	Sunday, May 17, AM
6:00	
7:00	
8:00	
9:00	**9:30 AM - 9:45 AM |** Finding and Fixing Progenitor Cell Programs for Lung Disease 9:30 AM - 11:30 AM **A19 (Mile High Ballroom 2C/3C (Lower Level)) 9:30 AM |** African Ancestry is Associated with Lung Function, Healthcare Utilization, and Airways Inflammation in African Americans with Asthma 9:30 AM - 11:30 AM **A21 (Capitol Ballroom 4 (Fourth Floor)) 9:30 AM |** Effects of Circadian Rhythm Disruption on Viral Pneumonia Severity 9:30 AM - 4:15 PM **A32 (Area C, Hall A-B (Upper Level)) 9:30 AM |** Levels of MUC5AC in Bronchoalveolar Lavage (BAL) Fluid as a Biomarker of Viral Respiratory Tract Infections in Lung Transplant Recipients 9:30 AM - 4:15 PM **A36 (Area G, Hall A-B (Upper Level))**
10:00	
11:00	
12:00	**12:30 PM - 12:45 PM |** Pragmatic Trial in Patient-Centered Asthma Management Approach(ASIST Trial) and Evidence to Action Network in Asthma Funded Sites 12:15 PM - 1:15 PM **L3 (Mile High Ballroom 2C/3C (Lower Level))**

	Sunday, May 17, PM
1:00	
2:00	**2:15 PM |** Longitudinal Assessments of Lung Function and Bronchial Hyperresponsiveness Following Severe RSV Bronchiolitis 2:15 PM - 4:15 PM **A106 (Room 401-402 (Street Level)) 2:15 PM |** Fibroblast-Specific FGF Signaling in Bleomycin-Induced Pulmonary Fibrosis 2:15 PM - 4:15 PM **A107 (Mile High Ballroom 1 A-B (Lower Level))**
3:00	
4:00	
5:00	
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8:00	

	Tuesday, May 19, AM
6:00	
7:00	
8:00	
9:00	**9:54 AM - 10:18 AM |** Evolution of Rapid Diagnostics for the Detection of Antibiotic-Resistant Gram Negative Bacteria 9:30 AM - 11:30 AM **C7 (Mile High Ballroom 2A/3A (Lower Level))**
10:00	**10:14 AM - 10:29 AM |** PRO: Thermoplasty Is an Effective Therapy in Severe Asthma **10:44 AM - 10:48 AM |** Rebuttal 9:30 AM - 11:30 AM **C5 (Centennial Ballroom A-C (Third Floor))**
11:00	
12:00	**12:15 PM - 12:45 PM |** Diagnostic Approach to the Peripheral Lung Nodule 12:15 PM - 1:15 PM **TSS2C (Capitol Ballroom 7 (Fourth Floor))**

	Tuesday, May 19, PM
1:00	
2:00	**2:15 PM |** Psychometric Properties of the Asthma Impact on Quality of Life Scale (A-IQOLS) and the Flanagan QOLS in Adults with Well-Controlled Asthma: Baseline Results in the LASST Trial 2:15 PM - 4:15 PM **C102 (Room 102/104/106 (Street Level)) 2:15 PM |** Fluid Balance in the ICU - Interventions to Minimize Fluids in Patients with Septic Shock 2:15 PM - 4:15 PM **C103 (Room 503-504 (Street Level))**
3:00	
4:00	
5:00	
6:00	
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8:00	

	Wednesday, May 20, AM
6:00	
7:00	
8:00	
9:00	**9:30 AM |** Outcomes Associated with Bacteremia in the Setting of MRSA Pneumonia: A Retrospective Cohort Study 9:30 AM - 11:30 AM **D22 (Room 503-504 (Street Level)) 9:30 AM |** Improving Acute Care Teams by Educating Residents Through Case Based Lectures and Simulation Center Training 9:30 AM - 3:30 PM **D34 (Area G, Hall A-B (Upper Level)) 9:30 AM |** Recruitment and Quality Control in Two Simultaneous Protocols **9:30 AM |** Perspectives on a Multi-Center Sarcoidosis Genomics Study **9:30 AM |** RNAseq in Sarcoidosis and Alpha-1 Antitrypsin Deficiency Patients 9:30 AM - 3:30 PM **D38 (Area G, Hall A-B (Upper Level)) 9:30 AM |** Autophagy Proteins Regulate Airway Epithelial Cell MUC5AC Secretion and ROS Production **9:30 AM |** Increased Systemic Paraoxonase Activity is an Adaptive Response in Asthma 9:30 AM - 3:30 PM **D44 (Area C, Hall A-B (Upper Level))**
10:00	**10:15 AM - 10:30 AM |** Therapeutic Approaches to Mucus Clearance 9:30 AM - 11:30 AM **D11 (Bellco Theatre Section 3 (Street Level))**
11:00	
12:00	

	Wednesday, May 20, PM
1:00	**1:30 PM |** Use of a Remote Inhaler Monitor Device to Measure Change in Inhaler Use with COPD Exacerbations 1:30 PM - 3:30 PM **D103 (Room 401-402 (Street Level))**
2:00	**2:15 PM - 2:30 PM |** Rare SERPINA1 Variants are Associated with Lung Function and Health Care Utilization in a Multi-Ethnic Population from the Severe Asthma Research Program (SARP) **2:30 PM - 2:45 PM |** CLCA1 Peptide Levels as Accurate Biomarkers of the Type 2 Immune Pathway and Disease Severity in Asthma 1:30 PM - 3:30 PM **D92 (Centennial Ballroom A-C (Third Floor))**
3:00	
4:00	
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8:00	

[L3] Outside Organization Session
PATIENT-CENTERED OUTCOME RESEARCH INSTITUTE PROJECTS IN OBSTRUCTIVE LUNG DISEASE
Moderators: K. Walker, MD, MPH, K. Sumino, MD, MPH
Mile High Ballroom 2C/3C (Lower Level), Colorado Convention Center, Sunday, May 17, 2015, 12:15 PM - 01:15 PM
Learning Objective 1: understand what Patient Centered Outcomes Research Institute (PCORI) is and its role as a funding agency in lung disease;
Learning Objective 2: learn what kind of PCORI funded projects are ongoing in obstructive lung disease;
Learning Objective 3: learn from researchers who are currently conducting PCORI funded studies on the how to design, fund, and implement patient centered outcome research.

[12:30 PM] Pragmatic Trial in Patient-Centered Asthma Management Approach(ASIST Trial) and Evidence to Action Network in Asthma Funded Sites
Speaker: K. Sumino, MD, MPH
St. Louis, MO/US

[A106] Poster Discussion Session
ASSESSING PEDIATRIC LUNG DISEASE: LUNG FUNCTION AND BEYOND
Moderators: P. Subbarao, MD, MSc, K.M. McDowell, MD, M.H. Jones, MD
Room 401-402 (Street Level), Colorado Convention Center, Sunday, May 17, 2015, 02:15 PM - 04:15 PM
Poster Viewing: 2:15-3:00
Discussion: 3:00-4:15

[Poster Board # 220] Longitudinal Assessments of Lung Function and Bronchial

Hyperresponsiveness Following Severe RSV Bronchiolitis, [Publication Number: A2335]
M. Kitcharoensakkul, M.D., M. Castro, MD, MPH, T. Schweiger, RN, B. Wilson, N/A, K. Schechtman, N/A, L.B. Bacharier, MD
St. Louis, MO/US

Rationale: It is well known that severe RSV bronchiolitis in infancy significantly increases risk of recurrent wheezing and asthma in later life. However, little is known about the long-term impact of severe RSV bronchiolitis on lung functions and bronchial hyperresponsiveness (BHR) of these children.

Methods: Of 206 children prospectively enrolled into the RSV Bronchiolitis in Early Life-1 (RBEL-1) cohort, 143 (69.4%) had ≥1 standard spirometry performed at mean ages of 5.4 (N=112), 6.6 (N=128), 7.4 (N=36), 8.4 (N=18), 10.8 (N=39), 12.6 (N=39) and 14.7 years (N=13). Standard deviation scores (z-scores) of forced expiratory volume in 1 sec (FEV1), forced vital capacity (FVC) and FEV1/FVC % predicted were calculated using published normative data. BHR was measured by methacholine challenge test (MCT) on 127 and 79 children at mean ages of 6.6 and 11.7 years, respectively. Abnormal BHR is defined as a provocative concentration of methacholine required to decrease FEV1 by 20% (PC20) of ≤8 mg/ml. The comparison of PC20 was analyzed by using Wilcoxon sign-rank test and a mixed model, repeated measures analysis of variance was used for longitudinal changes on z-scores of spirometry values.

Results: Of 143 children, 81 (56.6%) were male and 74 (51.7%) were Caucasian. The age at most recent spirometry was 10.0 ± 2.9 (5.0 -16.3) years. Significant longitudinal declines in z-scores of FEV1 and FVC were observed over the follow-up period ($p<0.004$), and did not differ by race, gender, or MD-diagnosed asthma. FEV1/FVC % predicted z-scores declined over time, but only in children with MD-diagnosed asthma, $p < 0.0001$. There was an increase in geometric mean PC20 from 0.51 ± 0.07 mg/ml at 6 years to 1.66 ± 0.36 mg/ml at 12 years, with the prevalence of abnormal BHR decreasing from 96% at 6 years to 78% at 12 years, $p=0.0003$. There is a positive, but weak correlation (0.31, $p=0.007$) between PC20 adjusted for FEV1, at 6 and 12 years.

Conclusion: Following severe RSV bronchiolitis, there is a significant decline in pre-bronchodilator lung function among these children across ages to puberty. Although abnormal BHR was observed in most patients at age 6, there is a decrease in the degree of their BHRs at age 12 and a small proportion normalized. The findings suggest long-term, and potentially progressive, impact of severe RSV bronchiolitis on lung function in early adolescence despite lower degrees of BHR. Ongoing follow-up will help clarify the long-term pulmonary sequelae of severe RSV bronchiolitis.

[A107] Poster Discussion Session
THE CONFLICT KITCHEN: FIBROBLAST PHENOTYPES
Moderators: J.C. Horowitz, MD, R.G. Jenkins, MD, PhD, D. Kass, MD
Mile High Ballroom 1 A-B (Lower Level), Colorado Convention Center, Sunday, May 17, 2015, 02:15 PM - 04:15 PM
Poster Viewing: 2:15-3:00
Discussion: 3:00-4:15

[Poster Board # 708] Fibroblast-Specific FGF Signaling in Bleomycin-Induced Pulmonary Fibrosis, [Publication Number: A2348]
R.D. Guzy, MD, PhD, D.M. Ornitz, MD, PhD
St. Louis, MO/US

Rationale: Idiopathic Pulmonary Fibrosis (IPF) is characterized by progressive pulmonary scarring, decline in lung function, and often results in death within three to five years after diagnosis. Recently

approved treatments for IPF target Fibroblast Growth Factor (FGF) signaling, however the mechanism through which FGFs contribute to pulmonary fibrosis remains unclear. In vitro, FGF signaling has been shown to be required for TGF-beta induced fibroblast proliferation and collagen production, but this has not been shown in lung fibroblasts in vivo. We hypothesized that FGF signaling in lung fibroblasts is required for the generation of pulmonary fibrosis in mice treated with bleomycin.

Methods: Mice with tamoxifen-inducible Cre recombinase driven by the promoter for procollagen Iα2 (Col1α2-CreER) were crossed with the ROSA26-mTmG reporter. Col1α2-CreER mice were also crossed with floxed alleles for FGF receptors 1, 2, and 3 to generate Fgfr1/2/3 fibroblast-specific conditional knockouts (Fgfr1/2/3Col1α2-CreER). Mice were treated with tamoxifen at P21 for 2 weeks, followed by a 4-week washout period. At 9 weeks of age, mice were administered intratracheal bleomycin (1 mg/kg) or PBS, and after 21 days lungs were harvested, inflation-fixed in 4% PFA, and embedded in OCT for frozen sections or paraffin for H&E staining. Sections were examined via immunofluorescence or H&E staining. In parallel experiments, RNA was harvested from whole lungs or lungs were dissociated for flow cytometry and cell sorting.

Results: Col1α2-CreER targets peribronchial and perivascular smooth muscle as well as interstitial fibroblasts under baseline conditions. Peribronchial smooth muscle cells targeted with Col1α2-CreER are Periosin+ and aSMA+, while interstitial fibroblasts targeted with Col1α2-CreER are PDGFRα+. Col1a2-CreER targeted cells collected via cell sorting express high levels of Col1α1, periostin, and αSMA. The lineage of cells targeted by Col1α2-CreER expand after bleomycin treatment, are concentrated in areas of fibrosis, and express αSMA. Fgfr1/2/3Col1α2-CreER mice have efficient deletion of FGFRs 1-3 in fibroblasts after tamoxifen treatment. Twenty-one days after bleomycin, Fgfr1/2/3Col1α2-CreER mice have a nearly significant trend towards improved survival, decreased collagen, and decreased hydroxyproline.

Conclusions: Col1α2-CreER targets peribronchial smooth muscle and interstitial fibroblasts in the lung which give rise to fibrotic tissue in the lung in response to bleomycin. These mice allow the study of fibroblast-specific genes and pathways involved in the pathogenesis of pulmonary fibrosis in vivo. Furthermore, intact FGFR signaling in fibroblasts appears to be required for collagen expression and fibrosis in response to bleomycin, implicating fibroblast-specific FGF signaling in the pathogenesis of pulmonary fibrosis.

[A19] Mini Symposium
PATHOLOGIC PROGRAMMING OF AIRWAY EPITHELIUM
Moderators: R.J. Freishtat, MD, MPH, H.A. Chapman, MD, S.D. Reynolds, PhD
Mile High Ballroom 2C/3C (Lower Level), Colorado Convention Center, Sunday, May 17, 2015, 09:30 AM - 11:30 AM

[9:30 AM] Finding and Fixing Progenitor Cell Programs for Lung Disease
Speaker: M.J. Holtzman, MD
St. Louis, MO/US

[A21] Poster Discussion Session
GENETIC REGULATION OF CHRONIC AIRWAY INFLAMMATION
Moderators: P.J. Lee, MD, B.A. Raby, MD, MPH, D.S. Postma, MD, PhD
Capitol Ballroom 4 (Fourth Floor), Hyatt Regency Denver at CCC, Sunday, May 17, 2015, 09:30 AM - 11:30 AM
Poster Viewing: 9:30-10:15
Discussion: 10:15-11:30

[Poster Board # 1010] African Ancestry is Associated with Lung Function, Healthcare Utilization, and Airways Inflammation in African Americans with Asthma, [Publication Number: A1061]

V.E. Ortega, MD[1], W.C. Moore, MD[1], J. Zein, MD[2], A.T. Hastie, PhD[1], E. Ampleford, PhD[1], S.P. Peters, MD, PhD[1], W.W. Busse, MD[3], M. Castro, MD, MPH[4], S.C. Erzurum, MD[2], E. Israel, MD[5], S.E. Wenzel, MD[6], G. Hawkins, PhD[1], E.R. Bleecker, MD[1], D.A. Meyers, PhD[1]

[1]Winston-Salem, NC/US, [2]Cleveland, OH/US, [3]Madison, WI/US, [4]St. Louis, MO/US, [5]Boston, MA/US, [6]Pittsburgh, PA/US

NIH NHLBI Severe Asthma Research Program

Introduction: African ancestry is inversely associated with baseline lung function in recently admixed populations of African descent, including African Americans (AA), an expected trend based on current, race-based predictive models. We hypothesize that genetic variation inherited from African ancestry underlies the increased asthma-related morbidity and mortality observed in AA compared to non-Hispanic Whites.

Methods: 331 self-identified African American asthmatics from the NHLBI Severe Asthma Research Program (SARP1-2) and 141 from the NHLBI Collaborative Study on the Genetics of Asthma (CSGA) were included. All subjects were genotyped with 95,296 single nucleotide polymorphisms to estimate global African ancestry using ADMIXTURE (Alexander DH 2009). Multivariate regression-based analyses were used to test for associations with African ancestry as a continuous variable and divided into quartiles. We estimated annual costs related to annual healthcare utilization using the Healthcare Cost and Utilization Project Nationwide Emergency Department Sample (HCUP-NEDS sponsored by the AHRQ) for 2011 adjusted to 2013 US dollars and annual medication costs using National Average Drug Acquisition Cost pricing.

Results: Analysis of pre-bronchodilator lung function by African ancestral quartiles identified that AA with percentage ancestry ≤70% (Q1) had an FEV1 at least 280ml higher and an FVC at least 350ml higher than subjects in the remaining three quartiles (Q2-Q4, Table 1). These inter-quartile trends were statistically significant for SARP, CSGA, and the combined cohort (FEV1 p=0.0003, FVC p=0.003, Table 1). In SARP, African ancestry was positively associated with sputum neutrophil percentage (ancestry coefficient=0.55, p=0.03), but not eosinophil percentage (p=0.65). AA with an ancestry of ≤70% (Q1, N=14) had a lower mean sputum neutrophil percentage than subjects in the remaining three quartiles (neutrophil percentage Q1=30% versus Q2-Q4=46%[N=105], p=0.02). Comparisons between AA with African ancestry >75% (AA>75%, N=264), AA<75% (N=62), and whites (N=758) from SARP showed that AA>75% were more likely to have experienced an asthma-related urgent outpatient visit (AA>75% vs whites: OR=1.56,p=0.03) or ED visit (OR=3.41,p=3.2x10-11) in the past year compared to whites after adjusting for annual medication costs. These associations were less significant between AA<75% and whites (urgent visits: OR=0.89,p=0.76; ED: OR=2.31,p=0.01). AA>75% had a greater healthcare costs related to urgent outpatient and ED visits in the past year ($547.22) compared to AA<75% ($461.50) and whites ($341.17, ptrend=3.26x10-5).

Conclusions: Differences in asthma-related healthcare utilization between AA and whites were primarily determined by AA with >75% African ancestry. Genetic variants related to African ancestry might impact asthma severity through mechanisms related to neutrophilic airways inflammation.

(a) African ancestry was divided into quartiles corresponding to intervals one and two standard deviations from a mean African ancestry of 80 percent. (b) SARP=NIH NHLBI Severe Asthma Research Program, CSGA=NIH NHLBI Collaborative Study on the Genetics of Asthma, Adjusted for age, sex, height, square of height, BMI, recruitment site, inhaled corticosteroid treatment in SARP, and study cohort for the combined analysis. Lung function expressed in liters (L) with standard deviations in

parentheses.

[A32] Thematic Poster Session
MICROBIAL INTERACTIONS AND HOST DEFENSE
Facilitators: D. Dockrell, MD, P.M. Hansbro, PhD, J. Klesney-Tait, MD, PhD, K.M. Robinson, DrMed
Area C, Hall A-B (Upper Level), Colorado Convention Center, Sunday, May 17, 2015, 09:30 AM - 04:15 PM
Poster Viewing: 11:30-1:15

[Poster Board # P178] Effects of Circadian Rhythm Disruption on Viral Pneumonia Severity, [Publication Number: A1316]
J. Haspel, MD-PhD, E. Agapov, MD, M.J. Holtzman, MD
St. Louis, MO/US

Introduction. Circadian rhythms are 24 hour oscillations in biological function that are generated by a cell intrinsic "clock mechanism" consisting of transcription-translation feedback loops. Recent work in our lab suggests that local circadian rhythms in the lung are tied to immune function, both during health and in the setting of systemic inflammation. However, little is known about the role that circadian rhythms play in the response to respiratory viruses. Therefore, we examined the effects of circadian rhythm disruption on viral pneumonia using a well-established mouse model.

Methods. Circadian rhythm defective male bmal1-null mice and wt liter mates were exposed to Sendai virus via intranasal administration and monitored post infection for three weeks. Daily weights, clinical appearance and lung tissue samples were obtained at various time points.

Results and Conclusions. Bmal1-null mice exhibited 100% mortality by day 8 post infection compared to 0% mortality for wt liter mates (observations out to day 21 post infection). The was a significant difference in absolute body weight loss and the rate of weight decline between the genotypes that was evident by day 3 post infection and continued throughout the period of observation (Fig. 1). These results suggest that circadian rhythm disruption exerts a significant effect on acute response to respiratory virus infection. Experiments are underway to examine the mechanism behind this phenomenon.

[A36] Thematic Poster Session
WITH A LITTLE HELP FROM MY FRIENDS: ALL ABOUT LUNG TRANSPLANT
Facilitators: K. Chan, MD, R.M. Kotloff, MD, J.A. Belperio, MD, R.D. Yusen, MD, MS
Area G, Hall A-B (Upper Level), Colorado Convention Center, Sunday, May 17, 2015, 09:30 AM - 04:15 PM
Poster Viewing: 11:30-1:15

[Poster Board # P814] Levels of MUC5AC in Bronchoalveolar Lavage (BAL) Fluid as a Biomarker of Viral Respiratory Tract Infections in Lung Transplant Recipients, [Publication Number: A1446]
B.C. Bemiss, MD[1], Y.G. Alevy, PhD[2], J. Tucker, BS[2], C. Mikols, BS[2], M.J. Walter, MD[2], M.M.

Chakinala, MD[2], C. Witt, MD[2], R.D. Yusen, MD, MS[2], E. Trulock, MD[2], R.R. Hachem, MD[2], M.J. Holtzman, MD[1], D.E. Byers, MD, PhD[2]
[1]St. Louis, MO/US, [2]Saint Louis, MO/US

Introduction:

Community acquired respiratory viral (CARV) infections contribute to the development of acute and chronic allograft injury following lung transplantation. One challenge has been to discern those patients with pathologic lower respiratory tract infections (LRTIs) from those with self-limited URTIs. In this pilot study, we examined the utility of an assay of airway mucus production, specifically inflammatory mucin MUC5AC generation, to identify LRTIs in serial bronchoscopic lung samples following transplantation.

Methods:

Single-center, prospective cohort pilot study of lung transplant recipients who developed a URTI in the outpatient setting during the period of April 2006 and May 2008. Nasal lavage samples were collected and examined by virus-specific PCR (EraGen® PLx virus panel). Bronchoalveolar lavage specimens were collected at 7-10, 30, and 90 days following PCR-proven URTI onset and stored at -80°C with protease inhibitors. At the time of study, BAL supernatant was thawed and examined by viral multiplex PCR (GenMark® Respiratory Virus Panel) and standardized ELISA for MUC5AC as well as CLCA1 and IL-33. Spirometry was monitored for 6 months after the URTI. All subjects consented to this study under a protocol approved by the institutional review board.

Results:

Of the 28 consented recipients, 3 died prior to completion of the study. Six subjects had PCR-confirmed viral URTIs a total of 10 times and underwent bronchoscopy collections. PCR assay of BAL samples showed respiratory syncytial virus (RSV, n=5), coronavirus NL63 (CV, n=2), influenza A H3N2 virus (IAV, n=2), and human rhinovirus (RV, n=1). Of these, 4 of the corresponding day 7-10 BAL specimens showed RSV (n=3) and IAV (n=1). MUC5AC levels were significantly increased in samples that were positive for RSV, IAV and RV, but not for CV, during the first week following URTI, compared to day 30 and day 90 samples. Total cell and neutrophil levels in BAL samples were also increased at day 7-10 compared to day 30 and day 90 but were not significantly associated with the presence of virus. The BAL sample levels of CLCA1 or IL-33 were not associated with viral detection. Only 1 of the 6 subjects that had a CARV LRTI developed a significant drop in FEV1 during the following 6 months.

Conclusions:

The levels of MUC5AC in BAL fluid are increased within the first week following PCR-confirmed viral URTI in lung transplant recipients. Therefore, excess production of MUC5AC may be a biomarker of more severe CARV infections that involve the lower airway.

[C7] Scientific Symposium
NEW STRATEGIES FOR THE MANAGEMENT OF ANTIBIOTIC-RESISTANT GRAM NEGATIVE BACTERIAL INFECTIONS
Moderator: M. Kollef, MD
Mile High Ballroom 2A/3A (Lower Level), Colorado Convention Center, Tuesday, May 19, 2015, 09:30 AM - 11:30 AM
Learning Objective 1: integrate new antibiotic options in caring for patients infected with antibiotic-resistant gram negative bacteria;

Learning Objective 2: more rapidly and accurately diagnose infections attributed to antibiotic-resistant gram negative bacteria;
Learning Objective 3: improve the quality of patient care with the use of enhanced informatics systems targeting the identification of patients at risk for infection with antibiotic-resistant gram negative bacteria.

[9:54 AM] Evolution of Rapid Diagnostics for the Detection of Antibiotic-Resistant Gram Negative Bacteria
Speaker: M. Kollef, MD
St. Louis, MO/US To describe the available and upcoming technologies for the rapid identification of antibiotic-resistasnt gram negative bacteria.

[C5] Scientific Symposium
CONTROVERSIES IN ASTHMA MANAGEMENT 2015
Moderators: N.N. Jarjour, MD, M. Kraft, MD
Centennial Ballroom A-C (Third Floor), Hyatt Regency Denver at CCC, Tuesday, May 19, 2015, 09:30 AM - 11:30 AM
Learning Objective 1: understand the usefulness and limitation of guiding asthma therapy by sputum EOS;
Learning Objective 2: comprehend the potential benefit of monoclonal antibodies in asthma;
Learning Objective 3: analyze the evidence for and against the use of thermoplasty for treatment of severe asthma.

[10:14 AM] PRO: Thermoplasty Is an Effective Therapy in Severe Asthma
Speaker: M. Castro, MD, MPH
Saint Louis, MO/US Thermoplasy has been shown to reduce asthma exacerbation and improve quality of life in severe asthma. Dr. Castro will defend the published studies to date supporting the use of BT in asthma.

[10:44 AM] Rebuttal
Speaker: M. Castro, MD, MPH
Saint Louis, MO/US

[C102] Poster Discussion Session
DEVELOPING AND VALIDATING METRICS AND TOOLS TO MEASURE AND IMPROVE RESPIRATORY HEALTH
Moderators: M.A. Valerio, MPH, PhD, D.R. Sullivan, MD, MA
Room 102/104/106 (Street Level), Colorado Convention Center, Tuesday, May 19, 2015, 02:15 PM - 04:15 PM
Poster Viewing: 2:15-3:00
Discussion: 3:00-4:15

[Poster Board # 101] Psychometric Properties of the Asthma Impact on Quality of Life Scale (A-IQOLS) and the Flanagan QOLS in Adults with Well-Controlled Asthma: Baseline Results in the LASST Trial, [Publication Number: A5189]

S. Wilson, PhD[1], R.A. Wise, MD[2], S.B. Knowles, Ph.D.[1], Q. Huang, M.S.[1], C.Y. Wei, M.S.[2], M. Castro, MD, MPH[3]
[1]Palo Alto, CA/US, [2]Baltimore, MD/US, [3]St. Louis, MO/US

RATIONALE:

Existing asthma-related quality of life (QoL) scales measure physical and emotional symptoms and functional status, but don't directly measure current QoL or the impact of asthma on QoL. The Flanagan QOLS, not previously used in asthma research, measures current QoL – how well individual's needs and wants are being satisfied (1=not at all, to 5=Very well) on each of 16 QoL dimensions. A new scale, the A-IQOLS allows individuals to rate the negative effect of asthma on their QoL (1=no, to 5=extremely negative effect) on the same 16 dimensions.

METHODS:

We examined psychometric properties of A-IQOLS and QOLS total scores (averages of their 16 dimension ratings) at the final baseline visit in 227 participants, ages 18-84 years, in the Long-acting Beta Agonist Step Down Trial, whose primary hypothesis is that, in patients whose asthma is stable and well-controlled on combination ICS/LABA (based on ACT score ≥20, FEV1≥70%, no exacerbations requiring medical attention, rescue medication use <16 puffs/wk., and unchanged controller regimen over the preceding 8 weeks), discontinuing LABA while continuing the same ICS dose will be inferior to continuing LABA and reducing ICS dose in preventing treatment failure during step-down therapy.

RESULTS:

Participants, mean(SD) age 43(13) years, were 67% female, 61% white, 31% black, 4% Asian, and 4% another race; 11% were Hispanic. A-IQOLS' and QOLS' internal consistency reliabilities (α) were high (Table 1). In this select population with well-controlled, stable asthma, few patients had A-IQOLS scores indicating slight or greater negative asthma impact); 95% of total scores were between 1.0-2.0. Even with this low variability, A-IQOLS scores were associated with the ACT, Marks AQLQ, and EQ5D. They were not associated with FEV1, ASUI, QOLS, or demographic characteristics. QOLS scores had greater variability, as in the general U.S. population, and were associated with ASUI, ACT, Marks AQLQ, EQ5D, age, and race (mean=3.8 in White, 3.9 in Black, 3.2 in Asian, and 4.2 in Other race). Distribution-based estimates of A-IQOLS and QOLS minimum important (i.e., reliably detectable) differences were calculated.

CONCLUSIONS:

Both the A-IQOLS and QOLS have strong construct validity as measures of, respectively, patients' perception of the impact of asthma on their quality of life and their current QoL and have high reliability. In patients whose asthma was well-controlled and stable, low A-IQOLS scores at baseline would be expected and were observed, supporting the possibility that the measure may be sensitive to treatment failure following step-down therapy.

					AIQOLS			QOLS		
Asthma Outcome Measures	Measure Mean (SD)	Range	α	MID1	r2	P	R	r2	P	R
Asthma Impact on Quality of Life (A-lQOLS)	1.22 (0.56)	1-4.9	0.98	0.28, 0.17	--	--	--	-0.02	0.78	0.0003
Flanagan Quality of Life Scale (QOLS)	3.79 (0.72)	1.7-5.0	0.92	0.36, 0.41	--	--	--	--	--	--
Percent Predicted FEV1 (PPFEV1) [pre-BD]	91.6 (13.4)	69-154	--	--	-0.01	0.90	0.00	0.02	0.81	0.003
Asthma Symptom Utility Index (ASUI)	0.94 (0.07)	0.61-1.0	--	--	-0.06	0.34	0.00	0.14	0.03	0.02
Asthma Control Test (ACT)	23.0 (1.7)	20-25	--	--	-0.18	0.005	0.03	0.21	0.002	0.04
Marks Asthma Quality of Life Questionnaire (AQLQ)	25.8 (6.5)	20-60	--	--	0.32	<0.0001	0.10	-0.26	0.0001	0.07
EuroQol-5D (EQ-5D-5L)	0.92 (0.11)	0.38-1.0	--	--	-0.23	0.0004	0.05	0.13	0.04	0.01
1MIDS estimated from 0.5*SD and 2*SEM. 2Pearson product moment correlation coefficient.										

[C103] Poster Discussion Session
OPTIMIZING LIMITED ICU RESOURCES
Moderators: J.M. Kahn, MD, MSc, H. Wunsch, MD, MSc, A. Combes, MD, PhD
Room 503-504 (Street Level), Colorado Convention Center, Tuesday, May 19, 2015, 02:15 PM - 04:15 PM
Poster Viewing: 2:15-3:00
Discussion: 3:00-4:15

[Poster Board # 510] Fluid Balance in the ICU - Interventions to Minimize Fluids in Patients with Septic Shock, [Publication Number: A5218]
C. Chen, MD, M. Kollef, MD
St. Louis, MO/US

Rationale: Since Rivers, et al. demonstrated that early goal-directed therapy improves survival in septic

shock, fluid resuscitation has become a mainstay of treatment. However, recent observational studies show that excessive positive fluid balance is independently associated with increased mortality. Additionally, achieving negative fluid balance within the first 3 days of intensive care unit admission correlates with increased likelihood of survival. We hypothesize that a protocol of daily fluid status assessment and minimization can decrease intravenous fluids administered and cumulative fluid balance in patients with septic shock determined to be volume non-responsive.

Methods: Patients with septic shock requiring vasopressors 12 hours after adequate initial fluid resuscitation were approached; pre-existing end-stage renal disease was excluded. Once consented, participants were randomized to usual care or daily fluid assessment. In the usual care arm, fluid management was by the primary team. Participants in the intervention arm had passive leg raise performed upon enrollment to determine fluid responsiveness using pulse pressure variation, maximal and minimal IVC diameters, stroke volume, and cardiac output as parameters. If participants were not volue responsive, continuous infusions were concentrated, fluid boluses discontinued, and diuresis encouraged. Daily fluid intake and output were recorded.

Results: At interim analysis, 70 of 90 planned participants had been enrolled. Participants in the usual care group received 9.1±5.4 L (mean ± standard deviation) by day 3; intervention group received 6.6±2.9 L (p=0.03). Those in the usual care group had a cumulative fluid balance of +4.9±6.6 L by day 3; intervention group had a cumulative fluid balance of +2.2±3.7 L (p=0.04). Total IV fluids administered was 11.1±6.8L in usual care group, 8.6±4.0 L in intervention group (p=0.06). Cumulative fluid balance was +3.9±8.3 L in usual care group, +1.4±5.1 L in intervention group (p=0.15).

There was no statistically significant difference between the two groups in maximal norepinephrine dose during enrollment (usual care 19±16 mcg/min, intervention group 24±19 mcg/min, p=0.32), use of vasopressin during enrollment (usual care 10 of 35 participants, intervention 12 of 35, p=0.55), or mean arterial pressure (usual care 71±6 mmHg, intervention 72±7 mmHg, p=0.82). There was no statistically significant difference in rate of renal replacement therapy between groups (usual care 12 of 35 participants, intervention 14 of 35, p=0.56).

Conclusions: Daily fluid assessment protocol is beneficial in decreasing IV fluids infused and overall fluid balance in patients with septic shock. Decreased IV fluids and fluid balance is not associated with more hypotension or renal failure.

[TSS2C] Thematic Seminar Series
ENDOBRONCHIAL ULTRASOUND
Capitol Ballroom 7 (Fourth Floor), Hyatt Regency Denver at CCC, Tuesday, May 19, 2015, 12:15 PM - 01:15 PM
Learning Objective 1: learn the role of EBUS in the staging of lung cancer;
Learning Objective 2: learn about the optimal performance of EBUS-guided transbronchial needle aspiration;
Learning Objective 3: learn the optimal approach to EBUS specimen handling.

[12:15 PM] Diagnostic Approach to the Peripheral Lung Nodule
Speaker: A.C. Chen, MD
St. Louis, MO/US

[D11] Scientific Symposium
TRANSLATING COPD DISCOVERIES TO THE CLINIC
Moderators: F.J. Martinez, MD, MS, J.A. Wedzicha, MD, PhD
Bellco Theatre Section 3 (Street Level), Colorado Convention Center, Wednesday, May 20, 2015, 09:30

AM - 11:30 AM
Learning Objective 1: understand the biological underpinnings to frequently seen clinical manifestations in COPD;
Learning Objective 2: appreciate how understanding these biological concepts are being translated into innovative therapies;
Learning Objective 3: understand and appreciate the timeline for the development of new therapeutic strategies in COPD.

[10:15 AM] Therapeutic Approaches to Mucus Clearance
Speaker: M.J. Holtzman, MD
St. Louis, MO/US

[D22] Poster Discussion Session
NOSOCOMIAL AND FUNGAL INFECTIONS
Moderators: C.M. Luna, MD, PhD, J.E. Chastre, MD, O. Epelbaum, MD
Room 503-504 (Street Level), Colorado Convention Center, Wednesday, May 20, 2015, 09:30 AM - 11:30 AM
Poster Viewing: 9:30-10:15
Discussion: 10:15-11:30

[Poster Board # 504] Outcomes Associated with Bacteremia in the Setting of MRSA Pneumonia: A Retrospective Cohort Study, [Publication Number: A5437]

A.F. Shorr, MD, MPH[1], M. Zilberberg, MD, MPH[2], S. Micek, PharmD[3], M. Kollef, MD[3]
[1]Washington, DC/US, [2]Goshen, MA/US, [3]St. Louis, MO/US

Introduction: Methicillin-resistant Staphylococcus aureus (MRSA) remains an important pathogen in pneumonia. Bacteremia may secondarily complicate MRSA pneumonia. The epidemiology and outcomes associated with bacteremia in the setting of MRSA pneumonia are unknown. We sought to describe the prevalence of bacteremia in MRSA pneumonia and the impact of concomitant bacteremia on hospital mortality and length of stay (LOS).

Methods: We conducted a single center retrospective cohort study (2008-2013) including adult patients hospitalized with pneumonia caused by MRSA. We defined pneumonia based on clinical criteria and all cases were culture confirmed. MRSA bacteremia was identified based on positive blood cultures. Pneumonia was categorized as either community-onset (CO, occurring at presentation or within 2 days of admission) or hospital-onset (HO, occurring >2 days after admission). We compared bacteremic and non-bacteremic groups with respect to their demographic and clinical characteristics and outcomes. A logistic regression and a generalized linear model (GLM) were constructed to examine the impact of bacteremia on hospital mortality and post-pneumonia onset LOS, respectively.

Results: Among the 765 patients with MRSA pneumonia (33.1% CO), 93 (12.2%) had concurrent bacteremia (37.6% CO). Patients with bacteremia were similar to non-bacteremic subjects based on demographic and clinical characteristics with the exception of frequency of a hospitalization within prior 180 days (48.4% bacteremic and 37.7% non-bacteremic, p=0.047), prevalence of chronic liver disease (17.2% vs. 9.5%, p=0.030), and the mean APACHE II score at the onset of pneumonia (17.5+6.0 vs. 16.1+6.0, p=0.045). Both unadjusted mortality (33.7% vs. 23.8%, p=0.067) and median post-pneumonia LOS (18.2 vs. 12.2 days , p<0.001) were greater in the bacteremic than the non-bacteremic group. In a logistic regression, bacteremia showed a trend toward an association with

increased mortality (odds ratio 1.56, 95% confidence interval 0.93 to 2.61). Concomitant bacteremia was independently associated with a 1.66 day increase in the post-pneumonia hospital LOS (95% confidence interval 1.41 to 1.90 days).

Conclusions: Concurrent bacteremia occurred with moderate frequency in the setting of hospitalization with MRSA pneumonia. Although bacteremia did not appear to independently impact mortality, this was likely due to our study's limited sample size. However, bacteremia complicating MRSA pneumonia added nearly two days to the hospital LOS.

[D34] Thematic Poster Session
INNOVATIONS IN PROFESSIONAL EDUCATION TO IMPROVE QUALITY OF CARE
Facilitators: M.R. Janevic, MPH, PhD, C.H. Weiss, MD, MS
Area G, Hall A-B (Upper Level), Colorado Convention Center, Wednesday, May 20, 2015, 09:30 AM - 03:30 PM
Poster Viewing: 11:30-1:15

[Poster Board # P773] Improving Acute Care Teams by Educating Residents Through Case Based Lectures and Simulation Center Training, [Publication Number: A5690]
A. Trivedi, MD, C. Mallow, MD, M. Kollef, MD
St. Louis, MO/US

RATIONALE: Rapid response teams or acute care teams (ACT) were established to prevent cardiopulmonary arrest and improve outcomes of acutely decompensating patients. These teams are advocated by regulatory agencies and have been implemented in most hospitals. The ACT at our hospital is led by a medicine resident and is comprised of an intensive care nurse, a respiratory therapist, and other medicine house staff members. Formal training for the medicine house staff was started in 2012 through a dedicated simulation center session. However, this only occurred once during their intern or second year. Because one session was thought to be inadequate, additional sessions were added this year with the goal of showing that resident comfort level and knowledge improve with further training.
METHODS: All residents in the internal medicine residency program attended a case based lecture that was interactive in nature and discussed several ACT scenarios. A survey was distributed prior to the educational session, labeled pre-test or P0. The survey assessed comfort level and incorporated 10 knowledge based questions. After the lecture, the residents completed a survey, labeled post-test #1 (P1). The interns will participate in simulation center training throughout the year and then complete a survey, labeled post-test #2 (P2). P0 and P1 were compared to measure the benefit of the case based lecture. Once the simulation center training is completed, all three surveys will be compared to determine the benefit of additional training.
RESULTS: Residents agreed in P0 and P1 that the knowledge obtained from simulation center training is more applicable than lectures. From P0 to P1 residents transitioned from feeling neutral to agreeing that case based lectures are more applicable than didactic lectures. From P0 to P1 residents' knowledge based average score improved from 6.89 to 8.68. This improvement was statistically significant with a p value of 0.0001.
CONCLUSION: The addition of one teaching session improved resident education in management of ACT scenarios as evidenced by the increase in knowledge based scores. House staff agreed that interactive teaching through cased based lectures and simulation center training is more applicable than didactic lectures. This relatively simple educational tool of a case based lecture can be utilized not only for ACT training, but also for other aspects of resident education. Simulation center training will be completed throughout the year to determine if there is an added benefit to resident comfort level and knowledge in managing acutely decompensating patients.

[D38] Thematic Poster Session
FLYING: REACHING NEW HEIGHTS IN SARCOIDOSIS
Facilitators: M.A. Judson, MD, A.K. Gerke, MD, G.E. Westney, MD, N.Y. Hamzeh, MD
Area G, Hall A-B (Upper Level), Colorado Convention Center, Wednesday, May 20, 2015, 09:30 AM - 03:30 PM
Poster Viewing: 11:30-1:15

[Poster Board # P790] Recruitment and Quality Control in Two Simultaneous Protocols, [Publication Number: A5817]

S. O'Neal, MA[1], N. Kaminski, MD[2], M. Becich, MD, PhD[1], H. Hochheiser, PhD[1], D.R. Moller, MD[3], K.F. Gibson, MD[1], C. Strange, MD[4], R.A. Sandhaus, MD, PhD[5], R. Senior, MD[6], E.S. Chen, MD[3], A. Morris, MD, MS[1], B. Methe, PhD[7], E. Ghedin, PhD[8], J.K. Leader, Ph.D.[1], N. Petro, _[1], H. Lynn, BS[2], Y. Zhang, PhD[1], L. Silfies, BS[1], D. Protivnak, MSIS[1], M. Martinez, MS[1], S.R. Wisniewski, PhD[1]
[1]Pittsburgh, PA/US, [2]New Haven, CT/US, [3]Baltimore, MD/US, [4]Charleston, SC/US, [5]Denver, CO/US, [6]St. Louis, MO/US, [7]Rockville, MD/US, [8]New York, NY/US
The GRADS Investigators

Introduction/Rationale: The goal of the NHLBI-funded (#5U01HL112707) Genomic Research in Alpha-1 Antitrypsin Deficiency and Sarcoidosis (GRADS) project is to enroll 400 research participants with Sarcoidosis and 150 with Alpha-1 Antitrypsin Deficiency in order to study the interactions among genomics, the lung microbiome, and the two disease phenotypes. The funding period is May 2012 through November 2015 and the enrollment period is August 2013 through June 2015.

Methods: Before the enrollment period began, two Protocol Development Committees crafted protocols for Alpha-1 and Sarcoidosis, outlining the hypothesis, specific aims, phenotypes, visit procedures, and data and samples to collect. A central Genomics and Informatics Center (GIC) and an independent Study Chair were part of these committees.

Once the protocols were established, seven clinical sites comprising nine recruiting centers across the U.S. began to recruit participants into the two protocols under the direction of the GIC. The site PIs and Coordinators identify, screen, and enroll participants from three Alpha-1 genotypes and nine Sarcoidosis phenotypes. The GIC monitors enrollment to make sure the genotypes and phenotypes are balanced to guarantee sufficient power to test study hypotheses.

While the clinical sites continue enrolling participants and conducting follow-up visits, the GIC is carrying out quality control procedures. Data managers at the University of Pittsburgh monitor data entry, completeness, and accuracy, and maintain a tracking system for biosamples. Computed Tomography (CT) scans and chest X-rays are transferred electronically and read by a radiology lab at the University of Pittsburgh.

Repositories at Yale University and the University of Pittsburgh receive biosample shipments from the clinical sites and distribute samples for analysis. Labs at Yale University, the University of Pittsburgh, New York University, and the J. Craig Venter Institute analyze blood and bronchoalveolar lavage samples and provide feedback to the clinical sites to maintain sample quality moving forward.

Results: Enrollment in both protocols is ahead of the targets and moving at a steady pace. Three out of the nine Sarcoidosis phenotypes have reached the total needed, so the clinical sites are focusing on the remaining phenotypes. The numbers are well-balanced among the three Alpha-1 genotypes. Thus

far, the samples are of high quality and are delivering results.

Conclusion: Enrolling multiple phenotypes and genotypes into two distinct protocols can be done well, even with a relatively small number of clinical sites. Quality control during the recruitment phase ensures that data and samples are collected appropriately and are of high quality.

[Poster Board # P792] Perspectives on a Multi-Center Sarcoidosis Genomics Study, [Publication Number: A5819]

H. Lynn, Bs[1], X. Yan, PhD[1], J. Deluliis, PhD[1], S. O'Neal, MA[2], M. Becich, MD, PhD[2], H. Hochheiser, PhD[2], D.R. Moller, MD[3], K.F. Gibson, MD[2], C.B. Strange, MD[4], R.A. Sandhaus, MD, PhD[5], R. Senior, MD[6], A. Wyllie, BS[1], A. Morris, MD[7], B. Methe, PhD[8], E. Ghedin, PhD[2], J.K. Leader, Ph.D.[2], N. Petro, _[2], L. Silfies, BS[2], Y. Zhang, PhD[2], E.S. Chen, MD[3], D. Protivnak, MSIS[2], M. Martinez, MS[2], S.R. Wisniewski, PhD[2], N. Kaminski, MD[1]

[1]New Haven, CT/US, [2]Pittsburgh, PA/US, [3]Baltimore, MD/US, [4]Charleston, SC/US, [5]Denver, CO/US, [6]St. Louis, MO/US, [7]Salt Lake City, UT/US, [8]Rockville, MD/US

GRADS Investigators

Introduction: Sarcoidosis is a systemic inflammatory and granulomatous disease that affects the lung. Alpha-1 Antitrypsin (A1AT) is a glycoprotein serine protease inhibitor that is not synthesized in lung endothelial cells and has to be taken up via endocytosis, and A1AT deficiency is a hereditary disorder that contributes to the premature onset of chronic pulmonary disease. Complex genetic factors underlay the pathogenesis and progression of these diseases.

Aim: The Genomic Research in Alpha-1 Antitrypsin Deficiency and Sarcoidosis (GRADS) study is a multi-center collaboration that aims to enroll 400 sarcoidosis and 150 A1AT patients to study the interactions between these two disorders. Recruitment across multiple centers allows for a larger population to be studied than could be attempted by any single center.

Methods: Patients were recruited at seven clinical sites and nine recruiting centers. CPT, serum, heparin plasma, Qiazol, PAXGene RNA, PAXGene DNA, and stool samples were collected for sarcoidosis and A1AT patients. For BAL, the following were collected from each patient: bronchoscope control, whole oral wash with PBS, Bronchial Wash, BAL for microbiome, BAL for virome, pooled wash (1 mL and 7 mL aliquots), Dry cell pellets (both unsuspended and resuspended in Qiazol), cytobrush in Qiazol, and microbrush in beadbeater. Total RNA was extracted from Qiazol from 202 A1AT and sarcoidosis and 112 BAL samples using Qiagen's miRNA easy kit and QiaCube machine. We constructed cDNA libraries after poly-A isolation and used the Ion Torrent system to perform RNA sequencing (RNA-seq) on 33 BAL samples.

Results: 197 of the initial 202 A1AT and sarcoidosis samples that were extracted had an average RIN of 8.4 and an average concentration of 245.96 ng/uL, making them adequate for RNA sequencing. For the 33 BAL samples, the average RIN was 7.58 and the average concentration was 141.00 ng/uL. RNA-seq was successful in 19 preliminary samples with an average of 26 million reads per sample that had an average mapping rate of 96.67%.

Conclusions: Total RNA extraction from the A1AT and sarcoidosis samples was more successful than total RNA extraction from the BAL samples. RNA-seq using the Ion Torrent system is a possibility for a large scale high-throughput study.

[Poster Board # P793] RNAseq in Sarcoidosis and Alpha-1 Antitrypsin Deficiency Patients, [Publication Number: A5820]

X. Yan, Ph.D[1], J. Delullis, BS[1], H. Lynn, BS[1], S. O'Neal, MA[2], M. Becich, MD, PhD[2], H. Hochheiser, PhD[2], D.R. Moller, MD[3], K.F. Gibson, MD[2], C. Strange, MD[4], R.A. Sandhaus, MD, PhD[5], R. Senior, MD[6], E.S. Chen, MD[3], A. Morris, MD, MS[2], B. Methe, PhD[7], E. Ghedin, PhD[8], J.K. Leader, MD[2], N. Petro, _[2], Y. Zhang, PhD[2], L. Silfies, BS[2], D. Protivnak, MSIS[2], M. Martinez, MS[2], S.R. Wisniewski, PhD[2], N. Kaminski, MD[1]

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The GRADS Investigators

RATIONALE: Alpha-1 Antitrypsin Deficiency (A1AT) and Sarcoidosis (SARC) are two under-recognized chronic lung disease. The Genomic Research in Alpha-1 Antitrypsin Deficiency and Sarcoidosis (GRADS) are collecting samples from both A1AT and SARC patients for parallel microbiome and transcriptome studies to identify biomarkers that indicate the current status of the lung diseases and predict their progression and response to the therapy. To understand the transcriptomic features of the diseases, we have analyzed the RNA sequencing data from the GRADS cohort and idiopathic pulmonary fibrosis (IPF) patients to understand the data quality and identify gene signatures that distinguish the two diseases and IPF.

METHODS: Samples were purified for mRNAs and further sequenced using the Ion Torrent Proton with PI Chip (Life Technology). Reads were mapped to Human Genome using a two stage mapping strategy suggested by Ion Torrent. The Fragments Per Kilobase of transcript per Million mapped reads (FPKMs) was estimated using Cufflinks. Principal component analysis (PCA) was applied to visualize the data and identify outlying samples. The IPF samples were previously profiled for gene expression using Agilent microarrays and the correlation between the RNA sequencing data and microarray data was assessed to better understand the accuracy of the sequencing technology. Finally, differentially expressed genes (DEGs) between the two diseases were identified using Cuffdiff. Pathways enriched for these DEGs were identified using GeneGO MetaCore.

RESULTS: The sequencing reads were shown to have high quality based on the quality assessment report by FastQC. Average base level mapping rate across the samples is 90.25%. Based on the IPF samples, the FPKMs estimated from the RNA sequencing data is highly correlated with the expression levels measured by the Agilent microarrays (Pearson Correlation Coefficient=0.71, p value=2.2e-16). Data visualization using PCA showed global transcriptomic differences between the three diseases. Taken together, the sequencing data has a high quality and the data does provide information on the differences between the three diseases. The FPKMs were compared across the three diseases to identify the differentially expressed genes. These genes were further enriched for biological pathway to better understand the pathobiology of the diseases.

CONCLUSIONS: Ion Torrent Proton provided high quality RNAseq data for our SARC, A1AT and IPF samples. Differentially expressed genes are identified between the three diseases and enriched for biologic pathways.

[D44] Thematic Poster Session

FIRST LINE OF DEFENSE: AIRWAY RESPONSE TO INFECTIONS AND IRRITANTS

Facilitators: A.O. Yildirim, DVM, PhD, R. Foronjy, MD, M.G. Drake, MD, M.F. Beers, MD

Area C, Hall A-B (Upper Level), Colorado Convention Center, Wednesday, May 20, 2015, 09:30 AM - 03:30 PM

Poster Viewing: 11:30-1:15

[Poster Board # P229] Autophagy Proteins Regulate Airway Epithelial Cell MUC5AC Secretion and ROS Production, [Publication Number: A6470]

J.D. Dickinson, MD[1], N. Malvin, B.S.[2], Y. Alevy, PhD[2], J. Jones, BS[1], M.C. Zimmerman, PhD[1], T. Stappenbeck, MD PhD[2], M.J. Holtzman, MD[2], S.L. Brody, MD[2]

[1]Omaha, NE/US, [2]St. Louis, MO/US

Airway diseases including cystic fibrosis, asthma, and chronic obstructive pulmonary disease are characterized by obstruction of small airways by excessive accumulation of the predominant inflammatory airway mucin MUC5AC. The induction of MUC5AC gene expression is driven by type 2 cytokines, notably IL-13, but whether these cytokines also regulate mucin secretion into the airway still needs to be determined. Autophagy, a highly conserved cellular function, has recently been found to be essential for protein secretion in a number of cell types, including colonic goblet cells. We hypothesized that autophagy proteins might also regulate mucin secretion in airway goblet cells under inflammatory conditions. To test this hypothesis, we developed human cell culture models wherein the levels of autophagy protein expression could be regulated. We studied primary-culture human tracheobronchial epithelial cells (hTECs) that were treated with IL-4 or IL-13. We found that the levels of MUC5AC were increased in concert with the autophagy activity marker LC3-II, providing evidence that autophagy is activated under these conditions. To test whether autophagy was required for MUC5AC secretion, we transduced hTECs with shRNA sequences to decrease expression of ATG5 and thereby block the assembly of autophagosome isolation membranes. We found that IL-13 caused accumulation of intracellular MUC5AC and mucus granules in hTECs that were transduced with ATG5 shRNA compared to control cells. Consistent with these findings, the levels of secreted MUC5AC in the apical supernatant was significantly decreased in ATG5 knockdown cells. We found a similar decrease in ATG14-deficient cells. We also assayed IL-13-treated cells for ROS production using the oxidant sensitive fluorogenic probe CM-H2DCFDA (DCF) and electron paramagnetic resonance (EPR) spectroscopy with a 1-hydroxy-3-methoxycarbonyl-2,2,5,5-tetramethylpyrrolidine (CMH) spin probe. We found that IL-13 treatment caused a dose-dependent increase in intracellular ROS production in hTECs. Moreover, IL-13-driven ROS production was significantly attenuated in ATG5- and ATG14-deficient hTECs, suggesting that autophagy might be required for ROS production. Together, our findings indicate that autophagy is crucial for airway mucin secretion in the setting of inflammation and IL-13 production, and that this pathway might involve intracellular ROS as a mediator of mucus secretion. We propose that autophagy is a key target for therapy in airway diseases characterized by high levels of type 2 cytokines.

[Poster Board # P214] Increased Systemic Paraoxonase Activity is an Adaptive Response in Asthma, [Publication Number: A5984]

E. Baldarelli, BA[1], J. DiDonato, PhD[1], B.M. Gaston, MD[2], W.G. Teague, MD[2], E.R. Bleecker, MD[2], W.W. Busse, MD[2], W.J. Calhoun, MD[2], M. Castro, MD, MPH[2], K.F. Chung, MD, PhD[2], D. Curran-Everett, phd[2], E. Israel, MD[2], W.C. Moore, M.D.[2], S.E. Wenzel, MD[2], W.N. Jarjour, MD[2], S.L. Hazen, MD, PhD[1], S.C. Erzurum, MD[1], S.A.A. Comhair, PhD[1]

[1]Cleveland, OH/US, [2]Bethesda, MD/US

Severe Asthma Research Project

Rational: Paraoxonase 1 (PON1) is a high density lipoprotein-associated enzyme with antioxidant and anti-inflammatory-related activities and essential for protection against lipid peroxidation of circulating lipoproteins. Systemic measures of PON1 activity include the hydrolysis of organo-phosphates, aromatic esters and lactones, and are named based upon the exogenous substrate provided during the assay (e.g. paraoxonase, arylesterase and lactonase). Systemic measures

of PON1 activities have been linked to risk of coronary heart disease in humans, and genetic studies in mice (transgenic and genetic deletion) reveal PON1 functions in a protective fashion during atherosclerosis. Our work has shown both enhanced oxidative stress and loss of intracellular antioxidant activities in asthma. Here, we hypothesized that circulating PON1 activities may be altered in asthma and related to lipid peroxidation products.

Method: Serum PON1 activities were measured in controls (n=85) and asthmatics (n=459) in the Severe Asthma Research Program (SARP). Arylesterase activity was measured using phenyl acetate as substrate, and the rate of hydrolysis determined at 270 nm using an extinction coefficient of 1310 M−1•cm−1. Paraoxonase activity was measured using paraoxon as substrate and the rate of generation of paranitrophenol was determined at 405 nm using an extinction coefficient of 17,000M−1•cm−1. Lactonase activity was measured using -thiobutyrolactone as substrate and the rate of generation of free thiols in serum was determined at 412 nm using DNTB. Urine F2-isoprostanes [(8-Isoprostaglandin F2 alpha (8-iso-PGF2 alpha)] were measured by stable isotope dilution LC/MS/MS.

Results: Paraoxonase and lactonase activities were significantly higher in asthma as compared to controls [lactonase (umole/min/ml): mean (SE), Control, 172.2(6.0); Asthma, 189.9 (2.8); p=0.008; paraoxonase (nmole/min/ml): mean (SE), Controls, 859.7 (61.5); Asthma, 1023.0 (29.1); p=0.01], irrespective of asthma severity (p>0.05). Arylesterase showed a similar trend but failed to reach significance [Arylesterase (umole/min/ml): mean (SE), Control, 98.0 (3.3); Asthma, 104.1 (1.5); p=0.09]. Urinary 8-iso-PGF2 alpha, a product of free radical-mediated lipid peroxidation, was higher in asthma [(ng/mg Cr) Mean (SE): Controls, 0.47 (0.03); Asthma, 0.57 (0.03); p=0.03). Lactonase and paroxonase activities were inversely related to the 8-IsoPGF2 alpha levels in asthma (all p<0.02).

Conclusion: Systemic measures of PON activity are increased in asthma and inversely associated with F2Isoprostanes, systemic indices of oxidant stress. To our knowledge, this is the first evidence of up-regulation of antioxidant capacity in asthma populations.

[D92] Mini Symposium
INFLAMMATORY PATHWAYS IN ASTHMA AND COPD
Moderators: G.L. Chupp, MD, F.J. Martinez, MD, MS, A.A. Zeki, MD
Centennial Ballroom A-C (Third Floor), Hyatt Regency Denver at CCC, Wednesday, May 20, 2015, 01:30 PM - 03:30 PM

[2:15 PM] Rare SERPINA1 Variants are Associated with Lung Function and Health Care Utilization in a Multi-Ethnic Population from the Severe Asthma Research Program (SARP), [Publication Page: A6057]

S. Pasha, MD[1], V.E. Ortega, MD[1], E.J. Ampleford, PhD[1], M.J. Bamshad, MD[2], K.C. Barnes, PhD[3], W.W. Busse, MD[4], M. Castro, MD, MPH[5], S.C. Erzurum, MD[6], E. Israel, MD[7], R.A. Mathias, ScD, ScM[3], D. Nickerson, PhD[2], S.E. Wenzel, MD[8], G. Hawkins, PhD[9], E.R. Bleecker, MD[1], D.A. Meyers, PhD[9]

[1]Winston-Salem, NC/US, [2]Seattle, WA/US, [3]Baltimore, MD/US, [4]Madison, WI/US, [5]St. Louis, MO/US, [6]Cleveland, OH/US, [7]Boston, MA/US, [8]Pittsburgh, PA/US, [9]Winston Salem, NC/US
NIH NHLBI Severe Asthma Research Program

Background: The most frequent PI types associated with α1-antitrypsin (α1AT) deficiency and an increased risk for COPD result from rare variants in the SERPINA1 gene: PI type S (Glu288Val) and PI Z (Glu366Lys). There has not been a study of rare SERPINA1 variants in asthma subjects despite an

overlap of asthma-related phenotypes in subjects with α1AT deficiency (Eden et al. CHEST 2003, Malerba et al. J Intern Med 2003). We hypothesize that rare SERPINA1 variants result in altered lung function and health care utilization in asthmatics.

Methods: 523 non-Hispanic White (NHW) and 344 African American (AA) asthmatics who met the criteria of <5 pack years of smoking (non-smokers at time of exam) from NHLBI SARP1-2 were genotyped for 19 SERPINA1 exonic variants (15 rare coding variants, allele frequency < 0.05 including PI types Z, F, V, and I) and 24 common variants. A subset of 191 African Americans had whole-exome sequencing. Regression-based analyses were performed adjusted by age, sex, BMI, and medication use.

Results: In NHW, PI Z was not associated with baseline lung function; however, in those with a history of cigarette smoking, PI Z heterozygotes (genotype CT, N=4) had a lower pre-bronchodilator FEV1 (Figure 1: 51% vs 75%, p=0.03) and FEV1/FVC ratio (0.59 vs 0.70, p=0.03) compared to ex-smokers without PI Z (CC, N=92). Among NHW ex-smokers, PI Z was associated with an increased risk for hospitalization (OR=21.1, 95%CI=2.1-519, p=0.009) and ICU admission (OR=11.2, 95%CI=1.1-116, p=0.04) in the past year, and a lifetime history of an ICU admission (OR=17.6, 95%CI=2.0-380, p=0.01). These associations were not identified in NHW non-smokers. AA asthmatics inherited three rare SERPINA1 variants not identified in NHW or the NHLBI Exome Variant Server (Asp365Asn, His293Gln, Pro221His). AA who inherited >1 rare variant (N=11) had a greater number of urgent or emergency department visits in the past year compared to those without a rare variant (N=93, p=0.02). AA compound heterozygotes (N=3, one PI S [Glu288Val]/His293Gln and two PI I [Arg63Cys]/Asp365Asn) were more likely to require ≥ three glucocorticoid bursts (p=0.02) in the past year or a lifetime history of ICU admission compared to those with 0-1 SERPINA1 rare variants (N=190, p=0.01).

Conclusions: The rare SERPINA1 variant, PI type Z, potentially impacts asthma severity in NHW through a gene-by environment interaction with minimum cigarette smoking. In AA with asthma, other rare SERPINA1 variants might have the potential to influence asthma severity.

[2:30 PM] CLCA1 Peptide Levels as Accurate Biomarkers of the Type 2 Immune Pathway and Disease Severity in Asthma, [Publication Page: A6058]

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Rational: Our studies of experimental models and patients suggest that chronic airway disease can be linked to a newly identified IL-13 to chloride channel calcium activated 1 (CLCA1) to MAPK13 signaling pathway to airway mucus production. To date, most of the clinical evidence derives from patients with COPD and uses lung explants harvested from lung transplant recipients and donors. Here we extend our observations to: (1) samples that are obtained from the airway less invasively using bronchoscopy; (2) samples that are obtained from patients with mild, moderate, and severe asthma; (3) samples that are analyzed using newly developed ELISAs to quantify the mature N-terminal and C-terminal fragments of CLCA1 that are secreted into the airway lumen.

Methods: Bronchoalveolar lavage (BAL) samples were collected by flexible fiberoptic bronchoscopy in mild-moderate (n= 15) and severe (n=13) asthmatics and control nonasthmatics (n=14). Samples of BAL fluid were centrifuged to remove cells and then were analyzed for levels of N-terminal CLCA1 (N-CLCA1, aa 1-695), C-terminal CLCA1 (C-CLCA1, aa 696-914), and the predominant inflammatory airway mucin MUC5AC using newly developed ELISAs for each target.

Results: N-CLCA1 and C-CLCA1 but not MUC5AC levels were significantly increased in samples from asthmatics compared to nonasthmatics. Moreover, N-CLCA1 and C-CLCA1 levels were more closely associated with disease severity than MUC5AC levels with >3-fold higher N-CLCA1 and <2-fold higher C-CLCA1 levels in samples from severe compared to mild-moderate asthmatics or nonasthmatics. N-CLCA1 levels were significantly higher than C-CLCA1 levels in all subject groups and were significantly correlated with MUC5AC levels ($p<0.0001$). In contrast to N-CLCA1, the eosinophil level in BAL (or serum) did not correlate with disease severity.

Conclusion: Our findings suggest that levels of N-CLCA1 are a sensitive and accurate marker of mucus production and disease severity in asthma relative to C-CLCA1 and MUC5AC itself in assays of airway fluid samples. The findings are consistent with CLCA1 self-cleavage and function in airway epithelial cells and imply a utility of N-CLCA1 levels to stratify patients for therapeutics aimed at attenuation of excess production of inflammatory airway mucus driven by type 2 immune responses.

[D103] Poster Discussion Session
COPD: FOCUS ON RESEARCH AND PATIENT CARE
Moderator: V.S. Fan, MD, MPH
Room 401-402 (Street Level), Colorado Convention Center, Wednesday, May 20, 2015, 01:30 PM - 03:30 PM
Poster Viewing: 1:30-2:15
Discussion: 2:15-3:30

[Poster Board # 218] Use of a Remote Inhaler Monitor Device to Measure Change in Inhaler Use with COPD Exacerbations, [Publication Number: A6181]

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Rationale: Remote monitoring of inhaler use is an emerging technology by which the provider can remotely monitor the time and location of inhaler use. We assessed the feasibility of its use for COPD patients and the pattern of inhaler use associated with episodes of COPD exacerbations.

Methods: We conducted a 12-week pilot study among COPD patients in which an GPS-enabled sensor recorded the date and time of each albuterol actuation. Self-reported COPD exacerbations and healthcare utilization were assessed monthly. Exacerbations were categorized as mild (symptom only), moderate (requiring prednisone and/or antibiotics), and severe (emergency department visits or hospitalizations). We used generalized estimating equations with a logit link to compare the odds of an exacerbation day to a day of non-exacerbation day by the frequency of albuterol use. Using the log transformed daily puffs we calculated the average odds associated with a percentage increase in albuterol use, after adjustment for baseline FEV1 percent predicted.

Measurements and Main Results: We enrolled 35 COPD patients (94.3% male and mean age: 66.5 +8.5) with a mean FEV1 % predicted of 44.9 + 17.2 . 42.9% reported a severe exacerbation in the past year, and 88.6% had more than two comorbidities. The average daily albuterol use was highly variable among patients, ranging from 1.5 to 16.3 puffs. 29 participants (82.9%) experienced >1 COPD exacerbation, of which 12 experienced at least one moderate to severe exacerbation. There was a median increase of 10.3% (interquartile range: -5.0 to 37.0%) in average daily puffs during exacerbation days compared to non-exacerbation days. For an average subject, a 50% increase in daily albuterol puffs was associated with an odds ratio (OR) of any exacerbation in the adjusted model of 1.14 (95% confidence interval [CI]: 1.07, 1.22). Among subjects with >1 moderate to severe

exacerbation, a 50% increase in use was associated with an OR of 1.30 (95% CI: 1.11,1.51). The device was well tolerated with 74.1% reporting satisfaction with the device. The device did not record any use for 30.9% of follow-up days, which could be due to no use, the device being turned off, or if the participant used their inhaler without the device.

Conclusions: Remote inhaler monitoring device was well tolerated and can be used to monitor inhaler use in older patients with COPD. Increased albuterol use captured by the device was associated with self-reported episodes of exacerbations.