in lung transplant medicine.

Abstract Title: microRNA181b is Protective in Murine Models of Sepsis by Limiting Gut Permeability

Authors: Arciniegas A, Varon J, Decorte J, Fandino L, Haemmig S, Yang D, Chang SC, Feinberg MW, Baron RM

Brigham and Women's Hospital

RATIONALE: microRNA181b (miR181b) has been shown to be an important regulator of inflammation through NFk-b. The role of miR181b in sepsis remains unclear. In order to elucidate possible mechanisms by which miR181b might contribute to sepsis related morbidity and mortality, we investigated outcomes and physiology in both global miR181b knockout (KO) mice in various murine models of sepsis and endotoxemia.

METHODS: Global miR181b KO mice were exposed to cecal ligation and puncture (CLP) (100% ligation, 2 holes with 19g needle), a model of polymicrobial sepsis, and mortality curves were generated. Tight junction transcripts were measured using rtPCR. Phagocytosis was assessed using co-culture of cells obtained via peritoneal lavage with green fluorescent protein (GFP) labelled e. coli via flow cytometry. To assess vascular permeability of the GI tract, mice were challenged with intraperitoneal LPS (40 mg/kg) 20 hours prior to sacrifice and then gavaged 6 hours prior to sacrifice with flourescein isothiocyante-dextran 4 (FD-4); blood was harvested and levels of FD-4 were measured fluoroscopically.

RESULTS: Global miR181b KO mice experienced earlier mortality after CLP when compared to controls with a Cumulative Median Survival of 95.25 hours Vs. 35 hours and Hazard Ratio: 2.721, 95% CI (1.28,5.79). In order to elucidate the cause of this phenotype, we investigated transcription of various tight junction transcripts in the cecum; all but one transcript was suppressed the KO mice (p=0.0012). There were no differences in phagocytosis between KO and controls. Global miR181b KO mice challenged with intraperitoneal LPS showed more evidence of endovascular leak as measured by FD-4 levels in the blood after gavage when compared to controls.

CONCLUSIONS: Absence of miR181b leads to early mortality in murine models of sepsis in an effect that appears to be mediated by increased endovascular leak in the GI tract. The effect does not appear to be mediated by impaired phagocytosis, as measured by uptake of GFP labelled e. coli by neutrophils or macrophages.

Antonio Arciniegas is a medical doctor from Colombia. A few years after graduation from medical school he joined Dr. Rebecca Baron's laboratory at the Brigham and Women's Hospital in Boston to study lung injury associated with sepsis and mechanical ventilation. During this time he has worked on a number of projects investigating mechanisms underlying lung injury and sepsis, which he has previously presented at the 2017 and 2018 ATS conferences. Now, he is grateful for being again a recipient of the MTDS award for 2020 for his work elucidating the role of 181b microRNA in gut permeability during polymicrobial sepsis.

Abstract Title: Assessment Of Ventilation Inhomogeneity After Recovery From Acute Chest Syndrome In Pediatric Patients With Sickle Cell Disease

Authors: Monique Bailey[1], Mansi Mehta[2], George Silva[3], Martha Wetzel[4], Tamara New[3], Marianne Yee[3], Angela James-Herry[3], and Lokesh Guglani[5]

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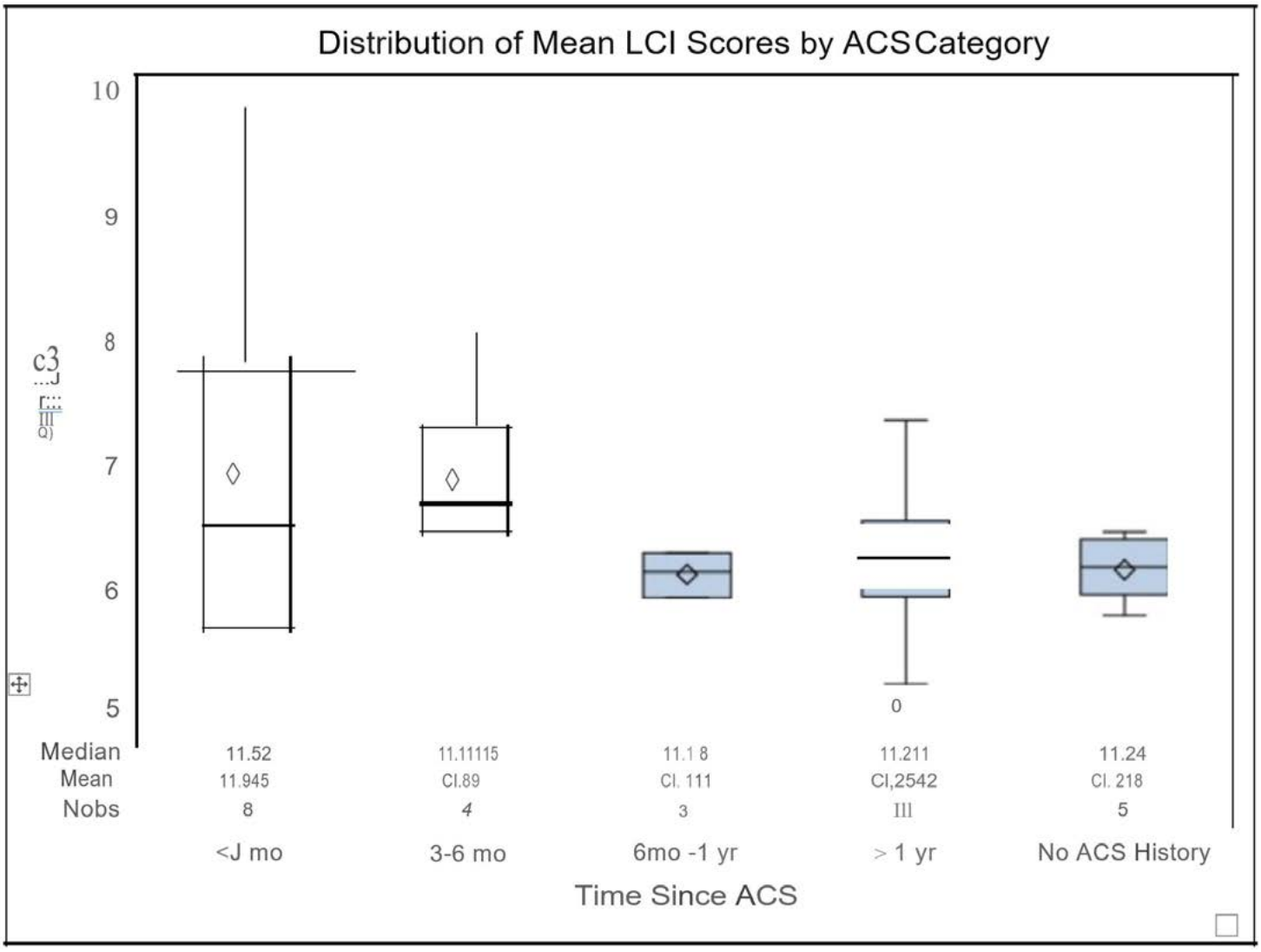
RATIONALE: Acute chest syndrome (ACS) is a complication of sickle cell disease that can lead to mortality in some cases and appreciable morbidity in others, including significant decreases in lung function. Lung Clearance Index (LCI) is a novel method of assessing small airway function using clearance of an inert tracer gas through multiple breath washout technique. The measured value of LCI is indicative of ventilation inhomogeneity in the small airways; thus, higher disease severity correlates with increasing LCI.

METHODS: This was an IRB approved, prospective case-control study comparing LCI values in sickle cell patients with differing ACS history. Sickle cell patients were recruited from the CHOA Aflac Sickle Cell clinic. Cases were defined as sickle cell patients aged 6-18 with a history of at least 3 episodes of ACS. Controls were defined as demographically matched patients with a history of

Figure: Lung Clearance Index Values by Acute Chest Syndrome Category



less than 3 episodes of ACS. Matching demographics included age, gender, race/ethnicity, Hb type, and age at diagnosis. Pulmonary and other comorbidities as well as their treatments were compared between groups as secondary measures. Each participant performed LCI testing using inert gas multiple breath washout technique with the Innovision® Innocor device, which is FDA approved for measurement of LCI. The recorded measurement for each test was an average of 2 to 3 trials with FRC values within 10% of each other. Participants also completed spirometry testing with a standard spirometry device as part of their routine clinical care.

RESULTS: We found no significant difference in mean LCI values between cases and controls ($p = 0.512$).Similarly, there was no significant difference in median FEV1 from PFTs between cases and controls ($p = 0.578$). The calculated effect size between mean LCI values among groups was small, with a magnitude of0.298. There was no correlation between LCI and time since last ACS episode for either the case or control group. High variance was observed in the LCI measurements taken closest to the last ACS episode (Figure).

CONCLUSIONS: Our data suggests there is no persistent ventilation inhomogeneity among pediatric sickle cell patients once they have recovered from ACS. Patients with a higher number of ACS episodes did not have significantly higher LCI values. As time progresses, LCI normalizes among groups regardless of the number of prior ACS events before the most recent episode. Future larger studies may focus on time course categories to confirm the apparent recovery of small airway lung function.

Monique Elizabeth Bailey is a native Georgian entering Pediatrics residency at MCG in Augusta, GA. She has an interest in primary care, loves to play video games and enjoys bike rides in her free time.

Abstract Title: Microbiome-Dependent Effects Influence Susceptibility to Lung Injury and Fibrosis

Authors: G. M. Barrón[1], C. L. Hrusch[1], V. Leone[2], N. Fei[2], K. A. M. Mills[1], M. K. Hollinger[1], E. B. Chang[2], J. Gilbert[3], A. I. Sperling[1]

[1]Medicine/PCCM, University of Chicago, Chicago, IL, United States, [2]Medicine/GI, University of Chicago Medicine, Chicago, IL, United States, [3]Health Sciences/Pediatrics, UCSD, San Diego, CA, United States.

RATIONALE: Idiopathic pulmonary fibrosis (IPF) is a devastating progressive lung disease that causes irreversible lung scarring and loss of pulmonary function. While the chemotherapeutic agent bleomycin (BLM) is used to model IPF and lung injury in mice, its effects are variable. This raises the question: what mechanisms govern the immunologic response to BLM-induced lung injury and fibrosis? We previously observed differences in survival and weight loss after BLM treatment in mice housed in two different UChicago mouse facilities. BLM treatment of C57BL/6 (B6) mice housed in Facility A had increased survival and decreased weight loss as compared to BLM treated B6 mice in Facility B. Additionally, mice in Facility B exhibited increased fibrosis compared to Facility A.

OBJECTIVE: To determine whether the responses to lung injury differ between the two facilities due to unique intestinal microbiome influences on the lung immune landscape.

METHODS: To identify differences in the gut microbiome promoted by each facility, untreated gnotobiotic B6 (ex-germ-free) mice were conventionalized by exposure to fecal matter from facility A or facility B. After 2 weeks, we collected fecal samples from each ex-germ-free mouse and performed 16S rRNA sequencing using the Illumina MiSeq platform and analyzed using QIIME2. The immune cell profiles in lung and spleen samples from ex-germ-free mice housed in facilities A and B were assessed via flow cytometry and analyzed using FlowJo and with machine learning algorithms, including t-SNE and PhenoGraph.

RESULTS: 16S rRNA sequencing revealed distinct fecal microbial community membership between the mice conventionalized with facility A vs. B gut microbes. Flow cytometric analysis of lung and spleen samples showed expansion of CD4+ T regulatory (Treg) cells (CD25+ Foxp3+) at baseline in Facility A mice as compared to Facility B counterparts. Further, naïve CD4+ conventional cell (Tconv) populations (CD44- CD62L+) and CD8+ central memory T cells (TCM) were more abundant in Facility B mice as compared to Facility A mice.

CONCLUSION: These results suggest intestinal microbes promoted in separate facilities can influence adaptive immune processes and outcomes in BLM-induced lung injury. The protective phenotype in Facility A is defined by an expansion of Treg cells and the exacerbated lung injury phenotype in Facility B is defined by increased naïve CD4+ Tconv and CD8+ TCM cells. Our data implicate the microbiota in shaping adaptive immune responses in the context of lung injury and fibrosis.

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Gabriel M. Barrón is currently an undergraduate researcher at the University of Chicago in the lab of Dr. Anne Sperling. His interests include leveraging computational methods to interrogate immunological processes as well as understanding the basis of how microbiota contribute to healthy and diseased states. Starting in the fall, Gabriel will begin to pursue his doctoral education at Stanford University in the field of Immunology. In his free time, he is often found candidly photographing the city and people of Chicago, finding the best Cuban cafes and biking along the lake (when it's not frozen).

Abstract Title: Pre-clinical And Clinical Pulmonary Hypertension Is Associated With Right Ventricular Endothelial-to-mesenchymal Transition Mediated Via Transcription Factor Snail: Therapeutic Role For In Vivo Snail Knockdown

Authors: V. R. Clark, J. Park, M. Zargari, E. Said, C. Makar, N. Yin, T. Le, D. Bagsik, J. Hong, G. Fishbein, L. Saddic, S. Umar

David Geffen School of Medicine at UCLA, Los Angeles, CA, United States.

BACKGROUND RV-failure (RVF), the main cause of death in pulmonary hypertension (PH) patients, is associated with distinct structural remodeling which is poorly understood. We performed transcriptome analysis of RV remodeling in two clinically relevant rat models of PH using RNASeq and investigated the role of transcription factor Snail in mediating Endothelial-to-Mesenchymal Transition (EndMT) in rats and explanted human RV tissue. We also performed in vivo knockdown of Snail as a therapeutic strategy for RVF.

METHODS Adult male Sprague Dawley rats (250-300g) received either a single s.c. injection of Monocrotaline (MCT, 60mg/kg, n=4; followed for 30-days) or Sugen (SU5416 20mg/kg, n=4; 10% O2 hypoxia for 3-weeks followed by normoxia for 2-weeks). PBS treated rats served as controls (CTRL, n=4). For in vivo Snail knockdown, MCT-rats either received Snail-siRNA (n=5; 5nM/injection every 3-4 days; 4-injections) or PBS (n=13) through tail vein from day 14- 30 after MCT. Echocardiography and RV-catheterization were performed terminally. RVs were stained with Trichrome and EndMT markers. RNASeq was performed on rat RV tissue. Differential expression analysis was conducted. Gene expression was assessed by RT-PCR. Human RV sections (CTRL n=3, PAH n=7) were stained with Trichrome and Snail antibody. Values are mean±SEM.

RESULTS PH was confirmed by increased RVSP(mmHg) in MCT(97.6±6.6) and Su/Hx(85.26±15.6) vs CTRL(37.1±1.3; $p<0.05$). Fulton-index was significantly increased in MCT (0.82±0.07) and Su/Hx(0.61±0.1) vs CTRL(0.27±0.01; $p<0.05$). MCT and Su/Hx had significant RV dilatation vs CTRL(RVID diastolic: MCT 3.5±0.3mm, SuHx 2.5±0.2 vs CTRL 1.3±0.1; $p<0.05$). PH patients had significantly elevated RVSP(80.7±9.9 mmHg) and reduced RV-function. Trichrome demonstrated increased RV-fibrosis in MCT and Su/Hx rats and PH patients. Double immunolabeling of RVs demonstrated colocalization of endothelial and smooth muscle markers, illustrating EndMT in RVs of MCT and Su/Hx and humans. RNASeq demonstrated EndMT as the top upregulated pathway in both MCT and Su/Hx RVs. Snail was significantly increased(~2-fold) in MCT and Su/Hx($p<0.05$) and demonstrated increased nuclear immunolabeling (activation) in humans. Other known EndMT-transcription factors Snai2, Twist1, and Zeb1 were unchanged. Based on RNASeq, we propose that increased TGFβ(~2-fold), CDKN2B(~3-fold) and PRSS23(~2-fold) upregulate Snail that recruits LOXL2(~2-3-fold increase), causing HistoneH3 oxidation(~1.5-fold decrease) and CBX5(~1.5-fold decrease) release leading to chromatin reorganization resulting in EndMT. Finally, MCT-rats treated with Snail-siRNA demonstrated decreased Snail expression, RVSP(67.78±7.0 vs.84.35±3.54 mmHg; $p<0.05$), and Fulton-index(0.44±.03 vs. 0.68±.04; $p<0.05$). Conclusions Pre-clinical and clinical PH-induced RVF is associated with EndMT mediatedvia Snail. Targeting Snail and its network may result in novel therapeutic strategies for PH-associated RVF.

Varina Clark is a medical student at the David Geffen School of Medicine (DGSOM) at UCLA from Mount Vernon, NY. She pursued her Sc.B. degree in Human Biology at Brown University. Her current research explores potential biomarkers that will help to lay the foundation for therapeutic targets for pulmonary hypertension-associated right ventricular failure. As a future clinician-investigator, her goal is to take an active role in the bench-to-bedside approach to treating debilitating diseases, addressing health disparities, improving health outcomes and providing culturally-responsive, comprehensive healthcare to patients.

Abstract Title: Risk Factors for Lung Cancer in Never Smokers: Insight from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial Dataset

Authors: Farouk Dako[1], Jason Hostetter[1], Jean Jeudy[1], Rydhwana Hossain[1], Paul Yi[2], Kenneth Wang[1,3], Charles White[1], Eliot Siegel[13]

[1]Department of Radiology, University of Maryland, Baltimore, MD, United States, [2]Department of Radiology, Johns Hopkins Hospital, Baltimore, MD, United States, [3]Department of Radiology, Veterans Affairs Medical Center, Baltimore, MD, United States.

RATIONALE: Lung cancer in never smokers LCINS accounts for up to 20% of lung cancer deaths and is the seventh leading cause of cancer mortality in the U.S. Factors for the incidence of LCINS are not well understood. Increasing availability of large datasets and the advancement of big data analysis techniques provide an opportunity for broader insight. The Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) Screening Trial enrolled 154,901 participants aged 55-74 between 1993 and 2001 to determine whether certain screening exams reduced cancer mortality. This dataset includes extensive information on participants including demographics, lifestyle, socioeconomic status and medical history from one of the largest screening trials in the U.S.

METHODS: Custom application with modern web frameworks was developed using a web-based interface to query a server-side database. Initial analysis of the PLCO dataset was performed to calculate the incidence of lung cancer in never smokers. Subsequent analysis was performed to evaluate associations between LCINS and multiple variables including race, gender, BMI, height, socioeconomic status, second-hand smoke exposure, exercise, family and personal history of lung cancer, alcohol consumption, fruit consumption, Beta carotene or vitamin A supplements, as well as multiple other variables.

RESULTS: Evaluation of the cohort revealed that 41% of participants are never smokers of cigarettes or cigars. The incidence of LCINS was 0.4%, one-tenth the 4% incidence reported in current and former smokers ($p<0.0001$). Adenocarcinoma was the predominant histopathology subtype, present in 68% of cases. Nonsmokers with income less than $50,000 were 1.8 times more likely to develop lung cancer compared to nonsmokers with income more than $50,000 ($p= 0.01$). Participants who drank alcohol were more than twice as likely to develop LCINS compared to those who reported abstinence (RR: 2.1, P= 0.027). Associations were also noted with BMI > 30, family history of lung cancer and prior personal history of any cancer, (RR: 0.7, p= 0.04), (RR: 1.7, p=0.019) and (RR: 1.6, p=0.048) respectively. No statistically significant correlation with developing lung cancer was noted with the variables of race, gender, second-hand smoke exposure, COPD, family history of any cancer, height, level of education, exercise levels, consumption of fruits and beta carotene or vitamin A supplements.

CONCLUSION Our study results demonstrate that lower income, alcohol use, family history of lung cancer and personal history of any cancer are associated with a higher likelihood of developing LCINS. No correlation was noted with other important variables such as race, gender and second-hand smoke exposure.

Farouk Dako is Cardiothoracic Radiology and Imaging Informatics fellow at University of Maryland in Baltimore with a passion for population health and health equity.

Abstract Title: Unraveling the Autofluorescence Properties Of Pulmonary Amyloids: Prelude to A Point-of-Care Detection Method In Critically Ill Patients

Authors: A. deWeever[1], M. S. Gwin[1], S. B. Voth[1], R. Balczon[2], T. Stevens[1]

[1]Physiology and Cell Biology, University of South Alabama College of Medicine, Mobile, AL, United States, 2Biochemistry and Molecular Biology, University of South Alabama College of Medicine, Mobile, AL, United States.

RATIONALE: Amyloids possess unexploited autofluorescence properties which could be useful for their detection in patients recovering from hospital acquired pneumonia (HAP). Recovering HAP patients have cytotoxic amyloids in their bronchoalveolar lavage fluid, blood, and cerebrospinal fluid. Pulmonary amyloids may be responsible for the cognitive decline and secondary organ failure patients experience after HAP. Infection of pulmonary microvascular endothelial cells (PMVECs) produces bacteria strain-dependent cytotoxic or antimicrobial amyloids which may have different fluorescence properties.

Currently, there are no detection methods for pulmonary amyloids at the bedside. Here we hypothesize that cytotoxic and antimicrobial amyloids can be detected and distinguished by their autofluorescence properties.

METHODS: PMVECS were infected with two strains of Pseudomonas aeruginosa, including ExoY+ (PA103ΔexoUexoT:: c pUCPexoY) and ΔPcrV (PA103ΔpcrV pUCPexoY) to generate amyloids with distinctive phenotypes. Infection with ExoY+ for 6 hours generates cytotoxic amyloids, while infection with ΔPcrV for 4 hours produces antimicrobial amyloids. To determine whether the autofluorescence properties are protein concentration-dependent, protein concentrations of the supernatants were standardized to 100 μg/mL. To assess whether fibrillar amyloids are responsible for the autofluorescent signature of ExoY+ and ΔPcrV supernatants, the supernatants were immunodepleted with the fibril- specific OC antibody. Fluorescence spectroscopy was performed to obtain the fluorescence spectra of the unstandardized, standardized, and immunodepleted ExoY+ and ΔPcrV supernatants, where supernatant was excited at 395 nm and emission collected from 430-600 nm at 5 nm increments.

RESULTS: The unstandardized fluorescence spectra of ExoY+ and ΔPcrV were indistinguishable; however, when standardized to 100 μg/mL, the fluorescence intensity of ΔPcrV supernatant containing antimicrobial amyloids was significantly greater than ExoY+ supernatant containing cytotoxic amyloids. The normalized emission spectra and peak emission wavelength of standardized ExoY+ and ΔPcrV supernatants were also distinct. Immunodepleting the supernatant with the OC antibody eliminated the fluorescence intensity of ΔPcrV supernatant but did not diminish the fluorescence intensity of the ExoY+ supernatant.

CONCLUSION: Our work suggests that the autofluorescence of amyloids can be developed as a point-of- care diagnostic tool in critical illness. Infection-derived antimicrobial amyloids can be detected by eliminating the autofluorescence through removal of fibrillar amyloid species. Interestingly, these results indicate that cytotoxic amyloids in the ExoY+ supernatant are not fibrils but are structurally distinct from antimicrobial amyloids. Work regarding the detection of cytotoxic amyloids in clinical samples is ongoing. Here we show that the autofluorescence properties of cytotoxic and antimicrobial pulmonary amyloids are distinct and can be harnessed for their label-free detection.

Althea deWeever is a doctoral candidate in the Center for Lung Biology at the University of South Alabama. She earned her Bachelor of Science in Polymer Science in 2015 at the University of Southern Mississippi. She is a member of Dr. Troy Stevens' laboratory, where she examines the structural basis of endothelial-derived cytotoxic amyloids. Althea is interested in both the structural and autofluorescence properties of cytotoxic amyloids generated in response to bacterial infection. The goal of her doctoral research is to: [1] understand the role of tau protein in the production of cytotoxic amyloids during the infection of pulmonary microvascular endothelial cells, and [2] develop a novel diagnostic utilizing amyloid autofluorescence for the detection of cytotoxic tau amyloids.

Abstract Title: Session Diagnosing and Treating Microaggressions in your Healthcare Team

Authors: Francesca Duncan, MD[1], Erin Crowley, MD[1]. Indiana University School of Medicine[1]. Indiana University School of Medicine[1].

Indiana University School of Medicine

DESCRIPTION: Microaggressions are subtle, intentional or unintentional discriminatory statements or actions made against a marginalized group of people. Some individuals rarely experience them, while other learners and colleagues encounter them daily. This interactive workshop will include a real-life re-enactment of a racist patient encounter, define microaggressions and other terms, and allow participants to role play challenging situations in their work environment while utilizing a tool to identify, address, and ameliorate microaggressions.

THE GREAT IMITATOR: Intravascular large B cell lymphoma is a subtype of lymphoma characterized by the proliferation of lymphoma cells within the lumen of small blood vessels, particularly capillaries. This typically occurs without any obvious extravascular tumor or circulating lymphoma cells in the blood. The clinical presentation varies and often includes symptoms related to organ dysfunction caused by occlusion of blood vessels by lymphoma cells. In the past, the diagnosis was usually only made on autopsy; however, the increase awareness of this rare subtype of lymphoma has resulted in more patients being diagnosed and ultimately treated. We discuss a case of intravascular large B cell lymphoma in a previously active male who presented with progressive dyspnea and unexplained hypoxia.

Patient is a 76 year old male who presented with two weeks of progressive dyspnea on exertion and at rest accompanied by hypoxia. Initial workup up included a spiral computed tomography which was negative for acute pulmonary embolism and unremarkable lung parenchymal disease. Transthoracic echocardiogram with bubble study showed a small right-to-left shunt and right heart catherization was normal. He was discharged on 4 liters without an explanation of the etiology of his symptoms. He returned one week later with worsening dyspnea. He had no fevers, chills, lower extremity swelling, orthopnea, or underlying lung disease. He was a former smoker with a 20 pack-per-year smoking history. He had repeat chest tomography, echocardiogram, and carboxyhemoglobin all within normal limits. His pulmonary function testing was notable for isolated severely decreased diffusing capacity. Admission white blood cell count was 5 and hemoglobin was 11. Patient was deemed high risk for respiratory failure and intubation with bronchoscopy, so decision made to trial high dose steroids. He continued to have progressive respiratory failure and ultimately succumbed from it. Autopsy report denoted patent foramen ovale and tumor cells were found to be involving the small vessels of the lungs, spleen, kidneys, adrenals, heart, and skin consistent with intravascular large b cell lymphoma.

Intravascular large B cell lymphoma is characterized as the proliferation of neoplastic lymphocytes only in the lumen of small vessels. Symptoms related to the nervous system and skin are usually noted and skin biopsy is performed when suspected. A step-wise approach to the diagnosis and management of hypoxia should be employed in all patients. An increase level of suspicion of pulmonary involvement should be considered in patients with hypoxia, progressive dyspnea, and non-diagnostic workup. Recent studies have suggested the use of transbronchial biopsy and positron emission tomography in the appropriate clinical context to aid in the diagnosis. An attempt at early diagnosis can potentially lead to timely initiation of therapy.

Dr. Francesca Duncan earned her medical degree at Meharry Medical College and completed a combined Internal Medicine – Pediatrics Residency Program at The Ohio State University. She is a 2nd year fellow in Pulmonary & Critical Care Medicine at Indiana University School of Medicine. Her research interest includes health disparities in lung cancer.

Abstract Title: Systemic Inflammation Increases with Progression of Pulmonary Arterial Hypertension

Authors: Mariana Dupont[1], Antonio D. Rodriguez Martin[2], Okaeri A. Hernandez[3], Savanna Lambert[4], Stefanie Krick[5], Jarrod Barnes[5] and Maria B. Grant[6]

Department of Optometry and Vision Science, School of Optometry, University of Alabama at Birmingham[1]; Department of Biology, College of Art and Science, University of Alabama at Birimgham[2]; Department of Clinical & Diagnostic Sciences, School of Health Professions, University of Alabama at Birmingham[3]; School of Public Health, University of Alabama Birmingham[4]; Department of Medicine, Division of Pulmonary Medicine, University of Alabama, Birmingham, Alabama [5];Department of Ophthalmology, University of Alabama, Birmingham, Alabama[6]

Plexiform lesions are considered antigenic lesion and represent unique histological inflammatory alterations of pulmonary arteries seen in individuals with severe pulmonary arterial hypertension (PAH). To better understand the impact of systemic inflammation on PAH, we examined peripheral blood mononuclear cell (PBMC) samples from PAH patients (n=33) and age and sex matched controls (n=28). PBMC samples were stained for CD14, CD34, CD45, CD64, CD192, CD195, CD309, and CX3CR1, processed using a BD Biosciences FACSCelesta flow cytometer, and analyzed using FlowJo software. Levels of neutrophils, the first responders to infections and tissue injury, were significantly increased in PAH subjects ($p<0.0001$) when compared to controls. Myeloid angiogenic cells, a bone marrow-derived progenitor population know to promoting tissue repair, showed a 1.5 fold increase in PAH subjects compared to controls ($p=0.0020$). Total monocyte counts were higher ($p<0.0001$), compared to controls, as were pro-inflammatory, classical monocytes expressing CCR5 (CD195) ($p=0.0236$). CCR5 regulates trafficking and effector functions of immune cells. Unexpectedly, mean fluorescence of CCR2 (CD192) on proinflammatory, classical monocytes was significantly decreased ($p<0.001$) in PAH subjects. In anti-inflammatory, non-classical monocytes of PAH subjects, CCR5 and CX3CR1 were both significantly increased ($p=0.0360$; $p=0.0002$, respectively) and CCR2 was significantly decreased ($p=0.0173$). PAH subjects also had a higher percentage of cells that exhibited the transition stage between anti-inflammatory and pro-inflammatory phenotype (intermediate monocytes) ($p=0.0024$). These intermediate monocytes also expressed a significant increase in CCR2 and CCR5 ($p<0.0001$; $p=0.0482$, respectively). Taken together, this study suggests that surface markers such as CCR5, CCR2, and CX3CR1 on monocytes of PAH subjects may provide a snapshot of the PAH subject's systemic inflammatory profile and, with additional studies, may provide a biomarker of PAH disease severity and/or progression.

Mariana DuPont is a 3rd year Ph.D. student at The University of Alabama at Birmingham. Over the past three years, she has worked to gain an understanding of the relationship between the retina and pulmonary vascular diseases. The overall goal is to develop a novel model via retinal vascular imaging that can be used as a window to Pulmonary Arterial Hypertension.

Abstract Title: Racial differences in health-related outcomes in Asthma-Chronic Obstructive Pulmonary Disease Overlap (ACO)

Authors: Chinedu O Ejike[1], Han Woo[1], Ashraf Fawzy[1], Laura M Paulin[2], Fernando J Martinez[3], MeiLan K Han[4], Carlos H Martinez[5], Alejandro A Diaz[6], Diego J Maselli[7], David T Wu[1], Emily P Brigham[1]; Meredith C McCormack[1], Dawn L DeMeo [6], Craig P Hersh[6], Nadia N Hansel[1], Nirupama Putcha[1].

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RATIONALE: There is no consensus on how to define Asthma COPD Overlap (ACO) and its clinical significance remains to be fully understood. Previous analysis of COPDGene has demonstrated an association of ACO status with adverse outcomes but little is known about how ACO and association with outcomes differs by race.

OBJECTIVES: To determine the racial differences in the association of ACO with respiratory outcomes in COPD subjects when using two differing definitions of ACO.

METHODS: We analyzed Non-Hispanic White (NHW) and black subjects with COPD (GOLD stage I-IV) in the COPDGene study. Subjects had ACO based on a physician diagnosis of asthma before 40 years 1 **OR** a physician diagnosis of asthma before 40 years with bronchodilator response (FEV1 > 200 ml and > 12%) and less than 15% emphysema seen on high-resolution CT (HRCT). 2 We used regression analysis with ACO status as the exposure of interest with the outcomes of interest including St. George's Respiratory Questionnaire (SGRQ), modified Medical Research Council (mMRC) score, distance walked in six-minutes (6MWD), predicted mortality based on BODE index, exacerbation frequency, % emphysema, air trapping and airway wall thickness, adjusting for patient characteristics (age, sex, current smoking status, pack years smoked, BMI) FEV1 % predicted and co-morbidities. Interaction terms were included for race (Black vs NHW) with ACO status. We also performed sensitivity analysis looking at the alternate definition of ACO. 2

RESULTS: In **4510** subjects with COPD, **467** met the criteria for ACO based on an asthma diagnosis before 40 years of which **174** were blacks (37%) and **293** NHW (63%).1 When using an alternate definition of ACO, with an asthma diagnosis before 40 years, bronchodilator response and % of emphysema seen on HRCT, **392** met the criteria, with **104** blacks (27%) and **288** NHW (73%) 2. Results show differences in distributions of race within ACO, with fewer blacks identified with ACO when using an alternate definition of ACO. Analysis show the association of ACO and outcomes (mMRC, BODE, 6MWD) were more pronounced among blacks than NHW when adjusted for patient characteristics, FEV1 % predicted and comorbid diseases. Blacks with ACO had worse outcomes when compared to NHW with ACO, irrespective of definition used but nominally worse when an alternate definition of ACO is used. There were no statistically significant interactions between ACO status and race for association with outcomes.

CONCLUSIONS: There are significant differences in racial distribution of ACO based on the definition of ACO used, highlighting the complexity of defining ACO.

REFERENCES

1. Hardin M et.al. The clinical and genetic features of the COPD asthma overlap syndrome. *Eur Respir J*. 2014 August; 44(2): 341–350.

2. Cosentino J et.al. Analysis of Asthma-Chronic Obstructive Pulmonary Disease Overlap Syndrome Defined on the Basis of Bronchodilator Response and Degree of Emphysema. Ann Am Thorac Soc. 2016 Sep; 13(9):1483-9.

Dr. Chinedu Ejike is a Nigerian-American with a MD/MPH degree. He is a fellow of ACP and SHM, and has clinical experience as an academic hospitalist in Ohio, Michigan and Maryland. Maryland. He is currently a Pulmonary Critical Care Fellow at John Hopkins University.

Abstract Title: MicroRNA Regulation of RGS4 in an Asthmatic Mouse Model of Allergic Inflammation

Author: Nathalie Fuentes[1], Morgan McCullough[1] and Kirk M. Druey[1]

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RATIONALE: Allergic asthma is the most common type of asthma. It is triggered by inhaled allergens and affects an approximate of 30 million people worldwide. Many host-derived inflammatory mediators present in asthmatic airways induce bronchospasm by acting on G protein-coupled receptors (GPCRs). GPCRs are negatively modulated by a large group of intracellular proteins called regulators of G protein signaling (RGS) proteins. RGS4, specifically, is expressed in respiratory epithelium and airway smooth muscle, with expression that increases in proportion to clinical severity. Rgs4-/- mice have reduced susceptibility to develop airway hyperresponsiveness compared to wild type (WT) mice. The role of post-transcriptional regulators, such as microRNAs (miRNAs), in RGS4 expression remain unknown. Here, we hypothesized that miRNAs are critical regulators of RGS4 expression and may thereby affect the phenotype of allergen-challenged mice.

METHODS: We challenged WT and Rgs4-/- mice intranasally with PBS or secreted filtrates of Aspergillus fumigatus (Af), a fungus that triggers type 2 immunity and is closely associated with severe asthma. Animals were treated three times per week over a two-week period. Total RNA was extracted from the lungs using the miRNeasy mini kit followed by miRNA sequencing analysis. Data analysis was performed using the R software and Ingenuity Pathway Analysis.

RESULTS: We identified five differentially expressed and statistically significant miRNAs (miR- 3535, miR-677-5p, miR-874-3p, miR-150-3p, miR-574-5p) in the lungs of WT mice compared to Rgs4-/- mice at homeostasis. We also found differentially expressed miRNA signatures in WT and Rgs4-/- mice challenged with Af. In silico pathway analyses identified biological networks (e.g. immune cell trafficking, inflammatory disease and response) affected by RGS4 and exposure to Af that ranged from direct predicted gene targeting to complex interactions with multiple intermediates. Interestingly, there were sex differences in miRNA expression and predicted regulatory networks in PBS-treated Rgs4-/- mice when compared to Af-treated Rgs4-/- mice.

CONCLUSIONS: Our results indicate that RGS4 can influence lung miRNA expression in response to Af exposure, indicating that RGS4-dependent miRNA regulation of inflammatory gene expression could affect the predisposition to develop allergic airway inflammation.

Dr. Nathalie Fuentes has a Ph.D. in Biomedical Sciences from Penn State College of Medicine. She is a post-doctoral fellow at the National Institute of Allergy and Infectious Diseases, NIH. Dr. Fuentes studies the role of microRNAs and G-protein-coupled receptors in the pathogenesis of asthma. She is originally from Caguas, Puerto Rico.

Abstract Title: Incidence of and Risk Factors for Infection-Associated Acute Kidney Injury in Northeast Thailand

Authors: Gabriela Galli[1], Pavan Bhatraju[2], Viriya Hantrakun[3], Chaiyaporn Boonsri[4], Prapit Teparrukkul[4], Direk Limmathurotsakul[3], T. Eoin West[2], Kristina E. Rudd[5]

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Research Funding Source: *National Heart, Lung and Blood Institute of the National Institutes of Health (R01HL113382) and Wellcome Trust (090219/Z/09/Z).*

RATIONALE: Infection-associated acute kidney injury (AKI) is associated with poor outcomes in some high-income countries (HICs). Data from low-resource settings, where causative infections and healthcare system capabilities may differ from HICs, are lacking. Our objective was 1) to determine the incidence of and risk factors for AKI, and 2) to assess features associated with poor outcome among those with AKI, among hospitalized adults with acute infection in northeast Thailand.

METHODS: Secondary analysis of the Ubon-Sepsis study, a prospective cohort study of Thai adults admitted to Sunpasitthiprasong Hospital 2013-2017 with community-acquired infection. All patients were enrolled within 24 hours of admission. Patients with ≥ 2 recorded serum creatinine (SCr) values were included. Those with prior dialysis were excluded. AKI was defined as new dialysis during admission, SCr change ≥ 0.3 mg/dL, or ≥ 50% SCr increase from baseline. Baseline characteristics, severity of illness, and initial clinical management of patients who did and did not have AKI, as well as AKI patients who did and did not die by 28 days, were compared using the chi-squared test. Multivariable logistic regression was used to identify features independently associated with 1) AKI development, and 2) 28-day mortality among AKI patients.

Table: Characteristics of Patient Cohorts

Parameters	Total Population (N=3,162)	AKI Cohort (n=1,674)	No AKI Cohort (n=1,488)
Demographics			
Age (years)(median[IQR])	61 (46-73)	61 (48-72)	61 (45-75)
Male gender (n[%])	1,808 (57.2)	1,010 (60.3)	798 (53.6)
Comorbidities			
Diabetes (n[%])	704 (22.3)	422 (25.2)	282 (19.0)
Congestive Heart Disease (n[%])	77 (2.4)	47 (2.8)	30 (2.0)
Hypertension (n[%])	832 (26.3)	470 (28.1)	362 (24.3)
Chronic Kidney Disease (n[%])	350 (11.1)	242 (14.5)	108 (7.3)
Severity of Illness Upon Study Enrollment			
Lowest Systolic BP (median[IQR])[a]	90 (73-106)	80 (70-100)	97 (80-110)
Blood Lactate (median[IQR])[a,b]	2.0 (1.4-3.3)	2.1 (1.6-3.8)	1.9 (1.3-2.8)
Highest Creatinine (median[IQR])[a,c]	1.6 (1.0-2.7)	2.2 (1.5-3.7)	1.1 (0.8-1.6)
Presence of Bacteremia (n[%])[a]	642 (20.3)	366 (21.9)	276 (18.6)
Infection Management			
ICU Admission within 24 hours (n[%])	562 (17.8)	366 (21.9)	196 (13.2)
Vasopressor Dependent (n[%])[a]	1,311 (41.5)	860 (51.4)	451 (30.3)
Fluids Administered >2 L (n[%])[a,d]	365 (24.5)	263 (27.8)	102 (18.7)
Clinical Outcomes			
28-day Mortality	661 (20.9)	369 (22.0)	292 (19.6)

[a] prior to and up to enrollment; [b] of the 3,109 patients with recorded lactate values; [c] all patients had at least one SCr recorded upon enrollment; [d]of the 1,492 patients with fluid values recorded (946 in the AKI group, 546 in no AKI group)

RESULTS: Of the 4989 patients in Ubon-Sepsis, 3162 were included. Incidence of infection-associated AKI was 53% (n=1674). Patients with AKI were older, with more comorbidities and higher illness severity than those without AKI (Table). After adjustment, development of AKI was associated with female sex (adjusted odds ratio [aOR]for males 0.41 [0.22-0.77], p=0.005), congestive heart disease (aOR 2.5 [1.30-4.82], p=0.006), and receipt of >2L intravenous fluids prior to study enrollment (aOR 5.69 [1.08-29.9], p=0.04). 28-day mortality among AKI patients was 22.0% (n=369/1674), versus 19.6% (n=292/1488) in those without AKI (p=0.1). The AKI patients who died were older, with more comorbidities and higher illness severity than those who survived. After adjustment, 28-day mortality was associated with older age (aOR 1.02 [1.02-1.03], p<0.001), female sex (aOR for males 0.75 [0.58-0.99], p=0.04), chronic kidney disease (aOR 1.74 [1.21-2.49], p=0.003), venous lactate (aOR 1.25 [1.19-1.30], p<0.001), bacteremia (aOR 1.99 [1.50-2.66], p<0.001), and ICU admission within 24 hours of hospital admission (aOR 1.88 [1.39-2.56], p<0.001).

CONCLUSIONS: Infection-associated AKI in northeast Thailand is common, though not associated with increased 28-day mortality. Older age, chronic comorbidities, and higher severity of illness upon hospital presentation were associated with the development of AKI and with 28-day mortality among patients with AKI.

Gabriela Galli is a rising third-year medical student who hopes to further develop her interests in critical care and low-resource settings through her research and future practice.

Abstract Title: Fibroblast Growth Factor Signaling as a mediator of inflammation and vascular remodeling in pulmonary diseases

Authors:: Jaleesa Garth[1], Molly Easter[1], Yuhua Wei[1], Rebecca Denson[1], Elex Harris[1,2], Eric Scott Helton[1], Ren-Jay Shei[1,2], Dongqi Xing[1,3], Michael Wells[1,3], Steven M. Rowe[1,3], Jarrod Barnes[1] and Stefanie Krick[1]

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RATIONALE: Fibroblast Growth Factor (FGF) 23 is a circulating pro-inflammatory mediator shown to bind FGF receptor (FGFR) 4 leading to the activation of phospholipase Cγ (PLCγ)/nuclear factor of activated T-cells (NFAT) signaling. Activation subsequently promotes inflammation and can lead to cardiovascular, liver, kidney, and lung dysfunction. Previously, we have demonstrated increased FGF23 serum levels and inflammation in chronic airway diseases such as cystic fibrosis (CF) and chronic obstructive pulmonary disease (COPD). We hypothesize that the FGF23-mediated increase in systemic and airway inflammation leads to pulmonary vascular remodeling. In this study, we examine the effects of FGF23/FGFR4 signaling on pulmonary vascular remodeling.

METHODS: Wild-type littermates and mice deficient in FGFR4 (Fgfr4-/-) were used for this study to examine baseline measurements in an in vitro primary cell culture and in vivo murine model. For the in vitro model, murine tracheal epithelial cells (MTECs) were harvested from wild-type and Fgfr4-/- mice. The isolated cells and supernatants were collected (undifferentiated) or transferred to filters and grown at air liquid interface until they developed beating cilia (differentiated). Analysis was done using micro optical coherence tomography (μOCT) (airway surface liquid volume depth and ciliary beat frequency), qRT PCR (IL-1β, IL-6, TGF-β, FGFR1, Klotho, FGF23), and Western Blot (PLCγ, ERK, αSMA, Col1A1). For the in vivo model, Fgfr4-/- and their wildtype littermates were analyzed for lung function using flexiVent, right heart catheterization for right ventricular pressure measurements, and bronchoaveloar lavage fluid for total cell count.

RESULTS: The μOCT analyses on differentiated MTECs revealed a decrease in airway surface liquid volume in Fgfr4-/-mice without differences in ciliary beat frequency. Additionally, qRT PCR data indicated an increase of IL-1β and TGF-β mRNA expression in both undifferentiated and differentiated Fgfr4-/- MTECs. Interestingly, IL-6 mRNA expression was increased in undifferentiated Fgfr4-/- MTECs but showed the inverse result when differentiated. In vivo morphometry studies indicated obstructive and emphysematous changes. Moreover, IL-1β as well as FGFR1 and Klotho mRNA levels were decreased in Fgfr4-/- mouse lungs.

CONCLUSION: In this study, we show that lack of FGFR4 can mediate pulmonary inflammation and vascular remodeling. Collectively, our data suggest that Fgfr4-/- mice might serve as a novel experimental murine model to study COPD related vascular remodeling. Further experiments are required to validate our findings.

Jaleesa Garth is a postdoctoral fellow at the University of Alabama at Birmingham (UAB). Jaleesa's current research focuses on the role of FGF23/FGFR4 signaling in the lung during chronic obstructive pulmonary disease and pulmonary hypertension. When Jaleesa is not in lab, she spends her time mentoring disadvantaged students in the Birmingham metro community. Jaleesa volunteers for the Office of Undergraduate research, teaches an interdisciplinary STEM curriculum to elementary students in the STREAM innovations after school program, and aids in several pipeline programs on and off UAB's campus. She strives to provide support, encouragement, and knowledge to minority students with interest in science and medicine.

Abstract Title: Cellular Responses Of ESAT-6 Antigens in Sarcoidosis Subjects.

Authors: Abena Green[1], Kenny Abel[1], Wonder Drake[1,2]

[1]Vanderbilt University School of Medicine, Department of Medicine, [2]Vanderbilt University School of Medicine, Department of Pathology, Microbiology and Immunology

RATIONALE: Sarcoidosis is an inflammatory disease of unknown origin resulting in the formation of non-necrotizing granulomas mainly involving the lungs, lymph nodes and skin. Sarcoidosis is pathologically similar to the disease tuberculosis. However, the antigens primarily responsible for sarcoidosis have yet to be identified. Previous research have demonstrated immune responses to mycobacterial antigens among sarcoidosis patients. The purpose of this investigation is to determine the role of 8 and 16 weeks of either antimycobacterial or placebo therapy on ESAT-6 immune responses.

METHODS: PBMC that were collected at week 8 and stored in liquid nitrogen until analysis were tested for immune recognition to ESAT-6. These immune responses were recorded by performing enzyme-linked immunospot (ELISPOT) assays for interferon-γ expression.

RESULTS: There were no significant distinctions at baseline ESAT-6-specific immune responses between subjects randomized to CLEAR II regimen and placebo (p=0.7, unpaired Student's T test). Concerning subjects randomized to placebo, there were no significant changes in ESAT-6-specific immune responses observed between baseline and WK8 (p=0.1, paired Student's T test), or baseline and WK16 (p=0.5, paired Student's T test). Concerning subjects randomized to CLEAR II, nearly distinctive declines were observed between ESAT-6-specific immune responses collected at baseline and WK8 (p=0.06, paired Student's T test) and significant declines were observed between cells collected at baseline and WK16 (p=0.02, paired Student's T test).

CONCLUSIONS: The results from this study suggest that there are quantifiable differences in ESAT-6-specific immune responses among subjects treated with antimycobacterial therapy versus placebo. Additionally, the optimal time period to view these immune system differences is after 16 weeks.

Abena Green is currently an aspiring physician-scientist and Biology major at Fisk University in Nashville, TN. She performed her research under Dr. Wonder Drake at Vanderbilt University Medical Center.

Abstract Title: Corticosteroids effect sphingolipid de novo synthesis in lung epithelial cells

Authors: Seyni Gueye-Ndiaye[1], Rika Gomi[1], Benjamin Kim[2], Tilla Worgall[2], Stefan Worgall[1]

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RATIONALE: Genome wide association studies have established the relationship between 17q21 risk alleles that effect expression of the sphingolipid synthesis regulator ORMDL3 and childhood asthma. We showed recently that in children with asthma, the presence of these risk alleles is also associated with decreased de novo sphingolipid synthesis. Corticosteroids are the first-line therapies for children with asthma during an acute exacerbation and for maintenance therapies. Corticosteroids are known to effect metabolism of sphingolipids via regulation of sphingomyelinase and sphingosine kinase, however not much is known about the effects of corticosteroids on the de novo sphingolipid pathway. Here we assess the effect of corticosteroids on sphingolipid metabolism in airway epithelial cells.

METHODS: A549 cells were treated for 8 -36 hours with dexamethasone at 0.2μM and 0.06μM concentrations, equivalent to historical peak serum levels following administration of oral prednisolone and inhaled steroids, respectively. Cells were maintained in DMEM and 1% fatty acid free bovine serum albumin. To assess the additional effect of infection with human rhinovirus (HRV) during asthma attacks, cells treated with 0.2μM dexamethasone were additionally infected with HRV16 at a multiplicity of infection (MOI) of 10. Sphinganine and dihydroceramides (DHCer16:0, DHCer18, DHCer24, DHCer24:1), sphingolipids that can only be generated by de novo synthesis, as well as ceramides (Cer16, Cer18, Cer18, Cer20, Cer24, Cer24:1) and sphingomyelins (SMC16, SMC18, SMC24:1) were quantified in cell lysates by HPLC tandem mass spectrometry and normalized to total protein content. One-way analysis of variance (ANOVA) was applied to determine the significance among groups, followed by post hoc tests with Bonferroni's correction.

RESULTS: Treatment with 0.2 μM dexamethasone increased cellular dihydroceramides (DHCer18, DHCer24, DHCer24:1) and ceramides (Cer16, Cer18, Cer20, all $p < 0.05$) at 24 h and 36 h. Masses of sphingosine were decreased ($p<0.05$) and there was no effect on sphinganine, ceramides (Cer22, Cer24, Cer24:1) or sphingomyelins (SM C16, SM C18, SM C24:1) compared to untreated controls. Treatment with 0.06 μM dexamethasone lowered sphingosine ($p<0.05$), but there was no effect on dihydroceramides, ceramides and sphingomyelins. Addition of HRV to 0.2μM dexamethasone had no additional effect on the effect of dexamethasone alone.

CONCLUSION: Corticosteroids effect de novo sphingolipid synthesis in lung epithelial cells at doses equivalent to those used during acute asthma exacerbations. These results will inform studies on sphingolipid metabolism in children with genetically decreased sphingolipid synthesis during asthma attacks.

Dr. Seyni Gueye-Ndiaye was born in Senegal and grew up in New Jersey. She received her Bachelor of Arts in biological sciences from Rutgers University. Dr. Gueye-Ndiaye then earned her medical degree and completed her pediatric residency at Robert Wood Johnson Medical School. She is currently in her last year of a pediatric pulmonary fellowship at New York-Presbyterian/Weill Cornell Medical Center. Upon completion of her fellowship, she will start a sleep medicine fellowship at Beth Israel Deaconess Medical Center/Boston Children's Hospital.

Her research interests include the mechanisms of how respiratory infections with human rhinovirus (HRV) trigger childhood asthma. Her research specifically aims to understand if HRV affects sphingolipid metabolism that is known to be altered with common 17q21 genetic variants, which influence expression of the sphingolipid regulator, ORMDL3 in childhood asthma.

Abstract Title: Obesity is associated with an altered airway microbiome and distinct airway microbiota-immune relationships in asthma

Authors: Ariangela J. Kozik PhD[1], Lesa Begley MS[1], Nicole Schafer BS[1], Siddharth Madapoosi BS[1,3], Kristopher Opron PhD[1], Njira Lugogo MD/MS[1], Michael Coffey MD[1], Alan Baptist MD/MPH[2], John Erb- Downward PhD[1], and Yvonne J. Huang MD[1]

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RATIONALE: Obesity-associated asthma is common, difficult to treat, and the biological mechanisms involved are poorly understood. Dysregulated immune responses and altered gut microbiota configurations have been associated with obesity and/or asthma. However, whether aberrant immune- airway microbiota relationships exist in relation to obese asthma phenotype is unclear. We hypothesized that characteristics of the airway microbiota and its associations with immune markers measured in the airway or blood, differ between obese and non-obese adults and further differ by asthmatic status among obese individuals (defined as body-mass index ≥ 30).

METHODS: Bacterial 16S rRNA gene sequencing was performed on induced sputum samples from a cohort of 60 adults enrolled in a prospective observational study at the University of Michigan. Host immune and metabolic responses were measured in plasma and sputum using assays on a Luminex platform. QIIME2 was used to identify bacterial exact sequence variants (ESVs), which were analyzed in R to determine relationships to clinical and immunologic features.

RESULTS: Obesity, irrespective of asthmatic status, was associated with significant differences in sputum microbial community structure (PERMANOVA, $p<0.01$) and composition, including a higher relative abundance of Prevotella ESVs. In this cohort enriched for mild-moderate asthmatics (mean FEV1% predicted= 89.3; mean blood eosinophils = 250), additional differences in sputum bacterial composition were identified between obese asthmatic and non-obese asthmatic subjects, such as a higher relative abundance in the former of Haemophilus, Actinobacillus, and Lactobacillus. Further, observed relationships between sputum microbiota and immune mediators measured in sputum or blood differed between obese and non-obese asthmatics and did not overlap. For example, among obese asthmatics, sputum bacterial diversity correlated with blood fractalkine (Shannon index; Spearman rho 0.70, padj 0.08) and specific ESVs associated with levels of blood IL-17A (Mogibacterium; rho 0.85, padj 0.02) and sputum GM-CSF (Alloprevotella; rho 0.82, padj 0.05). By contrast in non-obese asthmatics, ESVs of Leptotrichia positively associated with blood TNF-alpha and IL-7 (rho 0.70, padj 0.03), while Streptococcus was negatively associated with sputum IL1-beta (rho -0.70, padj 0.03).

CONCLUSIONS: Obesity itself is associated with an altered airway microbiome, which further differs in the setting of asthma. We speculate that obesity shapes a distinct immunological milieu that influences the airway microbiome, but that an asthmatic state further shapes immune-microbial interactions in the airways of obese individuals. These findings invite further investigation into functional consequences of these interactions and relationships to clinical outcomes in obesity-associated asthma.

Dr. Ariangela Kozik has a PhD in Comparative Pathobiology from Purdue University. She is currently a Postdoctoral Fellow at the University of Michigan. Her research focuses on the role of the airway microbiome in Asthma and COPD phenotype.

Abstract Title: Investigating Barriers To The Timely Diagnosis Of Pulmonary Arterial Hypertension

Authors: S. Krow, V. Prieto-Centurion, D. Fraidenburg

Division of Pulmonary Critical Care Sleep & Allergy, Department of Medicine, University of Illinois At Chicago, Chicago, IL, United States.

RATIONALE: Growing evidence suggests that health disparities significantly impact the care of minorities with pulmonary arterial hypertension (PAH). African American (AA) patients have more severe hemodynamic derangements, shorter walk distances and worse functional class at the time of diagnosis. Our current study seeks to identify delays in care from non-invasive testing with echocardiography (TTE) to diagnostic right heart catheterization (dRHC) among three different racial groups.

METHODS: We designed a retrospective, cross-sectional analysis study of PAH subjects identified from the University of Illinois at Chicago. Medical records were reviewed to determine date of first abnormal TTE (Tricuspid Regurgitation peak Velocity > 2.8 m/sec, right atrial or ventricular enlargement), most recent TTE, and dRHC. Subjects were stratified according to self-reported racial groups. One outlier was removed and missing data points were imputed based on group mean. Analysis of variance was used to analyze data among the groups and t-test to compare time intervals between AA and all other subjects.

RESULTS: 73 subjects with PAH were included; 35 AA, 24 European-American (EA), and 14 Hispanic- American (HA) subjects. The mean time delay from the date of the first available abnormal TTE to dRHC was 928 +/- 420 days for AA, 232 +/- 186 days for EA, and 365 +/- 497 days for HA subjects ($p = 0.02$).

There was a significantly increased time delay of 650 days in AA subjects compared to all others ($p=0.005$). The time delay between the most recent TTE until dRHC was 88 +/-45 days among AA, 51 +/- 30 days among EA, 43 +/- 16 days among HA ($p = 0.231$). There was a trend of 40 day increased time delay among AA subjects compared to all others ($p = 0.092$).

CONCLUSIONS: We identified significant racial disparity in the delay from the first abnormal TTE to the dRHC with AA subjects waiting nearly two additional years before being diagnosed with PAH. In each group, a mean delay exceeding six months suggests that PAH is going under-recognized on TTE. This small sample did not identify significant time differences from the most recent TTE to dRHC, yet a disturbing trend exists in which AA subjects waited, on average, 40 additional days before having dRHC. Future research into factors contributing to these disparities; such as access to care, patient mistrust, and implicit provider bias, will be invaluable to improving the timely diagnosis of PAH in all patients.

Solomon Krow was born to Ghanaian parents in the United Kingdom and raised in Barbados. After medical school in Jamaica, he finished residency at SUNY Downstate and is now a Pulmonary & Critical Care fellow at University of Illinois at Chicago.

Abstract Title: Engineered Polymer Platforms for Directing Endothelial Cell Function In Vitro

Authors: Vérida J. Léandre[1],[4], Liane Livi[2], Diane Hoffman-Kim[2], Elizabeth O. Harrington[3],[4]

[1]Integrative Studies PhD Program, Brown University, [2]Department of Molecular Physiology, Pharmacology and Biotechnology, Brown University, [3]Division of Pulmonary, Critical Care, Sleep Medicine, Department of Medicine, Warren Alpert Medical School of Brown University, [4]Providence VA Medical Center

RATIONALE: Pulmonary disease affects over 235 million people globally, killing >3 million people per year. In settings of disease, the lung undergoes multiple pathological processes including tissue and vessel remodeling; however, these are poorly understood processes. We sought to develop a biomimetic synthetic pulmonary vessel (BSPV) substrate system in which we modified the stiffness and topography and measured the effects on pulmonary endothelial cell function with the goal of informing the pathological processes in the pulmonary circulation in settings of disease.

METHODS: A replica molding technique was used to fabricate BSPV platforms with patterned surfaces presenting protruding topographical features of cells lining the vascular wall to living rat lung microvascular endothelial cells (RLMVEC). Pulmonary artery stiffening was modeled by tuning the elastic modulus of the BSPV platform. 15kPa platforms recapitulated normal conditions, while 40kPa platforms modeled severely remodeled pulmonary vasculature. Pulmonary artery muscularization and fibrosis were modeled by fabricating human lung myofibroblast (HLMF) and normal human lung fibroblast (NHLF) biomimetic platforms by taking the castings of these surfaces. Control surfaces were flat BSPV. The RLMVEC were seeded on these surfaces and cell functions were measured.

RESULTS: RLMVEC grown on BSPV platforms with engineered topography displayed normal rosette cobblestone morphology, while cells grown on flat platforms were less dense and resembled a stellate morphology not typically associated with healthy endothelial cells. RLMVEC grown on BSPV platforms preferentially attached to 15kPa BSPV platforms with HLMF topography, as compared to 15kPa flat BSPV platforms (n=3; p=0.0002). Similarly, RLMVEC preferentially attached to 40kPa normal BSPV platforms with NHLF topography, relative to 40kPa flat BSPV platforms (n=3; p=0.0015).

CONCLUSIONS: Topography of the BSPV platforms was an important parameter influencing the endothelial cells adhesive properties. Future experiments will elucidate the roles of biomechanical parameter on multiple endothelial cell functions.

Verida Leandre has been dedicated to medical science since the age of 6. A PhD student in Biomedical Science at Brown University, Verida is on a mission in researching ways to eliminate obesity by developing a cell based therapy. In addition to her research at Brown, she is a volunteer in an underserved elementary school in Providence and is an accomplished musician

Abstract Title: Chemical Activation of Protein Phosphatase 2A Slows Progression of Cigarette Smoke-Induced Loss of Lung Function

Author: Alnardo D. Lora[1], Michael Ohlmeyer[2], Ziyad Elgamal[1], Christopher Railwah[1], Robert F. Foronjy[1], Abdoulaye J. Dabo[1], Nathalie Baumlin[3], Matthias A. Salathe[3], and Patrick Geraghty[1]

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Source of Support: *This work was supported by grants made available to P.G. (Alpha-1 Foundation).*

Disclosure: *The authors declare no conflict of interest.*

RATIONALE: The activity of protein phosphatase 2A (PP2A), a serine threonine phosphatase, is inhibited in the lungs by prolonged exposure to cigarette smoke. Our group recently demonstrated that chemical activation of PP2A reduces loss of lung function in mice. Here we present data on an improved PP2A activator with enhanced bioavailability in a model with established COPD-like symptoms. The objective of this study was to investigate the effect of normalizing PP2A activity in mice already exposed to cigarette smoke and assess therapeutic effects on progression of lung function decline.

METHODS: A/J mice were exposed to cigarette smoke for 2 months. At the 2-month stage, mice twice daily received 5 mg/kg of a newly identified small molecule activator of PP2A (SMAP) by oral administration. The SMAP utilized here is a novel tricyclic-sulfonamide compound with improved metabolic stability and oral bioavailability. Animals received the compound and smoke exposure for 2 additional months. Forced oscillation and expiratory measurements were recorded in each animal. Additionally, human bronchial epithelial (HBE) cells isolated from non-smokers and COPD patients were exposed to the SMAP and PP2A responses were analyzed.

RESULTS: Long-term SMAP administration resulted in no notable toxicity in mice, with external appearance, behavior, and body weight similar to vehicle groups. As expected, exposure to cigarette smoke induced changes in pressure volume loops, airway inflammation, lung compliance, inspiratory capacity and FEV0.05/FVC. Importantly, treatment with SMAP reduced progression of these disease parameters in smoke-exposed mice. HBE cells treated with SMAP had restored PP2A signaling, confirmed by reduced ERK phosphorylation and elevated PP2A activity.

CONCLUSION: Our study indicates that the decrease in PP2A activity that occurs in COPD could be restored by SMAP administration to slow the rate of lung function decline. Restoration of lung PP2A activity represents a feasible therapeutic approach to counter smoke-induced lung disease.

Alnardo Lora is a 2nd year internal medicine resident at SUNY Downstate Medical Center in Brooklyn, NY. Currently, his research involves protein phosphatase 2A (PP2A) in cell and animal models as it relates to COPD, working alongside his mentor, Patrick Geraghty. In addition to lab-based research, Alnardo is actively involved in QI clinical projects targeting preventative health and health care delivery of culturally competent care within Brooklyn and is dedicated to improving patient quality of life within the community. He has excelled within his residency program, both academically and clinically, earning himself the award for "Intern of the Year" in 2019.

Alnardo earned his medical degree at Universidad Iberoamericana (UNIBE) in Dominican Republic. His expertise extends to population health management with advanced certifications in project management from Villanova University.

He plans to pursue a fellowship in pulmonology and critical care medicine.

Abstract Title: Adverse Childhood Experiences Increases Severe Asthma Symptoms in Children Receiving Care within a Safety Net Setting

Authors: Adali Martinez[1], Morgan Ye[1], Rosemarie de la Rosa,[1], Danielle Hessler[1], Mindy Benson[2], Rachel Gilgoff[3], Kadiatou Koita[3], Monica Bucci[3], Dayna Long[2], Neeta Thakur[1]

[1]University of California San Francisco, School of Medicine [2]UCSF Benioff, Children's Hospital Oakland, [3]Center for Youth Wellness

RATIONALE: Adverse Childhood Experiences (ACEs) have been shown to be associated with higher prevalence of asthma in children. Few studies have explored the relationship between ACEs and asthma symptom severity. As these exposures accumulate over childhood, their contribution to symptoms and poor asthma control may be under recognized.

METHODS: This is a cross--sectional study of baseline data from 153 participants (ages 0 to 11 years) with asthma from a larger cohort of children and their caregivers, enrolled in the Pediatric ACEs Screening and Resiliency Study in Oakland, California. Participants recruited during well--child primary care visits were screened for ACEs using the Pediatric ACEs and Related Life events Screener (PEARLS) Tool, a 17--item questionnaire covering abuse, neglect, household challenges, separation, caregiver illness or death, community violence and bullying, discrimination, food insecurity, and housing instability. The International Study of Asthma and Allergies in Childhood (ISAAC) core questionnaire was used to identify children with asthma and symptom burden. Medication use was self--report and collected using the Brief Medication Questionnaire. Multivariate and proportional odds logistical regressions models were used to examine the relationship between asthma symptoms and the number of adversities reported (total PEARLS Score), adjusting for maternal education, child age, and gender.

RESULTS: 132 (86.3%) of children with asthma reported at least 1 adversity, with 51% reporting 4 or more. The odds of reporting wheezing within the last 12 months increased by 14% for each unit increase in the PEARLS Score (aOR 1.14 95% CI 1.03--1.29). Adversities were also associated with increased odds of wheezing attacks (aOR 1.10, 95%CI 1.01--1.21), report of wheezing that woke child up from sleep (aOR 1.10, 95% CI 1.00--1.22), and inhaled corticosteroids (ICS) use (aOR 1.13; 95% CI 1.02--1.26), a common controller medication for asthma. Even after adjusting for ICS use, each unit increase in the PEARLS Score was associated with 13% increased odds of reported wheeze in the last 12 months (aOR 1.13 95%CI 1.01--1.27). No associations were observed with ED--visits or hospitalizations.

CONCLUSION: The association between ACEs and related adversities with asthma extends beyond prevalence. We found higher PEARLS Scores were associated with ICS use, frequent wheezing attacks, and interrupted sleep due to wheezing, all indicators of poorly controlled asthma. As California moves toward screening all children on Medicaid for early--life adversities, this study helps inform medical providers of the potential utility of such screening tools to identify children at high risk for experiencing severe asthma symptoms.

Adali Martinez is a second-year internal medicine resident at UCSF. She grew up in Barrio Logan, a vibrant immigrant community in San Diego. She attended UCSF Medical School and earned an MPH in Health Policy and Management from UC Berkeley.

Abstract Title: Predictors of LTEC/TEF in Children with Dysphagia

Author: Claudia Mattos, Pelton Phinizy, Kim Duffy, Steven Sobol, Joseph Piccione

Rowan University of Osteopathic Medicine

INTRODUCTION: Dysphagia and chronic pulmonary aspiration in children can be categorized as functional, structural or neurological in etiology. Laryngotracheoesophageal clefts (LTEC) and tracheoesophageal fistulae (TEF) represent the most common structural causes of aspiration. Identifying structural causes of aspiration early in life is critical to the prevention of pulmonary consequences of chronic aspiration including recurrent pneumonia and bronchiectasis. However, these anomalies are uncommon and diagnosis typically requires bronchoscopy under general anesthesia. Determining which children are at greatest risk for LTEC and TEF based on information available in the medical history and video fluoroscopic swallowing studies (VFSS) would enable clinicians to be more selective in performing bronchoscopy.

METHODS: Medical records of children aged 0 to 18 years who underwent flexible and rigid bronchoscopy for evaluation of dysphagia between January 1, 2012 and January 31, 2019 at the Children's Hospital of Philadelphia were reviewed. Data including demographics, diagnostic test results, inpatient and outpatient clinical notes and operative reports were collected and analyzed to identify predictors of laryngeal cleft (LTEC) and tracheoesophageal fistula (TEF).

RESULTS: Seventy-two children age 2 months to 9 years (median 17 months) met inclusion criteria. LTEC was identified in 19 (26%) and TEF (H-Type) was identified in 1 (1.3%). Of those with LTEC, 10% had a history of TEF repair. Approximately one-third of the cohort was born preterm (median gestational age 34 weeks). The proportion of LTEC in those born preterm was lower than that of those born full term (12% vs. 34%, $p = 0.03$). There was no statistically significant difference in LTEC rates for children based on age, midline defects, laryngomalacia, tracheomalacia, history of TEF repair, silent aspiration or thickness of barium aspirated during VFSS. Bronchoalveolar lavage fluid cytology, lipid laden macrophage proportions and culture results were similar among those with and without LTEC.

CONCLUSION: Children with dysphagia and chronic pulmonary aspiration who were born full term are approximately three times more likely to have LTEC than those born preterm. Dysphagia in children with a history of preterm birth is functional as opposed to structural in the vast majority. No other statistically significant predictors of LTEC were identified from the clinical history obtained prior to performing bronchoscopy in children with dysphagia.

Claudia Mattos is a third year medical student at Rowan SOM planning to pursue a career in pediatrics.

Abstract Title: The Association of HLA-C and Killer Cell Immunoglobulin-like Receptor Permutations on COPD Risk

Authors: T. Mkorombindo, T.N. Kim Thi, K. Yuan, Y. Zhang, J. Xue, G. Criner, J. Pilewski, M. McDonald, F.C. Sciurba, S.R. Duncan

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RATIONALE: Cytotoxic lymphocytes are implicated in COPD pathogenesis. The functions of Natural Killer (NK) Cells are modulated by interactions between killer-cell immunoglobulin-like receptors (KIR) on their surfaces and HLA-Class I molecules expressed on target cells. Different receptor–ligand interactions result in altered NK-cell-mediated immunity. We hypothesized HLA-Class I and KIR inheritance might influence risks for developing COPD. To assess whether HLA-Class I-KIR interactions affect COPD risk, we assessed inheritance and sought to validate with functional analysis.

METHODS: HLA Class I alleles and KIR genotypes were defined by PCR. These were assessed in the discovery and validation cohorts of COPD patients (n=393) and smokers with normal lung function (Smoke Controls [SC], n=343). NK Cell cytotoxicity was measured in ex vivo assays.

RESULTS: In both the discovery and validation cohorts, there was an over-representation of the activating KIR gene 2DS1 in COPD patients (OR 1.7, 95%CI 1.3-2.3, p=0.0005). Other observations include under-representation of HLA-C*12 in COPD patients (OR 0.5, 95%CI 0.3-0.8, p=0.002). Various combinations of HLA-KIR pairs had interactive effects on COPD risk, for example, the presence of KIR2DS1 with HLA-C*07 vs. HLA-C*12 without KIR2DS1 was highly associated with COPD prevalence (OR 6.6, 95%CI 2.8-15.7, p<0.0001), especially among HLA-C1 allotype (HLA-C*01/*03/*07/*08/*12/*14/*16) homozygotes (OR 12.7, 95%CI 2.7-60.6, p<0.0001). NK Cell-mediated cytotoxicity of COPD lymphocytes was enhanced by KIR stimulation (p=0.005), an observation not seen in the smoke controls. Additionally, KIR stimulation in lymphocytes from COPD patients was inversely correlated with expiratory airflow (r=-0.44, p=0.004).

CONCLUSIONS: HLA-C and KIR polymorphisms strongly influence COPD susceptibility. These findings highlight the potential importance of HLA-KIR interactions and the role of lymphocyte-mediated cytotoxicity in COPD pathogenesis. HLA-KIR typing has the potential to identify smokers at increased risk for COPD. These data also raise possibilities that HLA-KIR axis modulation may serve as a therapeutic target in COPD.

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Takudzwa Mkorombindo is interested in determinants of disparate outcomes in Chronic Obstructive Pulmonary disease. Having witnessed the disproportionate impact this disease has on marginalized communities and populations, he seeks to understand immunologic underpinnings that may be responsible for adverse COPD outcomes. Co-mentored by Mark Dransfield and Steven Duncan at the University of Alabama, he has a particular interest in the pathogenesis and identification of early disease. To do this, he works in the lab of Steven Duncan, evaluating the role of innate immunity in COPD and the role of natural killer cell receptors in the pathogenesis of COPD. Mkorombindo and his colleagues have identified interactions between HLA molecules and a subset of killer immunoglobulin-like receptors that are associated with an increased COPD risk. A Pulmonary and Critical care fellow, Mkorombindo's mission is to improve the outcomes of COPD patients by providing compassionate care and contributing to the growing body of evidence on mediators of COPD outcomes.

Abstract Title: Body Mass Index Does Not Influence Sensitization to Aeroallergens

Author: B. Nriagu, T. Thakur, B. Patchett and E.S. Schulman.

Drexel University School of Public Health and School of Medicine

BACKGROUND: It is known that obesity influences asthma and obese patients with asthma have more severe symptoms. However, the degree to which sensitization to specific allergens - which can worsen asthma symptoms is influenced by obesity remains largely unknown. We compared specific allergen sensitization among inner city asthmatics at two extremes of body mass index (BMI): ≤25kg/m2 vs ≥40kgm2.

METHODS: Retrospective chart review of patients from Drexel University Severe Asthma Clinics. After an initial visit and prior to a therapeutic intervention, subjects were tested for allergic sensitization using the ImmunoCAP® assay. Immunoglobulin E (IgE) levels, pulmonary function and other anthropometric parameters were collected at baseline. Allergic sensitization and pulmonary function were compared between patients with BMI ≤25kg/m2 and those with BMI ≥40kg/m2. We excluded patients with allergic bronchopulmonary aspergillosis (ABPA) from the study. The Fisher's-exact test was used to assess for differences in allergic sensitization between the two groups. We used the Benjamini and Hochberg correction to account for multiple comparisons.

RESULTS: In our study population of 153 asthmatic patients, 51% of patients (n=78) had a BMI of ≤25kg/m2 while 49% of patients(n=75) had a BMI of ≥40kg/m2. The mean BMI for patients with BMI ≤25kg/m2 and BMI ≥40kg/m2 was 22.3 + 2.3 (mean SD, range 16.3 – 25.0) and 47.4 + 6.8 (mean SD, range 40.0 – 72.14) respectively. For patients with BMI ≤25kg/m2, the mean age was 52.3 + 18.7 (mean SD, range 20 – 92); and 52.8 + 11.2 (mean SD, range 21 – 74) for patients with BMI ≥40kg/m2. The majority of patients who had a BMI ≤25kg/m2 and a BMI ≥40kg/m2 were Caucasians (46.8%) and African Americans (70.3%) respectively(p=0.001). Mean serum IgE in the BMI ≤25kg/m2 group was 484.5 + 832.9 IU/ml (range 0 – 2937 IU/ml) and in the BMI ≥40kg/m2 group, 319.1 + 650.3IU/ml (range 0 – 3722 IU/ml). Mean serum absolute eosinophil count in the BMI ≤25kg/m2 group was 221.6 + 198.7 (range 0 – 900) and in the BMI ≥40kg/m2 group, 190.4 + 184.4 (range 0 – 806). No significant differences in allergen sensitization was observed between the two groups for the 25 aeroallergens tested.

CONCLUSION: Although obesity is known to produce more symptoms in asthma, it does not affect sensitization to any specific allergen routinely tested. Our results suggest that among inner city asthmatics, obesity does not influence sensitization to allergens.

Bede Nriagu MD, MPH is a research fellow in the pulmonology division at Drexel University College of Medicine. He attended Drexel University where he obtained his MPH degree. Prior to that, he completed his MD from Nnamdi Azikiwe University, Nigeria. As a medical student, he served as the Editor-in-chief of the research journal of his medical school students' association.

Abstract Title: Adherence to Lung-RADS Recommendations in a National Cohort of US Veterans Screened for Lung Cancer

Authors: Eduardo Nunez, Tanner Caverly, Shirley Qian, Jacqueline Boudreau, Christopher Slatore, Jonathan Iaccarino, Donald Miller, Renda Soylemez Wiener

Boston University/Boston Medical Center

INTRODUCTION: In 2011, the National Lung Screening Trial (NLST) showed that yearly lung cancer screening (LCS) with low-dose computed tomography (LDCT) resulted in a 20% reduction in mortality from lung cancer. This benefit was, dependent on close follow-up and adherence to recommendations. There is limited current evidence on adherence to follow-up recommendations for LCS in the US population. Our objective was to analyze appropriate and timely follow-up in a national cohort of veterans screened for lung cancer based on Lung CT Screening Reporting & Data System (Lung-RADS) recommendations.

METHODS: We conducted a retrospective cohort analysis of veterans who were screened for lung cancer in any Veterans Affairs (VA) facility between 2015-2019 who also had Lung-RADS classification. We excluded patients who had insufficient time for follow up based on the recommended Lung-RADS time period. We used VA and Medicare claims data to look for evidence of expected follow-up tests including Chest CT, Positron Emission Tomography (PET) or invasive lung procedures. Our primary outcome was the presence of recommended next step in evaluation based on Lung-RADS categories (Table 1). Our secondary outcome was presence of expected evaluation within appropriate time frame, which was defined as within +/- 1 month of the Lung-RADS recommendation.

RESULTS: Overall, 16,558 veterans had lung cancer screening with Lung-RADS recommendations and enough time for follow-up. The population demographics were 95% male and 77% white with a mean age of 66.8 years. Of the 12,148 veterans in Lung-RADS categories 0,1 and 2, only 8,533 (70.2%) had the recommended annual screening. Veterans in Lung-RADS category 3, 4A and 4B/4X had higher rates of follow-up evaluation; 83.9%, 85.0%, 88.8% of veterans, respectively. However, in Lung-RADS category 3, 4A and 4B/4X, many veterans did not have their follow-up evaluation within the expected time frame: 47.2%, 47.1% and 48.3%, respectively. Across all groups, there were high numbers of veterans who had late evaluations; Lung-RADS 0,1,2 (21.5%), 3 (20.1%), 4A (29.2%), 4B or 4X (37.0%).

Table 1. Adherence to Lung-RADS Recommendation Stratified by Lung-RADS Group.

Lung-RADS	Expected Evaluation time period	N in LUNG-RADs Category	N (%) Early Evaluation	N (%) Expected Evaluation	N (%) Late Evaluation	N (%) No Evaluation
0, 1 or 2	f/u CT in 1 year	12148	1205 (9.9%)	4714 (38.8%)	2614 (21.5%)	3615 (29.8%)
3	f/u CT in 6 months	2443	268 (11%)	1289 (52.8%)	492 (20.1%)	394 (16.1%)
4A	f/u CT or PET in 3 months	1327	49 (3.7%)	691 (52.1%)	388 (29.2%)	199 (15.0%)
4B or 4X	f/u CT or PET OR invasive procedure in 0-3 months	640	N/A*	331 (51.7%)	237 (37.0%)	72 (11.3%)

*Early evaluation not applicable for Lung-RADS categories 4B and 4X since the time frame of recommended evaluation is within 0-3 months.

CONCLUSION : Our study shows that in a real world practice of veterans, there was sub-optimal follow-up to lung cancer screening recommendations regarding both the presence and the timing of the evaluation, raising the concern that the efficacy of NLST may be difficult to replicate. Future work should continue to focus on improving initial lung cancer screening uptake and subsequent adherence to recommendations.

Eduardo Nunez is a pulmonary and critical care fellow at Boston University/Boston Medical Center. His research interests include health care disparities, communication in the ICU and lung cancer screening. His current work focuses on identifying disparities and barriers to care that exist within lung cancer screening in the US, particularly in the VA Healthcare system. He is planning to continue this work by investigating successful characteristics of lung cancer screening programs and developing implementation strategies to help improve adherence to lung cancer screening and reduce disparities.

Abstract Title: Demographic, Environmental and Disease Self-Management Factors Associated with Asthma Exacerbations in the U.S. According to Asthma Call Back Survey Data

Authors: Ayomide Ojebuoboh[1], Omar Mansour[2], Lena Leszinsky[3], Rebecca Greenblatt[3], Blanca E.Himes[3]

1College of Arts and Sciences, Boston University, Boston, MA 2 Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 3Department of Biostatistics, Epidemiology and Informatics, University of Pennsylvania, Philadelphia, PA, [19104].

RATIONALE: Asthma exacerbations, episodes of worsening symptoms, requiring additional treatment, are a major source of asthma morbidity and healthcare costs. Disparities in exacerbations by race/ethnicity, sex, and income are known in the U.S., especially for African Americans, Puerto Ricans, women and those with low incomes. Several environmental factors, including cigarette smoke, mold, and dust mites, have been associated with asthma exacerbations. Decreasing exposure to such triggers, as well as improving disease self-management skills, are known to decrease asthma exacerbations. However, the relationship among demographic, environmental, and self-management factors in the U.S. is not fully understood. We used results from a national phone-based survey to better understand the factors that may contribute to disparities in asthma exacerbations.

METHODS: Asthma Call-Back Survey (ACBS) data from 2014 and 2015 corresponding to 23,741 respondents from 32 states and Puerto Rico was obtained (https://www.cdc.gov/brfss/annual_data/annual_data.htm). Exacerbations were defined as an affirmative response to a question of "having visited the ED or urgent care because of asthma at least once in the past 12 months." Logistic regression models with exacerbations as outcome and various demographic, environmental and self-management factors as predictors were created with the R Survey package, while considering survey design.

Table. Association between asthma self-management factors and asthma exacerbations.

Factor	Unadjusted ORs (95% CI)	Adjusted ORs (95% CI)
Ever taught to recognize early signs or symptoms of an asthma episode	1.77 (1.44, 2.19)**	1.63 (1.32, 2.02)**
Ever taught what to do during an asthma episode or attack	1.87 (1.47, 2.37)**	1.87 (1.44, 2.43)**
Ever taught how to use a peak flow meter to adjust daily meds	2.14 (1.73, 2.64)**	1.93 (1.57, 2.36)**
Ever given an asthma action plan	2.05 (1.62, 2.60)**	1.76(1.39, 2.22)**
Ever taken a course to manage asthma	2.78 (1.93, 4.00)**	2.19 (1.60, 2.99)**
Ever taught how to use the inhaler	0.95 (0.59, 1.53)	0.92 (0.53, 1.60)

*Adjusted ORs were determined by including age, race, sex, education, income, smoking status, BMI and health plan as additional covariates. CI: confidence interval. **p<0.01*

RESULTS: Consistent with previous studies, female sex, black race/ethnicity, low income, and obese body mass index (BMI) were significantly associated with increased exacerbations. In terms of asthma self-management, people with exacerbations in the previous year were more likely to have had various interventions related to recognizing symptoms, having an asthma action plan, and learning what to do during an asthma attack (Table). Most (20,443/21,499; 95%) respondents received inhaler technique guidance, which was not associated with exacerbations. Results to questions related to environmental factors found that persons with exacerbations were more likely to have been advised to change things in home, use mattress and pillow covers to control dust mites and have an air cleaner. According to unadjusted analyses, household mold and smoking inside the home were the most prominent environmental factors associated with exacerbations.

CONCLUSIONS: Persons with asthma exacerbations in the prior year had increased interventions that are appropriate to decrease exacerbations, with mold and smoking in the home being the most noticeable potential triggers. Longitudinal studies are necessary to determine whether the listed self-management strategies, as well as interventions to decrease exposure to mold and smoke in the home, have a sustained impact on decreasing future exacerbations.

Ayomide Ojebuoboh, an aspiring physician-scientist in epidemiology, is a senior at Boston University pursuing a B.A in Mathematics (Statistics Specialty) and a public health minor.

Abstract Title: L Il-36γ Is Cleaved By Pseudomonas Aeruginosa Derived Protease And Amplifies Neutrophilic Inflammation That Is Tempered By The Matricellular Protein Thrombospondin-1.

Authors: H. Penaloza[1], T. F. Olonisakin[1], Y. Qu[1], W. Bain[1], M. Hulver[1], Z. Xiong[1], T. J. Standiford[2], J. Lee[1];

[1]Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine, University of Pittsburgh, Pittsburgh, PA, United States, [2]Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of Michigan, Ann Arbor, MI, United States.

RATIONALE: IL-36γ, a member of the IL-1 cytokine family, is induced early during Pseudomonas aeruginosa (PA) infection. To be fully active, IL-36γ needs to be extracellularly processed by proteases like neutrophil elastase (NE). PA secretes proteases such as LasB that can amplify neutrophilic inflammation. However, whether LasB cleaves and activates IL-36γ remains unknown. Moreover, during early PA infection, thrombospondin-1 (TSP-1), a host matricellular protein, secreted locally by a variety of cells provides dual levels of protection by inhibiting LasB and NE activity. We hypothesized that PA-derived protease LasB amplifies neutrophilic inflammatory response through the cleavage of IL-36γ, which is e"ciently down-modulated by TSP-1.

METHODS: Cell-free supernatant (SN) of PA14, PA14lasB:: n5 transposon mutant lacking LasB, and small molecule LasB inhibitor were used to examine LasB cleavage of IL-36γ in the N-terminal sequence by SDS-page and Edman degradation. Wildtype (C57BL/6) and Thrombospondin-1 deficient (Thbs1-/-) mice were instilled with recombinant cleaved IL-36γ and neutrophil recruitment, lung MPO and BAL free NE activity were measured.

RESULTS: PA14 SN induces the cleavage of full- length IL-36γ, whereas PA14lasB:: n5 SN or PA14 SN in the presence of LasB inhibitor mitigated IL-36γ cleavage. While NE cleaves IL-36γ proximal to Y16, PA14 SN cleaves IL-36γ just proximal to M19. Recombinant cleaved IL-36γ (rcIL-36γ) but not full-length IL-36γ induces IL-6 and KC secretion by peritoneal macrophages in vitro. In vivo, rcIL-36γ delivery induces airspace neutrophil recruitment, and increased lung tissue MPO and BALF free NE activity that was accentuated in Thbs1-/- mice.

CONCLUSIONS: Although neutrophil-derived proteases such as NE can cleave IL-36γ, we show PA-derived protease LasB can directly cleave IL-36γ. Cleaved IL-36γ induces neutrophilic accumulation and free NE activity in the lung, providing a potential mechanism of inflammatory auto-amplification that is tempered by the matricellular protein TSP-1 during PA infection. Thus, targeting pathogen-derived proteases may break the cycle of pathogenic neutrophilic inflammation early during PA lung infection.

Hernan Penaloza has aPhD in Molecular Genetics and Microbiology at the Pontificia Universidad Católica de Chile (2018). Postdoctoral associate at the University of Pittsburgh. Research focuses on lung host-pathogen interaction and prevention of excessive lung injury

Abstract Title: Evaluating NLRP2 as a Mediator of Increased Susceptibility to Viral Infections following Ozone Exposures

Authors: Alexia Perryman, William Rivera Martin, Adam Speen, Ilona Jaspers

University of North Carolina Chapel Hill

BACKGROUND: Ground-level ozone is a prevalent air pollutant that can promote inflammation, exacerbate airway disease, and increase susceptibility to viral infections. At the molecular level, ozone reacts readily with components of the airway lining fluid and cell membranes (e.g. cholesterol, phospholipids, and proteins) to form oxidation products, which may contribute to these biological responses. Ozone-oxidized cholesterol products (oxysterols), such as highly reactive secosterol-A (SecoA), can adduct with cellular proteins and consequently modify their folding, promote aggregation, and alter function within the cell. Our lab previously performed a proteomic screen for SecoA adducted proteins in bronchial epithelial cells and found nucleotide-binding domain and leucine-rich repeat family pyrin containing 2 (NLRP2) to be modified. NLRP2 is a pattern recognition receptor that had been shown to negatively regulate pro-inflammatory signaling and antiviral immunity in different tissue types; however, how these functions translate to a role for NLRP2 within the bronchial epithelium and contribution to ozone-induced health effects is not known.

METHODS: To examine how NLRP2 regulates antiviral response in bronchial, shRNA mediated-knockdown (KD) of NLRP2 was performed in bronchial epithelial cells. Both scramble control cells and NLRP2 KD cells were treated with polyinosinic: olycytidylic (poly I: , 25 μg/mL), a viral mimic, for 24 hours. At 1,2,3, 8, and 24 hours of poly I: treatment, RNA and media were collected for analysis of antiviral gene expression (i.e. CXCL10). To determine if NLRP2 may contribute to enhanced susceptibility to viral infection following ozone exposure, wild type (WT) and NLRP2 knockout bronchial epithelial cells (KO) were cultured at an air-liquid interface and exposed to either air or ozone (0.4ppm) for 4 hours. At 1-hour post-exposure, RNA and basolateral media was harvested.

RESULTS: The peak for CXCL10 expression was observed at 8 hours following treatment with poly I: . KD of NLRP2 led to a significant decrease in CXCL10 mRNA and protein production in response to poly I: treatment at the 8 and 24 hour time points. Similarly, KO cells exhibited lower CXCL10 expression in both the air and ozone-exposed samples, while ozone significantly decreased CXCL10 production only in the WT cells.

CONCLUSION: Varied expression of NLRP2 across different epithelial cell types suggests a cell type dependent role for this NLR family member in mucosal surfaces, including the respiratory mucosa. Specifically, NLRP2 may serve as a positive modulator of CXCL10 expression and antiviral response in the bronchial epithelium. Furthermore, ozone-mediated decrease in antiviral gene expression may be mediated in part by NLRP2. Therefore, further investigation is needed to determine if SecoA adduction alters the function of NLRP2 in this regard and contributes to the enhanced susceptibility to viral infections following ozone exposure.

Alexia Perryman is a graduate student in the Curriculum in Toxicology & Environmental Medicine at University of North Carolina at Chapel Hill. There, she works in the lab of Dr. Ilona Jaspers studying the effect of ozone on the innate immune response and how responses vary in asthmatics.

Abstract Title: Adaptations of telehealth-delivered pulmonary rehabilitation for cognitively impaired COPD study participants.

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INTRODUCTION: Cognitive impairment (CI) is present between 10-61% of persons with COPD, and leads to worse outcomes including increased rates of re-hospitalization. COPD persons with CI have pronounced barriers to pulmonary rehabilitation (PR) participation; those requiring caregiver support for completion of tasks are typically not able to participate in standard pulmonary rehabilitation (office based PR). We describe adaptions to a telePR platform (telehealth-delivered PR in patients' homes) to enable participation by persons with concomitant CI and COPD.

METHODS: As part of a randomized control study comparing a referral to telePR vs. standard PR (SPR) we performed lab-based and in-field (in persons homes) usability testing including obtaining caregiver input for persons with CI. The telePR platform includes delivery of a tablet for teleconferencing with a respiratory therapist (RT), a stationary bike with exercise equipment and real-time vital sign monitors. The Mini-Mental State Examination (MMSE) assessment was conducted to test person's orientation, attention, memory, language and visual-spatial skills.

RESULTS: 57 persons (26 Hispanic and 31 African-American with mean age of 67.22±11.86 years), were recruited and randomized into telePR. MMSE scores were completed by 44 (77%) participants. Among these scores, 15 were abnormal ranging from 14 to 26 demonstrating mild-moderate CI. Persons were categorized by level of independent, intermediate, and dependent to predict level of support needed for telePR participation. The following adaptions were implemented to allow these persons with CI to participate in telePR: presenting exercise as graded tasks (RT starting sessions with simple instructions and gradual introduction of exercises over time); customizing icons on tablets to facilitate easier access to teleconference (larger icons, signaling icon of use and 1 click motion); providing a microkey remote control (6 buttons to easily turn on/off tablet, start/close, and restart teleconference and Nonin); replacing pulse oximeter by a Nonin wristwatch (sensor values directly sent to RT for real-time monitoring); and including a caregiver/research member during at least the first 3 sessions with some persons requiring presence at each sessions. As a result of these adaptions all 15 persons were able to complete the 8 weeks of telePR.

MMSE Score for Persons with COPD

	Persons Educational Level			2 Minute Step Test (2MST)	
	Some College or Higher (Total Number)	High School Graduate (Total Number)	8th Grade or Some High School (Total Number)	Day 1 (Average Number)	8 Weeks (Average Number)
Normal MMSE	8	10	11	42	50
Abnormal MMSE	6	4	5	43	53

CONCLUSION: PR can be an effective treatment for persons with COPD. TelePR can overcome access barriers to PR participation. For the 10-61% of COPD persons with concomitant CI, attendance at SPR is not possible. Our research demonstrates that additional adaptions to telePR can enable successful participation by these persons who arguably stand to benefit the most from PR.

Jennifer Polo is Research Coordinator at Northwell Health. As a Latina from an underserved community, she is committed to research on decision making for chronic lung diseases for among disparity populations.

Abstract Title: Characteristics and Outcomes of Pediatric Patients with Recurrent Respiratory Viral Infections

Authors: A.P. Rebaza[1], S. Bermejo[2], L. Sharma[2], J. Gomez-Villalobos[3], C. Dela Cruz[3]

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RATIONALE: Respiratory viral infections are common in the pediatric and adult population. Children may average four to eight respiratory infections annually. It is known that children with Respiratory Syncytial Virus (RSV) bronchiolitis have increased risk for asthma later in life. However, studies assessing long- term effects or outcomes of recurrent viral infections in the pediatric population are limited. With recent Influenza season highlighting multiple deaths around the country, it is worthwhile to investigate if recurrent respiratory viral infections are associated with worse clinical outcomes.

METHOD: In our retrospective analysis of clinical data obtained from Yale New Haven Hospital, we sought to characterize pediatric patients (0 to 21 years) who tested positive for respiratory viruses on viral panel and with single versus multiple hospital encounters over a five-year period. Demographics and clinical variables including comorbidities, respiratory support, antibiotic usage, labs, and maximum temperature during hospital encounter were obtained.

Table 1: Clinical Demographics of Pediatric Patients per Hospital Encounter Type

	Multiple Visits	Single Visits	Overall
	(n=861)	(n=2711)	(n=3572)
Gender			
	336*		
Female	142 (42.3%)	1201 (44.3%)	1343 (44.1%)
Male	194 (57.7%)	1510 (55.7%)	1704 (55.9%)
Race			
Black	100 (29.8%)	709 (26.2%)	809 (26.6%)
White	119 (35.4%)	1184 (43.7%)	1303 (42.8%)
Other	117 (34.8%)	818 (30.2%)	935 (30.7%)
Hispanic Ethnicity n (%)	117 (34.8%)	811 (29.9%)	928 (26.0%)
BMI			
Mean (SD)	19.0 (6.13)	18.9 (5.97)	18.9 (5.99)
Smoking Status			
Former Smoker	2 (0.6%)	41 (1.5%)	43 (1.2%)
Never	261 (77.7%)	1635 (60.3%)	1896 (53.1%)
Secondhand Smoke Exposure	30 (8.9%)	159 (5.9%)	189 (5.3%)
Unknown	37 (11.0%)	829 (30.6%)	866 (24.2%)
Active Smoker	6 (1.8%)	47 (1.7%)	53 (1.5%)
Age at Arrival (years)			
Mean (SD)	4.57 (5.86)	4.97 (6.54)	4.87 (6.38)
Deaths n (%)	0 (0%)	6 (0.2%)	6 (0.2%)
Length of Stay (days)			
Mean (SD)	5.00 (8.02)	4.07 (14.9)	4.35 (13.2)
Emergency Department Only	141 (16.4%)	1054 (38.9%)	1195 (33.5%)
Admission to ICU	306 (35.5%)	535 (19.7%)	841 (23.5%)

**Number of patients who made multiple visits (total visits 861)*

RESULTS: 3047 patients were included in final analysis which accounted for 3572 unique hospital encounters (see Table 1). Asthma was the most common comorbidity for the entire group, accounting for 29% of all patients, followed by bronchiolitis. Pneumonia was present in 15% of all patients. The most frequent virus isolated was Rhinovirus (34.6%) followed by RSV (24.8%). When divided into multiple and single encounters, Rhinovirus was most common in 48% and 30% of all multiple and single encounters, respectively. RSV followed at 18% and 27% of all multiple and single encounters, respectively. Secondhand smoke exposure (Table 1, p=0.038), length of stay, and Intensive Care Unit (ICU) admission was higher in the multiple group (Table 1, p<0.001 each). Emergency Department (ED) presentation was more frequent in the single group (Table 1, p<0.001). In terms of respiratory support, ventilator use, need for high-flow nasal cannula, and nasal cannula were higher in the multiple group (17.4% versus 5.6% in single group, 18.8% versus 10% in single group, 36.7% versus 25.5% in single group, respectively, p<0.001 each). Antibiotic usage was higher in multiple group (47% versus 31%, p<0.001). For laboratory measurements, mean eosinophil counts and arterial PCO2 was higher amongst the multiple encounter group (p=0.0008, p<0.001, respectively). There was no difference in max temperature between two groups.

CONCLUSION: Patients with recurrent hospital visits were clinically more severe compared to patients with single visits. Our data overall highlight differences seen in pediatric patients with recurrent and single hospital visits who were positive for respiratory viral infections.

Andre Rebaza is a 3rd year Pediatric Pulmonary fellow at Yale University. He is interested in respiratory viral infections and its burden on childhood disease. He is conducting both basic science and clinical projects on this topic.

Abstract Title: Protective Effect Of Monocarboxylate Transporters In Acute Lung Injury

Authors: V. Rubio, S. Zirbel, K. DeMasellis, G. Karpinsky, E. Coit, N. Burns, R. M. Tuder, C. U. Vohwinkel

University of Denver

RATIONALE: Acute lung injury (ALI) is an inflammatory lung disease, which manifests itself in patients as acute respiratory distress syndrome (ARDS). Presently, specific therapeutic approaches for ARDS are essentially unknown. Previous studies have shown that during the inflammatory response, alveolar type 2 cells (ATII) upregulate the production of lactate through HIF1A dependent glycolysis. Lactate, the end product of glycolysis can shift macrophages to an anti-inflammatory phenotype in several mouse models of ALI. However, the mechanism for lactate uptake by macrophages in the setting of ALI is unknown. Monocarboxylate transporters (MCTs), are a family of proton-linked plasma membrane transporters that carry molecules such as lactate and pyruvate, across biological membranes. Importing transporters MCT-1 and MCT-4 expression has been described in macrophages. We hypothesized that stimulating the macrophages with LPS would upregulate monocarboxylate transporters (MCTs) and inhibition of MCTs will prevent the lactate mediated increase of anti-inflammatory markers Arg-1 and IL-10.

METHODS: Bone marrow derived macrophages (BDMs) were isolated from C57/B6 mice. Human airway macrophages were isolated from BAL of lungs not suitable for transplantation and donated for medical research. L-Lactate was added to cultured cells 2 days after isolation (control experiments with pH-controlled PBS and D-Lactate). Macrophages were stimulated with lipopolysaccharide (LPS). Cytokine expression was determined by qPCR. MCT-1 was inhibited by MCT1 inhibitor III.

RESULTS : MCT-1 is expressed both murine BDMs and human airway macrophages. MCT-1 expression was increased in response to LPS stimulation. MCT-4 expression was low to undetectable in both macrophage types. In BDMs L-lactate did not change the cytokines expression. However, in human airway macrophages L-lactate added before or after LPS stimulation shifted the macrophages towards an anti-inflammatory phenotype with Arg-1 expression and with increased IL-10 and decreased IL-1 and IL-6 production. Inhibiting MCT1 prevented the lactate induced shift in macrophages phenotype. D-Lactate or pH controlled PBS did not affect Arg-1 expression or cytokine pattern.

CONCLUSIONS: Primary human airway macrophages upregulate the MCT-1 lactate transporter in response to inflammatory stimulation in order to import lactate into the cell. L-Lactate shifts airway macrophages (but not BDMs) from a pro-inflammatory phenotype to an anti-inflammatory phenotype, which indicates that the micro-environment is a critical determinant of macrophage function. These results suggest that altering the human airway macrophages phenotype via metabolic crosstalk with the alveolar epithelium metabolism may ameliorate excessive airway inflammation in ALI.

Victoria Rubio is a third year undergraduate student at the University of Denver majoring in Biochemistry. She has been studying acute lung injury at Children's Hospital Colorado/University of Colorado since the 2019 Summer Child Health Research Internship

Abstract Title: Repeat Rapid Response Calls: Associated with Increased Morbidity and Mortality

Author: Ann Marie Rusk, MD, Department of Pulmonary and Critical Care Medicine, Mayo Clinic Rochester, MN; Alice Gallo De Moraes, MD, Department of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN

RATIONALE: Many institutions have implemented a rapid response team (RRT) to aid in clinical management and escalation of care for unstable patients. Though there is data suggesting multiple RRT activations during a hospital stay is associated with increased mortality, there is a paucity of data addressing intensive care unit (ICU) morbidity. The aim of the following retrospective analysis was to examine mortality and markers of ICU morbidity for patients with two RRT calls activated within 24 hours compared to patients with one RRT activation.

METHODS: Retrospective review of 2307 RRT activations from January 1, 2019 through August 31, 2019 was completed. Charts were selected for review if there were greater than two RRT activations in one 24 hour period. 144 patients were found to have multiple rapid response calls within 24 hours. Outpatients and federal prisoners were excluded from review. A random number generator selected 140 RRT events for control. Patients were excluded from control if multiple rapid responses were activated during hospitalization, patients were found to be outpatients, or were federal prisoners. 40 patients were included in control. Variables outlined in table 1 to examine mortality and ICU interventions were reviewed. Chi square analysis was completed to assess for statistical significance with a significance level of 0.05

Parameters reviewed	*Multiple RRT Calls*	*One RRT Call*	*p value*
Average Hospital Length of Stay	20.3 days	7.0 days	
ICU Transfer	76.40%	37.50%	**0.00001**
Average ICU Length of Stay	3.1 days	0.77 days	
ICU mortality	17.10%	2.50%	**0.018193**
Hospital mortality	25.00%	7.50%	**0.016764**
Rescue NIPPV	39.30%	10%	**0.000502**
Endotracheal Intubation	27.90%	2.50%	**0.007261**
New Renal Replacement Therapy	8.57%	2.50%	0.190788
Vasopressor use	32.14%	12.50%	**0.01444**
Central Venous Catheter	38.46%	7.50%	**0.000148**
Arterial Line	42.14%	17.50%	**0.000048**
Change in Code Status	42.43%	17.50%	0.084694
Documented Goals of Care Discussion	38.57%	15.00%	**0.005287**
Cardiac arrest with Resucitation Attempt	8.57%	7.50%	0.828812
Average age	66.2 years	71.3 years	

Table 1: Highlighted p values indicate statistical significance between control and study arms.

RESULTS: Patients with two or more RRT activations in a 24 hour period had significantly higher mortality than control and significantly more invasive interventions, including non invasive positive pressure ventilation (NIPPV), endotracheal intubation, arterial line placement, vasopressor use, and central venous catheter placement. Multiple RRT activations were more likely to undergo a documented goals of care discussion. Length of stay was longer for patients with multiple RRT calls. There was a trend of higher mortality in women compared to men undergoing multiple RRT activations, however this did not reach statistical significance.

CONCLUSIONS: Patients undergoing multiple RRT activations in 24 hours were found to have longer length of stay and receive more invasive ICU interventions than control. Cause of higher mortality and utilization of invasive ICU interventions is unclear, but may be due to delay in escalation of care. Further review is required to explore possible contributing factors leading to increased morbidity and mortality.

Ann Rusk is a first year pulmonary and critical care fellow at the Mayo Clinic, Rochester campus. She graduated from the University of Minnesota medical school in 2015, and then completed her residency in Internal Medicine at the Medical College of Wisconsin where she was recognized as a chief resident. As an enrolled member of the Blackfeet Nation, support from her family and Tribal community has been pivotal for her career development. She hopes to promote health equity in Native Americans with her research and practice in the future.

Abstract Title: Impaired HSF1 Transactivation By Sumoylation Drives Cellular Senescence in Lung Fibroblast

Authors: Dominic Sales[1], K. Cuevas-Mora[1], W. Roque[2] F. Romero[1]

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RATIONALE: Loss of proteostasis and cellular senescence are key hallmarks of aging. Recent studies suggest that lung fibroblast from IPF patients showed features of cellular senescence, decline in heat shock protein 70 (HSP70) expression, and impaired cellular proteostasis. However, a direct cause-effect relationship are still mostly unknown.

OBJECTIVES: In this study, we sought to investigate whether the Heat Shock factor 1 (HSF1), a major transcription factor that regulates the cellular chaperones network and cytoplasmic proteostasis, contribute to cellular senescence in lung fibroblast.

METHODS: Cellular senescence was induced by exposing MLg mouse fibroblast to chronic low dose of H2O2 (100 mM) for 7 days. Cells lysates were collected for protein and gene expression analysis. Transcript and protein levels were assessed for several chaperones (HSP70, HSP40 and HSP27) and for various cellular senescence markers (p21, p53, p16, IL6, Mcp1, Tnfα, and Ilα). HSF1 total expression, p-HSF1ser 333, p-HSF1ser307 and HSF sumoylation (lysine 298) were measured by Western blot. The proteasome activity was measured using the AMC-tagged peptide substrate Suc-LLVY-aminoluciferin, Z-LRR-aminoluciferin, and Z-nLPnLD-aminoluciferin for the chymotrypsin-like, trysin-like and caspase-like activities, respectively. Protein aggregation was detected using a molecular rotor dye (Proteostat).

RESULTS: We found that chronic injured MLg fibroblast showed an upregulation in the expression of various cellular senescence markers, including β-Gal staining, the DNA damage marker γH2Ax, p21 and multiple senescence-associated secretory proteins (SASP), such as Il6, Mcp1, Tnfα, and Ilα. These changes were associated with impaired proteostasis, as judged by an increase in levels of p-HSF1ser307 and sumoylated HSF1, downregulation of protein chaperones, proteasome activity and increased cellular protein aggregation. Moreover, sustained pharmacology activation of HSF1 by small molecule proteostasis regulators (A3) induce heat shock proteins expression by activating HSF1 and reduced cellular senescence in MLg fibroblast.

CONCLUSION: Our data provide evidence that the HSF1-mediated proteostasis is important for driving lung fibroblast toward cellular senescence. We postulate that enhancing HSF1 activity could be effective in the treatment of senescence-associated lung diseases.

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Conflict of interest: No conflict of interest

Dominic Sales holds a Doctor of Philosophy, PhD, in microbiology and immunology. He has been published 15 times in a variety of journals.

Abstract Title: Association of Leukotriene Modifier Use and Bronchodilator Response in Puerto Rican and Mexican American Children with Asthma

Authors: Lesly-Anne Samedy-Bates, Sam S Oh, Marquitta White, Eunice Lee, Eric M Wohlford, Michael A LeNoir, Harold J Farber, Denise Serebrisky, Emerita Brigino-Buenaventura, William Rodriguez-Cintron, Kirsten Bibbins-Domingo, Rajesh Kumar, Shannon Thyne, Maria Pino-Yanes, José R Rodriguez-Santana, Luisa N Borrell and Esteban G Burchard

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RATIONALE: The National Asthma Education and Prevention Program recommends leukotriene modifiers (LM), plus a short-acting bronchodilator, as a therapy alternative for patients with persistent asthma and in the treatment of allergy symptoms. In the presence of tobacco secondhand smoke (SHS) exposure, an asthma and allergy irritant, greater improvement compared to inhaled corticosteroids (ICS) has been demonstrated in individuals treated with LM, suggesting that LM may be important in this setting. Few studies have examined if the augmentation of bronchodilator response (BDR) by LM use is equivalent in diverse ethnic groups. Our objective was to define subethnic-specific differences in the effect of LM on BDR and whether the response is modified by SHS exposure among Latino children with asthma.

METHODS: The association between LM use and BDR was evaluated in Latino populations with persistent asthma (841 Puerto Rican and 337 Mexican American children). Data were provided by the participants or the participant's parent/guardian using a questionnaire standardized by the American Thoracic Society (ATS). BDR to albuterol, measured via spirometry, was compared between participants using LM and those not using LM. Multivariable quantile regression analysis was used to determine the association between LM use and BDR and whether this association varies with SHS exposure. We adjusted for age, baseline forced expiratory volume in one second (FEV1) and use of controller medication, including long-acting B2-agonists, inhaled corticosteroids and oral steroids. Significance was determined at an alpha level of 0.05

RESULTS: Overall, Puerto Rican and Mexican American youth reported a comparable use of LM medication (30.9% vs. 26.7%, p=0.174). Puerto Rican children demonstrated a significantly lower baseline FEV1 (median 2.02L vs. 2.42, p<0.001) and lower percent predicted FEV1 (median 83.5% vs. 95.4%, p<0.001), compared to Mexican Americans. The association of LM use with BDR was significantly modified by SHS exposure status in Puerto Rican children, but not Mexican Americans. We observed a significant increase in BDR with LM use only in Puerto Ricans exposed to SHS (2.14%, p=0.035).

CONCLUSION: Our results demonstrate that LM therapy may not be an effective alternative in minority children with persistent asthma. LM use may be protective or ineffective in SHS exposure, contingent on the ethnic subgroups. Our findings have important implications for the alternative management of patients with persistent asthma, especially those exposed to SHS. This study reinforces the importance of investigating the influence of race/ethnicity on pharmacological response in order to improve asthma outcomes.

Lesly-Anne Samedy-Bates, PharmD, PhD, MS is a clinical pharmacologist whose researches focuses the role of the genetics in drug response in order to develop a more personalized, tailored approach to health care delivery and improved health outcomes. She is currently an NIH clinical pharmacology research fellow at UCSF, under the mentorship of Esteban Burchard, MD, MPH.

Abstract title: Oxidative stress, as measured by gene expression and airway glutathione, is increased in severe asthma and associated with racial background

Authors: Alexander J. Schuyler, Tadao Nagasaki, John B. Trudeau, Sally E. Wenzel

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RATIONALE: Gene-by-environment interactions could magnify health disparities when social context, including environmental inequalities, enhances adverse effects of genetic polymorphisms. Racial/ethnic disparities in asthma have been associated with environmental inequalities, such as disproportionately higher exposure to environmental toxicants. Environmental toxicants, typically strong oxidants, would lower intracellular antioxidants, like glutathione (GSH), and increase oxidized metabolites (GSSG) thereby worsening asthma. Variance in both genetic background and environmental exposure level would then determine individual responses to oxidative stress. We hypothesized that black compared to white asthmatic adults would show more evidence for oxidative stress as measured in airway epithelial cells (AECs) and bronchoalveolar fluid (BALF).

Table 1. Summary of 28 oxidative stress-related genes and their relationship with 1) asthma severity and 2) self-identified race in SA.

Gene	Function	SA vs. HC		SA: Black vs. White	
		p-value	Z-score	p-value	Z-score
ABCC1	Export of intracellular GSSG	**0.007**	**2.706**	0.280	0.602
CCBL1	Metabolism of cysteine conjugates	**0.019**	**2.354**	0.196	0.880
CD44	Stabilization of SLC7A11	**<0.001**	**3.981**	0.280	0.602
CST1	Inhibitor of cysteine proteases	**0.002**	**3.124**	0.447	0.139
CST2	Inhibitor of thiol proteases	0.186	1.324	0.177	-0.927
FETUB	Inhibitor of cysteine proteases	**0.003**	**2.928**	0.518	0.000
GCLC	First/rate-limiting step of de novo GSH biosynthesis (catalytic subunit)	0.741	-0.330	**0.022**	**1.991**
GCLM	First/rate-limiting step of de novo GSH biosynthesis (modifier subunit)	0.141	-1.474	0.250	0.694
GGT1	Hydrolysis of extracellular GSH to glutamate and cysteinyl-glycine	0.613	0.506	0.280	0.602
GLS1	Conversion of glutamine to glutamate (kidney-type)	0.416	-0.814	0.053	1.620
GLS2	Conversion of glutamine to glutamate (liver-type)	**0.009**	**-2.618**	0.343	0.677
GLUD1	Conversion of glutamate to α-ketoglutarate (mitochondrial)	**0.015**	**-2.442**	0.222	0.787
GLUD2	Conversion of glutamate to α-ketoglutarate (mitochondrial)	0.244	1.166	0.447	0.139
GPX4	Neutralization of intracellular 15-HpETE	0.194	-1.300	0.377	-0.324
GSR	NADPH-dependent reduction of intracellular GSSG	0.391	0.858	**0.004**	**2.546**
GSS	Second step of de novo GSH biosynthesis	0.416	0.814	0.343	0.677
NFE2L2	Regulation of antioxidant response elements (transcription factor)	0.441	0.770	0.149	-1.065
SLC1A1	Sodium-dependent uptake of glutamate and other amino acids	1.000	0.000	0.343	0.417
SLC1A2	Sodium-dependent uptake of glutamate and other amino acids	0.708	0.374	0.093	1.342
SLC1A3	Sodium-dependent uptake of glutamate and other amino acids	0.082	1.738	0.093	-1.342
SLC1A5	Sodium-dependent uptake of zwitterionic and neutral amino acids	**0.004**	**2.882**	**0.028**	**1.898**
SLC1A6	Sodium-dependent uptake of glutamate and other amino acids	0.887	-0.143	0.114	-1.211
SLC1A7	Sodium- and voltage-dependent uptake of glutamate	0.808	-0.242	0.437	0.139
SLC3A2	Sodium-independent uptake of large, neutral amino acids	0.301	1.034	0.078	1.435
SLC7A11	Sodium-independent exchange of cysteine for intracellular glutamate	0.244	1.166	0.250	0.694
TXN1	Reduction of protein thiols (cytoplasmic)	**0.037**	**2.090**	0.311	0.509
TXN2	Reduction of protein thiols (mitochondrial)	0.153	-1.430	0.482	-0.046
TXNRD1	NADPH-dependent reduction of oxidized thioredoxin	0.129	1.518	**0.013**	**2.176**

METHODS: Fresh AECs from bronchoscopic brushings and BALF were collected from asthmatic patients and healthy controls (HCs) recruited as part of the Immune Mechanisms of SA cohort (NIH/NHLBI P01-AI106684). Global RNA-Seq was performed on AECs. Following normalization and batch effect correction, log-normalized mRNA transcripts for 28 oxidative stress-related genes were reported [Table 1]. GSH and GSSG in AECs and BALF were measured by enzymatic assay. Severe asthma (SA) was defined by ERS-ATS criteria and mild/moderate asthma (MMA) included all others. Differences between groups were compared using Wilcoxon tests and associations between gene expression, race, sex, age and BMI were determined by generalized regression.

RESULTS: 20 SA patients, 26 MMA patients and 10 HCs were enrolled (73% female, self-identified race: 21% black, 4% Asian/Pacific Islander). A subset (n=50/56) had available BALF. Increased ABCC1, CCBL1, CD44, CST1, FETUB, SLC1A5 and TXN1 expression was observed in SA patients versus HCs, while GLUD1 and GLS2 were lower [Table 1]. When corrected for asthma severity, elevations in GCLC, GSR, SLC1A5 and TRXRD1 expression were observed in black versus white adults [Table 1]. Regression analyses confirmed the relationship between black race and GCLC (β=0.448, p=0.002), GSR (β=0.230, p=0.027) and TRXRD1 (β=0.352, p=0.022) expression in SA. Consistent with increased oxidative stress, higher BALF GSSG was observed in black versus white females (p=0.013, Z=2.484). Among all participants, those with high TRXRD1, high GSR and high GCLC expression (by median split) exhibited higher BALF GSSG (p=0.017, Z=2.115), lower intracellular GSH: SSG (p=0.012, Z=-2.201) and higher intracellular GSSG (p=0.031, Z=1.854), respectively.

CONCLUSION: Poorly control asthma is associated with increased expression of oxidative stress-related genes, with black adults showing more evidence for ongoing oxidative stress than white adults. Self-identified race, although a social construct, may be a proxy for inequities in environmental exposures, increased genetic risk or a combination of both.

Alex Schuyler (he/him/his) is an M.D./Ph.D. student at the University of Pittsburgh. Alex completed a B.S. in Biology and B.A. in East Asian Languages & Literature at Washington & Lee University. Between college and medical school, Alex worked in Dr. Thomas Platts-Mills' lab at the University of Virginia and studied IgE and IgG4 responses to mammalian allergens in various allergic diseases. During this time, Alex also served on the Executive Board of the local NAACP branch, as well as their Press, Publicity & Communications Chair.ing completed the first two years of medical school, Alex has temporarily traded in his stethoscope for a pipette in pursuit of a Ph.D. in Environmental & Occupational Health under the mentorship of Dr. Sally Wenzel. Alex's current research interests are socioenvironmental determinants of lung epithelium health and oxidative stress.

Outside of school, Alex sit on the Advisory Council for sisTer PGH, a black/transgender-lead organization that serves the local LGBTQIA+ community. Alex led data analytics for this group to help identify the needs of the Pittsburgh LGBTQIA+ community during the COVID-19 pandemic. Alex received the Sally Miller Award for Advocacy on Behalf of the Medically Underserved and the Trans Allyship Award in 2019.

Abstract Title: Impact of Asthma on Economic Productivity and Quality of Life in Urban Families in the United States

Authors: C. Socolovsky[1], C. Petty[2], M. Green[2], M. Samnaliev[2], W. Phipatanakul[3];

[1]Brigham and Women's Hospital, Boston, MA, United States, [2]Boston Children's Hospital, Boston, MA, United States, [3]Harvard Medical School, Boston Children's Hospital, Boston, MA, United States

RATIONALE: Asthma affects 6 million children in the United States, costing 3 billion dollars in lost wages and 83 billion dollars in health care utilization (HCU) per year. Inner city children experience higher asthma morbidity and mortality, driven by environmental exposures and socioeconomic determinants of health. The School Inner-City Asthma Intervention Study (SICAS-2) is a randomized controlled trial assessing the impact of HEPA air filtration and pest management in schools. We report participants' baseline quality of life, HCU and work productivity to understand the potential cost effectiveness of school environmental exposure reduction.

METHODS: SICAS-2 recruited inner city school-aged children with asthma (n= 214) in a randomized double-blind placebo controlled study evaluating air filter/purification with integrated pest management in school environments. Upon enrollment, each participant reported baseline symptom burden over the preceding 2 weeks and health care utilization (HCU) over the previous year, quantified by unplanned provider or emergency room visits. Participants also completed validated survey instruments, the Workers Productivity and Activity Impairment (WPAI) survey and EuroQol Five Dimensional Survey (EQ5D), to quantify impact of asthma on work productivity and quality of life, respectively. We used one-way analysis of variance to assess impact of race, household income or household education on these responses.

RESULTS: One third (32.86%) of participants reported one or more unplanned hospitalization or doctor's visit due to asthma in the past year. Amongst the 40% of participants who completed WPAI, 62% reported >4 hours of missed work per week and impaired work productivity due to their child's asthma. The majority of participants completed EQ5D (80%); approximately one fourth of caregivers reported their child experienced discomfort, depression or anxiety and were less able to participate usual activities due to asthma. 76% of the SICAS-2 population identified as a racial or ethnic minority; 40% had a household income less than 50,000 dollars; and 59% of caregivers had high school diploma or less. Higher income caregivers were more likely to report decreased productivity. Latino ethnicity and lower education were both associated to increased reports of limited mobility. Latino children also reported more depression or anxiety.

CONCLUSIONS: Baseline responses of the SICAS-2 participants suggest inner city children with asthma experience economic burden and decreased quality of life, both of which may be alleviated by decreasing school exposures. These data will be used to establish whether the SICAS-2 intervention is cost effective. Race, ethnicity and socioeconomic status may impact the degree of cost savings.

Dr. Carmela Socolovsky is interested in evaluating the impact of environmental exposures on pulmonary disparities to inform data-driven policy initiatives for vulnerable populations. She received her medical degree from The University of Chicago Pritzker School of Medicine in 2014 and completed Internal Medicine residency at Massachusetts General Hospital in 2017.

Abstract Title: YAP/TAZ Regulates TGF-beta/BMP Signaling In Pulmonary Artery Smooth Muscle Cells In Pulmonary Arterial Hypertension

Authors: P. Sosa[1], R. Rehman[2], P. B. Dieffenbach[2], A. M. Corcoran[2], L. E. Fredenburgh[2];

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RATIONALE: Enhanced TGF-# receptor signaling and impaired bone morphogenetic protein (BMP) receptor signaling play a key role in the pathogenesis of familial pulmonary arterial hypertension (FPAH) and idiopathic PAH (IPAH), however the mechanisms underlying the imbalance in TGF-#/BMP signaling in PAH remain incompletely understood. We have identified Yes-associated protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ) as pivotal regulators of sti"ness-dependent remodeling phenotypes in pulmonary artery smooth muscle cells (PASMC) in PAH. Prior work has demonstrated that YAP/TAZ may regulate TGF-# signaling and direct nucleocytoplasmic localization and activity of TGF-#-activated Smads in human embryonic stem cells and epithelial cells, however the role of YAP/TAZ in regulating TGF- #/BMP signaling in PASMC in PAH has not been examined.

OBJECTIVE: To investigate the role of YAP/TAZ signaling in regulation of TGF-#/BMP signaling in human PAH PASMC.

METHODS: PASMC isolated from explanted lungs of patients with IPAH, FPAH with BMPRII mutation, and control donors, were serum starved and exposed to normoxia or hypoxia (0.5% O2) for di"erent durations. In some experiments, cells were treated with recombinant TGF-# or BMP4. Supernatants were collected and ELISA was performed for TGF-#. RNA was isolated, converted to cDNA, and qPCR was performed for PAI-1, Id1, and YAP/TAZ dependent gene (Cyr61, CTGF) expression.

Immunocytochemistry was performed for Ki67 and YAP/TAZ. Cell number was also determined using the CyQuant NF Cell Proliferation Assay. PASMC were transfected with siRNA ON-TARGETplus SMARTpools targeting human YAP1 and TAZ. Id1 expression was also assessed via qPCR and Western blot in PASMC stably overexpressing constitutively active TAZ (TAZ4SA), YAP (YAP5SA), and control vector.

RESULTS: Secreted TGF-# levels were significantly higher in PAH PASMC compared with control PASMC under baseline normoxic conditions. Hypoxia increased TGF-# levels in IPAH and FPAH PASMC, but had no e"ect in control cells. PAI-1, CTGF, and Cyr61 expression were increased in IPAH and FPAH PASMC compared with control cells at baseline, and were induced by hypoxia in PAH, but not control, PASMC. YAP/TAZ nuclear activity was increased in IPAH and FPAH PASMC compared with control cells and correlated with increased Ki67 expression. Knockdown of YAP/TAZ attenuated TGF-# induction ofPAI-1, enhanced BMP4 induction of Id1 expression, and inhibited proliferation of PAH PASMC. Overexpression of nuclear TAZ or YAP dramatically suppressed Id1 expression in PASMC.

CONCLUSIONS: PAH PASMC have increased YAP/TAZ activation and TGF-# signaling, which are enhanced by exposure to hypoxia.

Piera Sosa is a second-year medical student at Meharry Medical College in Nashville, TN. She collaborates with Dr. Fredenburgh's laboratory at Brigham and Women's Hospital.

Abstract Title: Human Airway Surface Liquid Antimicrobial Activity And Response To Vitamin D Is Seasonal: Results From A Randomized Placebo-controlled Double-blind Trial

Authors: L. G. Vargas Buonfiglio[1], O. G. Vanegas Calderon[2], M. Cano[3], J. Simmering[1], P. M. Polgreen[1], J. Zabner[1], A. K. Gerke[1], A. P. Comellas[1]

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BACKGROUND: It is widely unknown why respiratory infections follow a seasonal pattern. Variations in Ultraviolet B (UVB) light during seasons affect the cutaneous synthesis of vitamin D. Serum vitamin D concentration influences the expression of airway surface liquid (ASL) antimicrobial peptides such as LL-37.

OBJECTIVE: Determine the effect of seasons on ASL antimicrobial activity and response to vitamin D supplementation.

METHODS: In a single centre, placebo-controlled, double-blind trial, 40 participants, 18-60 years old were randomized 1:1 to receive 90-days of 1000 IU vitamin D3 or placebo. We collected ASL via bronchoscopy and measured 25(OH)vitamin D serum concentration from participants before and after intervention across seasons. We measured ASL antimicrobial activity using bioluminescent Staphylococcus aureus (~5×106 colony forming units) and measured live bacteria by relative light units (RLU) after four minutes. We also investigated the role of LL-37 in this seasonal response by using a monoclonal neutralizing antibody.

RESULTS: We found that participants during summer and fall (n=20) compared to winter and spring (n=20) had: 1) decreased live bacteria after challenge (5542 ± 175.2 vs. 6585 ± 279 RLU, p= 0.003) and 2) higher serum vitamin D (35.3 ± 9.7 vs. 27±18.1 ng/mL, p= 0.026). Supplementation with vitamin D3 increased vitamin D levels and restored ASL antimicrobial activity only during the winter and spring period. The increased ASL antimicrobial activity seen during the summer-fall was abrogated by adding an LL-37 neutralizing antibody.

CONCLUSION: ASL kills bacteria more effectively during the summer-fall compared to the winter-spring. Supplementation of vitamin D3 only during winter-spring restores ASL antimicrobial activity likely by increasing the expression of antimicrobial peptides such as LL-37.

Luis Vargas Buonfiglio MD is a Venezuelan-born physician scientist with more than 10 years of research experience committed to the advance of pulmonary medicine by investigating mechanism of antimicrobial activity in the airways.

Abstract Title: Soldiers Deployed in Conflict Zones at Highest Risk for Incident Asthma

Author: Nicholas Villalobos MD, Clifford Qualls PhD, Akshay Sood MD, Jenny Mao MD

University of New Mexico

RATIONALE: Obese subjects are at high risk for incident asthma. The recent Millenium Cohort study confirmed this association in obese soldiers deployed during the Persian Gulf War. With this in mind, we sought to further define subgroups at greatest risk, among a large at-risk population of veterans with excess weight and diabetes and/or hypertension, who were deployed during the Operation Enduring Freedom/Iraqi Freedom (OEF/OIF) by the U.S. Military.

METHODS: A longitudinal data analysis of overweight (BMI >25) or Obese (BMI >30) veterans deployed during OEF/OIF was performed using an existing cohort of 47,959 American veterans, between Jan 1, 2000 and Feb 7, 2015. This cohort included subjects with excess weight and diabetes mellitus and/or hypertension, as documented by medical providers within the Veterans Affairs medical system. We employed a logistic regression model to analyze risk for incident asthma and perform formal tests of statistical interaction to identify subgroups at greatest risk.

RESULTS: The eligible group of veterans were mostly men (92.3%) with a large proportion of minorities (43.3%) and current smokers (49.6%). 77.2% of eligible veterans had hypertension; 29.5% had diabetes; and 58.0% were obese, at baseline. Mean BMI at baseline was 31.5 ± 4.5 kg/m2. 1,661 of 47,959 eligible at risk veterans (3.5%) developed incident asthma, which was significantly higher than those never deployed in OEF/OIF (2.6%) with unadjusted OR 1.33, 95% CI 1.26, 1.40; $p<0.001$; and after adjustment for propensity of deployment OR 1.11, 95% CI 1.05, 1.17; $p<0.001$. Through formal statistical tests for interactions between groups (Table 1), we found that the risk for developing deployment-related incident asthma was significantly higher in men than women, in non-minorities than minorities, in overweight than obese subjects, and in non-current smokers than current smokers (interaction P less than 0.01 for all analyses). The risk for developing deployment related incident asthma increased with increasing blood eosinophil percentage ($p<0.01$).

CONCLUSIONS: After adjusting for propensity of deployment, eligible veterans deployed during OEF/OIF were at high risk for incident asthma, and this risk was particularly high among men, non-minorities, overweight, noncurrent smokers, and those with higher blood eosinophil counts. These at-risk subgroups of soldiers need to be monitored during and after deployment in conflicts zones.

Table 1: Deployment associated risk for incident asthma in subgroups of populations of soldiers

Characteristic	Relative risk (95% confidence intervals)	Interaction P value
Women	0.99 (0.85, 1.14)	<0.001
Men	1.12 (1.06, 1.18)	
Minority	1.04 (0.96, 1.12)	<0.001
Non-minorities	1.15 (1.08, 1.24)	
Overweight	1.20 (1.10, 1.32)	0.005
Obese	1.07 (1.00, 1.14)	
Current smoker	1. 10 (1.02, 1.20)	<0.001
Non-current smoker	1.13 (1.05 1.21)	

Nicholas Villalobos is a first generation American citizen and Air Force Captain, involved in NM as a physician, business owner, and educator at the school of medicine. He is thankful for the opportunity to represent his program, and Mexican heritage.

Abstract Title: The loss of IL31RA-driven signaling attenuates lung function decline in pulmonary fibrosis

Author: Dan JK Yombo[1,2], Brijendra Singh[1,2,*], Nishant Gupta[3], Anil G. Jegga[4] and Satish K. Madala[1,2]

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BACKGROUND: Idiopathic Pulmonary Fibrosis (IPF) is a severe fibrotic lung disease characterized by excessive collagen deposition and the progressive decline in lung function. Multiple Th2-cytokines including IL-4 and IL-13 have been shown to contribute to lung remodeling and lung function decline in the pathogenesis of IPF. However, the mechanisms whereby Th2-cytokine polarized T cells exacerbates the severity of fibrotic lung disease remain undefined. Importantly, interleukin-31 (IL-31) is a newly identified cytokine produced by Th2 T cells but its role in pulmonary inflammation and fibrosis is unknown.

METHODS: We treated wildtype and IL31RA-/- mice with Bleomycin repetitively via the intradermal route for 4 weeks to induce lung fibrosis. We then assessed changes in lung function and histology. We performed total lung RNA-Seq analysis and RT-PCR to measure the expression of genes related to fibrosis. Also, we measured changes in IL-31 producing cells in the lungs and PBMCs of IPF patients and healthy controls.

RESULTS: The lack of IL-31 signaling did not alter inflammation and collagen staining during bleomycin-induced pulmonary fibrosis. Also, the loss of IL31RA signaling had no effect on the production of TH1, TH2 or TH17 cytokines in the lungs. Notably, we observed a significant improvement in the lung function of IL31RA-/- mice compared to wildtype mice treated with bleomycin. Our studies using chimeric bone-marrow transfers suggest that IL31 signaling in non-hematopoietic cells contributes to the lung function decline during bleomycin-induced pulmonary fibrosis. The percentage of IL31 producing CD4+ T cells was greater in PBMCs of IPF patients compared to control subjects.

CONCLUSION: Our findings indicate a critical role for IL31-IL31RA signaling in declining lung function during bleomycin-induced pulmonary fibrosis. Future efforts to target this signaling pathway may be beneficial in controlling the progression of IPF and have implications for preserving and improving lung function.

This study is funded by NIH (1R01 HL134801 and 1R21 AI137309)

Dr. Dan Yombo received his medical degree(MD) at The University of Kinshasa, Kinshasa DRC in 2008, where he practiced as an infectious disease clinician and epidemiologist. He pursued his graduate studies at Nagasaki University Institute of Tropical Medicine, in Japan, to obtain his master in Tropical Medicine in 2011, and completed his Ph.D. in Tropical Medicine, Infectious research. Dr. Dan has joined the Madala Lab at Cincinnati Children Hospital Medical Center, as a postdoctoral research fellow since 2018, under the supervision of Dr. Satish Kumar Madala.

His research is focused on exploring the role of interleukin 31 in pulmonary inflammation and fibrosis. The recent findings indicate that IL-31-positive Th2 T cells are increased in multiple chronic lung diseases including pulmonary fibrosis and allergic asthma. In particular, his new findings demonstrate that IL-31 is sufficient to induce lung function decline in a mouse model of bleomycin-induced pulmonary fibrosis.

Besides, he is interested in the pathophysiologic mechanisms of IL-31-driven airway hyperresponsiveness in an allergen-induced murine asthma model.