Department of Medicine
Research Symposium
March 24, 2017
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We would like to thank all the participants for sharing their innovative research, as well as those who coordinated and attended this event. Your support for our research mission is greatly appreciated.

Many thanks to the judges who contributed their time and effort to make the 11th annual Department of Medicine Research Symposium a successful event.

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Sincerely,

Jim Oates, M.D.  
Professor, Division of Rheumatology and Immunology  
Vice Chairman for Research

Edward Jauch, M.D.  
Professor, Division of Emergency Medicine
Department of Medicine Research Symposium
Award Recipients

2015

Craig Kutz, Graduate Student, Cardiology
Jennifer Scott, Graduate Student, Rheumatology & Immunology
Akash Naik, Medical Student (1st & 2nd Year), Surgery
Coti Phillips, Medical Student (1st & 2nd Year), Urology
Christian Hicks, Medical Student (3rd & 4th Year), Memorial Sloan-Kettering Cancer Center
Kathryn Appleton, Postdoctoral Fellow, Endocrinology
Neeti Kanodra, MD, Resident/Fellow, Pulmonary & Critical Care
Nithin Karakala, MD, and Takamitsu Saigusa, MD, Junior Faculty, Nephrology
Mara Lennard Richard, PhD, Other, Rheumatology & Immunology

Oral Presenters:
• Joy Buie, Rheumatology Immunology
• Melissa Cunningham, MD, Rheumatology & Immunology
• Lillianne Harris, PhD, Cardiology
• Mukoso Ozieh, MD, General Internal Medicine & Geriatrics

2016

Mohammed Dany, Graduate Student, Hematology/Oncology
Michael Lugo, Medical Student (1st & 2nd Year), Other
Muyi Li, Medical Student (3rd & 4th Year), Rheumatology & Immunology
Mona Haj, Postdoctoral Fellow, Gastroenterology & Hepatology
Sara Matar, MD, Resident/Fellow, Hematology/Oncology
Daena Peterson, MD, Resident/Fellow, Infectious Diseases
Sang-Ho Kwon, MD, Basic Junior Faculty, Nephrology
Rebekah Walker, PhD, Clinical Junior Faculty, General Internal Medicine

Oral Presenters:
• Erik Strungs, Endocrinology
• Keri Holmes-Maybank, MD, General Internal Medicine
• David Daly, MD, Cardiology
Age-related Changes in B cells Impact Immune Responses to Pneumococcal Vaccination in Aging HIV+ Individuals

Myra Happe, Jennifer Ohtola, Megan Bickford, Julie Westerink
Department of Medicine, Division of Infectious Diseases, Medical University of South Carolina, Charleston, SC

Introduction: The introduction of combined anti-retroviral therapy has increased longevity in HIV+ individuals resulting in a rapid growth of the aging HIV+ population. The increasing lifespan of HIV+ persons represents new challenges combining the immune deficiencies of HIV with those of aging. This results in high susceptibility to Streptococcus pneumoniae and poor recall and novel vaccine antigen responses likely caused by poorly characterized perturbations in B cells. The goal of this project is to characterize specific B cell deficiencies in aging HIV + individuals by studying B cell responses to highly pertinent vaccines, and to define mechanisms underlying poor vaccine responses in this unique population.

Methods: The HIV+ participants were recruited from MUSC. The age distributions of the participants were 21-40 and 50 -65 years of age (on cART with HIV viral loads<40); age matched healthy individuals served as control population. All participants received pneumococcal vaccination regimen PCV13 followed by PPV23. Blood samples were collected at five time points and were used for antibody titers, opsonophagocytic titer, antigen-specific B cell analysis by flow cytometry and Luminex assay.

Results/Conclusions: Serum antibody and opsonophagocytic studies demonstrated decreased responses to pneumococcal vaccination in HIV+ as compared to aged matched HIV- persons. In healthy young adults the predominant phenotype of polysaccharide (PPS) specific B cells were CD27+IgM+, while in elderly they were primarily CD27-IgM+ switched memory. The phenotype of PPS specific B cells in aging HIV+ consisted predominantly of CD27+IgM+ and resembled the phenotype of HIV- young individuals at significantly reduced numbers. Our preliminary studies demonstrated a lack of age related shift from IgM memory B cells to switched memory distinguishing the aging HIV+ persons from age-matched HIV-. Further analysis using single cell RT PCR is expected to expand our understanding of age-related B cell perturbations and potential mechanisms.

Category: Graduate Student, Basic Science
Mentor: Julie Westerink, M.D., Division of Infectious Diseases

This project was supported by the South Carolina Clinical & Translational Research (SCTR) Institute, with an academic home at the Medical University of South Carolina, through NIH Grant Numbers TL1 TR001451 and UL1 TR001450
ShinyGPA: An Interactive and Dynamic Visualization Toolkit for the Exploratory Analysis of Genetic Studies

Emma Kortemeier, Kelly Hunt, Paula Ramos, Hang Kim, and Dongjun Chung

Public Health Sciences: Biostatistics, MUSC

Rationale: As of this year, genome-wide association studies (GWAS) have identified over 20,000 single nucleotide polymorphisms (SNPs) associated with at least one disease or trait. Such achievements have provided various clinical and medical benefits with novel biomarkers and therapeutic targets. Recently, there has been accumulating evidence suggesting that different complex traits share common risk basis, a phenomenon known as pleiotropy. For example, 17% of genes reported in the GWAS Catalog are associated with more than one phenotype. Thus, a better understanding of pleiotropy can potentially be clinically beneficial as it may facilitate understanding of the common etiology of diseases and help improve therapies. However, effective interrogation of pleiotropic architecture still remains challenging, and it often requires employment of complicated statistical models.

Methods: In order to address these challenges, we are developing ShinyGPA, an interactive and dynamic visualization toolkit for exploratory analysis of genetic studies. Specifically, ShinyGPA maps phenotypes onto two-dimensional space based on the genetic relationship among these phenotypes. In addition, GPA-EDA provides remarkable flexibility in modifying visualization to help improve user interpretations.

Results: The application of ShinyGPA to GWAS datasets for 12 unique phenotypes indicates that clinically related phenotypes form clusters in the phenotype map generated by ShinyGPA. In addition, the visualization produced by ShinyGPA provides interesting hypotheses for relationships among groups of phenotypes, which require further investigation and in turn can be useful for the design of future genetic studies.

Conclusion: We expect that ShinyGPA will be a powerful and flexible off-the-shelf tool to elucidate the genetic relationship among phenotypes, which can contribute to the development and improvement of diagnoses and therapeutics for various diseases.

Category: Graduate Student, Basic Science
Mentor: Dongjun Chung, Ph.D., Department of Public Health Sciences
Class I Histone Deacetylases Localize to Cardiac Myocyte Mitochondria and Contribute to Ischemia Reperfusion Injury

Daniel J. Herr1, Sverre E. Aune1, Jennifer R. Bethard2, Lauren E. Ball2, and Donald R. Menick1,3*

1Department of Medicine, 2Department of Pharmacology, Medical University of South Carolina, Charleston, SC 29425, 3Ralph H. Johnson VA Medical Center

Introduction: Approximately half of the damage done to the heart by a myocardial infarction occurs during reperfusion of the ischemic region while the patient is in the care of the treatment team. While many different adjuvant treatments have been explored in an attempt to attenuate this ischemia-reperfusion (I/R) injury, little progress has been made in translating novel therapies to the clinic. Recently, it was discovered that epigenetic enzymes contribute to reperfusion-induced damage, but little is known about the exact mechanism by which they exacerbate I/R injury. Previously, we have shown that class I histone deacetylase (HDACs) activity acutely exacerbates I/R injury, and that inhibition of class I HDACs with MS-275 (entinostat) preserves left-ventricular (LV) function and substantially reduces the area of infarcted tissue in isolated rat hearts subjected to ischemia-reperfusion (IR) injury. Notably, this protective effect occurs whether MS-275 is given as a pretreatment or during the reperfusion phase alone. Given the acute nature of this protective effect, we hypothesized that class I HDACs mediate reperfusion injury by modulating the acetylation state of non-histone proteins in signaling cascades that are essential to cell survival.

Methods: To examine this, hearts from male Sprague-Dawley rats were subjected to ex vivo I/R injury +/- class I HDAC inhibition during reperfusion. We then performed biochemical analyses and mass spectrometry to analyze the changes in the acetylome between sham and I/R groups with and without class I HDAC inhibition.

Results: Unexpectedly, mass spectrometry analysis revealed significant changes in the acetylation state of multiple mitochondrial enzymes. Further biochemical studies show that class I HDACs localize to cardiac mitochondria and may directly modulate mitochondrial acetylation and mitochondrial function during I/R injury.

Conclusion: This study is the first to identify a class I HDAC that localizes to the mitochondria and emphasizes the importance of exploring class I HDAC inhibitors for protection against ischemia-reperfusion injury.

Category: Graduate Student, Basic Science
Mentor: Donald Menick, Ph.D., Division of Cardiology

Supported by VA merit award BX002327-01 to DRM. Additional support by F30 HL129629, T32 GM008716, T32 HL007260, and the SCTR Institute, NIH/NCATS Grant Number TL1 TR 000061 and UL1 TR 000062.
The Role of Lysyl Oxidase in Systemic Sclerosis

Xinh-Xinh Nguyen & Tetsuya Nishimoto, Takahisa Takihara, Logan Mlakar, Joseph Pilewski, Ellen Riemer, Jonathan Heywood, Amy Bradshaw, and Carol Feghali-Bostwick

Introduction: Systemic sclerosis (SSc, scleroderma) is a connective tissue disease characterized by progressive fibrosis of the skin and multiple visceral organs whose etiology is still unknown. Effective therapies for SSc are needed. Lysyl oxidase (LOX) is a copper-dependent amide oxidase that plays a critical role in the crosslinking of the extracellular matrix (ECM). Recent studies have shown increased circulating levels of LOX in SSc patients compared to healthy controls. In this study, we investigate the role of lysyl oxidase (LOX) in the pathophysiology of SSc.

Methods: LOX expression and protein levels were measured in vitro in primary human lung fibroblasts and ex vivo in human lung tissues maintained in organ culture following treatment with recombinant LOX (rLOX). Expression of extracellular matrix genes and the pro-fibrotic cytokine IL-6 was measured by real-time PCR and immunoblotting; collagen levels and crosslinking were measured using hydroxyproline assay. To differentiate the crosslinking activity of LOX from other potential effects, primary human fibroblasts were cultured with rLOX in the presence of the inhibitor, β-aminopropionitrile (BAPN).

Results: rLOX induced ECM production in lung fibroblasts in vitro and human lung maintained in organ culture ex vivo. The inhibition of LOX catalytic activity by BAPN failed to abrogate LOX-induced ECM production. In addition, LOX increased the production of IL-6 independently of catalytic activity. Neutralization of IL-6 reduced LOX-mediated induction of ECM levels.

Conclusions: LOX induces fibrosis via increase in ECM and IL-6. These effects are independent of the crosslinking activity of LOX and mediated via IL-6. Our findings suggest that inhibition of LOX may be a viable option for the treatment of lung fibrosis. Further, the use of human lung in organ culture establishes the relevance of our findings to human disease.

Category: Graduate Student, Basic Science
Mentor: Carol Feghali-Bostwick, Ph.D., Division of Rheumatology and Immunology
Transcriptomic analysis of the adult zebrafish liver in response to exposure to plasticizers and synthetic, steroidal estrogen.

Matthew Huff\textsuperscript{1,2}, E. Starr Hazard\textsuperscript{1,3}, Sean M Courtney\textsuperscript{1}, Gary Hardiman\textsuperscript{1,4}

\textsuperscript{1}MUSC Bioinformatics, Center for Genomic Medicine, \textsuperscript{2}MS in Biomedical Sciences Program, \textsuperscript{3}Library Science and Informatics, \textsuperscript{4}Departments of Medical and Public Health Sciences, Medical University of South Carolina (MUSC).

**Introduction:** Endocrine Disrupting Chemicals (EDCs) interact with nuclear hormone receptors and alter cell signaling. EDCs include plasticizers and synthetic estrogens or xenoestrogens (XE). Our hypothesis is that exposure to low XE doses impacts key cell signaling events posing potential human health risks. To test this hypothesis we exposed adult male zebrafish (\textit{Danio rerio}) to several xenoestrogens. The long term goal of this study is to characterize the adverse effects of EDC exposure using this model organism as a proxy for human health assessment.

**Methods:** Zebrafish were exposed to environmental levels of 17α-ethinyl estradiol (EE2), nonylphenol (NP), and (2-ethylhexyl) phthalate (DEHP), along with 17β-estradiol (E2) as a positive control, for three weeks. Liver RNA was extracted and the transcriptomes were analyzed using both DNA microarray (analog) and RNA sequencing (digital) approaches.

**Results:** Systems level analysis revealed altered hepatic transcriptomic profiles in exposed fish. Metabolic pathway was altered after exposure to all four XE ($q = 2.725E^{-15}$ for EE2, $3.673E^{-18}$ for DEHP, $5.846E^{-14}$ for E2, and $1.058E^{-13}$), Bonferroni adjusted q-values. Exposure to DEHP and EE2 enriched RB in Cancer ($1.8E^{-2}$ in EE2, $6.503E^{-2}$ in DEHP) and the HIF-1-alpha transcription network ($5.445E^{-2}$ in EE2, $4.706E^{-2}$ in DEHP). Exposure to EE2 enriched Pathways in Cancer ($1.375E^{-2}$). In E2 and NP, pathways relating to the important tumor suppressor gene p53 were altered, including p53-independent DNA damage response ($3.871E^{-4}$ in E2, $7.804E^{-6}$ in NP).

**Conclusions:** As EDCs become more prevalent in the environment, it is important that their effects on gene expression are fully characterized. This study has utilized transcriptomic analysis of the zebrafish model’s liver to successfully identify differential expression in key signaling pathways and uncovered pathways pertinent to cancer after exposure to EE2, DEHP and NP.

**Category:** Graduate Student, Basic Science

**Mentor:** Gary Hardiman, Ph.D., Division of Nephrology
Primary Cilia Contribute to Cardiac Valvular Diseases through DZIP1 and Exocyst Mutations

Diana Fulmer¹,², Katelynn Toomer¹, Lilong Guo¹,², Joshua Lipschutz², Russell Norris¹,²
¹Department of Regenerative Medicine and Cell Biology, ²Department of Medicine

Introduction: Mitral valve prolapse (MVP) and bicuspid aortic valve (BAV) disease are common clinical problems that affect 5-7% of the human population and result in more than 16,000 surgical procedures each year. The causes of these valve diseases remain poorly understood. However, through an international consortium focused on valvular heart disease, we now have compelling genetic and functional evidence that significantly advances our understanding of valve disease pathogenesis. Through various genetic approaches (linkage, deep sequencing, and genome wide association studies) we have identified multiple genes that cause both MVP and/or BAV. Pathway analyses have revealed that primary cilia may be a potential common link underlying both mitral and aortic valve disease. Primary cilia are small cellular appendages that function as antennae to sense the chemical and biomechanical extracellular environment. Here we present some of our new data, highlighting the identification of novel mutations in the cilia gene, DZIP1, in multiple families with non-syndromic MVP. We found Dzip1 to function in ciliogenesis through the regulation of the exocyst complex, an octameric protein network required for vesicular transport of cilia proteins from the golgi to the cell membrane. Genetic ablation experiments in murine and zebrafish models confirm the role of the exocyst, Dzip1, and cilia in the formation of normal valve architecture. These studies have provided an understanding of fundamental mechanisms underlying valve development and have established an etiological basis for valve diseases. Additionally, these studies, which capitalize on genetic data from valve disease patients, will be used as a platform for developing remedial therapies to treat these complex cardiac diseases in the future.

Methods: A valve specific Cre was used to genetically remove Dzip1, Ift88 (critical for ciliogenesis), and members of the exocyst complex. This Cre is cardiac specific and primarily expressed in the mitral and aortic valves. 3D reconstruction of histological slices of neonatal mitral and aortic valves were performed to quantify valve morphology in addition to performing immunohistochemistry stainings for markers of proliferation and/or differentiation. Biochemical experiments were performed to identify novel interactions between Dzip1 and the exocyst complex.

Results: Exoc5, a central exocyst protein, Ift88, and Dzip1 mutant mice all exhibit similar valvular phenotypes which resemble the human diseases (BAV and MVP). This phenotype includes increased size of valve leaflets, fusion of aortic cusps, increased proteoglycans (e.g. versican). Additionally, we have shown that Dzip1 is expressed at the basal body and can interact with the exocyst complex through Exoc4, and thus is likely involved in trafficking ciliary cargo to the membrane.

Conclusion: We show that Dzip1 functions as a molecular tether between the basal body, exocytic vesicles and the exocyst complex. As such, we have defined that DZIP1 mutations cause valve disease in humans, and likely do so through its ability to regulate the formation of primary cilia through an exocyst-dependent mechanism.

Category: Graduate Student, Basic Science
Mentor: Russell Norris, Ph.D., Department of Regenerative Medicine and Cell Biology
Distinct population differentiation levels in Gullah and non-Gullah African Americans relative to their African and European ancestral populations

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Introduction: Despite the higher prevalence of many common diseases, the fine-scale population structure of African Americans (AA) remains vaguely defined. Relative to other AA, the Gullah population has lower European admixture and higher ancestral homogeneity from the Sierra Leone (SL) area in West Africa. Since unusual population differentiation is indicative of natural selection, we sought to examine unusual population differentiation at the genome-wide scale in related African and AA populations.

Methods: We computed the fixation index (F̂ST) between populations to quantify the genetic distance between populations and to assess differentiation at individual SNPs. Using genotype data on 273 healthy Gullah AA, 401 healthy non-Gullah AA, 398 SL, and 159 YRI and 160 CEU from the HapMap3 Project, we computed the Weir and Cockerham’s (1984) F̂ST as implemented in VCFTOOLS between each AA and their ancestral populations.

Results: The genome-wide F̂ST estimates were higher between non-Gullah AA and their African ancestors (F̂ST=0.038) than between Gullah AA and their African ancestors (F̂ST=0.004), reflecting higher allele frequency differences between non-Gullah AA and their African ancestors than Gullah AA. Although non-Gullah AA showed identical F̂ST estimates with SL and YRI (F̂ST=0.038), Gullah AA showed a slightly higher estimate with YRI (F̂ST=0.0043) than SL (F̂ST=0.0034), supporting the Gullah’s genetic closeness to Africans, especially to SL. The F̂ST estimates were similar between both AA populations and CEU (F̂ST=0.10), indicating similar genetic differentiation from their European ancestors. Distinct sets of SNPs showed different evidence of selection in different populations.

Conclusion: This first report of population differentiation estimates in Gullah AA supports a closer genetic distance to African populations than other AA, especially to SL, but a similar distance to Europeans. Identification of regions with evidence of population differentiation, that may hence be under geographically restricted selection, might help elucidate the genetic basis for the ethnic disparities in disease prevalence.

Category: Graduate Student, Basic Science
Mentor: Paula Ramos, Ph.D., Division of Rheumatology and Immunology

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Pharmacokinetic studies in mice with a novel antifibrotic peptide M10

Tanjina Akter, 1,2 Yuichiro Shirai, 1 Ilia Atanelishvili, 1 Atsushi Noguchi, 1 Richard M. Silver, and 1 Galina S. Bogatkevich

1 Division of Rheumatology and Immunology, Department of Medicine, Medical University of South Carolina, Charleston, South Carolina, USA; 2 Nippon Medical School Department of Allergy and Rheumatology, Tokyo, Japan

Objective: Scleroderma associated pulmonary fibrosis is a complicated autoimmune disease, often leading cause of respiratory failure and death. The molecular mechanisms underlying the pathogenesis of lung fibrosis are not well understood and there is a great need for more effective treatment for this lethal disease. Recently we identified a small fragment of the c-Met receptor, designated as “M10”, as a peptide with strong antifibrotic properties. The current study was undertaken to study the pharmacokinetics of M10 in mice with bleomycin-induced pulmonary fibrosis.

Experimental Design: Pulmonary fibrosis was induced in C57BL6 male mice by intratracheal instillation of bleomycin (2.0U/kg). M10 was administrated by intraperitoneal injection, with a dose of 1mg/kg of mouse weight. Blood was collected at different time points (15 min, 30 min, 1hr, 2hr, 4hr, 24hr and 48hr) after M10 injection in presence of 6% (v/v) 0.1 M of sodium citrate. Concentration of M10 in mouse plasma was measured by using the indirect Enzyme-Linked Immunosorbent Assay (ELISA). Pharmaceutical grade synthetic M10 was used as a calibrator and commercially available anti-c-Met C12 antibody used to capture the M10 antigen.

Results: The detection limit of M10 in ELISA was 10ng/ml and a measuring limit was 250ng/ml. The recovery limit of M10 were 80% -120%; intra-assay coefficient of variation was 0.1% - 1.07% and inter-assay coefficient of variation was 0.7% - 1.12% over the buffer concentration tested 15-250 ng/ml. The peak of M10 concentration after a single intraperitoneal injection was achieved within 6 hours and declined to minimal levels by 48 hours. The experimentally obtained half-life for M10 was comparable to the theoretically predicted half-life for M10 by ProtLifePred software.

Conclusions: M10 exerts potent antifibrotic effects and significantly reduces the inflammation and fibrosis in bleomycin-induced mouse model of scleroderma-associated pulmonary fibrosis. Our pharmacokinetic data demonstrate that M10 has a very good stability and sustainability in plasma and may be considered as a potential therapeutic peptide in the treatment of pulmonary fibrosis and other fibroproliferative disorders.

Category: Graduate Student, Basic Science
Mentor: Galina Bogatkevich, M.D., Ph.D., Division of Rheumatology and Immunology
Human Antibody Responses to Pneumococcal Vaccination in Aging HIV+ Individuals

Megan Bickford, Myra Happe, Samuvel Devadoss, M.A. Julie Westerink
Department of Medicine, Division of Infectious Diseases, Department of Microbiology and Immunology, Medical University of South Carolina, Charleston SC

Introduction: *Streptococcus pneumoniae* is a major cause of morbidity and mortality in HIV-positive individuals. Despite the widespread use of anti-retroviral medications, the incidence of pneumococcal disease is 20-40 fold higher in the HIV+ population compared to HIV-.. Consequently, pneumococcal vaccination is recommended for all HIV+ individuals. In 2012 the FDA changed vaccine recommendation from a single vaccination with the 23-valent pneumococcal polysaccharide vaccine (PPV23) to a dual vaccination with 13-valent protein conjugate vaccine (PCV13) followed by PPV23. Studies demonstrating superiority of the PCV13/PPV23 regimen compared to PPV23 alone are limited and controversial. The goal of this study was to analyze and compare the immune response to PCV13/PPV23 versus PPV23 in HIV-positive individuals and age-matched HIV-negative persons.

Methods: The participants for this study were recruited from the University of Toledo and MUSC. We focused on aging HIV+ persons and all participants were 50-64 years of age. Participants were randomized to either PCV13 followed by PPV23 group or PPV23 only. Blood samples were collected prior to vaccination and thirty days following the administration of PPV23 to analyze antibody responses and opsonophagocytic activity to PPS3, 7 and 19A. Inflammatory markers were quantified by Luminex using day 0 serum samples.

Results/Conclusions: OPA titers and IgG antibody concentrations increased significantly from pre- to post-vaccination in all groups. In HIV+ there was no significant difference in antibody or opsonophagocytic response to serotypes 3, 7F or 19A between vaccine groups. In HIV- there was a significantly higher antibody response to serotype 19A only, but not to serotypes 3 and 7F in the group immunized with PCV13/PPV23. However, no significant differences were noted in opsonophagocytic activity between groups. Serum APRIL levels were significantly higher in HIV+ compared to HIV-. A positive correlation was noted between PPS3 OPA titers and IL6 concentrations in HIV- but not in HIV+.

Category: Graduate Student, Clinical Science
Mentor: Julie Westerink, M.D., Division of Infectious Diseases
Effects of Apolipoprotein E on Left Ventricular Geometry and Function

Andrew P. Hill\textsuperscript{1,2}, Hesham El-Shewy\textsuperscript{1}, Miran A. Jaffa\textsuperscript{1}, Sarah Garrett\textsuperscript{1}, Jeffrey A. Jones\textsuperscript{2}, Robert E. Stroud\textsuperscript{2}, Ayad A. Jaffa\textsuperscript{1}, Rupak Mukherjee\textsuperscript{2}

Divisions of Endocrinology\textsuperscript{1} and Cardiothoracic Surgery\textsuperscript{2}, MUSC, Charleston, South Carolina

Introduction
Dysregulation of cholesterol metabolism, which is a major risk factor for cardiovascular disease, is regulated partially by apolipoprotein E (ApoE) and mediated by growth factors such as connective tissue growth factor (CTGF). Although ApoE has been studied in various disease states, the time-dependent effects of ApoE deficiency on left ventricular (LV) geometry and function remain to be determined.

Methods/Results
Monthly echocardiography for 5 months was performed in wild type (WT; \(n=12\)) and mice deficient in ApoE (ApoE KO; \(n=16\)). Mice were fed normal chow starting at 2 months of age to measure end-diastolic volume (EDV), wall thickness (PWTd), ejection fraction (LVEF), and mass (LVMass). Age-matched body weights were similar in the two groups. EDV was similar between groups at 2 months of age (52.77\(\pm\)2.03 \(\mu\)L and 58.66\(\pm\)1.92 \(\mu\)L, respectively, \(p=\text{NS}\)), but higher in the ApoE KO mice beginning at four months (\(p<0.05\)). PWTd (0.88\(\pm\)0.03 vs 0.79 \(\pm\)0.02 mm, \(p<0.05\)) and LVMass (94.2\(\pm\)5.4 vs 76.4\(\pm\)3.0 mg, \(p<0.05\)) were higher in the ApoE KO mice at two months. LVEF was similar between groups at 2 months of age (61.3\(\pm\)2.0\% and 58.8\(\pm\)1.5\%, \(p=\text{NS}\)) and remained similar at subsequent time points (\(p=\text{NS}\)).

Conclusion
ApoE deficiency is associated with LV hypertrophy with no change in LV pump function through 6 months of age, suggesting an effect of ApoE on growth factors. These findings form the basis to examine the role of ApoE in modulating levels of growth factors, such as CTGF, and its effect on LV geometry and function with superimposed pathology, such as diabetes.

Category: Medical Student Year 1 & 2, Basic Science
Mentor: Ayad A Jaffa, Ph.D., Division of Endocrinology
**Long Term Mortality in Patients that Undergo Alcohol Septal Ablation for Treatment of Hypertrophic Cardiomyopathy in Early Life**

**Griffin BE, Heizer J, Waring AA, Wahlquist AH, Rier JD, Litwin SE, Nielsen CD, Fernandes V.**

**Introduction:** Hypertrophic Obstructive Cardiomyopathy (HOCM) is a relatively rare autosomal dominant disease affecting left ventricular function believed to present primarily in individuals 65 years or greater in age. There is very limited information regarding long-term outcomes following treatment of this disorder via Alcohol Septal Ablation (ASA), and it was not until the late 1980’s/early 1990’s that the standard treatment for HOCM underwent a drastic transition, from an invasive surgical septal myectomy to a much less hostile approach, ASA, which is now performed in the cardiac catheterization lab with minimal recovery time and much less associated risk. When observing the progressive deterioration caused by aging and exposure to every day environmental agents, that occurs in the body over time, it is of no great surprise that aging also plays a particularly significant role in predicting patient prognosis and mortality rates following ASA, and is also correlated with comorbid complications that may subsequently arise requiring additional interventions. Although deciphering and quantitatively measuring the factors that contribute to survival and successive quality of life is challenging and subjective, there is overwhelming evidence suggesting that age is highly correlated with long term mortality rates and the manner in which patients thrive and overcome this debilitating genetic disorder.

**Objective:** MUSC was one of the pioneer hospitals for the using ASA for treatment of HOCM, and we have compiled an extensive database that currently contains the earliest follow up information in the country for ASA. The goal of this study was to demonstrate how patient age contributed to overall survival and complications following ASA for treatment of HOCM.

**Methods:** A cohort of patients was retrospectively analyzed in this study. It consisted of 108 patients < 40 years of age divided into three groups, below the age of 20, 30, and 40 years of age. From the collected data for n = 108 patients who underwent ASA between 2000 and 2015, we examined factors such as repeat ASA, prior surgical septal myectomy, pre- and post-operative electrophysiology implantation, and created a survival curve using Kaplan-Meier technique.

**Results:** Among the patients under the age of 20, all 12 patients are still living with a mean of 12.61 years since their most recent ASA. They showed significant occurrence of device implantation post-operatively with 50% having received either an ICD or PCM and 18.18% having received both. In the patients between 20-30 years old, the average number of years since ASA was 11.62 out of 26 patients with only 3 deaths. Among individuals within the second age group 50% received post-operative device implantation with 11.54% having received both. In patients between the ages of 30 and 40 years, the mean number of years in living patients since ASA was 12.01 years and only 6 deaths out of 68 patients. 48.53% received post-operative device implantation, while 26.47% had devices prior.

**Conclusions:** The data was similar among the three age groups regarding the requirement of subsequent cardiac device implantation, survival time since ASA in living patients, and a consistent increase in the rate of mortality in those who sought treatment via ASA as the patient age group increased. The Kaplan-Meier survival curve showed a stable survival time from 0-11 years with a subsequent rapid decline between 11-15 years.

**Category:** Medical Student Year 1 & 2, Basic Science

**Mentor:** Valerian Fernandes, M.D., Division of Cardiology
**Relationship between the Affordable Care Act and Quality of Care in Patients with Diabetes**

**Arjun Varadarajan**

**Background:** Diabetes is a complex chronic disease requiring regular medical care in addition to ongoing self-management to minimize the risk of long-term complications. In the United States only slightly more than half of all adults with diabetes receive guideline consistent care, including regular examinations and blood work. The passing of the Affordable Care Act (ACA) provided access for more Americans to insurance, however, may not have addressed other factors impacting access to health care, including availability, accessibility, accommodation, and acceptability. This study investigated the relationship between insurance, access, and cost of care over time for patients with diabetes.

**Methods:** We used the Medical Expenditure Panel (MEPS) from 2002-2011 to examine the association between insurance, access, and cost, and direct healthcare service expenditures among adults with diabetes (aged ≥18 years). Access included having a usual source of care, having delay in care, or having delay in obtaining prescription medicine. Cost included inpatient, outpatient, office-based, prescription, and emergency costs. Panels were broken into three time categories: 2002-2005 (pre-ACA), 2006-2009 (pre-ACA), and 2010-2011 (post-ACA). Bivariate analyses and unadjusted means were used to compare the trends over time, and multiple regression was used to examine factors associated with health insurance, access, and cost.

**Results:** No significant change overtime was seen in insurance, delay in accessing care, or delay in obtaining prescription medications. A significant change was seen in having access to usual source of care (p=0.004), with a slight increase in those without a usual source of care (4.9% in 2002-2005 compared to 5.8% in 2010-2011). No significant change was seen in outpatient costs, or office-based visits, but inpatient costs decreased over time (p=0.04) and prescription cost increased between 2002-2005 and 2006-2009 (p=0.001). Emergency room costs significantly increased over time (p=0.003). Compared to those with private insurance, those who were uninsured had lower inpatient ($2,221 less), outpatient ($513 less), office-based ($1,442 less), and prescription costs ($1,627 less), but were not statistically different in emergency room costs.

**Conclusions:** The data shows that there was no major increase in insurance or access to care in patients with diabetes over the past 10 years. This may be due to a ceiling effect of insurance in this population. Expenditures have increased, and the uninsured are spending less, with the exception of emergency room costs suggesting the ER is still used as a major source of care despite the passage of the ACA.

**Category:** Medical Student Year 1 & 2, Basic Science

**Mentor:** Leonard Egede, M.D., MS, Division of General Internal Medicine
CRISPR-Cas9 genome-wide knockout screen reveals HUWE1-loss alters EGFR dependence in non-small cell lung cancer via alternate signaling and apoptosis changes

Christopher Duckworth

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**Introduction:** 83% of all lung cancer cases are non-small cell lung cancer (NSCLC), a startling majority which makes treatment development an urgent priority. Great strides in targeted therapy have recently been made with the advent of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs), which hone in on some NSCLC tumors' driving EGFR mutations. However, drug resistance tails initial improvement, and the mechanism has been difficult to characterize; hence, exploring novel actors is vital.

**Methods and Results:** We initiated a genome-scale CRISPR-Cas9 single-guide RNA (sgRNA) screen for an NSCLC cell line, HCC827, which is addicted to EGFR and sensitive to erlotinib. We infected the cells with our own pooled sgRNA library to generate a knockout population subjected to erlotinib (or DMSO) treatment. Genes enriched with sgRNAs were ranked using NGS and bio-statistical analysis. Top hits included genes previously shown to confer resistance to EGFR TKI's via loss-of-function, such as BAX – the loss of which has been reported to reduce apoptosis in NSCLC cells. One of the new candidate genes is an E3 ubiquitin-protein ligase, HUWE1. Suppression of HUWE1 by shRNA resulted in an increase in AKT and ERK1/2 signaling. Cell Titer-Glo luminescence assays confirmed associated proliferation. We then evaluated if Dox-inducible HUWE1 suppression enhanced tumor formation in athymic nude mice with or without erlotinib treatment. In-vivo, the shHUWE1-expressing, erlotinib-treated group of mice demonstrated superior tumor growth. Post-harvest, we used immunohistochemistry to address whether the HUWE1-knockdown group demonstrated similar AKT and ERK1/2 signaling; elevated Ki67 and CK7, as well as higher phospho-AKT and phospho-ERK in that group, were observed. The effect of HUWE1 loss on substrate interaction was assessed in-vitro. Interplay between HUWE1 loss and apoptosis in HCC827 cells was also evaluated using Annexin V staining with flow cytometry analysis. Suppressing HUWE1 resulted in higher SHOC2 and proto-oncogene phospho-RAF1 levels, as well as reduced apoptosis. Finally, potential means of bypassing resistance were explored using combined agents. Treating HCC827 cells with AZD6244 and BEZ235 in tandem with erlotinib proved efficacious.

**Discussion:** Increased AKT and ERK1/2 signaling, as well as apoptosis reduction, are alternate pathways for persistent NSCLC proliferation and survival. Both circumvent NSCLC tumor cells’ dependence on EGFR to resist EGFR TKI treatment. A complete understanding of this mechanism in the context of HUWE1 loss and further development of the aforementioned combinatorial therapy can produce supplemental ways of overcoming EGFR TKI resistance.

**Category:** Medical Student Year 1 & 2, Basic Science

**Mentor:** Hiu Wing Cheung, Ph.D., Department of Pathology and Laboratory Medicine
Rural-Urban Differences in Quality of Care Indicators among Adults with Diabetes

Darian Vernon, Kinfe Bishu, Joni S. Williams, Rebekah J. Walker, Leonard E. Egede
Medical University of South Carolina, Department of Medicine, Division of General Internal Medicine and Geriatrics and the Ralph H. Johnson VAMC

Background: Evidence suggests the prevalence of diabetes in adults living in rural areas is higher than that of those living in urban areas. Disparities in quality of care (QoC) indicators such as hemoglobin A1c testing, examining feet, getting eyes dilated, checking blood pressure, and visiting the doctor annually have been shown in patients with diabetes residing in rural versus urban areas. Therefore, the aim of this study was to assess differences in QoC indicators based on rural/urban status in a sample of adults with diabetes.

Methods: Data of 17,702 adults (aged ≥18 years) from the 2002-2011 Medical Expenditure Panel Survey Household Component (MEPS-HC) was used to examine the association between QoC indicators and Metropolitan Statistical Area (MSA) status. Five binary indicators were used as dependent variables to measure QoC. MSA was included as the primary independent variable to indicate whether or not the reporting unit was found in an MSA at the end of the year. Sample demographics by MSA status were assessed. Unadjusted analyses were computed for descriptive statistics and proportions of QoC indicators over time. Logistic regression evaluated associations between QoC indicators and MSA status, while controlling for confounders.

Results: Overall, 80% of the sample resided in an MSA, approximately 65% of the sample was NHW, 15% was NHB, 14% was Hispanic, and 7% identified with other races and ethnicities. Thirteen percent of the sample was 18-44 years of age, 47% was 45-64 years of age, and 40% was 65 years of age and older. Adjusted logistic regression models showed residents living in an MSA were 22% more likely to have their feet checked during the year (Odds ratio (OR)=1.22; 95% Confidence Interval (CI) 1.09, 1.38; p=0.001) compared to residents living in a non-MSA. Similarly, MSA residents were 15% more likely to have their eyes dilated in a given year (OR 1.15; 95% CI 1.03, 1.30; p=0.017) compared to non-MSA residents.

Conclusions: In this sample of adults with diabetes, urban residents were more likely to have their feet checked and their eyes dilated during a given year, when adjusting for relevant confounders. These findings add to the body of evidence showing disparate care between rural and urban residents and stress the need for equitable care to all adults with diabetes, regardless of residence, to stave off the debilitating effects of uncontrolled diabetes. Additional research is needed to explore the impact of these differences further.

Category: Medical Student Year 1 & 2, Clinical Science
Mentor: Leonard Egede, M.D., MS, Division of General Internal Medicine
Lifestyle Factors and Other Influences of Medical Students Choosing a Career in Emergency Medicine

Keith, K.C.; Reddy, S.; Bourne, C.L.

Background: Emergency Medicine (EM) has quickly grown to offer the fourth largest number of residency positions, behind internal medicine, family medicine, and pediatrics. EM has also become the fourth most common specialty choice among U.S. senior medical students, preceded only by internal medicine, pediatrics, and family medicine. EM physicians however, experience burnout at a rate more than three times the average doctor, and more so than anyone else inside or outside the medical field. Yet, EM remains one of the most highly sought out specialty choices each year for graduating medical students.

Methods: First and fourth-year students from 10 US medical schools were invited in 2012 and 2016 to participate in a 29 item (first year) and 31 item (fourth year) on-line survey about lifestyle specialty preferences and factors involved in selecting a specialty. Participants were asked to select their most and least preferred specialty choices. Respondents were sorted into three groups: selected EM at both time points, switched into EM, and switched out of EM. Descriptive data, Fisher’s exact, chi-square, and Kendall Taub analyses were conducted as appropriate to determine characteristics related to switching into or out of Emergency Medicine. Significance was determined to be P < .05.

Results: Of the 1,530 students eligible to complete the survey in 2012, 997 completed it; 788 out of 1575 completed in 2016. Students who stated a specialty preference in EM responded that "having a balance between work life and personal life" was a more important factor in their specialty choice than overall survey respondents (98% vs 83%; p=0.01). Most significantly, students whose desired specialty was EM responded that "having a low stress work day" was not an important consideration in choosing their specialty, at a rate markedly lower than students least interested in EM (3% vs 28%; p<0.001) and all other survey respondents (3% vs. 21%; p<0.001).

Conclusion: Survey results indicate students with an EM specialty preference place a high importance on schedule flexibility and control over working hours. However, this data presents a paradox when considered against the current labor force concerns of burnout, anxiety and depression among EM practitioners. This may perhaps be partially explained by the significantly lower priority of the daily stress exposure that EM students reported. Together, these factors should be utilized to design targeted career planning services and/or training programs.

Category: Medical Student Year 1 & 2, Clinical Science
Mentor: Christina Bourne, M.D., Division of Emergency Medicine
Non-Optic Vision: Beyond Synesthesia?

Matthew Roberts1, Joel Shenker2, Thomas Naselaris3, Nicki Pullman, Jane Joseph3, & Tom Jhou3

Introduction: Patient NS is a 30 year-old female who went blind in her early twenties as a result of S-cone syndrome, a degenerative retinal disorder. A few years after losing her vision, she started experiencing visual perceptions of her hands as she moved them and objects that came into contact with her hands. Over the course of a year, these cross-modal sensations evolved to become veridical visual experiences accurately representative of her hands, objects she touched, and to some degree, objects she could infer from her immediate surroundings.

Methods: Photic stimulation with occipital EEG recording was used to confirm lack of remaining retinal function. The patient was interviewed over multiple sessions to obtain reports of her visual phenomenology. For initial functional magnetic resonance imaging (fMRI), NS underwent three tasks: passive visual recording, moving her hand in front of her face, and imagining moving her hand in front of her face. These were compared to a sighted control.

Results: Interviews with NS revealed that her experiences appear to be distinct from mental imagery as they occurred automatically, remained consistent over time, and were proprioceptively mediated by her head position much like normal optical vision. Moreover, she could neither consciously force these visual experiences to occur without sensory inference nor prevent them from happening when haptically exploring an object. Her previous visual experiences contributed to a strong influence of top-down processing in her perceptions. Preliminary fMRI findings will also be reported.

Conclusion: Though individuals have previously been able to develop limited veridical acquired synesthesia following extensive practice over many years with the use of a special sensory device, none reported experiencing the richness of complexity or degree of top-down processing exhibited by NS. Thus, we posit that NS’s case may represent the first case of non-optic vision, a phenomenon beyond synesthesia altogether.

Category: Medical Student Year 1 & 2, Clinical Science
Mentor: Tom Jhou, Ph.D., Department of Neuroscience

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Racial and Ethnic Differences in Out-of-Pocket Expenses among Adults with Diabetes

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Medical University of South Carolina, Department of Medicine, Division of General Internal Medicine and Geriatrics and the Ralph H. Johnson VAMC

Background: Racial and ethnic minority groups have a higher prevalence of diabetes, worse complications, and poorer health outcomes compared to Non-Hispanic Whites (NHW). The objective of this study was to assess racial and ethnic differences in out-of-pocket (OOP) expenditures among a nationally representative sample of adults with diabetes.

Methods: Cross-sectional study of 17,702 adults (≥18 years) with diabetes from the 2002-2011 Medical Expenditure Panel Survey Household Component. Dependent variable was OOP expenses. The primary independent variable was race/ethnicity categorized into NHW, Non-Hispanic Black (NHB), Hispanic, or Other. Unadjusted means were computed to compare out-of-pocket expenses overtime and by race/ethnicity. A two-part regression model was used to estimate adjusted incremental OOP expenses.

Results: Nearly 65% of the sample was NHW, 15% was NHB, 14% was Hispanic, and 7% identified with another race or ethnicity. The average OOP for the sample from 2002-2005 was $2117.74, followed by $1665.10 for years 2006-2009, and $1391.22 for 2010-2011, suggesting OOP expenditures for the sample decreased significantly over time. Compared to NHW, all of the other racial and ethnic population groups had significantly lower OOP costs per year, adjusting for covariates. Compared to NHW, NHB had significantly lower OOP expenditures by more than $480 (95% CI: -621.30, -341.51; p<0.001). Hispanics had even lower OOP expenses at savings more than $590 compared to NHW (95% CI: -727.38, -455.00; p<0.001). The ‘Other’ category had the significantly lowest OOP expenses of nearly $645 compared to NHW (95% CI: -803.07, -484.47; p<0.001).

Conclusions: In this sample, OOP expenses decreased significantly overtime for all racial and ethnic groups; however, NHW had the most OOP expenses. These observed differences in OOP expenditures among different racial and ethnic groups might be due to higher healthcare utilization in NHW. Additional research is needed to understand these differences in costs in adults with diabetes.

Category: Medical Student Year 1 & 2, Clinical Science
Mentor: Leonard Egede, M.D., MS, Division of General Internal Medicine
The Effect Of Biologics On Subtalar Arthrodesis In The Setting Of Congenital Talocalcaneal Coalition

JA Tracey III, CE Gross, MS Myerson

Introduction
Tarsal coalitions are a rare occurrence; however, they are inevitably encountered in an orthopaedic foot and ankle practice. Joint sparing interposition procedures along with coalition resections in younger patients are considered when conservative treatment plans have failed, however primary arthrodesis still results in a large proportion of patients with recurring symptoms. Clinical outcomes tend to be favorable in this population undergoing arthrodesis, but the induction of modern biologics may lead to perfecting the arthrodesis rate and mitigating complications in high risk patients.

Methods
A retrospective analysis was conducted on 764 subtalar arthrodesis records occurring between 10/31/01 and 7/30/13. 36 (5%) were primary arthrodesis performed in the setting of talocalcaneal coalition. Of the 36 patients, 6 (17%) failed to have radiographs at their final follow-up and were excluded from the study. Clinical outcomes including revision procedures, delayed union, nonunion, and failure rates were recorded. The average age was 26 years old (+/- 10 years) with an average follow-up of 9 months.

Results
All 30 patients in the study had confirmed arthrodesis radiographically (100%). The Average time to fusion was 14 weeks (+/- 6 weeks). A single patient had delayed union (2.7%) with a comorbidity significant for heavy smoking. 24 (67%) patients had bone grafting included in their procedures: 2 femoral head allografts (5%), 15 autografts (42%), 6 demineralized bone matrices (17%), 1 partially demineralized bone matrix seeded with mesenchymal stem cells (3%). Two patients (5%) reported unresolved symptoms of pain and discomfort.

Conclusion
Subtalar Arthrodesis is a safe and reliable procedure when joint sparing options have failed in symptomatic talocalcaneal coalitions. Fusion rates as high as 100% are feasible when using rigid fixation and orthobiologics, even in high risk patients.
Fighting Cancer with Fat: Utilizing Ceramide Lipid to Induce Lethal Mitophagy

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Keywords: ceramide metabolism, mitophagy

Ceramide is the major lipid constituent of the stratum corneum providing the epidermal barrier property. Evidence shows that ceramide is also a bioactive signaling lipid that can mediate cancer cell death in response to chemotherapeutic agents. This study investigates ceramide’s role in the response of cancer cells to kinase inhibitors and aims at finding mechanism-based alternative strategies to overcome resistance. In a model consisting of Acute Myeloid Leukemia with mutations in FLT3 kinase, we found that kinase inhibition resulted in expression of Ceramide Synthase 1 and its translocation from cytosol to mitochondria to generate C\textsubscript{18}-ceramide. Mitochondrial C\textsubscript{18}-ceramide then binds to LC3B-II to recruit autophagosomal membranes for the execution of lethal mitophagy. This process was regulated by Drp1 activation and p-Drp1 S637 de-phosphorylation, whereby silencing Drp1 expression or preventing its S637 dephosphorylation blocked CerS1 translocation to mitochondria, prevented ceramide mitochondrial accumulation, halted lethal mitophagy, and protected from cell death. After we showed the importance of ceramide mitochondrial accumulation for mediating cell death, we proposed a synthetic lipid compound, LCL-461, composed of C\textsubscript{18}-ceramide conjugated to a pyridinium ring. We expected this compound to accumulate in mitochondria, induce lethal mitophagy, and have anti-cancerous effects. LCL-461 was effective in inducing cell death in cancer cell lines of different kinase mutation statuses and resistance profiles and in \textit{in vivo} xenografts and patient samples, with minimal cytotoxicity on primary bone marrow cells and keratinocytes. LCL-461 induced cell death via the same LC3B dependent lethal mitophagy mechanism. This highlights the potential of LCL-461 as an agent that can bypass kinase signaling by accumulating in mitochondria to induce lethal mitophagy and cancer cell death regardless of whether patients are sensitive or resistant to kinase targeted therapy.

\textit{Category}: Medical Student Year 3 & 4, Basic Science
\textit{Mentor}: Besim Ogretmen, Ph.D., Department of Biochemistry and Molecular Biology
Detecting High Hyperopia: The Plus Lens Test and the Spot Vision Screener

Samuel Feldman

Introduction: The early detection of hyperopia in children is very important, as children will develop long-term vision deficits if it is not corrected. The Plus Lens test is an easy, cheap, and supposedly effective method for detecting hyperopia. This test would allow school nurses and other ancillary pediatric services everywhere to detect hyperopia in children. Another method for detecting hyperopia is photoscreening. Photoscreeners are relatively expensive, but would be still be a good option for school systems looking to perform visual testing on many children. Very little research exists on the effectiveness of the Plus Lens test. The purpose of this research was to evaluate the usefulness of the Plus Lens (Goodlite Company, Elgin, IL) test and the Spot Vision Screener (Welch Allyn, Skaneateles Falls, NY) in detecting high hyperopia in a pediatric population.

Methods: Between June and August 2015, patients were screened with the Spot Vision Screener and the Plus Lens test prior to a scheduled pediatric ophthalmology visit. The following data were analyzed: demographic data, Plus Lens result, Spot Vision Screener result, cycloplegic refraction, and examination findings. Sensitivity/specificity and positive/negative predictive values were calculated for the Plus Lens test and Spot Vision Screener in detecting hyperopia as determined by the "gold-standard" cycloplegic refraction.

Results: A total of 109 children (average age: 82 months) were included. Compared to the ophthalmologist's cycloplegic refraction, the Spot Vision Screener sensitivity for +3.50 diopters (D) hyperopia was 31.25% and the specificity was 100%. The Plus Lens sensitivity for +3.50 D hyperopia was 43.75% and the specificity was 89.25%. Spot Vision Screener sensitivity increased with higher degrees of hyperopia.

Conclusions: In this preliminary study, the Plus Lens test and the Spot Vision Screener demonstrated moderate sensitivity with good specificity in detecting high hyperopia.

Category: Medical Student Year 3 & 4, Clinical Science
Mentor: Winfrey Peterseim, M.D., Department of Ophthalmology
Malignant fibrous histiocytoma: Surveillance, Epidemiology and End Results database suggests a relatively favorable prognosis in the head and neck

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Introduction: The malignant fibrous histiocytoma (MFH) is the most common soft tissue sarcoma of the head and neck. However, most of the current data on this tumor relies on small retrospective studies. This paper represents the largest study analyzing prognosis of this tumor in the head and neck to date.

Methods: Using the Surveillance, Epidemiology, and End Results (SEER) database, 395 patients with MFH of the head and neck were compared with 3968 patients with MFH of the trunk and extremities. Disease-specific survival was carried out comparing these two cohorts, with stratifications by tumor size and histologic grade.

Results: Head and neck MFH had a significantly higher disease-specific survival compared with trunk and extremity MFH. However, head and neck tumors were more frequently a smaller size ($p < .0001$) and lower grade ($p < .0001$). When stratified by tumor size and grade, disease-specific survival was not significant with the exception of grade III tumors.

Conclusion: Head and neck MFH presents at a smaller size and lower grade, likely due to earlier presentation in this region of the body. Because of this, head and neck MFH represents a more favorable survival prognosis compared with trunk and extremity MFH.

Category: Medical Student Year 3 & 4, Clinical Science
Mentor: Eric J. Lentsch, M.D., Department of Otolaryngology
Transfer personnel compliance with blood pressure thresholds for intracerebral hemorrhage patients during interfacility transfers.

Matt Berger, Dr. David French, Dr. Ed Jauch: Division of Emergency Medicine

Stroke is a leading cause of death in the United States and worldwide, and approximately 15% of all stroke deaths occur due to intracerebral hemorrhage (ICH) (Chakrabarty and Shivane 2008). Studies have shown that hematoma growth, especially early hematoma growth, is a key predictor of both mortality (Broderick, Brott et al. 1993) as well as morbidity (Brott, Broderick et al. 1997). Furthermore, elevated blood pressure is both a key risk factor for hemorrhagic stroke and a mechanism of hematoma expansion (Steiner, Kaste et al. 2006). Therefore, recognizing the importance of early management of elevated blood pressure for prevention of hematoma expansion as well as long term patient outcome, and knowing that many patients undergo long interfacility transfers to stroke centers after being diagnosed at an outside facility, EMS transfer personnel adherence to blood pressure control guidelines becomes a critical factor in hemorrhagic stroke management.

Our study aimed to evaluate adherence to recommended blood pressure management for patients with known ICH during interfacility transfers to MUSC. To this end we reviewed transport records of patients that were diagnosed with a spontaneous ICH at an outside facility and subsequently transferred to MUSC for treatment. We confirmed that the patient had a diagnosed ICH and then identified mode of transport (ground vs air), transport time, blood pressure during transfer and at arrival, medications given during transport, Glasgow Coma Scale and National Institutes of Health Stroke Scale on arrival, and final outcome.

We found that of 34 ICH patients, 16 had systolic blood pressure (SBP) over 160 mmHg during transport. Of these 16 patients, 6 were given antihypertensive medication during transport. This meant that only 37.5% of patients with elevated SBP received proper blood pressure management during transport to our stroke center. When analyzed by mode of transport, the 6 hypertensive ICH patients who received antihypertensive medication during interfacility transport were transferred by helicopter (often nicardipine infusion initiated before departure and titrated during transport) and the 10 who did not receive medication were transferred by ambulance. It should be noted however, that for two of the patients transported by ambulance, one requested labetalol and was denied due to bradycardia and one was given hydralazine and labetalol before transport. Both of these patients remained hypertensive during transport. We also found that for ICH patients who were hypertensive during interfacility transport and received antihypertensive medication, two thirds were discharged to home and a third were discharged to long term acute care or rehabilitation facility. This is contrasted with those patients who did not receive antihypertensive medication, of which 40% were discharged home and 60% were discharged to a rehabilitation facility. Finally, hypertensive ICH patients who received antihypertensives during transport had an average SBP of 153 mm/Hg on arrival at MUSC, versus an average SBP of 161 mm/Hg on arrival for those who did not.

Overall, our study demonstrates a need for improvement in blood pressure management for patients with ICH during interfacility transfers. Specifically, patients who were transferred via ambulance received suboptimal blood pressure management compared with those transferred by helicopter. This was alarming considering we analyzed patients who were hypertensive above a SBP of 160 mm/Hg, even though previous studies have demonstrated benefit in lowering systolic blood pressure in these patients below 150 mm/Hg (Steiner, Kaste et al. 2006) or even 140 mm/Hg (Anderson, Heeley et al. 2013). However, analysis of patients who were transported by helicopter showed better blood pressure management is possible and represents an opportunity for improvement for prehospital management of hemorrhagic stroke patients.

**Category:** Medical Students Year 3 & 4, Clinical Science

**Mentor:** David French, M.D., Division of Emergency Medicine
Hypermetabolism and the Complex Role of Lipids in Amyotrophic Lateral Sclerosis

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Introduction: Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease in adults that affects both upper and lower motor neurons and ultimately leads to death, usually by respiratory failure. It has been well reported that ALS is often marked by a hypermetabolic state, usually measured by the resting energy expenditure (REE)²,⁶,⁷,¹², ²⁵ Because of these findings, a mainstay of management is nutritional support, and lipids have been one of the most studied macronutrients in ALS.¹⁴,²² In this review, we aim to gather what is known about the role of lipids in ALS.

Methods: This review was performed using searches on PubMed, using “amyotrophic lateral sclerosis” or “ALS” with any combination of the following: “hypermetabolism,” “hypermetabolic,” “lipid,” “cholesterol,” “triglyceride” and “adipose.” Only articles published within the last 15 years with “amyotrophic lateral sclerosis” or “ALS” in the title were included in this review.

Results: Nine of the 25 articles selected for this review focused on hypermetabolism in ALS and the other 16 articles focused on the role of lipids in ALS. Within the sixteen articles concerning lipids, there were seven cohort studies, six cross sectional studies, one case control study, one review article, one meta-analysis, and three SOD1 mice studies.

Conclusion: Hypermetabolism is a phenomenon seen in patients with ALS and in animal models of ALS. In animal models, the increased metabolism appears to be related to the increased uptake and utilization of lipids in the muscles.¹¹,¹⁹ In patients with ALS, maintenance of body mass index is associated with a better prognosis; however, the role of lipids in the mechanism, progression, or prognosis of ALS is less clear.

Type of Project: Literature Review

Category: Medical Student Year 3 & 4, Clinical Science

Mentor: I-Hweii Amy Chen, M.D., Ph.D., Department of Neurology
The Natural History of Iron Deficiency Anemia

Dickey S and Rockey DC

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**Background:** In adults, iron deficiency anemia (IDA) is the most common cause of anemia in the United States. Current evidence suggests that in adult men and non-menstruating women with IDA, a gastrointestinal (GI) bleeding lesion should be suspected.

**Aims:** We aimed to better understand the natural history of IDA, in particular the long term outcome of patients diagnosed with IDA after bidirectional endoscopy including whether or not resolution occurred, follow-up as received, and what therapies were instituted.

**Methods:** Adult patients with IDA (ferritin value <50ng/mL and anemia) diagnosed between 2004 and 2008 and who underwent endoscopic evaluation as part of their diagnostic work-up were included in the study. These patients were followed from time of diagnosis through 2013 to analyze course of their disease.

**Results:** 96 patients were identified and had a mean follow-up of 6 years. 51 patients had either an upper or lower GI lesion thought to be responsible for IDA. Overall, 15 of the patients with endoscopic lesions and 17 of the patients without endoscopic lesions, totaling 32/96 (33%) of all of the patients, had complete resolution of their anemia. In the 64/96 (67%) who remained anemic after medical management, 23 received repeat endoscopies which found 13 new lesions in 8 patients. These lesions were all in the upper GI tract with most being esophageal varices. Among the patients who remained anemic, no new GI malignancies were found on repeat endoscopy.

**Conclusions:** When an adult patient presents with iron deficiency anemia and they are not a female still undergoing menstrual cycles, one must highly suspect a GI lesion, especially those of the upper GI tract. Even with medical management, there is a still a percentage of patients that remain iron deficient anemic; therefore, further investigation into the cause is warranted.

**Category:** Medical Student Year 3 & 4, Clinical Science

**Mentor:** Don C Rockey, M.D., Division of Gastroenterology and Hepatology
A Brief CPR-Training Program for High School Students Transiently Increases Likelihood of Bystander Intervention in Cardiac Arrest

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Background: Sudden Cardiac Arrest (SCA) affects over 300,000 Americans annually, and one of the keys to increased survival is rapid bystander intervention (Mozaffarian 2016), though this rarely occurs. Studies have demonstrated that compression-only CPR (CO-CPR) is an effective form of bystander intervention (Iwami 2015, Yao 2014, & Bobrow 2010). Further, students over 10 - 13 years of age can be taught to perform adequate chest compressions (Abelairas-Gomez 2014, Plant 2012, Bohn 2012, & Toner 2007), and the classes can be short but still effective (Panchal 2014, Nishiyama 2014 & Mpotos 2013). In some cases, appropriate intervention may be performed with verbal guidance, even for the untrained layperson (Beard 2014). Unfortunately, though retention of this skill knowledge is better with CO-CPR than standard CPR training (Nishiyama 2014), the degree of retention for high school students after the two-year period currently recommended for standard recertification is unclear.

Methods: Since 2013, MUSC has partnered with a large public high school (approximately 1000 students per grade) in Charleston County to assist with training ninth-grade high school students in CO-CPR during a 60-minute health class. For the first year of the program, we performed pre- and post-training surveys to assess attitudes and comfort with CPR and AED use and to guide and improve the program. We performed a similar survey of the first participants two years later to re-evaluate attitudes towards CPR and AED use.

Results: Before training, most students were not trained in CPR (56%) or AED use (81%), though 75% felt they could help an adult choking victim. In the setting of cardiac arrest, only 60% of respondents might start CPR. After training, 100% of respondents felt they knew how to perform CPR, 97% might start CPR, 89% were comfortable with AED use, and 96% felt they knew how to help a choking victim. Two years later, most respondents had not taken additional CPR training and only 37% felt comfortable with using an AED while 84% still felt comfortable helping a choking victim, though only 60% might start CPR.

Conclusions: A short training program in high school effectively increases knowledge of CPR, AED use and choking management, as well as the likelihood of bystander intervention in SCA, though this improvement is transient. Additional, more frequent educational initiatives are likely required to maintain this willingness to intervene in SCA.

Category: Medical Student Year 3 & 4, Clinical Science
Mentor: David French, M.D., Division of Emergency Medicine
Antibiotic Use in Patients with Systemic Lupus Erythematosus Compared to Rheumatoid Arthritis and Scleroderma

Muyi Li, Diane Kamen. *Department of Rheumatology, MUSC*

**Introduction:** Systemic Lupus Erythematosus (SLE) is a complex autoimmune disease triggered by environmental factors in genetically susceptible individuals. Patients are often immunosuppressed, and susceptible to opportunistic infections. Antibiotic treatment complicated due to higher frequencies of drug reactions. Our objective is to better characterize antibiotic use and drug allergies within this population, and observe differences in disease activity following use of antibiotics.

**Methods:** Subjects with SLE, rheumatoid arthritis (RA), and scleroderma were identified utilizing electronic medical record ICD-9/10 codes recorded from 01/2015 to 01/2016. Using EPIC SlicerDicer, we selected patients with these diagnoses who required certain antibiotics during this time. Further analysis examined antibiotic allergies and disease characteristics including medication use and laboratory values. Chi-square testing was performed and p-value <0.05 was considered statistically significant.

**Results:** The study population included 1976 SLE patients, 3094 RA patients, and 909 scleroderma patients with at least 1 visit in 2015. SLE patients were significantly more likely to have listed antibiotic than RA or scleroderma patients (Table 1). SLE patients were more likely to receive tetracyclines than Bactrim compared to RA or scleroderma patients as well (Table 2). Among SLE patients, those prescribed Bactrim were more likely to have been admitted during the past year, receive prednisone, and have lower C3 levels (31% vs. 21%, p=0.05).

**Conclusions:** SLE patients were more likely to have allergies listed for all antibiotics studied when compared to patients with 2 other autoimmune diseases seen over the same time period at MUSC. However, SLE patients were significantly more likely to receive tetracyclines and less likely to receive Bactrim than RA and scleroderma patients. Antibiotic usage in autoimmune disease, especially patients with SLE, faces many challenges due to increased adverse drug reactions, and should be taken into account when treating infections within this population.

**Table 1: Antibiotic allergies in SLE, RA, and scleroderma patients**

<table>
<thead>
<tr>
<th>ALLERGIES</th>
<th>SLE (n=1976)</th>
<th>RA (n=3094)</th>
<th>Scleroderma (n=909)</th>
<th>p-value (RA vs. SLE pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfas</td>
<td>271 (14)</td>
<td>358 (12)</td>
<td>115 (12)</td>
<td>0.02</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>92 (5)</td>
<td>107 (3)</td>
<td>36 (4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>43 (2)</td>
<td>38 (1)</td>
<td>6 (1)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

**Table 2: Antibiotic usage in SLE, RA, and scleroderma patients**

<table>
<thead>
<tr>
<th>ABX RECEIVED</th>
<th>SLE (n=1973)</th>
<th>RA (n=3094)</th>
<th>Scleroderma (n=909)</th>
<th>P-value (RA vs. SLE pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bactrim</td>
<td>87 (4)</td>
<td>203 (7)</td>
<td>77 (8)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>159 (8)</td>
<td>242 (8)</td>
<td>69 (8)</td>
<td>0.76</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>149 (8)</td>
<td>156 (5)</td>
<td>48 (5)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

**Category:** Medical Student Year 3 & 4, Clinical Science

**Mentor:** Diane Kamen, M.D., Division of Rheumatology and Immunology
Detecting High Hyperopia: The Plus Lens Test and the Spot Vision Screener

Samuel Feldman

Introduction:
The early detection of hyperopia in children is very important, as children will develop long-term vision deficits if it is not corrected. The Plus Lens test is an easy, cheap, and supposedly effective method for detecting hyperopia. This test would allow school nurses and other ancillary pediatric services everywhere to detect hyperopia in children. Another method for detecting hyperopia is photoscreening. Photoscreeners are relatively expensive, but would be still be a good option for school systems looking to perform visual testing on many children. Very little research exists on the effectiveness of the Plus Lens test. The purpose of this research was to evaluate the usefulness of the Plus Lens (Goodlite Company, Elgin, IL) test and the Spot Vision Screener (Welch Allyn, Skaneateles Falls, NY) in detecting high hyperopia in a pediatric population.

Methods:
Between June and August 2015, patients were screened with the Spot Vision Screener and the Plus Lens test prior to a scheduled pediatric ophthalmology visit. The following data were analyzed: demographic data, Plus Lens result, Spot Vision Screener result, cycloplegic refraction, and examination findings. Sensitivity/specificity and positive/negative predictive values were calculated for the Plus Lens test and Spot Vision Screener in detecting hyperopia as determined by the "gold-standard" cycloplegic refraction.

Results:
A total of 109 children (average age: 82 months) were included. Compared to the ophthalmologist's cycloplegic refraction, the Spot Vision Screener sensitivity for +3.50 diopters (D) hyperopia was 31.25% and the specificity was 100%. The Plus Lens sensitivity for +3.50 D hyperopia was 43.75% and the specificity was 89.25%. Spot Vision Screener sensitivity increased with higher degrees of hyperopia.

Conclusions:
In this preliminary study, the Plus Lens test and the Spot Vision Screener demonstrated moderate sensitivity with good specificity in detecting high hyperopia.
Histone deacetylase inhibition targets Wisp-1, a novel cardiac angiogenesis regulator, in post-MI myocardium.

Lillianne H. Wright¹, Daniel J. Herr¹, Symone S. Brown², Harinath Kasiganesan¹, Donald R. Menick¹,³

¹Medical University of South Carolina, College of Medicine, Cardiology. ²Medical University of South Carolina, College of Graduate Studies, SURP. ³Ralph H. Johnson VA Medical Center, SC.

Introduction: Re-establishing vasculature after a myocardial infarction (MI) may help to spare non-regenerative myocardium and subsequent cardiac function. Wisp-1 - a secreted matricellular protein that regulates collagen secretion and angiogenesis in certain cancers - promotes cell survival in cardiac myocytes in vitro. However, the potential role Wisp-1 plays post-MI, has not been evaluated. Histone deacetylase inhibitors (HDACi) attenuate adverse effects of an MI in small animal models but it is unclear which genes and or targets contribute to this benefit. Our preliminary data shows that Wisp-1 is upregulated 15-fold in response to MI injury compared to sham-operated mice. However, Wisp-1 is upregulated 45-fold in mice that are subjected to an MI injury and treated with the HDAC inhibitor, suberanilohydroxamic acid (SAHA). Therefore, we hypothesized that HDACi mediated upregulation of Wisp-1 contributes to beneficial angiogenesis, post-MI.

Methods: To test this, we subjected age and sex matched mice to ligation of the L.A.D. coronary artery or a sham operation. Mice were injected daily with either DMSO/vehicle, or the HDAC inhibitor, SAHA. Seven days post-MI, mice were euthanized and their heart tissue was assessed for the expression of Wisp-1 and microvasculature. We also assessed the impact of recombinant WISP-1 treatment and RNAi technologies on isolated human coronary artery endothelial cells (HCAECs).

Results: We observed that HDACi mediated upregulation of Wisp-1 is specifically found at the border zone of infarction and is proximal to increased microvasculature. In vitro studies show that recombinant WISP-1 protein promotes the expression of pro-angiogenic genotypic and phenotypic characteristics in HCAECs. Lastly, shRNA-targeted suppression of endogenous Wisp-1 functionally reduces endothelial cell network branching in vitro.

Conclusion: Therapeutic interventions after a heart attack can greatly impact the extent of infarct injury, cell survival and overall prognosis. Our studies shown here identify a novel pro-angiogenic target, Wisp-1, that may be useful in post-MI treatment modalities.

Category: Postdoctoral Fellow, Basic Science
Mentor: Donald Menick, Ph.D., Division of Cardiology
Immune Complex-Induced IL-6 Production by Lupus Prone Mesangial Cells Is Mediated By Neuraminidase Activity

Kamala P Sundararaj, Jessalyn L Rodgers and Tamara K. Nowling

Division of Rheumatology, Department of Medicine, Medical University of South Carolina.

Nearly 50% of patients with systemic lupus erythematosus (SLE or lupus) develop glomerulonephritis, a leading cause of morbidity and mortality in lupus patients. One of the earliest hallmarks of nephritis is the deposition of immune complexes in the glomeruli, which activates mesangial cells to produce an array of cytokines and chemokines that then lead to immune infiltration, inflammation and eventually tissue damage. We previously reported that glycosphingolipid (GSL) metabolism is altered in the kidney of lupus mice and humans with nephritis compared to their disease counterparts without nephritis and healthy controls. Specifically, we demonstrated an increase in lactosylceramide (LacCer), glucosylceramide (GlcCer), neuraminidase activity and Neu1 mRNA levels. These studies suggested that the catabolic pathway mediated by NEU activity was elevated in lupus nephritis. NEUs remove sialic acids from glycolipids and glycoproteins impacting cell signaling and function. Of the four mammalian NEUs, NEU1 shows the highest expression in kidney compared to the other NEUs followed by NEU3.

In this current study, we provide additional evidence that NEU-mediated GSL catabolism is elevated in the kidney of lupus mice with nephritis and demonstrate strong NEU1 expression in the expanding mesangial cells. Based on the mesangial cell-specific expression of NEU1, we examined the role of NEU activity and potential mechanisms by which NEU1 mediates the activation of lupus prone mesangial cells. We demonstrate that activation of MCs using either a mimic of immune-complexes or lupus serum increases IL-6 and MCP-1 production by both healthy and lupus prone primary MCs. The IL-6 production appears to be directly mediated by NEU activity and overexpression studies in an immortalized MC line indicates NEU1 specifically induces IL-6 production. Together our results suggest that NEU activity mediates IL-6 production by lupus prone MCs and targeting NEU activity or NEU1 specifically may be a therapeutic approach to reduce renal inflammation in lupus.

Category: Postdoctoral Fellow, Basic Science
Mentor: Tamara Nowling, Ph.D., Division of Rheumatology and Immunology
Deep Transcriptome Profiling – Comparisons and Contrasts.

da Silveira, WA¹; Hazard ES¹; Chung D², Hardiman, G¹.².³

¹MUSC Bioinformatics, Center for Genomics Medicine, ²Department of Public Health Sciences, ³Department of Medicine, Medical University of South Carolina (MUSC), Charleston SC.

Introduction: Different methods have evolved over the past five years to significantly determine differentially expressed (DE) genes from a comparison of the transcriptome under altered physiological conditions (e.g. healthy vs diseased). We wished to evaluate concordance amongst the most popular methodologies.

Methods: RNA-seq data from human lung adenocarcinoma cells (HCC827) expressing, or not, ZEB1 (a well-known epithelial-to-mesenchymal transition stimulator) were extracted from the GEO database. The sequence FASTQ files were assessed for quality using FASTQC and processed using Cutadapt and Trimmomatic. We exploited Tophat2 to align the reads to the reference GRCh37/hg19 human genome. We performed DE analysis using TUXEDO, which produces a transcriptome assembly, and lists DE genes. Additionally we tested three widely used count based methods (DEseq2, EdgeR and Limma/voom), after defining mRNA level read counts with Htseq. System level analyses were performed on all four approaches using Ingenuity Pathway Analysis (Qiagen).

Results: Employing a Bonferroni Hochberg adjusted $p$-value cut-off ≤ 0.1, TUXEDO uncovered 476 DE genes, DEseq2 found 186, EdgeR uncovered 540, and Limma/voom 155. When we examined DE gene lists from the different programs, DEseq2 provided the most overlap, i.e. 43% with TUXEDO, 58% with Limma/voom and 94.6% with edgeR. The edgeR analysis yielded the most comprehensive list of DE genes. TUXEDO revealed 59.6% overlap with EdgeR, DEseq2 94.6%, and Limma 81.2% respectively. Only 48% of edgeR DE genes were unique compared with just 0.01% with DEseq2. Only 19.4% of the mRNAs from Limma/voom overlapped the TUXEDO results, the lowest agreement observed. Even with this gene level discordance, systems analysis identified the same pattern of affected pathways.

Conclusion: Of all methods tested, DEseq2 was most concordant. Between these approaches, gene-level analysis of significance was not comparable, but system level analysis revealed high consistency.

Category: Postdoctoral Fellow, Basic Science
Mentor: Gary Hardiman, Ph.D., Division of Nephrology
Does Exposure to BPA Change the Epigenome of Zebrafish: A Focus on MicroRNAs.

Ludivine Renaud¹, William A. Da Silveira², E. Starr Hazard², Matthew Huff³ and Gary Hardiman¹, ², ⁴

¹Division of Nephrology, Department of Medicine, MUSC
²Center for Genomic Medicine, Bioinformatics MUSC
³College of Graduate Studies, MUSC
⁴Department of Public Health Sciences, MUSC

Introduction: Our society is addicted to plastic. We are exposed daily to plasticizers including Bisphenol A (BPA), an endocrine disruptor (ED) that mimics estrogen and impacts the ecosystem and human health. Our laboratory exploits Zebrafish (ZF) as a systems toxicology model. Along with histone modifications and DNA methylation, microRNAs are epigenetic factors and key regulators of gene expression during development and disease progression. The effect of EDs on microRNA profiles in aquatic species remains poorly characterized.

Hypothesis: Exposure to BPA during adulthood affects many microRNAs and their targeted genes, causing a cascade of deregulated pathways and disease.

Methods: Adult zebrafishes were exposed to 100 nM BPA for 3 weeks, mimicking chronic exposure. The liver was dissected, RNA and small RNAs were extracted and subjected to high throughput sequencing. We carried out differential expression analysis and compared BPA exposed to control fishes using bioinformatics pipelines. STEP1: For small RNAs, differently expressed (DE) miRNAs were identified using the CAP-miRSeq pipeline. STEP2: For mRNA, sequence reads were aligned to GRCz10 (ZF genome) using TopHat2. Read count assembly and DE analysis were performed using HTseq and DEseq2. Gorilla and REViGO provided Gene Ontology (GO) terms. Human homologs of ZF genes were obtained with Ensembl and analyzed using Advaita and TopFunn.

Results: STEP1: 29 miRNAs were DE in the liver of BPA exposed adults, including miR-122 which regulates hepatocyte differentiation. GO analysis revealed that BPA impacted reproductive processes. STEP2: The ‘humanized’ ZF data revealed that genes associated with non-alcoholic fatty liver disease (NAFLD), oxidative phosphorylation and cell cycle were significantly affected. Additionally, several miRNAs relevant in cancer were uncovered.

Conclusion: Short term exposure to elevated BPA levels has a significant impact on the liver miRNome in adult male zebrafish. Our data suggests that chronic BPA exposure has the potential to cause adverse effects in human.

Category: Postdoctoral Fellow, Basic Science
Mentor: Gary Hardiman, Ph.D., Division of Nephrology
Targeting Myosin 1c to Reduce Hepatic Fibrogenesis

Cindy Wang¹, Ehtesham Arif², Deepak Nihalani², and Wing-kin Syn¹,³, Division of Gastroenterology¹ and Nephrology², Department of Medicine, Medical University of South Carolina, Charleston, SC 29425; Ralph H. Johnson VA Medical Center³, Charleston, SC 29401

Introduction: Myosin 1c (Myo1c) is an unconventional myosin and plays a role in signal transduction and disease. Myo1c binds specifically to PI(4,5)P2, the substrate of phosphoinositide 3-kinase (PI3K), suggesting a role for Myo1c in regulating the PI3K pathway. We previously reported that the activation of the PI3K-Akt pathway promotes hepatic fibrogenesis. On the basis that both hepatic stellate cells (HSCs, the liver pericytes) and liver progenitors (LPs) are major effectors of liver repair, we hypothesized that Myo1c expression in HSCs and LPs modulates fibrogenesis.

Methods: The mouse HSC (GRX) and LP (603) lines were used. Myo1c was depleted by shRNA-mediated knockdown (KD) or inhibited using pentachloropseudilin (PCIP), a Myo1c inhibitor. Gene expression was evaluated by quantitative real-time polymerase chain reaction and Western blotting; cell migration and viability were assessed using the scratch assay and the Cell Counting Kit-8, respectively.

Results: Depletion of Myo1c in HSC and LPs increased expression of αSMA, Col1a1, Vimentin, and Snail (fibrogenic genes), and increased levels of phospho-Smad2 proteins (TGF-β1 pathway activation) and phospho-Akt under basal conditions; by contrast, these were reversed (i.e. repressed) under TGF-β1 stimulation. Similar changes were observed when HSCs were treated with PCIP. Myo1c KD was also associated with reduced cell proliferation and migration under basal conditions.

Conclusion: Genetic depletion or pharmacologic inhibition of Myo1c repressed fibrogenic genes in both HSC and LPs under TGF-β1 stimulation, suggesting that Myo1c is a major regulator of liver fibrosis. Our data further suggest that these effects may be PI3K-Akt and TGF-β dependent. Further studies will be necessary to confirm the importance of Myo1c in murine models of liver disease.

Category: Postdoctoral Fellow, Basic Science
Mentor: Wing-Kin Syn, M.B..Ch.B., Division of Gastroenterology and Hepatology
Evaluating the Effects of Selective Estrogen Receptor Modulators (SERMs in Bone Marrow Derived Dendritic Cells

Mara L. Lennard Richard a, Jena R. Wirth a, Melissa A. Cunningham a, Gary S. Gilkeson a

a Department of Medicine, Division of Rheumatology & Immunology, Medical University of South Carolina, Charleston, SC 29425, USA

Introduction: Systemic lupus erythematosus (SLE) is a chronic, inflammatory, autoimmune disease with a profound sex bias, affecting females of reproductive age 9:1 over males. ERα plays a significant role in SLE disease pathogenesis; lupus mice with a deletion of the ERα AF-1 activation domain have significantly prolonged survival and less renal disease. Treatment options for SLE patients are limited and many have severe or toxic side effects. The development of novel therapeutic targets is of great clinical importance. Ligand bound ERα impacts several immune cell types and affects the transcription of inflammatory mediators. Several new selective estrogen receptor modulators (SERMs) were developed that selectively induce non-genomic effects of ERs in breast cancer such that they retain metabolic/bone and vascular protection without impacting fertility or reproductive tissue. Their effects in immune cells have not yet been investigated.

Methods: In this study, the effects of several SERMs were tested on bone marrow derived dendritic cells (BMDCs) isolated from NZM2410 lupus prone mice prior to the onset of disease. mRNA levels of proinflammatory cytokines important in SLE pathogenesis were measured in the cells. To assess the non-genomic effects of these particular SERMs on ERα in immune cells, phosphorylation of ERK kinase was analyzed as a marker of MAPK pathway activation.

Results and Conclusions: Our results demonstrate that these novel SERMs reduce mRNA expression of IL6 and MCP-1 in TLR-stimulated BMDCs after 24 hours. Their effect on the cells does not appear to be as potent as estrogen at this time point. Future results from this study will determine the potential role of SERMs in modulating the effects of ERα in immune cells, characterize the non-genomic effects of ERα in immune cells and lay the foundation for the potential use of these compounds in the treatment SLE and other immune mediated diseases.

Category: Postdoctoral Fellow, Basic Science
Mentor: Gary Gilkeson, M.D., Division of Rheumatology and Immunology
Exploring the TGF-β1 regulated secretome using a proteomic approach

Maya Malaab, Ryan T. Kendall, John E. Baatz and Carol Feghali-Bostwick

Department of Medicine, Division of Rheumatology and Immunology, Medical University of South Carolina, Charleston, SC

Introduction: Transforming Growth factor superfamily member (TGF)-β is an autocrine and paracrine cytokine involved in the pathogenesis of a broad spectrum of pathologies including cancerous and fibrotic diseases across organs. In two of these fibrotic disorders, Systemic Sclerosis (SSc) and Idiopathic pulmonary fibrosis (IPF), TGF-β has been found to be upregulated. And although TGF-β has been proven to play a pivotal role in these disorders, the effect of its upregulation on downstream targets has not yet been well defined in human lung fibroblasts.

Methods & Results: Using fluorescent two-dimensional gel electrophoresis (DIGE), we identified downstream effectors of TGF-β1 in primary human lung fibroblasts. Of particular interest, the extracellular chaperone clusterin was downregulated by TGF-β. This was then verified through western blotting and qPCR using primary human lung fibroblasts and total human lung tissue maintained in organ culture ex vivo. Clusterin expression was also decreased in primary lung fibroblasts derived from lung tissues of patients with SSc and IPF.

Conclusion: Given that one of the many functions of clusterin is the clearance of extracellular debris, a reduction in clusterin in a fibrotic milieu has implications for the pathogenesis of fibrotic diseases.

Category: Postdoctoral Fellow, Basic Science
Mentor: Carol Feghali-Bostwick, Ph.D., Division of Rheumatology and Immunology
Association of Dietary Magnesium Intake with Depression among Individuals at High Risk of Suicide: Participants Enrolled in the Better Resiliency Among Veterans & Non-Veterans with Omega-3’s (BRAVO) Study

Kristen B. Johnson, PhD, RDN¹, Bernadette P. Marriott, PhD¹
¹Department of Medicine, Division of Gastroenterology/Hepatology, Medical University of South Carolina, Charleston, SC

Introduction: Depression is associated with increased risk of chronic conditions, higher incidence of suicide, and increased healthcare utilization (1). Earlier reports suggest higher dietary magnesium (Mg) intake may be associated with reduced depressive symptoms (2). We assessed the association of Mg intake with depression among participants at risk of suicide in the BRAVO study.

Methods: Dietary Mg from 107 adults was determined using the first 24-hour recall from Automated Multiple Pass Method (AMPM) dietary assessment data (3). Dietary Mg intake was compared to recommendations [Estimated Average Requirement (EAR)] (4). Depression was measured by the Beck Depression Inventory II (BDI). T-tests, Wilcoxon-Mann-Whitney, and chi-square tests were used to determine differences among those meeting vs. not meeting the Mg EAR. Linear regression was used to determine the independent and predictive association of magnesium intake with depression (BDI total score).

Results: Mg intake of over half of the study participants (57%; n = 61; mean 221.4 ± 62.2 mg) did not meet the Mg EAR. Of the 107 adults, mean BDI score was 20.8 ± 10.1, and 67% had a BDI score >16 indicating borderline to severe depression. Participants whose dietary Mg intake did not meet the EAR had higher mean BDI scores (21.5 ± 8.8) than participants whose dietary Mg intake met the EAR (19.9 ± 11.6), but the difference was not statistically significant (p = 0.4). No significant association was found between Mg intake and BDI scores with linear regression (Adjusted R²=0.1393, Model F (5, 94) = 4.21, p = 0.0017).

Conclusion: While over half of the study participants did not meet the EAR for Mg intake and 73% evidenced depression, we did not find a significant association between Mg intake and BDI scores in this study.

REFERENCES


Category: Postdoctoral Fellow, Basic Science
Mentor: Bernadette Marriott, Ph.D., Division of Gastroenterology and Hepatology
Association between snoring and metabolic biomarkers in the continuous NHANES database

Musab Nusrat, Suchit Kumbhare, Charlie Strange, Chitra Lal Division of Pulmonary, Critical Care, Allergy and Sleep Medicine, Medical University of South Carolina, Charleston, SC

Introduction: Snoring is a common problem and affects approximately 90 million Americans. It leads to fragmented sleep, poor daytime function, and disruption in the bed partner’s sleep. Snoring is often associated with obstructive sleep apnea (OSA) which is a more severe form of sleep-disordered breathing. Several studies have shown an association between obstructive sleep apnea (OSA) and derangements in metabolic biomarkers, however they did not distinguish the effects of snoring from the effects of the OSA. We hypothesized that snoring, independent of OSA, is associated with abnormalities in serum levels of metabolic biomarkers.

Methods: This retrospective study used publicly available data from the continuous National Health and Nutrition Examination Survey (NHANES) database. Demographic characteristics and relevant laboratory data of adult (≥ 18 years) respondents from the years 2005-2008 were analyzed. The study population was divided into 4 mutually exclusive groups by self-reported diagnoses: non-snorers, occasional snorers, habitual snorers (as defined by snoring ≥ 4 nights/week) and subjects diagnosed with OSA. As the data was not normal in distribution, non-parametric analysis was done by the Kruskal Wallis method. Continuous variables are reported as median with interquartile range and categorical variables are reported as percentages.

Results: A total of 11795 respondents were included in the study; 51.4% were females. Non-snorers were younger than occasional snorers, habitual snorers and those with OSA [41 years (25, 65) vs 45(31, 62), vs. 50 (36, 63) vs. 57 (44, 67); p < 0.0001 in groups 1-4 respectively (table 1). Snorers were more likely to be male and had a higher BMI than non-snorers. Diabetes was more common in habitual snorers as compared to occasional snorers and non-snorers, 13.1% vs. 9.2% vs. 8.8 % respectively; p <0.0001. Most of the evaluated biomarkers showed abnormal levels in snorers as compared to non-snorers. A complete list of evaluated biomarkers is shown:

<table>
<thead>
<tr>
<th></th>
<th>Non-snorers</th>
<th>Occasional</th>
<th>Habitual</th>
<th>Diagnosed OSA</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>41 (25, 65)</td>
<td>45 (31, 62)</td>
<td>50 (36, 63)</td>
<td>57 (44, 67)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender, Male</td>
<td>1838 (39.8)</td>
<td>1789 (48.9)</td>
<td>1810 (59.5)</td>
<td>305 (63.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>25.9 (22.7, 29.9)</td>
<td>27.4 (24.0, 31.4)</td>
<td>29.7 (26.1, 34.2)</td>
<td>33.6 (29.3, 39.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ferritin (mg/dl)</td>
<td>33 (17, 59)</td>
<td>34 (18, 61)</td>
<td>41 (19, 76)</td>
<td>40.5 (18, 70)</td>
<td>0.0009</td>
</tr>
<tr>
<td>Urine albumin (mg/dl)</td>
<td>8.5 (4.5, 17.5)</td>
<td>7.5 (4.2, 16.0)</td>
<td>8.9 (4.8, 19.8)</td>
<td>11.5 (6.0, 31.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Transferrin receptor (mg/dl)</td>
<td>3.3 (2.7, 4.2)</td>
<td>3.4 (2.7, 4.3)</td>
<td>3.4 (2.7, 4.5)</td>
<td>3.6 (3.0, 4.8)</td>
<td>0.008</td>
</tr>
<tr>
<td>Vitamin D (mg/dl)</td>
<td>54.4 (39.8, 71.3)</td>
<td>56.8 (39.8, 68.9)</td>
<td>54.4 (39.8, 68.9)</td>
<td>51.9 (39.8, 61.6)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Conclusion: Self-reported habitual snoring independent of OSA is associated with abnormal levels of several metabolic and inflammatory biomarkers. Future large prospective studies are needed to further delineate the association between snoring and metabolic biomarkers.

Category: Resident/Fellow, Basic Science
Mentor: Carol Feghali-Bostwick, Ph.D., Division of Rheumatology and Immunology
Effect of Concussion Education on Female Soccer Players

Elizabeth Barton MD (presenter), Chris Sacha, Keith Borg MD PhD
Affiliation: Division of Emergency Medicine, Medical University of South Carolina

Introduction: Concussions are brain injuries that affect many athletes and can lead to short and long-term complications. Given the risks associated with sports-related concussions, especially in the setting of underreporting, the purpose of this investigation was to evaluate if an educational intervention designed to teach young athletes about concussions would affect both the athletes’ knowledge about and attitudes toward concussions.

Methods: This is a retrospective review of survey data gathered from 25 female soccer players between the ages of 13 and 16 years old on club and junior varsity soccer teams in Charleston, South Carolina.

An education video about concussions was created and participants completed surveys pre- and post-viewing of the video. The main outcome measures were changes in knowledge about and attitudes toward concussions.

Results: When comparing scores for knowledge before and after the video, we found a difference in knowledge acquired specifically regarding the dangers of returning to play while symptomatic with a concussion (p=0.000047). We did not, though, find a significant change in general knowledge.

There were two sections on the survey targeted at eliciting the participants’ attitudes toward concussions. The first set of data queried the athletes on their perceptions of the importance of concussions. We found a significant increase in realizing the importance of concussions after watching the video (p=0.0146). The second set allowed the participants to quantify how comfortable they were with reporting a concussion, and we found a significant increase in the athletes’ favorable attitudes toward reporting concussions (p = 0.0451).

Conclusions: An educational video provides improvement in both athletes’ knowledge about the risk of returning to play while symptomatic and attitudes toward concussions. A key next step is for longer studies to evaluate whether knowledge and attitudes are retained over time.

Significance: An educational video is a valuable adjunct to teach young athletes about concussions.

Category: Resident/Fellow, Basic Science
Mentor: Keith Borg, M.D., Ph.D., Division of Emergency Medicine
Effects of IL-6 on Estradiol Production in Dermal Fibroblasts

DeAnna Baker Frost, MD/PhD*‡ and Carol Feghali Bostwick, PhD**‡

*Rheumatology Fellow,” ‡Professor of Medicine Endowed Chair, Kitty Trask Holt Endowed Chair for Scleroderma, ‡Medical University of South Carolina, Department of Medicine, Department of Medicine Division of Rheumatology 96 Jonathan Lucas Street Charleston, SC 29425

Background: Systemic Sclerosis (SSc) is characterized by increased synthesis of extracellular matrix (ECM) components in the skin, resulting in morbidity. In SSc, there is increased IL-6 in circulation and dermal fibroblast milieu. Like most autoimmune diseases, SSc has a female predominance that increases during childbearing years, while estrogen levels are higher. Post-menopausal SSc patients have higher circulating estradiol levels compared to age matched controls. Estradiol has pro-fibrotic activity in skin and aromatase (CYP19), an enzyme in skin used for the aromatization of androgens into estrogens. In activated fibroblasts, IL-6 activates the transcription factor STAT3, with its binding sites upstream of the aromatase gene. Due to the predominance of IL-6 in SSc dermal fibroblasts, and increased estrogens in SSc patients, we hypothesized that estradiol production is increased in SSc dermal fibroblasts.

Methods: Primary adult dermal fibroblasts from healthy and SSc patients were stimulated with IL-6 and its soluble receptor, sIL6R, for 48 hours. Dermal fibroblasts isolated from SSc patients satisfied the 2013 ACR/EULAR criteria for SSc diagnosis. Transcript levels of aromatase were measured using reverse transcriptase PCR. Estradiol was measured using an ELISA-based testosterone conversion assay. Statistical significance was determined using non-parametric analysis.

Results: Healthy dermal fibroblasts stimulated with IL-6 and sIL6R had increased aromatase mRNA compared to SSc dermal fibroblasts. Aromatase mRNA levels in SSc dermal fibroblasts responded to IL-6 stimulation to a lower level. However, SSc dermal fibroblasts had increased estradiol production after stimulation with IL-6 and sIL6R compared to healthy dermal fibroblasts.

Conclusion: Healthy dermal fibroblasts produce higher levels of aromatase in response to IL-6 and receptor stimulation, but SSc fibroblasts have higher estradiol production, likely due to chronic exposure to high levels of IL-6 produced in an autocrine manner. Our findings implicate increased estradiol production in the pathogenesis of SSc via conversion of testosterone into pro-fibrotic estradiol.

Category: Resident/Fellow, Basic Science
Mentor: Carol Feghali-Bostwick, Ph.D., Division of Rheumatology and Immunology
How long should you delay insertion of a long term central venous catheter (LTCVC) in patients with bloodstream infection (BSI)?

E Kagan, MD, F.S Nolte Ph.D., D(ABMM), F(AAM), R. Kilgore, MD, C. D. Salgado, MD, MS, J R Cantey, MD.

Background: Guidelines detail when it is appropriate to remove a CVC in patients with BSI and suggest placement of a new CVC, often needed for further treatment, can proceed when “additional blood cultures show no growth,” the timeframe is not well defined. There is theoretical risk of relapsed BSI after therapy if organisms are still circulating in the blood and adhere to new LTCVC. We sought to determine the BC time to detection (TTD) for common orgs to identify a safe timeframe for LTCVC insertion.

Methods: We conducted a retrospective cohort study of positive (+) BC for Candida albicans & glabrata, Enterococcus faecalis & faecium, Staphylococcus aureus & coagulase-negative, Escherichia coli, Klebsiella pneumoniae, & Pseudomonas aeruginosa from 4/1/15 to 3/31/16. Data retrieved from the microbiology laboratory information system and the BACTEC system was used. TTD was recorded for each (+) BC in hours (hrs) and the mean TTD was calculated by species.

Results: 922 BC were (+) for our common organisms. Mean TTD collectively was 16.3 hrs; 34.4 hrs for Candida species, 18.2 hrs for gram positives and 12.8 hrs for gram negatives. Overall, 815 (88.4%) BC were (+) within 24 hrs, 889 (89.6%) w/in 48 hrs, 913 (99.0%) w/in 72 hrs, and 916 (99.3%) w/in 90 hrs (Table).

Conclusions: With the exception of Candida glabrata, most BC show no growth beyond 72 hrs after inoculation and thus insertion of a LTVC after this time period should mitigate risk for relapsed BSI. Further studies of candidemia due to non-albicans species are needed to determine optimal timing of LTCVC insertion.

Category: Resident/Fellow, Clinical Science
Mentor: Evgenia Kagan, M.D., Division of Infectious Diseases
An Elevated Body Mass Index is Associated with Lower Serum Adalimumab Levels in IBD patients

Jen Seminerio-Diehl, M.D., MUSC Department of Gastroenterology; Matt Rolfsen, M.D., MUSC Department of Internal Medicine

Introduction: Adalimumab and infliximab are commonly used biologic agents in IBD, and therapeutic drug monitoring can optimize treatment. Studies have shown that low trough levels < 4.9 ug/mL are associated with loss of response to adalimumab. An increased body weight may change the pharmacokinetics of adalimumab in IBD. The primary aim of this study was to determine if body mass index correlated with adalimumab drug levels in IBD patients.

Methods: A database was compiled via retrospective chart review of 488 IBD patients seen at our Digestive Disease Center (DDC) between July 2013 and March 2016. Variables in the database include patient’s weight, medications, serum adalimumab and infliximab levels, dates of medication administration, endoscopic findings, and lab data. 352 patients had a BMI <30 kg/m², while 136 had BMI >30 kg/m². Of the 352 patients with BMI <30 kg/m², 95 had adalimumab levels drawn (27%) while in 136 patients with BMI > 30 kg/m², 42 had adalimumab levels drawn (31%).

Results: Using ANOVA to compare the two groups, there was a significant association with lower adalimumab levels in patient with BMI >30 kg/m² when compared to those with BMI <30 kg/m² (p = 0.009). Average adalimumab levels in these two groups were 11.8 ug/mL and 8.8 ug/mL, respectively. This association remained significant when a multivariate analysis was done breaking down BMI into increments of 5 kg/m² (p = 0.02).

Conclusion: In a cohort of patients with inflammatory bowel disease there is a significant difference in serum adalimumab levels based on weight with a BMI >30 kg/m² showing a statistically significant lower value. Whether adjustments in adalimumab dosing are required for patients with high BMI is unclear and further studies are being planned.

Category: Resident/Fellow, Clinical Science
Mentor: Jen Seminerio-Diehl, M.D., Division of Gastroenterology and Hepatology
Change in Mycophenolate and Tacrolimus Exposure by Transplant Vintage and Race

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Introduction: There is strong evidence that both tacrolimus (FK) and mycophenolate (MMF) have improved outcomes in kidney transplantation; yet, the impact of exposure of these immunosuppressants on outcomes and racial disparities is not well studied.

Methods: Eight-year longitudinal cohort study of kidney transplant (KTX) recipients. Inpatient tacrolimus and mycophenolate levels and dosing were assessed and compared across transplant vintage (txp yr) stratified by race (non-AA vs. AA). Pediatrics, non-FK/MMF regimens and non-renal transplants were excluded. Standard univariate tests and multivariable regression models were used to analyze data.

Results: Between 2005 and 2013, 1,217 KTX recipients with MMF/FK exposure data were included with follow up through 2015. More than half (53.7%) were African Americans (AA). The mean MMF dose was 1672±463 mg/day during the first 3 years post-transplant. Transplant vintage did not appreciably impact MMF dosing in non-AAs (0.7 mg/day/year, p=0.903), while MMF dosing significantly decreased in AAs across txp yr (-20.5 mg/day/year, p<0.001, Figure 1). AAs also had a significant increase in the rate of MMF being held or discontinued based on txp yr, which did not change in non-AAs (Figure 2). Mean FK levels were lower in AAs vs. non-AAs in 2005. However, over time, there was a slight decrease in non-AAs (-0.03 ng/mL/year, p=0.279) and a slight increase in AAs (+0.03 ng/mL/year, p=0.247), such that mean FK levels were similar by 2013 (Figure 3). In terms of outcomes, higher FK levels were protective against rejection in AAs only, but were protective against death censored graft loss in both AAs and non-AAs. MMF dosing had no appreciable impact on outcomes in AAs, but higher MMF dosing was a significant risk factor for death-censored graft loss in non-AAs (Table 1).

Conclusion: These data demonstrate that the FK and MMF exposure has significantly changed over time and differed by race. In non-AAs, those transplanted more recently tended to have lower FK exposure with similar MMF exposure. In AAs, MMF exposure has decreased in recent years, while FK exposure has slightly increased. The impact of FK and MMF exposure on outcomes also differ by race and these results likely reflect the providers’ improved understanding of immunosuppressant tolerability by recipient race.

Category: Resident/Fellow, Clinical Science
Mentor: David J. Taber, PharmD, BCPS, Department of Surgery
Severity of Gastrointestinal Bleeding in Patients Treated with Direct-Acting Oral Anticoagulants (DOACs)

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Medical University of South Carolina, Charleston, SC, United States.

**Background:** Direct-acting oral anticoagulants (DOACs), which have recently been approved for stroke prevention in non-valvular atrial fibrillation and treatment of venous thromboembolism, have become increasingly preferred over warfarin given their predictable pharmacodynamics and lack of required monitoring. DOACs have been shown to be associated with an increased frequency of gastrointestinal bleeding (GIB) compared to warfarin, but the severity of GIB in these patients is poorly understood.

**Methods:** We retrospectively evaluated medical records of patients with diagnosis codes of GIB (n=8,496) from 2010-2016. We identified 61 patients with GIB episodes while treated with DOACs (rivaroxaban, dabigatran, or apixaban) and 119 patients with GIB while on warfarin. We randomly selected a control group of 242 patients with GIB on no anticoagulation from the same data set. Outcomes included hospitalizations, blood transfusions, GIB requiring either endoscopic or surgical intervention, and 30-day mortality.

**Results:** The DOAC, warfarin, and control groups were similar in terms of age and underlying comorbidity (Charlson Comorbidity Index). The DOAC group had more concomitant aspirin use than the warfarin group (Table 1). GIB was classified as upper (n=166), lower (n=69), anorectal (n=168), and other (n=19). The DOAC group had a trend toward fewer hospitalizations (51% vs 64%, p=0.07) and required transfusions less frequently (28% vs 42%, p=0.04) compared with the warfarin group (Table 2). The DOAC and control groups were similar with regard to hospitalizations and blood transfusions. There were no significant differences between any groups in 30-day mortality or need for intervention.

**Conclusion:** Although prior studies have shown a higher frequency of GIB in patients treated with DOACs compared to warfarin, our data suggest that the severity of GIB in patients taking DOACs may be less, with fewer transfusions and a trend toward fewer hospitalizations. This was despite significantly greater concomitant aspirin use in the DOAC group.

**Category:** Resident/Fellow, Clinical Science

**Mentor:** Don C. Rockey, M.D., Division of Gastroenterology and Hepatology
ED HIV and Hepatitis C Screening

Gregory Hall MD, Elizabeth Barton MD, Alexandra Monroe MD, Robert Houck

Introduction: In South Carolina, 700 new cases of HIV and 4,000 cases of Hepatitis C (HCV) are identified annually. Our Emergency Department (ED) sees over 62,000 patients/year, many of whom are unfunded or underfunded, making it a prime location for screening patients for HIV and HCV. Many of these patients would otherwise not be screened, be unaware of their infection, and would likely contribute to the spread of disease. We hypothesize that by incorporating a best practice alert (BPA) into our electronic medical record (EMR), we can improve our ability to identify patients in need of screening for HIV and HCV during triage at our ED.

Methods: We designed a BPA to be integrated into our EMR and alert the Triage Nurse when a patient has not had an HIV, HCV, or both tests in the last year. Our BPA will query the patients’ prior laboratory reports, alert the nurse regarding eligible patients, and allow testing to be directly ordered. Patients will be informed of the notification and told that they may opt out of the testing. A patient navigator will assist patients with positive screens to obtain appropriate care. Triage nurses will be educated by our Epic education team and champions. During the study we will monitor our progress toward our goals according to The Model for Improvement (PDSA cycles).

Results: We will generate weekly reports of our screening for HIV and HCV and compare the number of screens performed before the new BPA alert to the number of screens performed after implementation. Preliminary results using the BPA showed a quadrupling of the rate of HIV testing during the first two weeks of January, 2017 compared to pre-intervention data.

Conclusions: Screening for HIV and HCV in patients who come to the ED is an important intervention which can improve public health. Use of an EMR which incorporates a BPA facilitates identification of patients in need of screening.

Category: Resident/Fellow, Clinical Science
Mentor: Gregory Hall, M.D., Division of Emergency Medicine
An Emergency Department Antibiogram for Urinary Tract Isolates

Leanne Radecki  
Chara Calhoun  
Division of Emergency Medicine

Introduction: One of the most frequent infections that Emergency Physicians encounter is acute uncomplicated cystitis. The most common pathogen that is isolated from acute cystitis is *Escherichia Coli* (E. Coli). Bacterial and local resistance patterns to common antibiotics has become an evolving problem. Hospital antibiograms are developed to aid clinicians in effectively treating urinary tract infections, however they are based on inpatient culture isolates rather than those that are treated and discharged from the Emergency Department (ED). We assume that those patients that are seen in the Emergency Department with uncomplicated acute cystitis differ substantially from those who are admitted to the hospital with a urinary tract infection, especially in terms of antimicrobial resistance. Our hypothesis was that those who were discharged with acute cystitis from the ED have isolates with greater susceptibility than those from the hospital antibiogram.

Methods: A retrospective review of urinary culture isolates was performed on patients discharged from the Emergency Department from 1/1/16 to 11/30/16. The data was gathered and compiled using Theradoc Safety Simulation. An antibiogram was created which was compared against the hospital’s antibiogram for urine isolates.

Results: As expected, *Escherichia Coli* was the most common urinary isolate from urine cultures from patients discharged from the Emergency Department. The results showed that the susceptibility to medications in comparison to the hospital antibiogram were similar in terms of treating *Escherichia Coli*.

Conclusion: Our data from an 11 month period does not show any significant difference between the susceptibility of E. Coli from Emergency Department acute uncomplicated cystitis in comparison to the inpatient hospital isolates. More data should be gathered over time to account for any trends in susceptibility from ED urine isolates.

Category: Resident/Fellow, Clinical Science  
Mentor: Gregory Hall, M.D., Division of Emergency Medicine
Changing epidemiology of lower gastrointestinal hemorrhage in the last decade: a nationwide analysis

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Background & Aims: Lower gastrointestinal hemorrhage (LGIH) is common and carries substantial morbidity and mortality requiring frequent hospitalizations. Our objective was to investigate trends in etiology and outcome of LGIH in hospitalized patients in the United States.

Methods: This was a retrospective, observational cohort study of the Nationwide Inpatient Sample (NIS) from 2002-2012. LGIH was identified in hospitalizations with any listed ICD-9-CM diagnosis of LGIH. Colonoscopy and age 18 years or older were required for inclusion. Cases with multiple diagnoses of LGIB or any diagnosis of UGIB were excluded. Changes over time and p-values were calculated using linear regression.

Results: The hospitalization rate of LGIH in the U.S. decreased by 28% from 2002 to 2012, from 61 to 46/100,000 population (p≤0.01) (Table). The most common causes of LGIH were “unknown” and diverticular bleeds. The frequency of all causes of LGIH decreased, however, the greatest declines occurred for inflammatory bowel disease (IBD) and “other”, which decreased by 51% and 47%, respectively (p≤0.01). The all-cause inpatient mortality rate of LGIH decreased 26% from 2.0 per 100 cases in 2002 to 1.4 in 2012 (p≤0.01). The greatest decline occurred for hemorrhoidal and infectious causes, which both decreased by 39% (p=0.02, p≤0.01).

Conclusions: The epidemiology of LGIH hemorrhage appears to be shifting, with a significant decline in both the hospitalization and mortality rate from 2002 to 2012. This trend raises the possibility that there have been improvements in hemostatic techniques and overall care in hospitalized patients with LGIH. The great improvements in hospitalization rates for IBD patients raise the possibility of improved outpatient care and more effective therapies for these disorders.

| Category: Resident/Fellow, Clinical Science |
| Mentor: Don C. Rockey, M.D., Division of Gastroenterology and Hepatology |
Unique Characteristics of Scleroderma in the Lowcountry of South Carolina

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Introduction: Systemic sclerosis (SSc) is a rare autoimmune disease categorized on the basis of skin involvement as either limited or diffuse cutaneous, the latter of which manifests in more severe skin and internal organ involvement. SSc disproportionately affects women and literature suggests African American (AA) patients experience autoimmune diseases differently than other ethnic/racial groups. We sought to test this hypothesis utilizing a longitudinal cohort of SSc patients, comparing disease characteristics between AAs and non-AAs.

Methods: Data was collected as part of an ongoing IRB-approved longitudinal registry of SSc at MUSC, including demographics, clinical disease manifestations, and other medical history. Patients were seen over a 12-year period at the MUSC Division of Rheumatology outpatient clinics. Retrospective chart review was additionally performed to confirm age of onset, SSc disease type, and selected criteria for SSc to assess severity of disease. Pearson’s chi-squared and Fisher’s Exact testing was performed for categorical measures. Two-sample t-tests were performed for continuous measures. Significance set at alpha =0.05.

Results: A total of 236 patients with SSc (80.9% female, 35.2% black) were identified. AA patients developed SSc at a significantly younger age compared to the non-AA patient subset (41.8±13.3 yrs., 48.7±13.2 yrs., respectively, p<0.001). Females developed SSc at a younger age than males (45.1±13.9 yrs., 51.3±11.0 yrs, p=0.006). Diffuse SSc was significantly more common in AA patients (p<0.001). Males in both population groups were more likely to have diffuse SSc than limited SSc (68.3%, p=0.002).

Although not statistically significant, the following trends were shown: A higher percentage of non-AA patients experienced dysphagia (17.0% p=NS); AA patients had a higher prevalence of restrictive lung disease based on forced vital capacity forced vital capacity predicted <70% (46.0% versus 31.9% p=NS) as well as digital ulcers (17.5% p=NS). Overall mortality was 7.2% in AA patients compared to only 3.9% in non-AA patients (p=NS).

Conclusion: In conclusion, we found that AA SSc patients are younger and more often have diffuse cutaneous disease than non-AA SSc patients, consistent with findings among other AA populations. Although not statistically significant, AA patients trended towards a higher prevalence of restrictive lung pattern and a higher mortality rate. These data support the conclusion that AAs have more severe disease with a more unfavorable SSc prognosis. Further investigation into the multifactorial causes for this disparity is needed in order to identify strategies to reduce them.

Category: Resident/Fellow, Clinical Science
Mentor: Diane Kamen, M.D., Division of Rheumatology and Immunology
Intracardiac Pressures Measured Using an Implantable Hemodynamic Monitor: Relationship to Mortality in Patients with Chronic Heart Failure

Stephanie El Hajj, MD; Catalin F. Baicu, Ph.D; Tom D. Bennett, Ph.D; Fred J. Kueffer, MS; William T. Abraham, MD; Robert C. Bourge, MD; Lynne Stevenson, MD; Michael R. Zile, MD

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Background: The purpose of this analysis was to examine whether implantable hemodynamic monitor – derived baseline estimated pulmonary artery diastolic pressure (ePAD) and change from baseline ePAD were independent predictors of all-cause mortality in patients with chronic heart failure.

Methods and Results: Retrospective analysis used data from three studies (n=790 patients, 216 deaths). Baseline ePAD was related to mortality using a multivariable model including baseline and demographic data. Changes in ePAD defined as change from baseline to 6 months and from baseline to 14 days prior to death or exit from study were related to subsequent mortality, and analysis was adjusted for baseline ePAD. Area under the pressure vs time curve (AUC) during 180 days prior to death or exit from study was related to mortality. Baseline ePAD, independent of other covariates, was a significant predictor of mortality (HR=1.07, 95% CI=1.05-1.09, p<0.0001). Change in ePAD was an independent predictor of mortality (HR=1.07, 95% CI=1.05-1.10, p=0.0008). Increased ePAD=3, 4, or 5 mmHg from baseline to 6 months was associated with increased mortality risk= 23.8%, 32.9%, or 42.8%. Change in ePAD from baseline to 14 days prior to death or exit from study was higher in patients that died 3.0±8 vs 1.7±10 mmHg, p=0.003. AUC in the final 180 days prior to death or exit was higher in patients that died vs. those alive at end of study (185±668 vs 17±482 mmHg days, p=0.006).

Conclusions: Implantable hemodynamic monitor – derived baseline ePAD and change from baseline ePAD were independent predictors of mortality in chronic heart failure patients.

Category: Resident/Fellow, Clinical Science
Mentor: Michael R. Zile, M.D., Division of Cardiology
Role of Sphingosine Kinase 1 in Regulation of Store-Operated Calcium Channels

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Introduction: Sphingosine kinase 1 (SK1)/sphingosine 1-phosphate (S1P) pathway has been reported to play a role in regulation of vascular tone by mobilization of intracellular Ca\(^{2+}\). We demonstrated recently that SK1/S1P mediates transmembrane Ca\(^{2+}\) flux through store-operated Ca\(^{2+}\) channel (SOC). However, the exact mechanism by which SK1 mediates regulation of SOC is not well defined.

Methods & Results: SOC is composed of two molecular components; stromal interaction molecules (STIM), and Orai proteins. STIM function as Ca\(^{2+}\) sensors within the ER, and Orai proteins at PM. Depletion of Ca\(^{2+}\) from ER leads to oligomerization and translocation of STIM to bind Orai at the PM to activate Ca\(^{2+}\) flux. We found that S1P triggers SOC-dependent Ca\(^{2+}\) influx indicating that SK1/S1P axis regulates SOC via a novel intracellular mechanism and independent of G protein-coupled S1P receptors. We first employed confocal microscopy and by BRET assay to investigate the role of SK1/S1P on STIM1/Orai1 assembly. Inhibition of SK1 inhibited colocalization of GFP.STIM1 and mCherry Orai1, and decreased NET BRET values of STIM1-FlAsH and Orai1-Rluc in transiently transfected HEK293 cells stimulated with angiotensin II (AngII). Our molecular modeling simulation predicted direct binding of S1P to STIM1. In vitro binding assay revealed binding of S1P to STIM1 in the membrane fractions of vascular smooth muscle cell lysates. Direct mutation of the predicted S1P binding sites to STIM1 markedly inhibited AngII and intracellular S1P-dependent Ca\(^{2+}\) flux without affecting Ca\(^{2+}\) release from intracellular stores. Preliminary circular dichroism study revealed binding of S1P to STIM1 and not to its mutant protein suggesting a direct binding of S1P and STIM1.

Conclusion: Collectively, these findings reveal a mechanistic insight into regulation of SOC via modulation of STIM1 by intracellular SK1/S1P axis.

Category: Basic Junior Faculty, Basic Science
Mentor: Louis Luttrell, M.D., Division of Endocrinology
Mesenchymal Stem Cells: Phenotype Modulation in the Treatment of Scleroderma by Cell Injection

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Introduction: Mesenchymal stem cells (MSCs) are non-hematopoietic multipotent progenitor cells. The injection of MSCs has been proposed to be a potential treatment for a variety of diseases including scleroderma (SSc). We believe that this approach has value, but can be vastly improved by modulating the function of MSCs. We propose to test the hypothesis that modifying the function of MSCs with perturbants of CXCR4 and CCR5 function can be used to enhance the beneficial effects of MSC injection.

Methods: The study was approved by the MUSC IRB for Human Subject Research. MSCs (also called adipose derived stem cells, ADSCs) were isolated from fat tissue. MSCs were cultured either in maintenance medium or adipocyte induction medium for ten days with or without addition of TGFβ, CCR5 inhibitor (maraviroc (MVC)), or CXCR4 inhibitor (AMD3100). α-smooth muscle actin (ASMA), caveolin-1, and fatty acid binding protein 4 (FABP4) expression were determined by Western blot and immunohistochemistry.

Results: MSCs from healthy subjects or saline treated mice contain relatively high levels of caveolin-1 and low levels of the myofibroblast marker ASMA, while the converse is true for MSCs from SSc patients or bleomycin treated mice. A fibrogenic phenotype can also be induced in control MSCs by TGFβ treatment. MSCs can differentiate into adipocytes when treated with Inducing Medium containing troglitazone. While TGFβ promotes the fibrogenic differentiation of MSCs, it inhibits their adipogenic differentiation. We find that the CCR5 antagonist MVC and the CXCR4 antagonist AMD3100 are each capable of inhibiting fibrogenic differentiation induced by TGFβ or of reversing the inhibition of adipogenic differentiation induced by TGFβ.

Conclusions: MSCs from mice or humans with fibrotic disease exhibit enhanced fibrogenic differentiation and inhibited adipogenic differentiation. Modulation of the fate of MSCs by chemokine receptor antagonists has potential for improving the treatment of SSc.

Category: Basic Junior Faculty, Basic Science
Mentor: Stanley Hoffman, Ph.D., Division of Rheumatology and Immunology
Selective disruption of ERα expression in dendritic cells of lupus-prone mice results in female-specific reduced survival

Melissa A. Cunningham, Jena R. Wirth, Jackie Eudaly, and Gary S. Gilkeson
Division of Rheumatology and Immunology

Introduction: SLE is a disease that disproportionately affects females. The etiology of the sex bias in this disease is unclear. We previously showed that a functional knockout of estrogen receptor alpha (ERαKO) resulted in significantly reduced renal disease and increased survival in murine lupus. The mechanism of this effect, which requires estrogen, is not known. Interestingly, an ERα-/-(null mutant) mouse is not similarly protected. We and others have demonstrated a role for ERα in dendritic cell (DC) development. Here we show that selective genetic disruption of ERα in DCs of lupus prone mice results in a survival difference, but only in females, who die prematurely compared with intact females.

Methods: Floxed-ERα and Cre-CD11c strains were backcrossed onto the NZM2410 lupus-prone background for 12 generations. Animals were validated by sorting CD11c+ DCs from Flt3L-cultured bone marrow; CrePos/Floxed-ERα mice had ERα mRNA levels reduced by ~90% in DCs. Mice were sacrificed at 52 wks, or earlier if they had high proteinuria or >10% weight loss. On a separate cohort of animals, spleen cells were isolated and flow cytometry was performed to determine number and subset of DCs.

Results: CrePos/Floxed-ERα (DC-specific ERαKO) and CreNeg/Floxed-ERα animals (n=24, males and females) were studied. There was no significant difference in survival between the 2 groups. Considered separately, however, female survival was significantly different. Median age at death was 30.0 wks (± 1.807) n=6 for the CrePos and 40.4 wks (± 3.891) n=7 for the CreNeg females (p<0.042). At 52 weeks: CrePos (DC-specific ERαKO) 0/6 were alive (0%) vs. CreNeg – 3/7 were alive (43%). Preliminary flow cytometry results revealed an increased percent of CD11b+CD11c+ cDCs in CrePos vs. CreNeg mice.

Conclusion: Selective deletion of ERα in DCs of female lupus-prone mice results in reduced survival, but only in female animals. These mice have increased numbers of spleen inflammatory cDCs, which may partially explain the phenotype. This data joins a growing body of evidence that estrogen and ERα play critical roles in modulating immune cell development and function impacting autoimmune disease.

Category: Clinical Junior Faculty, Basic Science
Mentor: Gary Gilkeson, M.D., Division of Rheumatology and Immunology
Podocyte-specific deletion of motor protein Myo1c protects podocytes from injury

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Introduction: Podocyte proteins Nephrin and Neph1 are the critical components of kidney’s filtration barrier commonly known as slit diaphragm. The membrane organization of these proteins is significantly altered in various glomerular disorders and contributes towards disease pathology. We previously identified motor protein Myo1c as a novel component of slit diaphragm that interacts with Nephrin and Neph1 and has been implicated in intracellular trafficking of these proteins. Despite several biochemical and structural studies, the in vivo function of Myo1c in podocytes and glomerulus remains unknown.

Methods: To understand the in vivo function of Myo1c in podocytes, we generated Myo1c conditional mice, which were used to genetically delete Myo1c specifically in podocytes (Myo1c⁶/⁶pod-CreTg/+ ) by mating them with podocin cre mice. The response of these mice to various chronic and acute glomerular injuries was investigated. Urine of these mice was analyzed by determining Albumin/Creatinine ratio, and the kidney sections were analyzed by Transmission and Scanning Electron Microscopies. To further clarify the mechanisms involved, immuno-staining of kidney sections was performed using various antibodies followed by confocal microscopic analysis.

Results: The analysis of Myo1c⁶/⁶pod-CreTg/+ mice showed no proteinuria or functional abnormality when aged to 12 months. However, when bred to an adriamycin-sensitive background, these mice were resistant to adriamycin-induced glomerulopathy; they did not develop proteinuria and podocyte effacement as compared to the controls. Furthermore, Myo1c⁶/⁶pod-CreTg/+ mice were resistant to acute glomerular injury inducing agents including protamine sulphate and nephrotoxic serum. To highlight the mechanism of this protection, we investigated if loss of Myo1c affects injury-induced distribution and phosphorylation of Nephrin and Neph1. Interestingly, immunofluorescence analysis of kidney sections and isolated glomeruli showed a significant injury-induced loss of Nephrin and Neph1 expression in podocytes of control mice, but not in the Myo1c⁶/⁶pod-CreTg/+ mice. Furthermore, injury-induced phosphorylation of Nephrin and Neph1 was significantly attenuated in Myo1c⁶/⁶pod-CreTg/+ mice. In addition, we use a molecular inhibitor to show that inhibiting Myo1c motor activity attenuated injury response in podocytes.

Conclusion: Collectively, these results suggest that loss of Myo1c decreases podocytes sensitivity to injury suggesting Myo1c as a novel therapeutic target in the treatment of podocytopathy.

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Category: Basic Junior Faculty, Basic Science
Mentor: Deepak Nihalani, Ph.D., Division of Nephrology
Correlation of Blood Transcriptome with Outcome After Antiviral Treatment of Hepatitis C Virus Infection

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Introduction: Combination treatment with direct acting antivirals (DAA) results in a sustained virologic response (SVR), synonymous with cure, in most patients infected with hepatitis C virus (HCV). Some patients experience virologic relapse after treatment for unclear reasons. The ability to predict relapse and identify biomarkers allowing shorter treatment would have practical clinical implications. We previously identified differences in hepatic gene expression that correlated with outcome. Here, we hypothesized that analysis of whole blood gene expression would inform mechanisms of relapse.

Methods: We analyzed cryopreserved paired whole blood collected before and after treatment (prior to relapse) from 40 chronically infected HCV patients (n=26 SVR, n=14 relapse) treated in a DAA clinical trial. mRNA was extracted using the PAXgene Blood miRNA Kit with quality determined by Agilent Bioanalyzer (median RIN 7.2). Expression of 579 unique immune-related transcripts was determined using the Nanostring Human Immunology v2 Panel. Data were analyzed with parametric approaches (SPSS software). NSolver Advanced Analysis Software 3.0 was used for immune cell type profiling of gene expression results.

Results: Considering all 40 patients, expression of 216 of 579 genes changed significantly during treatment. Comparing SVR vs. relapse patients, differential expression was observed for 42 pre-treatment and 25 end-of-treatment mRNAs. Intriguingly, genes involved in inhibition of host immunity had higher pre-treatment (CD244, CTLA4-TM, SOCS1, SOCS3) and end-of-treatment (PD1, SOCS3) expression in relapers. Immune cell type abundance predicted by gene expression suggested a decline in B-cell, CD4+ Th1-cell, and total, exhausted, and cytotoxic CD8+ T-cell frequencies over the course of treatment, data that correlated with independent flow cytometric observations. Interestingly, there was a trend (p=0.08) towards higher expression of an exhausted CD8+ T-lymphocyte profile at the end of treatment in relapers.

Conclusions: Whole blood expression of genes associated with impaired host immunity are associated with relapse after DAA treatment of HCV infection.

Category: Clinical Junior Faculty, Basic Science
Strategies to Improve Safety and Outcomes Utilizing Systems-Based Hematologists in IVC Filter Placement and Management in an Academic Medical Center

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Introduction: There are multiple clinical scenarios that may require placement of inferior vena cava filters (IVCF). Both the Society of Interventional Radiology (SIR) and the American College of Chest Physicians have released guidelines for IVCF use. Several publications have reported high rates of retrievable IVCF complications. The purpose of this study was to report our healthcare system use of IVCF.

Methods: A retrospective review of all IVCF placement performed between July 2014 and December 2015 was conducted.

Results: A total of 181 IVCF were placed; 26 (14.4%) permanent IVCF, 143 (79.0%) retrievable IVCF, 12 (6.6%) unknown. Mean age at IVCF placement was 59.34 years (range: 19–85); 46.4% were male. Ninety-six (53.0%) patients had active cancer. Surgical Services and Medical Services requested IVCF placements in 112 (61.9%) patients and 69 (38.1%) patients, respectively. Only 13 (7.2%) patients had a hematology consultation prior to IVCF placement. Per SIR guidelines, 60.2% (n=109) of IVCF were placed for absolute indications, 15.5% (n=28) for relative indications, 14.4% (n=26) prophylactically and 9.9% (n=18) with no clear indications. Of the 143 retrievable IVCF, 21 patients died during their hospitalization or were discharged to hospice. Of the remaining 122 cases, documentation of the presence of an IVCF was present in 107 (87.7%) discharge summaries, and outlined instructions for filter retrieval were seen in 19 (15.6%) cases. Only 29 (23.8%) IVCF were retrieved at a mean interval of 159 days (range: 4-511 days). Of the 21 patients that had IVCF placed prophylactically, only 7 (33.3%) IVCF were retrieved.

Conclusion: There remains a lack of awareness of IVCF evidence-based indications and a lack of structured system for IVCF tracking in some clinical services, resulting in poor IVCF retrieval rates. The presence of a systems-based hematologist may help improve safety and outcomes in IVCF placement and management.

Category: Clinical Junior Faculty, Clinical Science

Mentor: Charles S. Greenberg, M.D., Division of Hematology and Oncology
Development of a Formalized Professional Wellness and Development Residency Curriculum- Comparison of Faculty and Resident Perceived Topic Importance

Diann M. Krywko, MD, FACEP, Jeffrey P. Caporossi, MD, Christine M. Carr, MD, CPE, FACEP, Steven H. Saef, MD, MSCR, FACEP
Division of Emergency Medicine, Department of Medicine, MUSC, Charleston, SC

Introduction: Educators and residents have advocated for formal teaching of wellness and professional development (W&PD) during residency training. Currently there exists no standard curriculum in Emergency Medicine (EM) addressing this important subject. Our objective was to ascertain the extent to which faculty and residents value inclusion of proposed topics regarding W&PD in an EM curriculum and to compare differences between groups.

Methods: The study was conducted during July, 2016 via a REDCap® survey distributed to all faculty and residents in EM at our institution. Participants were instructed to indicate on a visual analog scale (VAS) from 0-100 how essential they believed it was to teach 35 individual topics pertaining to W&PD. The questionnaire was divided into 4 domains: Personal, Clinical, Professional, and Academic. Mean values for each item were determined and results for faculty and residents were compared using Students t-Test.

Results: Response rates were as follows: Residents 13/18 (72%); Faculty 22/35 (63%). Items with highest mean values for faculty were: [Item (VAS score)]: Teamwork (84.1); Burnout (83.9); Caring for Difficult Patients (82.4); Working efficiently (82.2); Communication skills (81.1). Items with highest mean values for residents were: Working efficiently (83.5); Contract negotiations (81.6); Learning post-residency (78.5); Career advancement (77.9); Taking the boards (77.1). Significant differences were noted between faculty and residents for the following items [Faculty mean, Resident mean; p-value]: Teamwork: 84.2, 61.6; <0.001; Substance abuse: 73.6, 51.7; 0.03; Communication skills: 81.1, 66.2; 0.03; Significant others: 75.3, 52.9; 0.04.

Conclusion: EM faculty and residents did not differ in the extent to which they valued inclusion of many topics in a W&PD curriculum. Personal items seemed to dominate faculty priorities while residents seemed to place more emphasis on professional topics. Faculty believed inclusion of Teamwork, Substance abuse, Communication skills, and Significant others as more important than did residents. Our results can be utilized to inform the development of a formal EM curriculum in W&PD by residency educators.

Category: Clinical Junior Faculty, Clinical Science
Mentor: Steven H. Saef, M.D., MSCR, FACEP, Division of Emergency Medicine
Health Information Exchange: What do Emergency Physicians think?

Cathy L. Melvin, Steven H. Saef, Holly Pierce, Christine M. Carr. Medical University of South Carolina, Charleston, SC

Study Objectives: Our regional health information exchange (HIE), serves 4 major hospital systems including 11 Emergency Departments (EDs) in our region and is accessible to all Emergency Physicians (EPs) in those systems. We sought to understand the reasons for low HIE utilization (2.3% in previous studies) and explore options for improving it.

Methods: We surveyed ED clinicians to learn their perceptions of the usability and functionality of our HIE, the quality of information available, the value of clinician time spent using the HIE, its ease of use, and areas for improvement. Respondents used a visual analogue scale (VAS) from 1 (strongly disagree) to 100 (strongly agree) to indicate their level of agreement with each of 21 items. Mean VAS scores were calculated for each item. We defined “strong agreement” as a mean VAS score of 70 or higher for positively framed items (meaning the higher the score, the better) or a mean VAS score of 30 or lower for negatively framed items (meaning the lower the score, the better). Weak agreement was indicated by the obverse, particularly mean values below 70 for positively framed items and above 30 for negatively framed items. Survey items were grouped into 3 domains: “Usability”, “Functionality”, and “Patient and Clinical Issues”. The survey was constructed in REDCap ©Vanderbilt University and distributed by email to all ED clinicians who had access to our HIE at all participating sites. Participation was entirely voluntary and anonymous.

Results: Of 231 ED clinicians surveyed, 51 (22.1%) completed the survey including 48 who used the HIE. Regarding “Usability”, respondents were in strong agreement that they would like to use the HIE for every patient they saw, that it was easy to use, that they felt very confident using it, that they didn’t need to learn a lot prior to use and that the information received from the HIE made the time taken to log on worth the effort. Regarding “Functionality”, participants indicated strong agreement that if the HIE provided good information and was easy to use, they would use it for every patient they saw, that the information obtained about their patients was usually sufficient to be useful clinically, that the HIE was a very valuable addition to their practice, that it improved their efficiency, that it improved the quality of care they offered, and that they would prefer the HIE to be embedded in the EMR at their hospital. Regarding “Patient and Clinical Issues”, respondents indicated strong agreement that HIE was most useful for patients with more complex diagnoses or for patients thought to be seeking narcotics for inappropriate reasons. They also agreed that their expectation of finding information about their patients in the HIE prompted its use.

Conclusion: Results showed most ED clinicians thought our HIE was easy to use and that it added value to their work but they also wanted it better integrated into their hospitals’ EMR. The study was heavily influenced by selection bias in that participants were those who used the HIE and chose to complete the survey. These findings may be helpful in promoting HIE use among those who have not yet adopted it into their daily practice. Efforts should be made to embed access to HIE into hospital-based EMRs.

Category: Clinical Junior Faculty, Clinical Science
Mentor: Renee Martin, Ph.D., Department of Biostatistics and Epidemiology
Quality Improvement Intervention on High Utilizer Inpatients Admitted to Internal Medicine Services

Samuel O. Schumann III, MD; Marc E. Heincelman MD; Patrick D. Mauldin PhD; Jignwen Zhang; Zemin Su; Justin E. Marsden; Don C. Rockey MD, William P. Moran MD, MS

Background: The value-based care movement places considerable pressure on healthcare systems to deliver high quality medical care while decreasing overall costs. Numerous studies have demonstrated that the top 10% high cost patients, labeled high utilizers (HU), disproportionately consume an exceedingly large amount of medical resources. For unclear reasons, the attrition rate for patients meeting HU status is high (> 70% at one year) and an individual HU patient’s extreme resource utilization is likely to be short lived. Therefore efforts to reduce utilization based on intensive case management of a fixed population may not impact the majority of high utilizer patients who access a health system. Using predictive modeling, inpatients at risk for a high utilizer hospitalization can be identified early based on admission variables. Historically nursing charges, a surrogate for length of stay (LOS), has been the most costly resource used during a high utilizer admission. The objective of this study was to develop a quality improvement guideline intervention aimed at decreasing length of stay and the unnecessary utilization of other inpatient resources for patients identified at risk for a high utilizer admission.

Methods: A quality improvement guideline intervention study was performed on all patients ≥ 18 years old admitted to internal medicine services from October 1st, 2015 – April 11th, 2016. An established predictive model (AUROC = 0.80) was used to analyze admission variables and identify patients at risk for a HU admission in real time. A predictive model estimator score of ≥ 0.15 was used to define patients at risk for a high utilizer admission, giving the model a sensitivity of 55% and specificity of 84%. An estimator score of ≥ 0.15 was also projected to identify 2 patients per day at risk for a HU admission, which was a patient volume appropriate for the scope of the intervention. Certain patients meeting pre-specified criteria were excluded from the study, such as new solid organ or bone marrow transplant recipients. Patients with a HU estimator score ≥ 0.15 and not excluded were enrolled in the study and received intervention in three areas: early palliative care consultation, early pharmD medication reconciliation, and recommendations to follow Choosing Wisely guidelines for lab tests, chest x-rays and blood transfusions. The top 10% high cost patients admitted to internal medicine services from July 1st, 2013 – June 30th, 2014 were used as the comparison group. Primary outcome was a reduction in length of stay. Secondary outcomes included pharmaceutical charges, laboratory charges, total hospital costs and disposition.

Results: 373 patients were identified by the predictive model as being at risk for a HU admission (1.92 patients were identified per day). 130 patients were enrolled in the quality improvement guideline intervention and received all 3 areas of intervention (early palliative care, pharmD medication reconciliation and choosing wisely education). 243 patients were excluded. In the comparison group 7,571 patients were admitted to internal medicine services and 757 were the top 10% high cost patients. The mean LOS for HU patients enrolled in the guideline intervention was 10.3 days compared to a historical mean LOS of 25.4 days (p Value 0.0183). The median LOS for HU patients enrolled in the guideline intervention was 6.1 ± 13.2 days, compared to a historical median LOS of 19.5 ± 32.5 days.

Conclusions: Patients at risk for a high utilizer admission can be identified in real-time based on admission variables. Guideline based interventions can then be deployed early in an admission to improve the value of care and decrease length of stay.

Category: Resident/Fellow, Clinical Science
Mentor: William Moran, M.D., Division of General Internal Medicine
Quality Improvement Intervention on Internal Medicine High Utilizer Inpatients

Marc E. Heincelman MD; Samuel O. Schumann III MD; Patrick D. Mauldin PhD; Jingwen Zhang; Zemin Su; Justin E. Marsden; William P. Moran MD, MS; Don C. Rockey MD

Medical University of South Carolina, Division of General Internal Medicine

Introduction: The value based care movement places considerable pressure on healthcare systems to deliver high quality medical care while decreasing costs. Studies have demonstrated that the top 10% high cost patients, labeled high utilizers (HU), disproportionately consume an exceedingly large amount of resources. For unclear reasons, the attrition rate for patients meeting HU status is high (> 70% at one year) and an individual HU patient’s extreme resource utilization is likely to be short lived. Thus, efforts to reduce utilization based on intensive case management of a fixed population may not impact the majority of high utilizer patients who access a health system. Using predictive modeling, inpatients at risk for a high utilization hospitalization can be identified early based on admission variables. Historically nursing charges, a surrogate for length of stay (LOS), has been the most costly resource during a high utilizer admission. The objective of this study is to develop a quality improvement (QI) guideline intervention aimed at decreasing length of stay and the unnecessary utilization of other inpatient resources for patients identified at risk for a high utilizer admission.

Methods: A QI guideline intervention study was performed on all patients admitted to internal medicine services from October 2015 – April 2016. An established predictive model (AUROC = 0.80) was used to analyze admission variables and identify patients at risk for a HU admission. A predictive model estimator score of ≥ 0.15 was used to define patients at risk for a high utilizer admission, giving the model a specificity of 84%. All patients with a predictive model estimator score of ≥ 0.15 were considered to be at risk for a high utilizer admission. On a daily basis, patients with the top two highest estimator scores that did not have a pre-specified exclusion criteria were enrolled in our study arm. The remaining patients with a HU estimator score ≥ 0.15 were placed in our control arm. Patients enrolled in the study arm received intervention in three areas: early palliative care consultation, early pharmD medication reconciliation, and recommendations to follow Choosing Wisely guidelines for lab tests. Primary outcome was a reduction in length of stay. Secondary outcomes included total hospital costs, pharmaceutical charges, and laboratory charges.

Results: 373 met criteria for being at risk for a HU admission. 130 patients were enrolled in the QI guideline intervention study arm and received all 3 areas of intervention. 243 patients were included in the control arm. The mean LOS for HU patients enrolled in the guideline intervention was 10 days compared to a mean LOS of 14 days in the control (p=.01). The median LOS for HU patients enrolled in the guideline intervention was 6 days, compared to 8 days in the control.

Conclusions: Patients at risk for a HU admission can be identified in real-time based on admission variables. Guideline based interventions can then be deployed early to decrease length of stay.

Category: Clinical Junior Faculty, Clinical Science
Mentor: Don C. Rockey, M.D., Division of Gastroenterology and Immunology
The differences between Systemic Sclerosis associated pulmonary arterial hypertension (SSc-PAH) and Idiopathic pulmonary arterial hypertension (IPAH): a quantitative lung morphometric analysis.

Rahul G Argula¹, Russell A Harley², Richard M Silver³, Charlie B Strange¹, Viswanathan Ramakrishnan³, Carol Feghali-Bostwick⁴.

1.Division of Pulmonary and Critical Care, 2.Division of Pathology and laboratory medicine, 3. Department of Public health sciences, 4. Division of Rheumatology. Medical University of South Carolina, Charleston, SC – 29425

Introduction: Pulmonary arterial hypertension (PAH) is a disease of progressive pulmonary arterial remodeling resulting in increased pulmonary vascular resistance (PVR) to blood flow, which leads to elevated pulmonary arterial (PA) pressures, and progressive right ventricular dysfunction, failure and death. SSc-PAH patients have a significantly higher mortality when compared to other forms of PAH such as idiopathic pulmonary arterial hypertension (IPAH) patients. The goal of this pilot project was to understand the pathological and biological differences between the pulmonary vasculopathies of SSc-PAH and IPAH using quantitative lung morphometry.

Methods: We utilized bio-banked SSc-PAH (n=24) and IPAH(n=9) lung tissue specimens from the MUSC/Pittsburgh lung repository. We also used 13 non-IPAH/SSc-PAH, deceased donor lung specimens as controls. We then conducted a quantitative lung morphometry study comparing the above lung specimens. H & E (Hematoxylin and Eosin) and VVG (Verhoeff Van Gieson) lung sections from the specimens were analyzed for the following: 1. Plexiform lesions, 2. Interstitial cellularity, 3. Interstitial fibrosis, 4. Small vessel intimal proliferation, 5. Pulmonary vein intimal proliferation, 6. Smooth muscle hypertrophy.

Results: 5/9(55.5%) IPAH lungs had notable plexiform lesions while 1(7.7%) control specimen (severe emphysema) and 1/24 (4.2%) SSc-PAH specimen had plexiform lesions. The SSc-PAH lung specimens were statistically significantly different when compared to the IPAH lung specimens with respect to: a) the number of plexiform lesions (4.2% vs 55.%, p=0.003), b) interstitial cellularity score (5.4 vs 2.1, p=0.005), c) interstitial fibrosis score (8.4 vs 0.6, p<0.0001). The SSc-PAH and IPAH lung specimens did not differ significantly with respect to a) small vessel intimal proliferation score (7.3 vs 7.1, p =0.99), b) pulmonary vein intimal proliferation score (4.1 vs 2.3, p = 0.21), c) arteriolar smooth muscle hypertrophy score (4.29 vs 5.78, p = 0.23).

Conclusion: Our analysis suggests that SSc-PAH patients have a distinct vasculopathy when compared to IPAH patients. These differences could have implications with regard to their disease progression and response to pulmonary arterial vasodilators.

Category: Clinical Junior Faculty, Clinical Science
Mentor: Carol Feghali-Bostwick, Ph.D., Division of Rheumatology and Immunology
Gain-framed text messaging is more motivational than weekly phone calls in advanced stage lung cancer.

**Brett Bade MD, Lindsey Owens, Alana Rojewski PhD, Benjamin Toll PhD, Gerard Silvestri MS MD**

Medical University of South Carolina
Department of Medicine
Division of Pulmonary, Critical Care, and Sleep Medicine

**Introduction:** Physical activity (PA) improves quality of life in patients with lung cancer. Lung cancer patients prefer low-impact exercise, though adherence is low. Activity adherence may be improved using a low-impact and personized regimen. Previously, weekly phone calls provided walking prescriptions for patients with advanced stage lung cancer and measured daily step counts with FitBit® accelerometers. Many subjects never wore the device, and missing step counts were frequent. In this study, a teaching session and twice/daily gain-framed text messages (emphasizing the benefits of a particular action) were provided.

**Methods:** Adult patients (n=6) with advanced stage lung cancer and access to a smartphone were enrolled. Over 28 days, twice/daily motivational and gain-framed text messages were sent. FitBit® Flex devices monitored daily step counts. After 1 week average daily step count was calculated, and a slow increase in step count (i.e., 400 steps/day above the average) was recommended. Simple statistics were used to compare the data collection between subjects receiving weekly phone calls compared those receiving twice/daily text messages.

**Results:** Subjects receiving weekly phone calls (n=29) did not wear the FitBit accelerometer in 24% of cases. All subjects receiving twice/daily text messages (n=6) used the device. Using weekly phone calls, daily step count was not collected for 37% of days. Sending twice/daily text messages, daily step count was not collected for only 3.6% of days. Subjects receiving weekly phone calls less frequently increased their step count compared to subjects receiving text messages over 4 weeks (48% vs 100%; see Table).

**Conclusion:** In a small sample, sending twice/daily motivational and gain-framed text messages increases the number of subjects wearing an accelerometer and reduces the frequency of missing data by 10-fold. Subjects receiving twice/daily text messages increased their activity over 28 days. In advanced stage lung cancer patients, daily gain-framed text messaging appears to be more motivating than weekly phone calls.

**Table:**

<table>
<thead>
<tr>
<th>Category</th>
<th>Twice Daily Text Messaging (n=6)</th>
<th>Weekly Phone Calls (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects never using the device</td>
<td>0% (0/6)</td>
<td>24% (7/29)</td>
</tr>
<tr>
<td>Days no step counts were collected</td>
<td>3.6% (6/168)</td>
<td>37% (304/812)</td>
</tr>
<tr>
<td>Subjects increasing step count (last vs first week)</td>
<td>83% (5/6)</td>
<td>34% (10/29)</td>
</tr>
<tr>
<td>Subjects increasing step count at all</td>
<td>100% (6/6)</td>
<td>48% (14/29)</td>
</tr>
</tbody>
</table>

**Category:** Clinical Junior Faculty, Clinical Science
**Mentor:** Gerard Silvestri, Division of Rheumatology and Immunology
Introduction: The Internal Medicine (IM) residency community widely agrees on the need to transform resident ambulatory training. Ideally, this would occur within highly functional ambulatory care settings, incorporating interprofessional teams. The Patient Centered Medical Home (PCMH) provides a unique opportunity for such training to occur. Interprofessional, case-based team meetings focused on patient care may address the non-traditional knowledge, skills and attitudes required for successful PCMH practice in modern healthcare systems.

Methods: In 2012, our IM residency training program separated inpatient and ambulatory activities using a block format. Ambulatory training occurs in our hospital-based, National Committee for Quality Assurance (NCQA) certified Level 3 PCMH staffed by a team including nursing, PharmD's, social worker and administrative support. The practice is supported by an electronic medical record and serves approximately 11,000 patients.

Beginning January 2012, clinic faculty have led brief weekly, case-based interprofessional team meetings utilizing the effective behaviors of team leadership as described by Salas and colleagues. Attendance by all categorical residents is required. Resident patient panels, including measures of chronic disease control, are distributed and discussed at least quarterly. Team meeting content generally falls into three categories: case review, practice process review, or resident panel review. Interprofessional teams generate implementable solutions utilizing a rapid sequence improvement process with results documented since inception.

Results: The 2011 Society of General Internal Medicine PCMH Education Summit defined 25 IM resident PCMH entrustable professional activities (EPA’s) using the NCQA standards as an organizing framework. Independent reviews of our Team Meeting content areas from January 2012 – December 2016 show that subject matter spanned all of the PCMH standards and the majority of EPA’s. 107 separate topics were discussed over this time period.

Conclusion: Brief interprofessional team meetings are feasible in an IM resident clinic and cover all PCMH EPA’s. Resident experience with each ranged from knowledge acquisition to skill demonstration. Participation from all team roles, a structured rapid sequence improvement process, and tracking of results are key components of continued success. The interprofessional team meeting has resulted in improved quality measures of patient care, enhanced team communication, and alteration of our practice environment. As direct care providers, IM residents serve a key role in the team meeting and may be able to utilize these skills in future practice environments.

Category: Clinical Junior Faculty, Clinical Science
Mentor: Elisha Brownfield, M.D., Division of General Internal Medicine
Evaluation of Rapid Polymerase Chain Reaction (PCR)-Based Organism Identification (OI) of Gram Positive Cocci (GPC) for Patients with a Single Positive Blood Culture (SPBC)

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\textsuperscript{2} Division of Infectious Diseases, College of Medicine  
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Background: For patients with a SPBC growing GPC, OI provides supportive information for differentiating contamination from true bacteremia. Whereby, once the identity of the GPC organism is known, clinicians can tailor antibiotic therapy to optimize patient outcomes. We investigated the effect of rapid PCR-based OI of SPBC with GPC on vancomycin (VAN) prescribing patterns and patient outcomes, as compared to conventional OI techniques.

Methods: This retrospective quasi-experimental study of adult patients with a SPBC with GPC compared conventional OI (pre-BCID; 8/1/12-10/31/12) with OI on the FilmArray Blood Culture Identification Panel (post-BCID; 8/1/14-10/31/14). Antimicrobial stewardship reviewed PBC in both groups. The FilmArray BCID provides OI for 19 bacteria (including \textit{Staphylococcus aureus}, coagulase-negative staphylococci [CoNS], \textit{Enterococcus} spp., \textit{Streptococcus} spp. [\textit{S. pyogenes}, agalactiae, and pneumoniae]), as well as gram-positive antimicrobial resistance genes (\textit{mecA} and \textit{vanA/B}). The primary outcome was to determine the effect of BCID on VAN prescribing patterns. Secondary endpoints assessed were the incidence of nephrotoxicity, length of stay (LOS), readmission rate, mortality, and hospital costs. Patients were excluded if they had more than 1 PBC in a 24 hour period, were transferred from a facility with known PBC with the same organism, or had expired or been on hospice care prior to blood culture positivity.

Results: A total of 188 patients (86 pre-BCID, 102 post-BCID) had a SPBC with GPC. OI was known 21 hours sooner in the post-BCID group (P < 0.001). CoNS were the most commonly isolated organisms (73.4%). Post-BCID had higher Charlson comorbidity scores (5.0 vs 4.0; \( P = 0.04 \)) and more concomitant infections (53\% vs 37\%; \( P = 0.03 \)). Pitt bacteremia score and ICU admission were comparable between groups. In patients with CoNS, VAN use (55\% vs 44\%), overall duration of VAN (1.3 vs 1.6 days), and time from culture positivity to VAN discontinuation (1.2 vs 1.1 days) were not different between pre-BCID and post-BCID. Incidence of acute kidney injury in the post-BCID group (14\%) was similar to the pre-BCID group (13\%). Groups did not differ in LOS, readmission, mortality, and hospital costs (\( P > 0.05 \)).

Conclusion: Earlier identification of likely blood culture contaminants did not appear to significantly influence prescribing patterns of VAN. Baseline antimicrobial stewardship review of positive blood cultures may have lessened the opportunity for detectable differences between groups in this analysis.

Category: Clinical Junior Faculty, Clinical Science
Use of an Outreach Coordinator to Reengage and Retain Patients at Risk of Falling Out of HIV Care, Does the Amount of Time Matter?

Madelyne C. Bean, PharmD¹, Linda Scott, LPC¹, Lauren E. Richey, MD, MPH¹

¹Division of Infectious Disease, Department of Medicine, Medical University of South Carolina, Charleston, SC

**Background:** Multiple studies have shown that retention in care is a problem among patients living with HIV and the reasons for falling out of care and poor retention are varied. Within our clinic there are many poorly retained patients and the purpose of this project was to determine if early phone and letter interventions by an outreach coordinator could improve retention in patients at risk of falling out of care.

**Methods:** Patients were included if they were at risk of falling out of care, defined as having a no show to an HIV clinic visit in 2015 and receiving an intervention by the outreach coordinator. Retention in care was defined by the HRSA definition (2 visits to an HIV provider 90 days apart).

**Results:** Out of 1242 patients, 61(5%) patients were at risk in 2015. The mean age was 40 years (range 22 to 62). Thirty-four (56%) were male and 49 (80%) were African-American. Fifty (82%) had a visit and 22(36%) met the HRSA definition of retention. Fifty (82%) received a phone intervention, and most patients received a call for outreach (89%) although some also received calls for visit reminders (26%) and missed visit follow-up (7%). Thirty three (54%) received a letter intervention. The mean time per patient was 59 minutes; therefore, it took 2.7 hours to achieve each retained patient or 1.2 hours for each patient with a visit.

**Conclusion:** Using an outreach coordinator to contact patients at risk of falling out of care with a simple phone and letter intervention, is a cost effective way to reengage and retain people living with HIV in care.

**Category:** Clinical Junior Faculty, Clinical Science
Use of an Outreach Coordinator to Reengage and Retain Patients with HIV in Care

Madelyne Ann Bean

Background: Retention in care is a large problem in our population. The purpose of this project was to see if an outreach coordinator could both re-engage patients who had fallen out of care and improve long-term retention in care.

Methods: We identified patients who attended our multidisciplinary HIV clinic in the past five years and did not meet the HRSA definition of retention in care in 2014 (2 visits to an HIV provider 90 days apart) and determined if the patients had transferred care, died, been incarcerated, or fallen out of care. The outreach coordinator used phone, letters, and home visits to reengage patients who had fallen out of care. Patients, with whom contact was made, were reminded of appointments and called to reschedule missed appointments. The intervention and data collection continued through the end of 2015. Visit constancy was defined as having a visit in both the first and second six month interval of 2015.

Results: For 2014 population who did not meet the HRSA definition of retention in care, 233 patients were not retained in care. Of them 77(33%) transferred care, 14(6%) died, 14(6%) were incarcerated, and 128(55%) had fallen out of care. Intervention occurred in most patients [127(99%)]. Continued outreach in 2015 resulted in 55(43%) patients attending at least one visit in 2015 and 5(4%) scheduling but never attending a visit. Of the remaining 68 patients, 3(2%) attended a visit in early 2016, 3(2%) died, 3(2%) were imprisoned, and 3(2%) moved. In 2015, 27(21%) met the HRSA definition of retention in care and 25(20%) met visit constancy. This demonstrated an overall response to the intervention in 63 out of 119(53%), after the denominator adjusted for reclassification.

Conclusion: An outreach coordinator is an effective intervention to reengage patients in HIV care, but retention remained low, possibly reflecting unaddressed barriers to care that would require additional interventions to overcome.

Category: Clinical Junior Faculty, Clinical Science
Mentor: Lauren Richey, M.D., MPH, Division of Infectious Diseases
Asthma COPD overlap syndrome and COPD are associated with higher mortality rates in US: Data from the Third National Health and Nutrition Examination Survey (NHANES III)

Suchit Kumbhare, M.B.B.S, MS, Charlie Strange MD, Division of Pulmonary, Critical Care, Allergy and Sleep medicine

Introduction: Asthma COPD overlap syndrome (ACOS) is increasingly recognized as a distinct clinical entity and is associated with higher co-morbidities compared to those with asthma and COPD alone. However, very little is known about the mortality related to ACOS in the US general population. Our aim was to investigate mortality among patient with ACOS and compare it with those with asthma and COPD in the US population.

Methods: We examined questions using the third National Health and Nutrition Examination Survey III (NHANES III) database linked to the National Death Index. The data from 10,554 participants were stratified into four groups, those with Asthma, COPD, ACOS, and those without any obstructive lung disease. We examined baseline demographics, then used multivariate logistic regression to model the impact of demographics, smoking, and self-reported physician diagnosed lung disease on mortality generating odds ratios (OR) and confidence intervals (CI).

Results: Among 10,554 participants, 286 (2.7%), 664 (6.3%), and 214 (2.0%) participants self-reported diagnoses of asthma, COPD and asthma-COPD overlap syndrome respectively. Patients with COPD were older (62.8 ± 14.3 years) than other groups. The ACOS group described the worst health status (57.9% with poor or fair grade) compared to the groups with asthma (33%), COPD (46.5%), and those without these diagnoses (26.2%). The mortality rate was higher in the ACOS group (OR=2.5, 95% CI 1.4-4.6) vs COPD (OR=2.0, 95% CI 1.6-2.6) vs Asthma (OR1.4, 95% CI 0.8-1.6) when compared to those without obstructive lung disease. Age, Gender, BMI and smoking also impacted mortality.

Conclusion: The study demonstrates significantly higher mortality in Asthma-COPD overlap syndrome. This finding suggests that these patients have worse prognosis than either Asthma or COPD alone and it should be recognized as a distinct clinical entity.

Type of project: Epidemiology

Category: Other, Clinical Science

Mentor: Charlie Strange, M.D., Division of Pulmonary and Critical Care
Next Generation Sequencing of Alpha-1 Antitrypsin Deficiency MZ Individuals Shows Frequent Bi-allelic Mutations.

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Rationale: Individuals who have a single Z allelic mutation in the SERPINA1 gene that codes for alpha-1 antitrypsin (AAT) are at increased risk for COPD if they have ever-smoked. Whether additional genetic variants alter the risk for COPD in this population remains unknown. This study sequenced SERPINA1 genes of 104 previously identified MZ individuals, with and without COPD, to determine whether previously undetected variants impact disease expression and severity.

Methods: Participants provided documentation of a prior MZ result, by genotyping or protease inhibitor (Pi) phenotyping, and documentation of a serum AAT level in the lower quartile for the MZ cohort. Participants completed a smoking history and COPD Severity Score (Range 0-33) using REDCap data capture and performed an at-home finger stick test. Next Generation Sequencing (NGS) was performed in the Biocerna, LLC laboratory blinded to participant identity and symptomology.

Results: A second clinically reportable SERPINA1 alteration was identified in 6 (5.8%) participants. One each of ZZ, SZ, FZ, ZSmunich, ZM2obernburg and Z/rs141620200 G>T genotypes were identified. In reconciling the initial MZ results with discordant NGS results: the ZZ individual was on augmentation therapy when determined MZ by Pi typing; the others had limited targeted genotyping that yielded MZ results. ZZ, SZ and FZ genotypes are of known clinical significance. Smunich is a likely pathogenic variant. M2obernburg and rs141620200 G>T are variants of uncertain significance (VUS).

<table>
<thead>
<tr>
<th>NGS SERPINA1 Genotype</th>
<th>Participant Age</th>
<th>Ever-Smoked</th>
<th>COPD Severity Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZZ</td>
<td>59</td>
<td>Yes</td>
<td>17</td>
</tr>
<tr>
<td>SZ</td>
<td>18</td>
<td>No</td>
<td>2</td>
</tr>
<tr>
<td>FZ</td>
<td>58</td>
<td>No</td>
<td>12</td>
</tr>
<tr>
<td>ZSmunich</td>
<td>57</td>
<td>Yes</td>
<td>4</td>
</tr>
<tr>
<td>ZM2obernburg</td>
<td>34</td>
<td>Yes</td>
<td>3</td>
</tr>
<tr>
<td>Z/rs141620200 G&gt;T</td>
<td>65</td>
<td>No</td>
<td>3</td>
</tr>
</tbody>
</table>

Conclusions: Some previously assessed MZ individuals have additional SERPINA1 gene abnormalities. AATD genomic nomenclature is unconventional: a normal M allele is reported in the absence of the evaluated specific mutation(s) in targeted genotyping. Pi phenotyping may be confounded by augmentation therapy and liver transplantation; patient history may not be provided to the lab and not all clinicians are aware of these clinical interferences. The clinical utility of NGS to identify SERPINA1 variants has not been studied in large series; however, these results remind clinicians to consider the clinical circumstances and laboratory methods when selecting an AATD test.

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Category: Other, Clinical Science
Mentor: Charlie Strange, M.D., Division of Pulmonary and Critical Care