Staphylococcus Aureus Colonization Is Associated with Increased Atopy and Inhaled Steroid Use in Patients with Atopic Dermatitis and Asthma

Peter Uong, MD1, Douglas Curran-Everett, PhD1, and Donald Y. M. Leung, MD, PhD, FAAAAI2; 1National Jewish Health, Denver, CO, 2K926i, National Jewish Health, Denver, CO.

RATIONALE: Staphylococcus aureus (S. aureus) colonization has been associated with severe atopic dermatitis (AD), and in experimental models, has been shown to increase IgE and corticosteroid insensitivity. We tested the hypothesis that S. aureus colonization may also contribute to increased environmental allergen sensitization and severity of asthma.

METHODS: We reviewed the patient research database at National Jewish Health and found 557 patients (less than or equal to 18 years of age) with a concurrent diagnosis of AD and asthma who had been cultured for S. aureus. We queried for total and allergen specific serum IgE levels, positive skin tests to inhalant allergens, exhaled nitric oxide (eNO), asthma control test (ACT) scores, and medications prescribed.

RESULTS: Of the 557 patients with AD and asthma who were cultured for S. aureus, 459 subjects had positive S. aureus cultures (average age 6.4 years old; 66% males) and 98 subjects had negative S. aureus cultures (average age 5.3 years old; 62% males).

Subjects with S. aureus colonization, as compared to S. aureus negative subjects, had significantly higher total serum IgE (P < .001), percent positive skin prick tests for aeroallergens (P = .003), and higher eNO (P = .05). Importantly, asthmatics colonized with S. aureus required a higher daily dose of inhaled corticosteroids (P = .02) despite similar ACT scores (P = .92).

CONCLUSIONS: Our data suggests that S. aureus colonization in asthmatics with concomitant AD is associated with increased IgE responses to environmental allergens, increased eNO, and increased inhaled corticosteroid use. We postulate that S. aureus colonization contributes to systemic allergy and corticosteroid insensitivity.

Oxidative stress induces fibrotic reactions in Atp8b1 mutant mice through abnormal behavior of Club cells

Jutaro Fukumoto, MD, PhD. Andrew J. Cooke, MD, Ramani Soundararajan, PhD, Richard F. Lockey, MD, FAAAAI, and Narasaih Koliputi, PhD; Division of Allergy and Immunology, Department of Internal Medicine, Morsani College of Medicine, University of South Florida, Tampa, FL.

RATIONALE: Atp8b1 is a cardiolielin transporter in the apical membrane of lung epithelial cells. While the role of Atp8b1 in pneumonia-induced acute lung injury (ALI) has been well studied, its potential role in oxidative stress (hyperoxia)-induced ALI and recovery from it are poorly understood.

METHODS: WT mice and Atp8b1L1208V/G1308V mutants (functionally deficient; referred to as Atp8b1 mutant mice hereinafter) were exposed to 100% O2. A portion of mice were euthanized 48 hrs after exposure for sample collection (acute inflammatory phase). The remaining mice were euthanized after an additional 12 days under normoxia (post-inflammatory recovery phase). Cell apoptosis, proliferation, inflammatory response, and tissue fibrosis were evaluated using bronchoalveolar lavage (BAL) fluid and lung tissue samples. Human lung samples from patients with idiopathic pulmonary fibrosis (IPF) and COPD were subjected to immunohistochemical labeling for Club cell markers, CCSP and Claudin-10 (Cldn10).

RESULTS: H&E-stained and TUNEL-stained lung sections from WT and Atp8b1 mutant mice revealed that Atp8b1 mutant mice under hyperoxia display accelerated alveolar cell death and patchy proliferation of bronchiolar epithelial cells. BAL analysis and immunohistochemical labeling for Ki-67 revealed that TUNEL-negative Club cells proliferate in Atp8b1 mutant lungs under inflammatory conditions, which was followed by fibrotic reactions during the recovery phase. Clinical relevance of Club cell aberration to IPF was confirmed by marked pleomorphism and wide distribution of Cldn10-positive Club cells in IPF lungs.

CONCLUSIONS: Oxidative stress induces aberrant fibrionic reactions in Atp8b1 mutant mice. This model can be a new format to unravel the role of Club cells in the development of IPF.

Chronic Rhinitis Is A Strong Clinical Predictor for Early Hospital Readmission Of Chronic Obstructive Lung Disease Patients

Umesh Singh, MD, PhD1, Victoria Wangia-Anderson, PhD2, Linda Levin, PhD3, and Jonathan A. Bernstein, MD, FAAAAI1,2; 1University of Cincinnati College of Medicine, Cincinnati, OH, 2University of Cincinnati, College of Allied Health Sciences, Cincinnati, OH, 3Bernstein Allergy Group, Inc, Cincinnati, OH.

RATIONALE: Hospital performance measures are determined by 30-day readmission rates (30d-RR) for specific medical conditions. Purpose of this study was to assess the 30d-RR for chronic obstructive lung disease (COLD) using a large university hospital patient database.

METHODS: De-identified patient records of hospital encounters, demographics and comorbidities admitted with a primary diagnosis of asthma or chronic obstructive pulmonary disease (i.e., COLD) from the University of Cincinnati Hospitals (UCH) between October, 2012 and July, 2016 were analyzed to determine the 30d-RR compared to the national average of 22.1%. Age and mortality-adjusted comorbidities as risk factors for 30d-RR were determined in multivariate logistic regression analysis. Adjustment for medical complexity and social vulnerability was not performed due to missing data.

RESULTS: Of the 11,311 hospital encounters for 5,735 COLD patients, 2,104 (18.6%) were readmitted within 30d. The mean age of readmitted patients (n=2,087) and non-readmitted patients (n=3,648) were 53.2 vs. 50.6 years, respectively (p<.001). No difference in average length of stay was observed between these two groups (1.74 vs. 1.68 days), however, a significantly greater percentage of readmitted patients (4.1%) versus non-readmitted (2.7%) patients died over this period. Logistic regression analysis identified chronic rhinitis (OR=2.7; p<.0001), diabetes mellitus (OR=1.3; p<.0014), cardiac arrhythmia (OR=1.7; p<.0001), anemia (OR=1.5; p<.0001), tobacco use (OR=1.5; p<.0001), or obesity (OR=1.6; p<.0001) significantly increased the 30d-RR.

CONCLUSIONS: The 30d-RR for COLD at UCH was 18.6% which is better than the national average. Interestingly, the comorbidities identified, most notably chronic rhinitis, are novel and suggest that their treatment should be prioritized in these high risk patients to further reduce 30d-RR.
**IL-22 Generated in Response to Cutaneous Sensitization Drives Neutrophilic Airway Inflammation Following Antigen Inhalation in a Mouse Model of Atopic Dermatitis**

Juan-Manuel Leyva-Castillo, Juhan Yoon, and Raif Geha; Division of Immunology, Children’s Hospital and Department of Pediatrics, Harvard Medical School, Boston, MA.

**RATIONALE:** Asthma is a heterogeneous chronic pulmonary inflammatory disease, commonly preceded by atopic dermatitis (AD). We have recently shown that systemic IL-22 is induced by epicutaneous (EC) sensitization in a mouse model of AD. We examined whether this IL-22 response contributes to airway inflammation triggered by antigen inhalation in EC sensitized mice.

**METHODS:** Wild type (WT) and Il22−/− mice were subjected to EC sensitization with ovalbumin (OVA) or saline followed by intranasal (i.n.) OVA challenge. WT mice were adoptively transferred with OVA TCR-specific Th22 from WT or Il22−/− mice and i.n. challenged with OVA. rIL-22, rIL-17A and rTNFa, alone or in combination were instilled intranasally in WT mice. Airway inflammation, mRNA levels in the lungs and airway hyper-responsiveness (AHR) were examined.

**RESULTS:** EC OVA sensitization promoted IL-22 production in the lungs after i.n. challenge. EC OVA sensitized Il22−/− mice exhibited diminished eosinophil and neutrophil airway infiltration and decreased AHR following i.n. OVA challenge. Moreover, Il22−/− mice exhibited enhanced IFNγ, but normal IL-13 and IL-17 production in the lungs. Adoptive transfer of in vitro polarized WT but not IL-22 deficient TCR-OVA specific Th22 cells, which co-express IL-17A and TNFa, promoted a neutrophil-dominated airway inflammation, increased Cxcl1 and Cxcl3 mRNA and enhanced AHR. Intranasal instillation of IL-22 in combination with TNFa, but not IL-17A, caused neutrophilic airway inflammation with increased Cxcl1 and Cxcl3 mRNA and enhanced AHR.

**CONCLUSIONS:** EC sensitization promotes the generation of antigen-specific Th22 cells, which drive neutrophil-dominated airway inflammation and AHR following antigen inhalation, suggesting that IL-22 plays an important role in the atopic march.

**The activation of transient receptor potential melastatin 8 (TRPM8) receptors induces airway inflammation in bronchial asthma**

Joo-Hee Kim1, Young-Sook Jang1, Ji Young Park1, Yong Il Hwang1, Sung-ho Park1, Seung-Hun Jang1, Ki-Suck Jung1, and Hae-Sim Park, MD, PhD2; 1Hallym University Medical Center, Anyang, Korea, The Republic of. 2Department of Allergy and Clinical Immunology, Ajou University School of Medicine, Suwon, Korea, The Republic of.

**RATIONALE:** The airway epithelium is exposed to a range of irritants in which can trigger airway inflammation. Cold air is a major environmental factor that exacerbates bronchial asthma, and transient receptor potential melastatin family member 8 (TRPM8) receptor is a cold- and menthol-sensing cation channel expressed in sensory neurons as well as bronchial epithelial cells. We sought to explore the role of TRPM8 receptor expressed in bronchial epithelial cells in airway inflammation.

**METHODS:** Human airway epithelial cell line, BEAS-2B, was treated with menthol, TRPM8 antagonist (BCTC, N-(4-tert-butylphenyl)-4-((3-chloropyridin-2-yl) Piperazine-1-carboxamide) and dexamethasone in dose- and time-dependent manner. The mRNA of TRPM8 and several cytokines was determined by real-time quantitative PCR. ELISA of TRPM8 and real-time PCR for epithelial derived cytokines (TSLP, IL-25, and 33) were performed using the induced sputum of asthmatics and normal controls.

**RESULTS:** TRPM8 receptor was expressed primarily in bronchial epithelial cells at both mRNA and protein levels with statistical significances. Activation of the TRPM8 receptors by menthol was coupled with enhanced expression of the inflammatory cytokines of IL-4, 6, 8, 13, 33 and treatment with BCTC and dexamethasone attenuated the expression of inflammatory cytokines. TRPM8 protein expression was significantly increased in patients with asthma compared with healthy controls using ELISA of sputum supernatants. There were positive correlations between TRPM8 mRNA level and TSLP, IL-25, and -33 in the sputum of asthmatics.

**CONCLUSIONS:** Activation of TRPM8 receptor of bronchial epithelial cells induces airway inflammatory cytokines, suggesting the TRPM8 receptor may involve in cold induced asthma exacerbations.
7 Presence of Cytomegalovirus DNA in the Whole Blood Is Associated with the Risk of Bronchial Asthma

Marek L. Kowalski1, Aleksandra Wardzynska2, Mirosława Studzińska3, Malgorzata Pawelczyk1, Zbigniew Jan Lesnokowski1, and Edyta Paradrowska1; 1Department of Immunology, Rheumatology & Allergy, Medical University of Lodz, Lodz, Poland, 2Department of Immunology, Rheumatology & Allergy, Medical University of Lodz, Lodz, Poland, 3Laboratory of Molecular Virology and Biological Chemistry, Lodz, Poland.

RATIONALE: Cytomegalovirus (CMV) is a recognised cause of morbidity in immunocompromised individuals. CMV seropositivity has been associated with signs of immunosenescence and systemic inflammation in the elderly. We aimed to assess the presence of CMV DNA in the blood of elderly and non-elderly patients with bronchial asthma.

METHODS: Eighty five elderly asthmatics (above 65 years of age) and 74 younger asthma patients (aged 30-50) were recruited and underwent clinical and laboratory evaluation. Control group consisted of 63 adults over 65 years old and 56 subjects aged 30-50 without chronic respiratory disease. Real-time PCR (RT-PCR) for quantitation of CMV DNA was performed with the commercial CMV detection kit (detection limit > 500 copies/mL) and with an in-house assay targeting the UL53 gene (detection limit >100 copies/mL).

RESULTS: Commercial CMV assay was positive in 18% of elderly and 1.3% non-elderly asthma patients, but was negative in all control samples. Custom made RT-PCR assay detected low levels of CMV DNA in 42.1% of asthma patients and in 12.6%, of control subjects (p<0.001). The test positivity was higher in elderly asthmatics than in younger patients (52.9% vs. 29.7%, p=0.003), and higher in elderly control subjects than in younger controls (22.2% vs. 1.8%, p<0.001). Presence of CMV DNA was associated with an increased risk of asthma: OR=5.1 (95% CI: 2.7-9.4, p<0.001) for the whole population tested and OR=21.6 (95%CI: 2.8-166.1; p<0.001) for non-elderly subjects.

CONCLUSIONS: CMV replication at low level is highly prevalent in elderly asthmatics and is associated with risk of asthma.

8 IL10 Genetic Variants Are Associated With House Dust Mite-Allergy But Not Directly On Asthma In A Severe Asthma Case-Control Study

Hellen Freitas Fonseca1, Ryan Santos Costa1, Tamires Cana Brasil Carneiro1, Regina Santos Nascimento1, Gerson Almeida Queiroz, Sr, AnaQue Oliveira Pires1, Alvaro Augusto Cruz Filho1, and Camila Alexandrina Figueiredo1, Sr1; 1Institute of Health Sciences, Federal University of Bahia, Salvador, Bahia, Brazil, Salvador, Brazil, 2Institute of Health Sciences, Federal University of Bahia, Salvador, Salvador, Brazil, 2Institute of Health Sciences, Federal University of Bahia, Salvador, Salvador, Brazil, 3Institute of Health Sciences, Federal University of Bahia, Salvador, Salvador, Brazil, 4Federal University of Bahia, Salvador, Brazil, School of Medicine, Federal University of Bahia, Salvador, Salvador, Brazil, 5School of Medicine, Federal University of Bahia, Salvador, Salvador, Brazil.

RATIONALE: IL10 is a key immune regulatory cytokine to control immune reactions and has been linked to asthma and atopy. Polymorphisms (SNPs) in the IL10 may affect the production of this cytokine and thus asthma/allergy occurrence. This work evaluates the associations between IL10 SNPs, different asthma phenotypes, markers of allergy and IL10 levels in a case-control study for severe asthma in adults living in Salvador, Brazil.

METHODS: DNA was extracted from peripheral blood from 1,406 subjects (448 mild asthma, 503 severe asthma and 455 healthy individuals) recruited in a case-control study for severe asthma in adults living in Salvador, Brazil. The IL10 SNPs were typed by using TaqMan probe. The study included 4 SNPs (rs3024496) negatively associated with SPT to Dermatophagoaides farinae (OR=0.77; CI 0.65-0.91) and SPT to D. pteronyssinus (OR=0.83; CI 0.70-0.99) both in additive model. The SNP rs3024491 was negatively associated to D. farinae (OR=0.81; CI 0.67–0.97) skin reactivity. None of the asthma phenotypes studied (including severe asthma) were associated with IL10 SNPs (p>0.05).

CONCLUSIONS: IL10 SNPs were associated negatively with skin test to allergen, an indicator of allergic sensitization in a Brazilian population confirming the possible role of this gene in atopy but not directly in asthma.

9 Effect of age and asthma on Treg cell function

Janette Birmingham1, Juan Wnisievsky, MD, DrPH2, and Paula J. Busse, MD, FAACAP, 1Mount Sinai School of Medicine, New York, 2Icahn School of Medicine Mount Sinai, New York, 3Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY.

RATIONALE: Regulatory T-cells (Tregs) may control inflammation in younger asthma patients. Older asthma patients (>60 years) have increased morbidity and mortality. However, Treg function is not well established in the latter group.

METHODS: To evaluate Treg function with aging and asthma, peripheral blood mononuclear cells (PBMC) were collected from a subset of younger (n=14) and older (n=15) subjects from a cohort of inner-city asthma patients in which sputum and asthma control (ACT) has been measured. To control for the effect of aging itself, PBMCs were collected from younger (n=5) and older (n=7) non-asthma subjects. Tregs were isolated from PBMCs; autologous PBMCs CFSE-labeled, and cultured with anti-CD3/anti-CD28; and the Treg function assessed by measuring suppression at decreasing ratios of Tregs/PBMCs. Sputum Treg function was assessed by flow cytomtery (MFIs).

RESULTS: Despite worse asthma control in the older (ACT=15.1) vs younger patients (ACT=19.3, P<0.03), and increased hospitalizations, ER and urgent care visits in the past 12 months, there were not significant differences in the function of peripheral and sputum Tregs between ages of patients.

CONCLUSIONS: These findings suggest that despite poorer asthma outcomes in older patients with asthma, age-related differences in Treg have a minimal contribution.

10 Wnt7b/Beta-Catenin Signal Pathway Associated with Airway Remodeling of Asthma Rats

Weixi Zhang, MD, PhD1, Tingting Zhu, MD1, Xiaoxiao Jia, MD1, Cuuye Weng, MD, MD1, Changchong Li, MD1, and Wei Zhao, MD, PhD2; 1Mount Sinai School of Medicine, New York, 2Icahn School of Medicine at Mount Sinai, New York, NY.

RATIONALE: Wnt signaling pathway that regulates function of multiple tissue and cell types is involved in the pathogenesis of bronchial asthma. This study was designed to explore the role of Wnt/beta-catenin signaling in airway remodeling of asthma.

METHODS: Sprague-Dawley rats were sensitized intraperitoneally with ovalbumin (OVA) on day 1 and 8, followed by aerosol OVA challenge every other day for 8 weeks. Sham control received normal saline in both phases. HE staining was used to examine lung histological structure change. Bronchial wall thickness (Wat) and bronchial smooth muscle thickness (Wam) were measured by Image-Pro plus 5.0 image analysis system. The expression of Wnt7b, beta-catenin and c-Myc was determined by immunohistochemistry (IHC) for protein level and qRT-PCR for mRNA level.

RESULTS: Asthma group showed significant increase of Wat and Wam. The protein expression of Wnt7b (0.17 ± 0.05), beta-catenin (0.33 ± 0.07) and c-Myc (0.41 ± 0.13) in asthma group was much higher than control group (0.07 ± 0.02, 0.19 ± 0.03 and 0.20 ± 0.04, P<0.01). mRNA expression of Wnt7b, beta-catenin, and c-Myc was elevated (P<0.01). A strong positive correlation was noticed between Wat protein and Wnt7b, beta-catenin, c-Myc (r=0.808, 0.821, and 0.787, respectively); also between Wat and Wnt7b, beta-catenin, c-Myc (r=0.847, 0.834, and 0.853, respectively).

CONCLUSIONS: The elevation of Wnt7b, beta-catenin, and c-Myc was closely associated with thickening of bronchi and smooth muscle in rat model of asthma. Data suggest that Wnt/beta-catenin signaling pathway may play an important role in airway remodeling of asthma.
11 Variants in **OXA1L** Gene Are Associated With Asthma and Atopy in a Latin Population

Anaque Oliveira Pires¹, Milicia Jesus Silva¹, Maria Borges Rabelo Santana¹, Raimon Rios Silva¹, Hugo Bernardino Ferreira Silva, Sr², Norma Vilani Queiroz Carneiro², Gerson Almeida Queiroz, Sr³, Héllen Freitas Fonseca³, Sandro Oliveira Dias³, Ryan Santos Costa², Mauricio Lima Barreto⁴, and Camila Alexandrina Figueiredo²

¹Institute of Health Sciences, Federal University of Bahia, Salvador, Brazil, ²Institute of Health Sciences, Federal University of Bahia, Salvador, Brazil, ³Institute of Health Sciences, Federal University of Bahia, Salvador, Brazil, ⁴Institute of Health Sciences, Federal University of Bahia, Salvador, Brazil, ⁵State University of Santa Cruz, Ilhéus, Brazil, ⁶Oswaldo Cruz Foundation, Salvador, Brazil.

**Rationale:** Asthma and atopy are considered complex diseases linked to the environmental and genetic factors. The **OXA1L** is involved in the biogenesis of proteins from mitochondria membrane. Changes in oxidative stress and calcium homeostasis in bronchial smooth muscle cells increase mitochondrial biogenesis, cell proliferation, and remodeling of the airways. Thus, we hypothesize that genetic variants in **OXA1L** are associated with asthma and atopy in an admixture population from Brazil.

**Methods:** DNA from 1,307 individuals was genotyped using Illumina Human 2.5-8 Omni Bead chip. Logistic regression analyses were performed to verify the association of polymorphisms in **OXA1L** with asthma and allergy markers using PLINK 1.9 software adjusted for sex, age, and ancestry markers in an additive model. *In silico* gene expression analysis was performed in whole blood tissue using GTEx browser.

**Results:** The allele of rs4981436 in **OXA1L** was positively associated with asthma (OR=1.41; CI:1.08-1.84; p=.012). Additionally, the G allele of rs8572 was positively associated with skin prick test to *D. pteronyssinus* (OR=1.33; CI:1.05-1.70; p=.020), *Periplaneta americana* (OR=1.32; CI:1.03-1.70; p=.029) and dog epithelium (OR=2.21; CI:1.02-4.82; p=.045). The same allele (G for rs8572) was also positively associated with anti-*D. pteronyssinus* specific IgE (OR=1.27; CI:1.10-1.56; p=.027). In relation to the *in silico* gene expression analysis, the G allele of rs8572 led to a higher gene expression in Whole Blood tissue.

**Conclusions:** Polymorphisms in **OXA1L** were positively associated with asthma and allergy markers in our population. At least in part, this association can be explained by the increased expression of this gene observed herein.

12 **IL1RL1** Variants rs1041973 and rs873022 are Associated With Allergy Markers and Soluble ST2 Production in a Brazilian Population

Gerson Almeida Queiroz, Sr¹, Ryan Santos Costa², Valdirene Leao Carneiro¹, Talita Santos Jesus², Neuzia Maria Alcântara-Neves², Anaque Oliveira Pires³, Héllen Freitas Fonseca³, Mauricio Lima Barreto³, and Camila Alexandrina Figueiredo²

¹Institute of Health Sciences, Federal University of Bahia, Salvador, Brazil, ²Institute of Health Sciences, Federal University of Bahia, Salvador, Brazil, ³Institute of Health Sciences, Federal University of Bahia, Salvador, Brazil.

**Rationale:** Asthma and other allergic diseases are caused by type 1 hypersensitivity reaction, initiated by IgE antibody-mediated mechanisms and inflammatory cells. Interleukin-33 (IL-33) appears to be a potent inducer of Th2 response, since it promotes the release of IL-4, IL-5 and IL-13, contributing to inflammation in asthma. The polymorphisms in the IL-33 and IL1RL1 are the most replicated genes in Genome-Wide Association Studies (GWAS) for allergic conditions worldwide. The aim of this study was to associate polymorphisms (SNPs) in the IL1RL1 gene with allergy markers in a Brazilian population.

**Methods:** DNA of 1,253 subjects were genotyped using Illumina 2.5 Human Omni Beadchip. Logistic regressions between **IL1RL1** polymorphisms with allergy markers were performed using PLINK software 1.9 adjusted for sex, age, hemilinfection and ancestry markers, in dominant model. The concentrations of plasma levels soluble ST2 (sST2) were measured by sandwich ELISA.

**Results:** The A allele of rs1041973 was positively associated with IL-5 production (OR=1.36; CI 1.09-1.84, p=.044), with positive SPT (OR=1.48, CI 1.08-2.03, p=.014) and specific IgE levels (OR=1.40, CI 1.07-1.84, p=.013), both for *B. tropicalis* mite. In addition, sST2 levels in serum from atopic subjects were higher in AA genotype for rs1041973 compared with individuals with AC and CC genotypes (p<.05). On the other hand, the T allele of rs873022 was negatively associated with sIgE levels for *B. tropicalis* (OR=0.72, CI 0.54-0.98, p=.035).

**Conclusions:** Variants in **IL1RL1** are associated with allergy markers, at least in part, due to the decreased levels of sST2.

13 A Common Pattern of Peripheral Airway Responsiveness in Asthma and Allergic Rhinitis

Alain Michils, MD¹, Amaryllis Haccuria, MD², Andrei Malinovschi, MD³, and Alain Van Muylem, PhD¹

¹Erasm University Hospital, Brussels, Belgium, ²Uppsala University, Uppsala, Sweden.

**Rationale:** Allergic rhinitis (AR) is a risk factor for developing asthma. Moreover, AR is often associated with bronchial hyper-responsiveness (BHR) usually assessed by FEV1 decrease during airway challenge (i.e. capturing proximal airway response). The aim of this study was to compare the peripheral component of airway responsiveness in asthma and AR.

**Methods:** FENO, FEV1, and the slope of phase III of the single breath washout test (SBWT) of Helium (He) and sulfur hexafluoride (SF6) were measured in 32 patients with asthma, 20 patients with AR and 20 healthy controls (HC), before and after sputum induction procedure which is similar to airway challenge with hypertonic saline. FENO decreases and He and SF6 slopes increases were both previously shown to be sensitive to airway caliber change occurring in lung periphery during airway challenges. Changes (D) were expressed as relative changes from baseline (%). *Results:* Mean FEV1 decrease was greater in the asthma group compared to AR and HC populations (16.5% vs 6.5% and 4.5% respectively (p<.01). FENO decrease was larger in asthma and AR populations than in HC group (58.6% and 50.8% vs 37.4% respectively (p<.001). DSSF6 > DSSH were observed in both rhinitis (p=.008) and asthma (p<.001), whereas DSSH = DSSH in HC (p=.962).

**Conclusions:** A common pattern of peripheral airway responsiveness distinct from that of HC is documented in patients with asthma or rhinitis, supporting the ‘one airway one disease’ concept physiologically. It is likely that the involvement of both proximal and peripheral airways distinguish airway responsiveness in asthma from airway responsiveness in allergic rhinitis.
14 Identification of steroid response signature among patients with mild to moderate asthma using differential protein expression analysis.

Tanvi Patel, MD1, Lata Kachalia, MS, MEd, PhD2, and William J. Calhoun, MD3, 1UTMB, League City, TX, 2UTMB, Galveston, TX.

RATIONALE: Asthma is a heterogeneous disorder with several phenotypes. We proposed to identify a unique steroid response signature in mild-to-moderate asthmatics, and postulated that asthmatics without ICS (A-S) would express higher inflammatory cytokine levels, and asthmatics on ICS (A+S) would express protein patterns similar to normal (N) patients.

METHODS: We enrolled 6 N, 6 A-S and 11 A+S patients. All patients underwent bronchoscopy with bronchoalveolar lavage (BAL). BAL fluid was analyzed for 22 cytokines using the Bio-Rad Bio-Plex Pro Assay. Each cytokine was expressed as a percentage of the mean for that cytokine. Analysis was performed using one-way ANOVA, using log-transformed data.

RESULTS: Seven of 22 cytokites were detectable. Combined inflammatory cytokite expression decreased between N, A-S, and A+S groups (159%, 111%, 62%, respectively; p<0.05), and combined anti-inflammatory cytokite expression did not differ. Compared to A-S, A+S patients expressed lower levels of IL-10 (85% vs. 71%, p=0.037) and MIG (86% vs. 35%, p=0.005). IL-8 expression varied between N, A-S and A+S patients (83%, 168%, 57%; p=0.001). There were no statistically significant differences in IL-10, IL-1Ra, G-CSF or VEGF expression.

CONCLUSIONS: Except for IL-8, pro-inflammatory cytokite expression was decreased in A-S and A+S, compared to the N group. IL-8, IP-10 and MIG were identified as steroid responsive cytokines, as their detection levels were reduced in the A+S compared to the A-S group. The explanation for lower cytokine levels in A-S and A+S subjects may suggest in vivo proteolysis, or other effect. This data suggests that protein expression patterns may recognize steroid responsive genes in asthma.

15 Impact of Environmental Factors on Recurrent Asthma Exacerbations among Inner-City Schoolchildren from the Pittsburgh Region

Deborah A. Gentile, MD1, Nicole Sossong2, Tricia Morphe3, Albert Presto4, and Jennifer Elliott5; 1Allegheny Singer Research Institute, Pittsburgh, PA, 2Allegheny Singer Research Institute, Pittsburgh, 3Morphe Consulting, Seattle, 4Carnegie Mellon University, Pittsburgh, 5Duquesne University, Pittsburgh.

RATIONALE: Pediatric asthma is a public health concern in the inner-city of Pittsburgh. The purpose of this study was to determine factors influencing the occurrence of repeated episodes of asthma among Pittsburgh school children.

METHODS: This study was approved by the Allegheny Singer Research Institute IRB. Informed consent/assent was obtained from all subjects prior to participation. Students aged 4-13 years with asthma were enrolled from fifteen Pittsburgh schools. Parents were surveyed using an abbreviated, validated survey to assess asthma control. Relationships between potential contributing factors were explored using logistic regression analyses.

RESULTS: 166 subjects were enrolled (53.6% African American, 48.8% female, 64.8% public insurance, and mean± age 9.2±1.8 years). 35% had repeated episodes of asthma in the prior year. NO2 exposure was the only unadjusted factor that influenced odds of repeated asthma exacerbations (OR=1.35 per one unit increase; P<0.05). Adjusted analysis showed that influence of NO2 exposure on odds of repeated asthma exacerbations became a significant factor after 9 years of age (OR=1.72, P<0.05 in children age 10; P=0.05 in children < 9 years). Chronic stress corresponded to 6 times higher odds of repeated exacerbations (OR=6.10, P<0.05), among children with private insurance and lower than average NOx exposure.

CONCLUSIONS: Results indicate a high rate of repeated exacerbations of asthma among school children from the inner-city of Pittsburgh. Identified contributors to uncontrolled disease include outdoor air pollution, chronic stress in those not on public health insurance nor exposed to higher than average NOx levels. Future studies need to focus on improving asthma outcomes in at-risk populations.

16 Entire Course Monitoring and Evaluation of Asthma Attack Following Allergen Airway Challenge In A Rat Model

Xingdong Zhang, Jingjiao Tao, and Chuan Qin; Chinese Academy of Medical Sciences, Beijing, China.

RATIONALE: For airway measurement following specific allergen challenge, anesthetization and artificial ventilation were necessary with traditional method in rodent asthma models and it was hard to naturally record the entire course of asthma attack including early-(EAR) and late-phase asthmatic responses (LAR). Ergo, a new asthma animal model to meet our research requirement is necessary.

METHODS: Brown Norway rats were immunized subcutaneously with 0.01, 0.1, 1, and 10 mg of ovalbumin in saline and mixed with aluminum hydroxide (alum) on days 0 and 5. Sera were collected for specific IgE analyses. Airway challenge with aerosolized 5% ovalbumin was conducted in conscious rats on day 35. Airway measurement was performed with whole-body plethysmography and enhanced pause (a parameter from the expiratory phase) was recorded continuously for 16 hours (covering the entire period of asthma attack).

RESULTS: Rats developed dose-dependent specific IgE and asthmatic responses following airway challenge. The group sensitized with 10 mg ovalbumin plus 100 mg alum steadily developed EAR and LAR. EAR developed immediately following challenge and ended within the first hour. LAR initiated 1 to 2 hours after challenge and lasted from 2 hours to 14 hours. The airway responses can be inhibited if animals were treated with dexamethasone before challenge.

CONCLUSIONS: Entire course of asthma attack was successfully recorded in the conscious rat model especially LAR can be observed. This model may be a useful tool for asthma studies especially for evaluating or finding antiasthma drugs.

17 Does Bioaerosol Exposure Increase the Risk of Pediatric Asthma?

Nadia Thura1, Eugene Hershorn, MD1, Lourdes Forster, MD1, Sumitha Khatri, MD2, and Naresh Kumar, PhD3; 1University of Miami Miller School of Medicine, Miami, FL, 2Respiratory Institute, Cleveland Clinic, Cleveland, 3University of Miami Miller School of Medicine, Department of Public Health Sciences, Miami, FL.

RATIONALE: Miami, FL has high levels of year-round bioaerosols in the form of indoor molds and outdoor pollens. Elevated exposure to bioaerosols can sensitize subjects with predisposition for developing allergies and/or asthma, especially those unexposed previously. We hypothesize that migrants, especially those from higher latitudes, are at a greater risk of developing allergies and asthma after migrating to Miami.

METHODS: An online survey designed with Qualtrics software was administered using iPads in two general pediatric clinics at the University of Miami. The survey includes questions on demographics, migration status, past diagnosis and symptoms of asthma or other allergic respiratory disease, medications, and environmental factors such as exposure to secondhand smoke, pets, and other indoor allergens sources.

RESULTS: A total of 109 (~ 70%) of 162 parents/guardians who were approached participated in the survey. Twenty percent (22 of 109) of children had physician-diagnosed asthma, and 31% of children without an asthma diagnosis reported wheezing in the past. Therefore, diagnosed and possible undiagnosed pediatric asthma prevalence was as high as 45%. Among 109 subjects, 11 were migrants. Although the prevalence of physician-diagnosed asthma among migrants and non-migrants was not significantly different, 27% of migrant children (3 of 11) had physician-diagnosed asthma as compared to 20% (19 of 98) of non-migrants.

CONCLUSIONS: While the small sample size limits the ability to draw certain conclusions, this research provides important findings concerning the sensitization to bioaerosols in the context of migration to Miami and management of pediatric asthma.
Mycoplasm and Chlamydia infection related cough and bronchial responsiveness in children

Sun Hee Choi, MD1, Yeong-Ho Rha, MD, PhD2, and Kysung Suk Lee, MD3, 1Kyung Hee University Hospital at Gangdong, Seoul, South Korea, 2Kyung Hee University Hospital, Seoul, South Korea, 3CHA Bundang Medical Center, CHA University, School of Medicine, Seongnam-si, Gyeonggi-do, Korea; Department of Pediatrics, CHA University Bundang Medical Center, Seongnam, South Korea.

RATIONALE: Asthma is characterized by cough and bronchial hyperresponsiveness (BHR). Chlamydia pneumoniae and Mycoplasma pneumoniae causes persistent cough and has been considered to be associated with asthma in previous studies. We investigate the characteristics of cough and BHR associated with both infection.

METHODS: The patients with persistent cough who were performed allergy test, serologic tests for C. Pneumoniae. M. pneumoniae and methacholine bronchoprovocation tests from 2010 to 2015 were recruited. They were divided into infection and non-infection group.

RESULTS: Total of 112 patients were recruited. Number of infection group and non-infection group were 69, and 43, respectively. MPT were performed in 29 patients in infection group and 21 patients showed BHR (<1.6 mg PC20 FEV1). Forty three of non-infection group were considered to have asthma (intermittent or mild persistent). There were no difference between two groups in terms of cough duration (5.1 vs 6.3 wks), atopy (specific IgE to inhalant allergen), methacholine PC20 FEV1 (11.7 vs 8.2 mg/mL), % Pred FEV1 (101.5 vs 100), FEV1/FVC (0.88 vs 0.88) and peripheral blood total eosinophil count (TEC) (213 vs 257/μL). Age of infection group was younger than non-infection group (5.9 vs 8.0 yr, P value=0.001).

CONCLUSIONS: In this study, we found that younger age might be a risk factor for development of infection related BHR. We could not differentiate cough and BHR with Mycoplasma or Chlamydia infection from non-infection group (asthma) by allergy test, BPT or TEC. Further investigations using large number of patients are needed to identify the pathogenesis of infection related BHR.

The Exposure to Ambient Ozone Affects Clinical Symptom in Asthmatic Adults

Min-Young Jung, MD1,2, Young-min Kim, PhD1,2, Jihyun Kim, MD, PhD1,2, Inbo Oh, PhD3, Byung-Jae Lee, MD, PhD4, Dong-Chull Choi, MD, PhD4, Byoung-Hak Jeon, PhD3, Hae-Kwan Cheong, MD, PhD4, and Kangmo Ahn, MD, PhD2, 1Environmental Health Center for Atopic Diseases, Samsung Medical Center, Seoul, Korea, The Republic of; 2Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, The Republic of; 3Environmental Health Center, University of Ulsan College of Medicine, Ulsan, Korea, The Republic of; 4Department of Internal Medicine, Sungkyunkwan University School of Medicine, Seoul, Korea, The Republic of.

RATIONALE: We evaluated the effect of ambient ozone (O3) on asthma symptoms in adults based on high-resolution exposure assessment of O3.

METHODS: We recruited 45 asthmatic patients (10 men and 35 women aged over 19 years) living in Seoul Metropolitan Area, Korea and followed between April and July in 2014. Asthma symptoms, i.e. chest discomfort, nocturnal cough, wheezing, and awakening at night were recorded daily, and the presence of at least 1 symptom was considered as positive. We assessed daily O3 level for residential area using Community Multi-scale Air Quality (CMAQ) modeling system with spatial resolution of 1 km. Generalized linear mixed model was used to evaluate the effect of O3 on the asthma symptoms after controlling for age, sex, outdoor temperature, outdoor humidity, ambient particulate matters (PM10), nitrogen dioxide (NO2), and tobacco smoke.

RESULTS: The symptom records of 3,441 person-days were collected. An increase in O3 by 10 ppb seemed to show the association with an increase in 10.8% (95% CI: -2.48 to 25.96) of asthmatic symptoms on the same day, and no lag effects were observed. The effect of O3 exposure on the asthma symptoms in women was robust with statistical significance. The asthma symptoms in women increased by 17.2% (95% CI: 1.3 to 35.6) per 10 ppb of O3 increase, whereas no statistical significance was found in men.

CONCLUSIONS: Our results suggest that exposure to O3 aggravates asthma symptoms particularly in women.

RESPIRATORY ALLERGY DUE TO MILLET IN BIRD-KEEPERS: TWO CASES REPORT

Elena Mederos Luis1, 2Alicia Enriquez Matas, MD, 2Ismael Garcia-Moguel3, 1Lys Herrera Herrera, 4Natividad De las Cuevas Moreno3, 2Conuelo Rodriguez Fernandez; 1HOSPITAL UNIVERSITARIO 12 DE OCTUBRE, MADRID, Spain, 2HOSPITAL UNIVERSITARIO 12 DE OCTUBRE, Madrid, Spain, 3Hospital Universitario 12 de Octubre, Madrid, Spain.

RATIONALE: Millet (Panicum miliaceum) belongs to the family of grasses (Poaceae). Type I sensitization to millet can lead to asthma by inhalation and to anaphylaxis by ingestion of millet-containing food. Furthermore, the existence of cross reactivity with other different seeds has been reported.

METHODS: We report two cases of patients with personal history of seasonal allergic rhinoconjunctivitis and asthma to pollens. They kept parakeets at home, therefore they didn’t refer symptoms at exposure initially. Few years later, as they developed perennial respiratory symptoms even when cleaning the cage in case 1, allergy tests to bird allergens and seeds-containing bird’s food were carried out by skin prick-by-prick test (SPT), specific IgE (ImmunoCap 250 Thermofisher system) and immunoblot analysis.

RESULTS: Case1. SPT to millet, hsemseed and linseed were positive; millet, canary grass and sesame seed specific IgE were positive and avian proteins specific IgE were negative.

Case2. SPT to millet, canary grass, hsemseed, oats and sesame seed were positive; millet, canary grass, oats and sesame seed specific IgE were positive and avian proteins specific IgE were negative.

The immunoblot analysis against specific IgE antibodies showed an own allergenic pattern for each patient with some coinciding bands between 10 to 75 kd.

In case1, after removing the parakeets, the respiratory symptoms improved.

In case2, the patient decided to maintain the parakeets at home avoiding its daily care and improving the respiratory symptoms.

CONCLUSIONS: Asthma and rhinoconjunctivitis after inhalation of millet in bird’s food are rare, but should be considered as potential cause of respiratory allergy in bird-keepers.

Body Mass Index Correlates with Total Serum IgE Levels in Healthy Adults and those with Allergy/ Asthma.

Roshni Naik, MD, Maria-Anna Vastardi, MD, Helen G. Durkin, PhD, and Rauno Joks, MD, SUNY Downstate Medical Center, Brooklyn, NY.

RATIONALE: Obesity is associated with increased Th1 responses in adipose tissue and Th2 responses in peripheral blood. We determined the relationship of body mass index (BMI) to total serum IgE levels.

METHODS: Blood levels of total serum IgE levels were measured (IU/mL, fluoroenzymeimmunoassay) and BMI (kg/m2) determined for 31 adults (16 female, 13 with allergy/asthma and 18 healthy control subjects, mean age 38.8 yrs±14.0). Spearman correlations were determined.

RESULTS: There is a significant association of BMI with total serum IgE level (R=0.47, p=0.007) for the entire group.

CONCLUSIONS: The immune responses of obesity are associated with IgE production and may contribute to allergy/asthma in adults.
22 Contributing Factor of Asthma for Developing Severe Dengue

Luisa I. Alvarado, Johanna Velez, Ernesto Santini, Mariana Tavarez, Nicole Rodriguez, Luzelida Vargas, Janice Perez, and Yvima Velazquez; Hospital Episcopal San Lucas, Ponce.

RATIONALE: Dengue is a self-limited, viral infection transmitted by mosquitoes with clinical presentations, from undifferentiated fever to severe dengue that may cause death. Epidemiologic studies had associated asthma with severe dengue, our study aims to describe demographic characteristics and clinical manifestations of laboratory confirmed dengue cases with past medical history of asthma.

METHODS: Data was collected from patients enrolled in the Sentinel Enhanced Dengue Surveillance System (SEDSS) established in St. Luke’s Episcopal Hospitals in Ponce and Guayama, Puerto Rico from May 7, 2012 to May 6, 2015. We compared asthmatic cases with intermittent and persistent disease to determine their risk for severe dengue. SEDSS collects clinical and demographic data and specimens for testing with RT-PCR appropriate for dengue virus.

RESULTS: Of 1,691 enrolled patients with history of asthma, 169 had confirmed dengue. 50.9% were male; median age 14.0 years (range: 1 – 73). 77.5% were under 19 years. 46.7% were admitted to the hospital. 55.7% were between 10-19 years. One case was transferred to another institution (0.6%) no deaths were reported. Common symptoms upon presentation were headache (148, 88.1%), fever (126, 76.4%), muscle pain (114, 68.7%), facial flush (100, 59%) and rash (81, 50.3%).

CONCLUSIONS: Patients with a history of asthma and laboratory confirmed dengue had similar symptoms as dengue cases described in the medical literature. Admission rates were high for this group, further analysis is being conducted to characterize and compare asthma severity among patients enrolled in SEDSS who developed severe dengue during their clinical course.

23 Plasma 15-Hydroxyeicosatetraenoic Acid Predicts Treatment Outcomes in Aspirin-Exacerbated Respiratory Disease

Elina Jerschow, MD, FAAAAI1, Matthew Edin, PhD2, Teresa Pelletier3, Waleed Abuzeid4, Nadeem Akbar4, Marc Gibber4, Marvin Fried4, Fred B. Li4, Artiom Gruzdev, PhD5, J. Alecly Brubady5, Weigup Han, PhD6, Golda Hudes, MD, PhD7, Taha Keskin, MD8, Victor Schuster4, Simon Spivack4, Darryl Zeldin, MD5, and David Rosenstreich, MD2; 1Albert Einstein College of Medicine/Montefiore Medical Center, New York, NY, 2National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle, NC, 3Albert Einstein College of Medicine, Bronx, NY, 4Albert Einstein College of Medicine/ Montefiore Medical Center, Bronx, NY, 5National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle, NC, 6Albert Einstein College of Medicine, Bronx, NY, 7Albert Einstein College of Medicine/ Montefiore Medical Center, Bronx, NY.

RATIONALE: Aspirin desensitization followed by daily aspirin provides therapeutic benefits to patients with aspirin exacerbated respiratory disease (AERD). It is not well understood how eicosanoid levels change during aspirin treatment. We investigated associations between clinical outcomes of aspirin treatment and plasma eicosanoid levels in AERD patients.

METHODS: Thirty-nine AERD patients were offered aspirin treatment (650 mg twice daily) for four weeks. Respiratory parameters and plasma levels of multiple eicosanoids were recorded at baseline and after four weeks of aspirin therapy using the Asthma Control Test (ACT) and Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). Respiratory function was evaluated using the forced expiratory volume in 1 second (FEV1) and nasal peak flow (NPF).

RESULTS: After aspirin treatment, respiratory symptoms improved in sixteen patients, worsened in twelve patients, and did not change in four. Seven patients were unable to complete the desensitization protocol. Patients with symptom improvement had higher baseline plasma 15-hydroxyeicosatetraenoic acid (15-HETE) levels than patients with symptom worsening: 7006 (IQR 6056-8688) vs. 4800 (IQR 4238-5575) pg/ml, p=0.0005. Baseline 15-HETE plasma levels positively correlated with the change in ACT score (r=0.61, p=0.001) and in FEV1 after four weeks of aspirin treatment (r=0.49, p=0.01). It inversely correlated with RQLQ score (r=-0.58, p<0.002). Peripheral eosinophilia counts after four weeks of aspirin treatment inversely correlated with the change in ACT score (r=-0.45, p=0.02) and change in FEV1 (r=-0.68, p=0.0001).

CONCLUSIONS: In AERD patients, low baseline 15-HETE plasma levels and increased eosinophilia during aspirin treatment are associated with worsening of respiratory symptoms and function.
25 Decreased Asthma Exacerbations and Hospitalizations in PROSPERO (Prospective Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab)

Bradley W. Chipps, MD1, William Busse, MD2, Allan T. Luskin, MD3, Robert S. Zeiger, MD, PhD4, FAAAAI4, Benjamin L. Trzaskoma, MS5, Noelle M. Griffin, PhD6, Evgeniya Antonova, MS, PhD7, Susan L. Limb, MD7, and Thomas B. Casale, MD, FAAAAI8. 1Capital Allergy and Respiratory Disease Center, Sacramento, CA, 2University of Wisconsin School of Medicine and Public Health, Madison, WI, 3HealthyAirways, Madison, WI, 4Kaiser Permanente Southern California, San Diego and Pasadena, CA, 5Genentech, Inc., South San Francisco, CA, 6University of South Florida, Tampa, FL.

RATIONAL: Real-world data are important to supplement clinical trial data in heterogeneous diseases like asthma. We report the results of a US-based, multicenter, prospective, 48-week observational registry of patients with allergic asthma initiating treatment with omalizumab (PROSPERO: NCT01922037).

METHODS: Patients with asthma ≥12 years old identified as omalizumab candidates by their treating physicians, with access to treatment through insurance or other funding, were enrolled. Asthma-related exacerbations and health care use were recorded monthly over 48 weeks. Patients also underwent semi-annual spirometry and Type 2 biomarker testing (blood eosinophils, serum peroxidin, and FeNO).

RESULTS: 806 patients were enrolled (mean age 47.3 years, 64% female, 70% White, 16% Black/African American). 86% completed ≥26 months of the study, 77% completed the study. Patients reported a mean 3.0 asthma exacerbations in the prior year that required OCS use, ED visit, or hospitalization; 61% reported ≥2 exacerbations and 22% reported ≥1 asthma-related hospitalizations in the past year. At Month 12, a mean rate of 0.8 exacerbations per year was observed; 19% reported ≥2 exacerbations and 4% reported ≥1 hospitalizations. Predictors of experiencing an exacerbation included an exacerbation in the past year, higher FeNO, and lower FEV1 at baseline. Baseline elevation of a Type 2 biomarker was associated with FEV1 improvement (+70 to 90 mL in patients ≥18 years). Adverse events appeared consistent with the safety profile described in the current product label.

CONCLUSIONS: In a real-world setting, patients treated with omalizumab had an improvement in asthma control as demonstrated by decreased asthma exacerbations and hospitalizations compared with baseline.

26 Efficacy of Reslizumab in Asthma Patients with Aspirin Sensitivity and Elevated Blood Eosinophils

Rohit Katial1, Flavia Hoyte2, Matthew Germinaro, MD3, and Mirna McDonald4. 1National Jewish Health, Denver, CO, 2National Jewish Health, Denver, 3Teva Pharmaceuticals, Frazer, PA, 4Teva Pharmaceuticals, West Chester.

RATIONAL: Aspirin Exacerbated Respiratory Disease (AERD) consists of chronic rhinosinusitis with nasal polyps (CRSwNP), severe asthma, and intolerance to aspirin (ASA) and other NSAIDs. Eosinophilic inflammation plays an important role in AERD. Our aim was to determine the effect of reslizumab on clinical asthma exacerbations (CAE) in patients with inadequately controlled asthma and historical ASA sensitivity.

METHODS: The methodology and outcomes of studies 3082 and 3083 have been previously reported (Castro M, et al. Lancet Resp Med 2015). Patients with asthma and elevated blood eosinophils (>400 cells/μL) who remained inadequately controlled with medium-dose inhaled corticosteroid were randomized to placebo or reslizumab (3mg/kg [IV] Q4W) for 52 weeks. In this analysis, pooled results assessed change in CAE frequency for patients with ASA sensitivity.

RESULTS: 11% (n = 103/953) of patients had historical ASA sensitivity. Data for concurrent sinus disease were not available for the entire group, but 56 of these patients (6%) were known to also have CRSwNP. Patients with ASA sensitivity who received reslizumab (n = 48) had a 62% reduction in the annual rate of CAE versus placebo (RR 0.38 [95% CI 0.21, 0.70]). Patients with ASA sensitivity and known CRSwNP who received reslizumab (n = 28) had a 79% reduction in the annual rate of CAE versus placebo (RR 0.21 [95% CI 0.08, 0.58]). Both groups achieved clinically meaningful improvements in forced expiratory volume in 1 second.

CONCLUSIONS: Patients with inadequately controlled asthma, elevated blood eosinophils, and ASA sensitivity (≥CRSwNP) received significant therapeutic benefit, providing further support for the use of reslizumab in this clinical setting.

27 Efficacy Of Mepolizumab In Patients With Severe Eosinophilic Asthma And Nasal Polyps

Mark C. Liu1, Oliver N. Keene2, Steven W. Yancey, MS3, Daniel J. Bratton4, and Frank C. Albers5, 1Johns Hopkins Asthma and Allergy Center, Baltimore, MD, 2GSK, Stockley Park, United Kingdom, 3GSK, Research Triangle Park, NC.

RATIONAL: Severe eosinophilic asthma (SEA) and nasal polyps (NP) are characterized by eosinophilic inflammation. Mepolizumab is an approved treatment for SEA, but is of interest to understand the efficacy of mepolizumab in patients with SEA and co-existing NP.

METHODS: This was a meta-analysis of DREAM (NCT01000506) and MENSa (NCT01691521), which assessed the efficacy of mepolizumab versus placebo in patients with SEA with or without NP at baseline. The primary endpoint of this meta-analysis was the annual rate of clinically significant exacerbations. Secondary endpoints included pre- and post-bronchodilator FEV1, Asthma Control Questionnaire (ACQ-5), and St George’s Respiratory Questionnaire (SGRQ; MENSa only). Data from both studies were combined using an inverse-variance weighted fixed-effects meta-analysis. Data are presented for combined 75 mg intravenous and 100 mg subcutaneous mepolizumab doses.

RESULTS: A total of 884 patients were included in this analysis, of whom 120 (14%) had NP at baseline. Patients with NP had higher blood eosinophil counts at baseline than patients without NP (geometric mean [SD log]: 380 (0.954) vs 260 (1.000) cells/μL, respectively). The reduction in exacerbations with mepolizumab compared with placebo was 59% for patients with NP (rate ratio [95% CI]: 0.41 [0.25-0.67]) and 48% for patients without NP (0.52 [0.42-0.64]). Mepolizumab improved ACQ-5, SGRQ, pre- and post-bronchodilator FEV1 versus placebo in both groups, with larger point estimates in the NP group.

CONCLUSIONS: Efficacy of mepolizumab was not affected by the presence of NP, making it a viable treatment option for patients with concurrent SEA and NP. Funded by GSK (205786).
28 New Oral Treatments for Asthma through Tissue-Specific Modulation of the GABAA Receptor

Leggy Arnold1, Gloria Forkuo1, Amanda Niemann1, Olivia B. Yu1, Margaret L. Guthrie1, Revathi Kodali1, Nina Yuan1, Rajwana Jahan1, Michael S. Stephen1, Charles W. Emala1, Gene T. Yocum1, James M. Cook1, and Mitchell H. Grayson, MD, FAAAI1, 1University of Wisconsin Milwaukee, Milwaukee, WI, 2Columbia University, New York, 3Columbia University, New York, 4700 Children’s Drive, Nationwide Children’s Hospital / The Ohio State University, Columbus, OH.

RATIONALE: This study addresses the unmet need for an oral, safe, non-steroidal asthma treatment. The hypothesis is that GABAARs in airway smooth muscle (ASM) and inflammatory cells can be targeted by subtype-selective GABAAR ligands to tissue-selectively induce ASM relaxation and immunosuppression.

METHODS: New drug candidates were characterized by electrophysiology and microsome, S9, and blood plasma stability assays. Pharmacokinetic studies in mice are used to identify in vivo stability and distribution. Murine pharmacodynamic models are used to quantify sensorimotor effects (rotarod), disease specific airway hyperresponsiveness, airway mucus production, and airway eosinophilia. ASM muscle relaxation was tested in ex vivo lung tissue. The immune modulatory effect of subtype-selective GABAAR ligands was evaluated by flow cytometry.

RESULTS: A α5 subtype-selective GABAAR ligand showed excellent PK when given orally. The compound did not cross the BBB, thus no sensorimotor effects were observed. The compound inhibited eosinophila and reduced the number of inflammatory cells. Significant muscle relaxation was observed ex vivo in trachea rings and reduced airway hyperresponsiveness was observed in mice. Importantly, this is the first oral treatment for asthma specifically targeting muscle relaxation and inflammation. In addition, a novel α4 subtype-selective GABAAR ligand was identified with equally excellent stability in vitro and in vivo. Reduced airway hyperresponsiveness was observed at low concentrations of methacholine. The anti-inflammatory properties were significant but immune cell populations were regulated differently.

CONCLUSIONS: α4 and α5-selective GABAAR modulators have a great potential as novel orally active drug candidates for asthma to alleviate symptoms of airway hyperresponsiveness mediated by ASM constriction, hypereosinophilia, and inflammation.

29 Clinically Significant Improvements in Asthma Patient-Reported Outcomes: Results from the Prospective Observational Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab (PROSPERO) Study

Erika G. Gonzalez-Reyes, MD1, Allan T. Luskin, MD2, William Busse, MD3, Thomas B. Casale, MD, FAAAI1, Bradley E. Chipp, MD3, Evgeniya Antonova, MS, PhD4, Susan L. Limb, MD5, Benjamin L. Trzaskoma, MS6, Noelle M. Griffin, PhD6, and Robert S. Zeiger, MD, PhD, FAAAI7. 1Children’s Hospital of San Antonio- Baylor College of Medicine, San Antonio, TX, 2Healthy-Airways, Madison, WI, 3University of Wisconsin School of Medicine and Public Health, Madison, WI, 4University of South Florida, Tampa, FL, 5Capital Allergy and Respiratory Disease Center, Sacramento, CA, 6Genentech, Inc., South San Francisco, CA, 7Kaiser Permanente Southern California, San Diego and Pasadena, CA.

RATIONALE: Real-world data on patient-reported outcomes in asthma patients receiving omalizumab treatment are limited. This study aims to bridge that gap.

METHODS: PROSPERO, a US-based, multicenter, prospective, 12-month, observational study, enrolled patients ≥ 12 years old with asthma who initiated omalizumab therapy between 6/2013-3/2015 (clinicaltrials.gov: NCT01922057). At baseline and throughout the study, patients completed the following validated questionnaires: Asthma Control Test (ACT), Asthma Quality of Life Questionnaire (AQLQ), Work Productivity and Activity Impairment (WPAI)-Asthma Questionnaire, and Mini Rhinoconjunctivitis Quality of Life Questionnaire (miniRQLQ). Changes from baseline at month 12 are reported for each questionnaire.

RESULTS: Among 806 enrolled patients, 622 (77.2%) completed the study. Patients were primarily female (63.5%), white (70.3%), obese (48.5%), diagnosed with moderate (48.1%) or severe (47.8%) asthma and never smoked (65%); 61% of patients reported 2 exacerbations in the 12 months prior to enrollment.

At baseline, patients reported mean [SD] scores: ACT (13.9 [5.0]), AQLQ (4.0 [1.4]), miniRQLQ (2.7 [1.4]), and % WPAI Overall Work Impairment (33.5 [28.7]), and % Daily Activity Impairment (47.7 [28.9]).

At the end of the study patients reported clinically meaningful mean [SD] changes from baseline in ACT (4.4 [4.9]), AQLQ (1.3 [1.3]), and miniRQLQ (-1.0 [1.3]) and all WPAI domains, including % Overall Work Impairment (-16.4 [29.6]) and % Daily Activity Impairment (-20.80 [32.4]).

CONCLUSIONS: In a real world setting, patients receiving omalizumab reported at month 12, clinically meaningful improvement from baseline in asthma control, asthma- and rhinoconjunctivitis-related quality of life, and decline in work and daily activity impairment.

30 Meta-analysis of Mepolizumab Global Studies Suggest Consistent Therapeutic Response Across a Range of Demographic Sub-groups

Steven W. Yancey, MS1, Neced B. Gunsoy2, Eric S. Bradford1, Frank C. Albers1, Charlene M. Prazma, PhD3, Richard Follows1, Oliver N. Keene4, and Ian Padvor4. 1GSK, Research Triangle Park, NC, 2GSK, Uxbridge, United Kingdom, 3GSK, Stockley Park, United Kingdom, 4University of Oxford, Oxford, United Kingdom.

RATIONALE: A retrospective analysis was conducted to explore treatment responses to mepolizumab across a broad range of subgroups with severe eosinophilic asthma (SEA).

METHODS: A meta-analysis of two randomized, double-blind, placebo-controlled studies (N=1192; MEA112997/MEA115588) with mepolizumab or placebo plus standard of care given every 4 weeks to SEA patients treated with high dose ICS plus a controller with or without maintenance oral corticosteroids, a history of ≥2 exacerbations in the previous year and evidence of eosinophilic inflammation. This post-hoc analysis was conducted using a negative binomial regression model, accounting for study. All mepolizumab doses were combined for this analysis.

RESULTS: The overall ratio of exacerbation rates with mepolizumab (n=846) compared with placebo (n=346) was 0.53 (95% CI: 0.44 to 0.62, p<0.001). Among females (n=715) and males (n=477), rate ratios were 0.56 (0.45, 0.70) and 0.45 (0.34, 0.60) respectively. Among African-Americans/Africans (n=39), Asian (n=141) and Whites (n=1004), rate ratios were 0.61 (0.24, 1.58), 0.39 (0.25, 0.61) and 0.55 (0.45, 0.66), respectively. Among adolescent patients (ages 12–17) in MEA115588 (n=25), the rate ratio was 0.68 (0.17, 2.68). The safety profile was generally comparable across the subgroups.

CONCLUSIONS: Sub-group analysis showed consistent response in the reduction of clinically significant exacerbations. No unique safety signals emerged from the sub-groups. These post-hoc analyses suggest that the safety and efficacy profile of mepolizumab is consistent across a broad range of sub-groups, indicating that an eosinophilic phenotype in severe asthma identifies a common endotype that is therapeutically responsive to targeting IL-5 and reducing eosinophilic inflammation. Funding: GSK(NCT01000506/NCT01691521).
AB10 Abstracts

31 Patient-Reported Outcomes and Quality of Life Improved with Fluticasone Propionate and Fluticasone Propionate/Salmeterol Multidose Dry Powder Inhalers Versus Placebo in Patients with Persistent Asthma

Gordon Raphael, MD1, Gloria Yu, MS2, Anat Sakov, PhD3, Siyu Liu, MD, PhD2, and Cynthia Caracta, MD, FCCP4; 1Bethesda Allergy, Asthma and Research Center, Bethesda, MD, 2National Hospital Organization Tokyo Medical Center, Tokyo, Japan, 3Teva Pharmaceuticals, Frazer, PA, 4Teva Pharmaceuticals, Netanya, Israel.

RATIONALE: Patient-reported outcomes, including quality of life, were evaluated in patients receiving fluticasone propionate (FP) and fluticasone propionate/salmeterol (FS) via a novel multidose dry powder inhaler (MDPI).

METHODS: This phase 3, double-blind, parallel-group study (FSS-AS-301; NCT02139644) evaluated asthmatic patients (ages ≥12 years) using inhaled corticosteroids (ICS) or ICS/long-acting beta2-agonists. After a 14- to 21-day run-in during which patients received albuterol metered-dose inhaler for rescue, beclomethasone dipropionate metered-dose inhaler, 40 mcg twice daily (BID), and placebo MDPI BID, patients randomly received Fp MDPI 50 mcg, Fp MDPI 100 mcg, FS MDPI 50/12.5 mcg, FS MDPI 100/12.5 mcg, or placebo BID for 12 weeks. Efficacy and safety outcomes were previously reported. Patient-reported outcomes including asthma symptoms, rescue medication use, Asthma Quality of Life Questionnaire (AQLQ) scores (patients ≥18 years), and adverse events are reported.

RESULTS: The full analysis and safety populations included 640 and 641 patients, respectively. All active treatments significantly improved asthma symptom scores (p<0.05) and significantly decreased rescue medication use (p<0.05) versus placebo over 12 weeks. Improvements in AQLQ from baseline to endpoint for active treatment groups were significantly greater versus placebo (p<0.05). AQLQ improvements from baseline achieved the minimal important difference (≥0.5) for all active treatment groups. Comparisons between Fp MDPI and FS MDPI were not significant for any assessed outcome except AQLQ for Fp MDPI 100 mcg versus FS MDPI 100/12.5 mcg (p<0.05). Adverse events were similar across all groups.

CONCLUSIONS: Low- and mid-dose Fp MDPI and FS MDPI significantly improved patient-reported outcomes and quality of life versus placebo.

Funding: Teva Pharmaceuticals.

32 Benralizumab Reduces Exacerbations in Japanese Patients with Severe, Uncontrolled Asthma: Subgroup Analysis of the CALIMA Trial

J Mark FitzGerald1; Ken Ohta2, Mitsuru Adachi3, Yuji Tohda4, Tadashi Kamei5, Motokazu Kato5, Masayuki Takamuna5, Tadahiro Kukuno5, Nobuyuki Imai5, Yanping Wu6, Magnus Aurivillius7, and Mitchell Goldman8; 1Vancouver General Hospital, UBC Institute for Heart and Lung Health, Vancouver, BC, Canada, 2National Hospital Organization Tokyo National Hospital, Tokyo, Japan, 3International University of Health and Welfare Sanno Hospital, Tokyo, Japan, 4Kindai University Faculty of Medicine, Osaka, Japan, 5Kamei Respiratory Clinic, Takamatsu, Japan, 6Kishiwada City Hospital, Osaka, Japan, 7Kyowa Hakko Kirin Co., Ltd., Tokyo, Japan, 8AstraZeneca, Gaithersburg, MD, 9AstraZeneca, Malmö, Sweden.

RATIONALE: In the Phase III CALIMA trial, benralizumab significantly reduced asthma exacerbations, improved lung function, and alleviated symptoms for patients with severe, uncontrolled, eosinophilic asthma. This subanalysis evaluated benralizumab’s efficacy and safety for Japanese patients who participated in CALIMA.

METHODS: CALIMA (NCT01914757) was a randomized controlled trial of 1,306 patients (aged 12–75 years) with severe asthma uncontrolled by medium- to high-dose inhaled corticosteroids (ICS) and long-acting β2-agonists. Patients received 56 weeks benralizumab 30 mg SC either every 4 weeks (Q4W) or every 8 weeks (Q8W; first 3 doses Q4W), or placebo SC Q4W. Primary analysis population was 728 patients receiving high-dose ICS with baseline blood eosinophils ≥300 cells/μL. This sub-analysis covered Japanese patients from this group.

RESULTS: Of 83 patients randomized in Japan, 46 were receiving high-dose ICS and had baseline blood eosinophils ≥300 cells/μL. Benralizumab reduced the annual rate of asthma exacerbations by 66% (Q4W; rate 0.83, rate ratio 0.34 [95% CI 0.11–0.99], n=15) and 83% (Q8W; rate 0.42, rate ratio 0.17 [0.05–0.60], n=15), vs. placebo (rate 2.45, n=16); increased pre-bronchodilator FEV1 by 0.334 L (Q4W; 95% CI 0.020–0.647) and 0.198 L (Q8W; 95% CI –0.118 to 0.514), vs. placebo; and decreased total asthma symptom score by –0.17 (Q4W; 95% CI –0.82 to 0.48) and –0.24 (Q8W; 95% CI –0.87 to 0.40), vs. placebo. Incidence of adverse events was consistent with the overall CALIMA group.

CONCLUSIONS: Benralizumab reduced annual asthma exacerbation rates, increased FEV1, decreased symptoms, and was generally well-tolerated for Japanese patients with severe, uncontrolled, eosinophilic asthma.

FEBRUARY 2017
34 Observational study in asthmatics patients after reduction/withdrawal of Omalizumab for good asthma control: real life experience from a Severe Asthma Unit

Jose Alessandro Bastidas Parlanti, Dorkas M. Márquez, Irina Boboaea, MD, Lys Herrera Herrera, Ismael García Moguel, and Consuelo Rodríguez Fernández; Hospital Universitario 12 de Octubre, Madrid, Spain.

RATIONALE: The optimal duration of treatment with Omalizumab (OMA) in patients with severe asthma is not established. The aim of this study is to assess asthma control after reduction or withdrawal of OMA in patients who have completed at least 5 years of treatment.

METHODS: Patients with severe asthma treated with OMA ≥ 5 years, who had good or excellent global evaluation of treatment effectiveness (GETE), Asthma Control Test (ACT) ≥ 20, no severe exacerbations in the previous year, and stable lung function, underwent a progressive OMA dose reduction protocol. We herein present data from those patients who have now completed at least one year follow-up after decrease or withdrawal of OMA.

RESULTS: From the 24 patients treated for at least 5 years with OMA, 12 patients were selected according to the protocol inclusion criteria. 5/12 patients discontinued OMA offhandedly: 1 for pregnancy, 3 on their own initiative, and 1 reduced progressively the dose over one year-period until complete suspension. After an average of 17 months of follow-up, none of them required to restart Omalizumab. 2 patients had severe exacerbations in the first three months after the reduction of the dose, reprising their previous doses. In the other 5 patients, OMA doses have been reduced by 50-75%, maintaining all of them good asthma control after an average of 19 months of follow-up.

CONCLUSIONS: In our series, most patients treated with OMA ≥ 5 years with good asthma control have tolerated reduction or cessation of OMA. Nevertheless, larger studies with long-term follow-up are further required.

35 Effect of Weight Reduction on Respiratory Function in Obese Children without Asthma

Keigo Kainuma, MD1, Keiko Kameda2, Yu Kuwabara, MD1, Mizuho Nagao, MD1, and Takao Fujisawa, MD, PhD2; 1Allergy Center and Institute for Clinical Research, Mie National Hospital, Tsu, Japan; 2International Clinical Research Center, Mie National Hospital, Tsu, Japan.

RATIONALE: Obesity has been implicated in asthma morbidity in adults and children but causal mechanisms, especially in relation with respiratory physiologic, are not well understood. We investigated the effect of weight reduction on respiratory function by spirometry and forced oscillation technique (FOBT) in obese children without asthma.

METHODS: We enrolled 20 obese children aged 7-16 years who joined the weight reduction program in Mie National Hospital in 2014-2015. They have now completed at least one year follow-up after decrease or withdrawal of OMA.

RESULTS: Paired t test was used to compare the changes of the parameters. Ance analysis (BIA) were performed as well as body weight and height. Three months without taking any medication and surgery. Before and after the weight reduction program in Mie National Hospital in 2014-2015. They have now completed at least one year follow-up after decrease or withdrawal of OMA.

CONCLUSIONS: In the allergic group, 66% had blood eosinophils>300/mm3, with 45%≥300/mm3 and 33%≥400/mm3. In the non-allergic group, 65% had blood eosinophils>150/mm3, with 41%≥300/mm3 and 27%≥400/mm3. In the SA exhibiting ≥300/mm3 eosinophils, 71% were atopic while 68% of patients with eosinophilia <300/mm3 were sensitized. 48% of patients with total IgE levels between 76 and 700UI/L had blood eosinophil>300/mm3. According to Belgian reimbursement criteria for anti-IgE (total IgE, 76-700) and anti-IL5 (≥300/mm3), 44% of patients are potentially eligible for anti-IL5, while among candidates to anti-IgE, 50% are eligible for both biotherapy (table-figure).

CONCLUSIONS: The majority of our SA displayed IgE sensitization, irrespectively of blood eosinophilis. The subpopulations of patients eligible to each biotherapy largely overlap, indicating the need for more sophisticated phenotyping including clinical characteristics and novel biomarkers to predict which biotherapy is the most appropriate.

36 Belgian Severe Asthma Registry. Which Biotherapy to Choose According to Inflammatory Characteristics?

Florence N. Schleich, MD, PhD1, Guy Brussel, MD, PhD2, Renaud Louis3, Olivier Vandenplas1, Alain Michils, MD2, Charles Filet1, Rudi Peche, MD1, and Guy F. P. Joos, MD, PhD3; 1CHU Saint-Tilman Liege, Liege, Belgium; 2Gent University, Gent, Belgium; 3CHU Saint-Tilman, Liege, Liege, Belgium; 4Université Catholique De Louvain, Yvoir, Belgium; 5Erasme University Hospital, Brussels, Belgium; 6Laboratoire de Allergy and Mucosal Immunology, Cliniques Universitaires St-Luc, Brussels, Belgium; 7CHU Vesale, Montigny Le Tilleul, Belgium; 8Ghent University Hospital, Gent, Belgium.

RATIONALE: The Belgian severe asthma registry is a web-based registry including demographic, functional and inflammatory data of severe asthmatics (SA), for whom pulmonologists may now propose anti-IgE or anti-IL5 according to evidence of its allergic or eosinophilic nature. The overlap between these two phenotypes remains poorly investigated. We aimed to evaluate the prevalence of both features separately or concomitantly in this population.

METHODS: The cross-sectional analyses included 350 SA as defined by the ATS (2000) from 9 Belgian centers, with at least one year follow up.

RESULTS: The detailed clinical characteristics of our population have been reported previously (Schleich, RespirMed2014). The proportion of allergic asthma was 76% (IgE≥3.35 for at least one common allergen) and the median blood eosinophils was 240/mm3. In the allergic group, 66% had blood eosinophils>300/mm3, with 45%≥300/mm3 and 33%≥400/mm3. In the non-allergic group, 65% had blood eosinophils>150/mm3, with 41%≥300/mm3 and 27%≥400/mm3. In the SA exhibiting ≥300/mm3 eosinophils, 71% were atopic while 68% of patients with eosinophilia <300/mm3 were sensitized. 48% of patients with total IgE levels between 76 and 700UI/L had blood eosinophil>300/mm3. According to Belgian reimbursement criteria for anti-IgE (total IgE, 76-700) and anti-IL5 (≥300/mm3), 44% of patients are potentially eligible for anti-IL5, while among candidates to anti-IgE, 50% are eligible for both biotherapy (table-figure).

CONCLUSIONS: The majority of our SA displayed IgE sensitization, irrespectively of blood eosinophilis. The subpopulations of patients eligible to each biotherapy largely overlap, indicating the need for more sophisticated phenotyping including clinical characteristics and novel biomarkers to predict which biotherapy is the most appropriate.

37 Real-Life Study of Efficacy and Safety of Omalizumab in Asthma: A 7-Year Follow-up from an Arabian Gulf Country

Mona Al-Ahmad1, and Nermina Arifhodzic2; 1Microbiology Department, Faculty of Medicine, Kuwait University, Kuwait; 2Al-Rashid Allergy Center, Ministry of Health, Kuwait.

RATIONALE: To evaluate the long term (up to 7 years) effectiveness and safety of omalizumab in patients with moderate - severe allergic asthma - in real-life world.

METHODS: Data from 80 patients on treatment with omalizumab ≥ 4 years have been evaluated. Patients are progressively enrolled from 2008-2012 and followed till 2016. Evaluation included subjective and objective parameters of asthma control, reduction in medication use, and documented ER visits/hospitalization. All parameters were compared with data in the year prior omalizumab. results are demonstrated for year 1st, 4th and at 7th years of therapy.

RESULTS: Out of 80 patients, 65 (81.25%), of both genders, mean age of 45.4 ± 13.6, reached study end point. Twenty-one (21.3%) reached 4 years, thirteen (20%) 5 years, while 31 (47.7%) are in 6 and 7 years. Almost 60 % were fully compliant throughout treatment. We had premature patient’s loss (18.75%) including 2 deaths. Mean total IgE was 406.5 ± 302.8. Excellent response was seen in 63.5% of patients (p<0.001), moderate response was in 20%, while 13.8% were non-responder. We had a significant improvement in ACT score (p=0.001). Improvement in FEV1 was statistically significant (p<0.0001) but slower. Unlike SABA rescue use, we only had 36.9% of patients who reduced ICS at end point. ER/unscheduled visits and hospitalization were reduced significantly (p<0.001), which markedly influenced the reduction in oral corticosteroid burst (83.3%), p<0.001. No significant major adverse reactions.

CONCLUSIONS: Omalizumab was effective and safe when used as long-term add on therapy in patients with moderate-severe asthma.
The Opposing Roles of Let-7c and Mir-125-b2 in Human Hematopoietic Stem Cell Maintenance and Proliferation

Vanessa L. Bundy, MD, PhD1; Salemiz Sandoval1, Christopher Seet1, Chintan Parekh2, Edward He1, Yuhua Zhu1, Lisa A. Kohn2, Dinesh Rao1, and Gay Crooks1; 1University of California, Los Angeles, CA, 2University of Southern California, Los Angeles, CA.

RATIONALE: Hematopoietic stem cells (HSCs) possess extensive self-renewal, proliferation and differentiation capacities that enable them to sustain long-term repopulation of all hematopoietic cell types. This process requires an intricate balance between self-renewal and differentiation. Micro RNAs (miRNAs) are known to regulate transcription, but precise molecular networks affecting HSC maintenance remain poorly understood.

METHODS: Our laboratory used microarray to identify a genomic cluster of miRNAs (miR-99a/let-7c/miR-125b2) that is highly expressed in hematopoietic stem cells and almost absent in progenitors and mature cells. To elucidate the impact of miRNA expression in human HSCs, we generated lentiviral overexpression vectors for let-7c, miR-125b2, miR99a and the entire cluster. “Sponge” inhibition vectors were generated for let-7c and miR-125b2. Vector-mediated gene transfer studies included in vitro assays of differentiation, long-term culture initiation cells (LTC-ICs), proliferation and survival assays and in vivo mouse transplantation assays.

RESULTS: Let-7c overexpression decreased CD34+ cells, reduced LTC-ICs and increased myeloid cell output. MiR-125b2 overexpression expanded CD34+ cells and LTC-ICs. Cluster overexpression revealed an intermediate phenotype between Let-7c and mir-125b in vitro and in vivo (primary and secondary transplant) assays. Let-7c inhibition showed markedly increased cell proliferation and CD34+ cell output, with decreased myeloid differentiation.

CONCLUSIONS: Our data suggest that let-7c may function within the cluster to modulate the profound proliferative effects of mir-125b2 activity in HSCs. We hypothesize that sponge inhibition of let-7c enhances HSC proliferation due to unopposed mir-125b2. Future studies will use RNA-Seq to explore the transcriptional networks through which let-7c and mir-125b2 modify the behavior of HSCs.

Optimization of High-Dimensional Phenotyping of B Cells For Studying Rhinovirus Infection

Jacob D. Eccles1, Katarzyna Niespodziana, PhD2, Rudolf Valenta, MD2, Ronald Turner, MD3, and Judith A. Woodfolk, MBChB, PhD, FAAAAI1; 1University of Virginia, Charlottesville, VA, 2Medical University of Vienna, Vienna, Austria.

RATIONALE: Human rhinoviruses (RV) are responsible for an estimated half-billion colds per year within the US and are a major trigger of acute asthma. It is unknown why adaptive responses fail to induce lasting protection despite the development of serum neutralizing antibodies. We aimed to develop an experimental approach to rigorously interrogate the B-cell repertoire in RV-seropositive individuals that could be readily adapted to an experimental infection model.

METHODS: Recombinant capsid proteins of RV-A16 (VP1-4) and intact virus purified to high concentration by ultracentrifugation and cobalt-affinity chromatography were labeled for B-cell detection using PBMCs obtained from subjects who were seropositive for RV-A16. A 40-marker antibody panel was developed for mass cytometry. Samples were barcoded to enable multiplexing and to eliminate batch effects, using discrete combinations of palladium isotopes on anti-CD45 antibodies prepared in-house.

RESULTS: Circulating RV-specific B cells were identified using capsid proteins, but not intact virus, by multi-color flow cytometry thereby providing proof-of-concept for their presence in the periphery. In contrast to protocols requiring cell fixation and permeabilization, CD45-based barcoding of samples analyzed by mass cytometry preserved surface epitopes. These included markers vital to delineating naive and memory B cell subsets (IgD, CD27), plasma cells (CD138), and lymphoid versus non-lymphoid trafficking types (CXCR5). Robust barcode signals resulted in minimal cells omitted from analysis.

CONCLUSIONS: Our multiplex approach provides an efficient, sample-sparing method for high-dimensional phenotyping of B cells, including those that are RV-specific. Potential applications include monitoring of B cells during RV infection, and broader use in interventional studies in humans.

IL-10 Differentially Affects IgE and IgG4 Production Through Distinct Mechanisms

Adora A. Lin, MD, PhD, and Thomas B. Nutman, MD; National Institutes of Health, Bethesda, MD.

RATIONALE: Control of allergic disease is associated with decreased allergen-specific IgE and increased allergen-specific IgG4. Although IL-10 has been shown to contribute to changes in the IgE/IgG4 balance, the mechanisms underlying these changes are largely unknown. The present study explored how IL-10 differentially regulates human IgE and IgG4 production.

METHODS: PBMCs and highly purified total (CD3-CD19+CD20+), antigen-naive (CD3-CD19+CD21+CD27-), and antigen-experienced (CD3-CD19+CD21+CD27+) B cells were cultured with combinations of IL-4, IL-10, and anti-CD40. Quantitative PCR was performed for Cε and Cγ4 germline transcripts (GLTs). IgG and IgE isotypes were quantified from culture supernatants using multiplexed immunoassays.

RESULTS: In PBMC cultures, IL-4 induced production of both IgE and IgG4 (IgE: mean 16.2-fold above baseline; IgG4: mean 4.7-fold). At the transcriptional level, IL-4 increased expression of Cε and Cγ4 GLTs to 54.1-fold and 5.3-fold above baseline, respectively. Addition of IL-10 significantly (p<0.01) reduced IL-4-induced IgE production to 4.6-fold and expression of Cε GLTs to 24.7-fold above baseline, without affecting IgG4 production or expression of Cγ4 GLTs. In cultures of isolated total B cells and B cell subsets, IL-10 had no significant effect on IL-4-induced IgE production; however, IL-10 markedly increased IL-4-induced IgG4 production over 20-fold. IL-4-induced transcription of Cε and Cγ4 GLTs in isolated B cells was not affected by IL-10.

CONCLUSIONS: IL-10 acts indirectly through accessory cells present in PBMCs to downregulate IL-4–induced production of IgE. In contrast, IL-10 can act directly on B cells to upregulate IL-4–induced production of IgG4, with its effects on isolated B cells being downstream of germline transcription.
41 Hyperglycemia on the Phosphereral Blood Mononuclear Cells Cytokine Production

Ammar K. Daoud, MD, FAAAAI1, Nasreen A. Saada2, Nizar Abu Harfil1, and Khalid J. A. A. Zubiad1. 1Faculty of Medicine – JUST, Amman, Jordan; 2Faculty of Medicine, Jordan University of Science and Technology (J.U.S.T.), Irbid, Jordan; 3Faculty of Medicine – JUST, Irbid, Jordan; 4Faculty of Science – JUST, Irbid, Jordan. 1Graduate Studies Faculty – JUST, Irbid, Jordan. RATIONALE: We wanted to study the effects of chronic in vivo and acute in vitro hyperglycemia on the production of cytokines by peripheral blood mononuclear cells. METHODS: 10 uncontrolled Type II Diabetes Mellitus patients (HbA1c >8%) and 5 healthy sex and age matched controls were enrolled. PBMN cells were cultured in RPMI1640 culture medium with 3 glucose concentrations (0, 200, and 600 mg/dL) stimulated by 1 μg/mL of LPS. The levels of 7 more recently identified cytokines were measured by ELISA kits (IL-17, IL-18, IL-19, IL-20, IL-21, IL-22 and IL-33). Appropriate statistical tests were applied for the different comparisons. RESULTS: Our results showed that all studied interleukins (except IL-19 and IL-33) revealed no significant difference at all glucose concentrations (0,200, and 600mg/dl) between diabetic group and non-diabetic group. IL-19 and IL-33 showed significant results at 0 mg/dl glucose between diabetic group and non-diabetic group. IL-17, IL-20, and IL-33 levels showed no significant results in the presence or absence of glucose in both groups while IL-18 and IL-22 levels revealed significant results in both groups. IL-19 and IL-21 revealed significant difference in diabetic group only. CONCLUSIONS: Diabetes type II did not affect all studied interleukins levels except IL-19 and IL-33 levels that were increased. Moreover, some interleukins levels such as IL-17, IL-20, and IL-33 were not affected by different glucose concentrations. However, other interleukins such as IL-18, IL-19, IL-21, and IL-22 levels were affected by different glucose concentrations (their levels were increased except IL-19 levels, which was decreased).

42 Role of Lesional BCL6hiPD-1hi T Follicular Helper Cells As a Cardinal B-Cell Helper to Produce IgG4 in IgG4-Related Disease

Ryuta Kamekura, MD, PhD1,2, Kenichi Takano, MD, PhD2, Motohisa Yamamoto, MD, PhD1, Koji Kawata, DVM, PhD1, Sumito Jitsukawa1,2, Tomonori Nagaya, MD, PhD2, Fumie Ito1,2, Chieko Tsuomatsu, MD, PhD2, Hiroki Takahashi, MD, PhD1, Tetsuo Himi, MD, PhD2, and Shingo Ichimiya, MD, PhD1. 1Department of Human Immunology, Research Institute for Frontier Medicine, Sapporo Medical University School of Medicine, Sapporo, Japan, 2Department of Otolaryngology, Sapporo Medical University School of Medicine, Sapporo, Japan. RATIONALE: IgG4-related disease (IgG4-RD) shows a chronic fibroinflammatory condition characterized by spread to various systemic organs, resulting in dysfunctions associated with IgG4 such as dacryoadenitis and sialoadenitis and type 1 autoimmune pancreatitis. However, the pathogenesis of IgG4-RD remains unknown. Therefore, we examined T follicular helper (Tfh) cells in tissue lesions of IgG4-RD. METHODS: Tfh (CD4+CXCR5+) cells in tissues of submandibular glands (SMGs) from patients with IgG4-related dacryoadenitis and sialoadenitis (IgG4-DS, n = 6), normal SMGs (n = 6), nasal polyps (n = 3), and palatine tonsils (n = 6) were analyzed. Expression of programmed death 1 (PD-1) and inducible T-cell co-stimulator in Tfh cells from those subjects was examined by flow cytometry. Sorted Tfh cells from IgG4-DS SMGs were characterized and compared with tonsillar and circulating Tfh cells. Functional analyses of sorted Tfh cells from IgG4-DS SMGs were also performed. RESULTS: Patients with IgG4-DS exhibited increased infiltration of activated Tfh cells highly expressing PD-1 in their SMGs. Lesional Tfh cells in IgG4-DS had higher expression of B-cell lymphoma (BCL) 6 and higher capacity to help B cells produce IgG4 than did tonsillar Tfh cells. We also found that the percentage of PD-1hi Tfh cells in blood from patients with IgG4-DS was elevated compared with that in healthy volunteers and was correlated with clinical parameters. CONCLUSIONS: Our findings indicate that BCL6hiPD-1hi Tfh cells in tissue lesions of IgG4-RD have features distinct from those in lymphoid counterparts or blood and potentially regulate local IgG4 production in IgG4-RD.

43 Three lymphocyte subsets (CD45+ CD4- CD8-IFN gamma+ (CD16/56+), CD3+ CD4+ IL-4+ IFN gamma-, CD3+ CD6+ CD60+ IL-4+ IFN gamma-) are required for human specific memory IgE responses

Tsz Wah Ho1, Charles Kim2, Bryan McCarthy, MD3, Seto M. Chice, MS4, Ayla Safran1, Yitzchok Norowitz2, Maja Nowakowski, PhD2, Stephan Kohlhoff, MD3, Rauno Joks, MD, FAAAAI1, Tamar A. Smith-Norowitz, PhD2, and Helen G. Durkin, MD2. 1Center for Allergy and Asthma Research, Brooklyn, NY, 2Center for Allergy and Asthma Research at SUNY Downstate Medical Center, Brooklyn, NY, 3SUNY Downstate Dept of Pediatrics, Brooklyn, NY. RATIONALE: CD4+ T cells and their cytokines (IL-4, IL-13) are required for induction of human IgE responses. We reported that two T cell subsets (CD4+, CD8+CD60+) which express IL-4, and five additional cytokines (IL-2, 10, 12, IFN alpha, IFN gamma, but not IL-13) are required for induction of human ragweed specific memory IgE responses by PBMC of ragweed sensitized humans. It is unknown if CD4 or CD8+CD60+ T cells are sources of the IFN gamma required for induction of memory IgE responses. METHODS: Blood was obtained from serum IgE+ ragweed sensitized humans (n = 6) and the distributions of lymphocyte subsets determined (flow cytometry). Distributions of PBMC lymphocyte subsets expressing IL-4 or IFN gamma were determined ± incubation for 2-6 hr with varying concentrations of PMA. RESULTS: CD4+ and CD8+CD60+ T cells expressed IL-4 (5, 5% of CD45+ lymphocytes), but neither CD4+, CD8+ nor CD8+CD60+ T cells expressed IFN gamma (<1%). However, CD4+ CD4- CD8- CD80- lymphocytes (CD16/56+ NK cells) (NK cells?) expressed IFN gamma (3% of CD45+). CONCLUSIONS: CD4+IL-4+, CD8+CD60+IL-4+T cells, and CD45+CD8-CD60+IFN gamma+ cells are required for memory IgE responses.

44 The Dynamics and Function of Regulatory B Cells in Thoracic Adipose Depots

Rajeev Dalal1,2, and Lan Wu, MD1,2. 1New York Institute of Technology College of Osteopathic Medicine, Old Westbury, NY, 2Vanderbilt University Medical Center, Nashville, TN. RATIONALE: Regulatory B cells (Bregs) can influence inflammatory responses through endogenous production of anti-inflammatory cytokines, e.g. IL-10. We previously investigated these cells in perigonadal adipose tissue and reported a protective role against obesity-induced inflammation and insulin resistance. We hypothesized that Bregs are enriched in the thoracic compartment and can function as IL-10 producing cells. METHODS: We isolated the stromal vascular fractions from pericardial, periaortic, and perigonadal adipose depots of wild type (WT) B6 mice at 4.6, and 8 weeks of age and analyzed the samples by flow cytometry. A separate intracellular staining procedure was performed for detecting IL-10. RESULTS: The percentage of Bregs in the perigonadal depot rises throughout development (10.69 ± 5.40421% at 4 weeks, 13.975 ± 2.75616% at 6 weeks, 15.585 ± 6.07088% at 6 weeks, 34.925 ± 2.16083% at 8 weeks). The prevalence of Bregs in periaortic mirrors that in the perigonadal depot (11.7775 ± 5.65177% at 4 weeks, 15.023408% at 8 weeks). The enrichment of Bregs in the pericardial adipose depot occurs prior to that in perigonadal and periaortic depots (52.175 ± 3.85778% at 4 weeks, 43.475 ± 1.647998% at 6 weeks, 31.075 ± 3.619139% at 8 weeks). We detected significantly more IL-10+ Bregs in unstimulated adipose tissue of WT mice compared to that of IL-10 knockout mice (0.319 ± 0.094377% vs. 0.07195 ± 0.023408%). CONCLUSIONS: These results will aid our efforts in exploring therapeutic strategies targeting Bregs in obesity-associated diseases, such as type 2 diabetes.
**Impact of Diet on Secretion of IL-1β and of IL-1RA by Adipocytes and Other Immune Cells**

Roman Khanferyan¹, N. Riger¹, S. Apyratin¹, V. Sjomin¹, and Lawrence M. Dubuske, MD, FAAAI²,¹; ¹Federal Scientific-Research Center of Nutrition and Biotechnology, Moscow, Russian Federation; ²George Washington University School of Medicine, Washington, DC; ³Immunology Research Institute of New England, Gardner, MA.

**RATIONALE:** Adipocytes produce cytokines, which may regulate phagocytosis, cooperating with macrophages initiating immune responses. This study assesses the influence of various diets on secretion of IL-1β and IL-1 receptor antagonist (IL-1RA) by rat adipocytes, PBMC and the adherent fraction of spleen cells (AFSC).

**METHODS:** Wistar rats were fed for 63 days with various diets supplemented with: a) high concentrations of carbohydrates; b) high concentrations of fats; and c) high concentration of carbohydrates + fats. Control animals were fed using standard balanced diet. IL-1b and IL-1RA from blood sera and supernatants of adipocytes, PBMC and AFSC were assessed by ELISA.

**RESULTS:** The serum levels of IL-1b and of IL-1RA of animals fed the various diets did not differ. Production of IL-1b by cultivated adipocytes (0.251 pg/ml) was 4.7 fold greater than PBMC and 5.8 fold greater than by AFSC (p<0.05 for both). Secretion of IL-1RA by adipocytes was 4 fold less than PBMC and 4.3 fold less than AFSC in all experimental groups.

**CONCLUSIONS:** While various diets did not influence serum concentration of IL-1b and of IL-1RA, cultivated adipocytes produced increased concentrations of IL-1b and lower concentrations of IL-1RA in comparison to PBMC and AFSC. IL-1b and of IL-1RA produced by adipocytes, PBMC, and AFSC was not impacted by various diets.

---

**IL-10 Prevents the Production of Type 2 Cytokines in Human Group 2 Innate Lymphoid Cells**

Noriko Ogasawara, MD, PhD¹, Julie A. Poposki, MS¹, Aiko I. Klingler, PhD³, Bruce K. Tan, MD, MS², Kathryn E. Hulse, PhD¹, Whitney W. Stevens, MD, PhD³, Anju T. Peters, MD, FAAAI², Leslie C. Grammer, MD, FAAAI¹, Robert P. Schleimer, PhD, FAAAI¹,², Kevin C. Welch, MD², Stephanie S. Smith, MD², David B. Conley, MD², Pejman Soroosh, PhD³, Tetsuo Himi, MD, PhD², Robert C. Kern, MD¹,², and Atsushi Katoh, PhD²,³; ¹Division of Allergy-Immunology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL; ²Department of Otolaryngology, Northwestern University Feinberg School of Medicine, Chicago, IL; ³Division of Allergy-Immunology, Department of Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL; ⁴Janssen Research and Development, San Diego, CA; ⁵Department of Otolaryngology, Sapporo Medical University School of Medicine, Sapporo, Japan.

**RATIONALE:** Group 2 innate lymphoid cells (ILC2) play an important role in the initiation and amplification of type 2 inflammation and are elevated in type 2 inflammatory diseases including asthma and chronic rhinosinusitis with nasal polyps. IL-10 is an important immunosuppressive cytokine and is known to suppress Th2 cell-mediated type 2 inflammation in allergic diseases. However, its role in ILC2-mediated inflammation in humans is still largely unknown.

**METHODS:** We investigated the presence of the IL-10 receptor subunits, IL-10RA and IL-10RB, in human ILC2 from blood, tonsil and nasal polyps (NP) and the phosphorylation of STAT3 by IL-10 in ILC2 by flow cytometry. Purified blood ILC2 were stimulated with 10 ng/ml IL-33 and 10 ng/ml thymic stromal lymphopoietin (TSLP) in the presence or absence of 1-10 ng/ml IL-10 and the production of type 2 cytokines from ILC2 was evaluated by Luminex.

**RESULTS:** Flow cytometric analysis revealed the expression of IL-10RA and IL-10RB on ILC2 from blood (n=6), tonsil (n=6) and NP (n=5).

---

**IL-10 dose-dependently induced phosphorylation of STAT3 in blood ILC2 (p<0.05, n=5). IL-10 significantly suppressed IL-33 and TSLP-mediated production of type 2 cytokines including IL-4, IL-5, IL-9 and IL-13 in blood ILC2s (p<0.01, n=6). We also found that IL-10 suppressed IL-33-mediated morphological changes of ILC2.**

**CONCLUSIONS:** Functional IL-10 receptor is expressed on human ILC2 and IL-10 suppresses the production of type 2 cytokines in ILC2. Induction of IL-10 may have a beneficial role in both Th2 cell- and ILC2-mediated inflammation in type 2 inflammatory diseases.
48 Early-life Lactobacillus rhamnosus GG Supplementation of High-risk for Asthma Infants Reprograms Gut Microbiota Development and promotes regulatory T-cells

Juliana Durack1, Nikole E. Kimes1, Din Lin2, Michelle McKean1, Marcus Rauch2, Michael D. Cabana1, and S. V. Lynch1, tUniversity of California, San Francisco, San Francisco, CA.

RATIONALE: Neonatal gut microbiota perturbation is associated with childhood allergic asthma development. Daily Lactobacillus rhamnosus GG supplementation of high-risk (HR) for asthma infants from birth may impact the compositional and functional development of the gut microbiome in a manner that promotes immune tolerance.

METHODS: Longitudinal stool samples from 25 HR infants (randomized to receive 1x10^9 LGG or placebo daily, from birth to 6mo), and 29 healthy control (HC) infants were subjected to 16S rRNA-based microbiota and un-targeted liquid chromatography mass spectrometry metabolic profiling. A dendritic-cell/T-cell co-culture assay was used to assess the capacity of sterile fecal water from a subset of 6mo and 12mo samples to promote T-regulatory cell populations and IL10 production.

RESULTS: Compared to healthy controls, placebo-treated HR subjects exhibited delayed bacterial diversification over the first year of life, which was abrogated in LGG supplemented subjects. Compared to the placebo arm, LGG supplementation was associated with gut bacterial communities and fecal metabolic profiles more similar to healthy control subjects. At 6 months LGG-supplemented subjects exhibited enrichment of a range of anti-inflammatory metabolites, and sterile fecal water prepared from these participants promoted expansion of CD4+CD25+Foxp3+ (T-regulatory) cells and IL10 ex vivo. These effects were lost at 12 months, 6 months following cessation of LGG supplementation.

CONCLUSIONS: Daily LGG supplementation in early life partially rescues gut microbiome and metabolome deficiencies associated with high-risk for asthma subjects. Sustained supplementation or supplementation with a cocktail of bacteria typically depleted in HR infants may be necessary to prevent allergic asthma in childhood.

49 Surfactant Protein-D (SP-D) Is a Lung Specific Regulator of Group 2 Innate Lymphoid Cells (ILC2)

Cameron H. Flayer, Moyar Qing Ge, PhD, Peter B. Kovacs, Sean Ott, and Angela Haczk, MD, PhD, FAAAAAI; University of California, Davis, Davis, CA.

RATIONALE: We previously showed that ILC2 were required for recruitment of neutrophils and eosinophils into the lung following ozone (O3) inhalation. SP-D is an immunoprotective protein released by airway epithelial cells. We found that presence of SP-D was necessary to resolve airway inflammation after O3. The relationship between SP-D and ILC2 in the lung has not been investigated before. We hypothesized that SP-D suppresses ILC2 activation by O3.

METHODS: C57BL/6 (WT) and SP-D-/- mice were exposed to 3 ppm O3 for 2 hours and euthanized 12 hours later. Bronchoalveolar lavage (BAL) was collected and measured for inflammatory cell influx and cytokines (ELISA). Lungs were harvested and gene expression (qPCR) of ILC-acti- vating cytokines (IL-33, TSLP, IL-25) and ILC transcription factors (GATA-3, Bcl11b, RORγt) was measured for inflammatory cell influx and cytokines (ELISA). BALCs were collected and measured for inflammatory cell influx and cytokines (ELISA). Surfactant protein-D (SP-D) was measured by qPCR.

RESULTS: SP-D+ mice had heightened and prolonged airway neutrophilia after O3 exposure, that corresponded with significantly reduced ILC2 count in the BAL. O3 induced ILC2-activating cytokines in the lung (qPCR) and inhibited ILC2 suppressor IFNγ in the BAL of both WT and SP-D-/- mice. Lack of SP-D was associated with increased lung IL-33 mRNA expression elevated ILC2 counts and higher ST2 (IL-33 receptor) GATA-3, Bcl11b and lower RORγt expression by ILC2.

CONCLUSIONS: We propose that in the absence of SP-D, ILC2 are “primed” for response to O3, explaining why SP-D-/- mice are more susceptible to the effects of O3 than WT mice.

50 Effects of Annona muricata L. (soursop) seeds oil improves in model in vivo and in vitro of type 1 diabetes mellitus

Laise Cedraz Pinto1, Ana Tereza Cerqueira-limani, Samara dos Santos Suzart1, Raiane Souza1, Bruna Tosta1, Hugo Bernardino Ferreira Silva, Sr2, Anaque Oliveira Pires2, Gerson Queiroz2, Rainmon RIOS Silva2, Tatiane Teixeira1, Keina Maciele Dourado2, Veturia Oliveira Costa2, Vanda Baqueiro2, Caroline Oliveira de Souza2, Janice Izabel Druzian2, Karina Carla de Paula Medeiros2, Cresio de Aração Danus Alves3, Mariangela Vieira Lopes3, and Camila Alexandra Figueiredo4, 1Institute of Health Sciences, Federal University of Bahia, Salvador, Brazil, 2Federal University of Bahia, Salvador, Brazil, 3Clinical Laboratory LABCHECAP, Salvador, Brazil, 4Clinical Laboratory LABCHECAP, Salvador, Brazil, 5Faculty of Pharmacy, Federal University of Bahia, Salvador, Brazil, 6Federal University of Rio Grande do Norte, Salvador, Brazil, 7Department of Life Sciences, State University of Bahia, Salvador, Brazil.

RATIONALE: Type 1 diabetes mellitus (T1D) is a metabolic disorder and caused by an autoimmune reaction against pancreatic β cells. Annona muricata L. has several medicinal properties, such antidiabetic effects. In this work, we hypothesized that the A. muricata seeds oil (AmSO) possess immunomodulatory and can improve inflammatory markers in T1D in vivo and in vitro.

METHODS: Fatty acid profile to AmSO was evaluated by gas chromatography. Spleenocyte viability exposure to AmSO was evaluated by MTT-tetrazolium and Resazurin. Whole blood cell viability exposure to AmSO was evaluated by Resazurin. AmSO was given orally in Balb/c mice for 48 days and mice were randomly divided into four groups; control group, Stz group, Stz-AmSO (1.0 mg/Kg) and AmSO group (1.0mg/Kg). T1D was STZ-induced intraperitoneally (3x-100 mg/Kg). Blood glucose, serum insulin, area of pancreatic islets, ALT, creatinine, histopathological analysis were evaluated. IL-10, IL-4, and IL-17 production in splenocyte cultures upon AmSO exposure from diabetic mice was determined by ELISA. IFN-γ and IL-10 also was determined in whole blood cells culture from 12 T1D diabetics patients upon AmSO exposure.

RESULTS: AmSO contain 39% of oleic acid and 33% of linoleic. AmSO showed anti-hyperglycemic effect (p<0.01), preservation of the area of pancreatic islets (p<0.001), preservation of liver tissue and partial recovery glycogen, increase of IL-4 and IL-10 in splenocytes culture (125μg/mL, p<0.01) and decrease of IFN-γ (125, 62.5 and 31μg/mL, p<0.05) in whole blood cell from T1D patients.

CONCLUSIONS: AmSO has immunomodulatory potential for the treatment and/or prevention of T1D.

All abstracts are strictly embargoed until the date of presentation at the 2017 Annual Meeting.
**Human Metapneumovirus Small Hydrophobic Protein Inhibits Interferon Induction in Plasmacytoid Dendritic Cells via TLR7 Signaling Pathway**

Anar Dossambekova, MD, Deepthi Kolli, PhD, Dana L. Esham, MD, Tianshuang Liu, MS, and Antonella Casola, MD, 1University of Texas Medical Branch, Galveston, TX, 2Adena Regional Medical Center, Chillicothe, OH.

**RATIONALE:** Human metapneumovirus (hMPV) is a leading cause of upper and lower respiratory tract infections in infants, elderly and immunocompromised patients. hMPV encodes a small hydrophobic (SH) protein thought to be important in immunopathogenesis, although the exact function is unknown. Plasmacytoid dendritic cells represent an important source of IFN produced upon entry of viral and viral pathogens.

**METHODS:** Human pDCs were infected with recombinant hMPV, either wild type (rhMPV-WT) or lacking SH protein expression (rhMPV-ΔSH), followed by measurement of type I IFN in the supernatants by ELISA. IFN secretion was also measured from spleen pDCs from TLR7-/- mice following hMPV infection. HEK293 cells, which stably express TLR7, were transfected with a luciferase-tagged IFN-α promoter, MyD88, IKK-α and either TRAF6 or TRAF3 expression plasmids in the presence of SH expression plasmid or empty vector, and treated with recombinant IFN-α to induce TLR7 expression.

**RESULTS:** Increased production of IFN-α and β by rhMPV-ΔSH infected pDCs vs rhMPV-WT infected pDCs suggests that SH protein inhibits type I IFN production in these cells. Compared to wt mice, neither TLR7-/− or MyD88-/−/− mice produced type I IFNs after hMPV infection. SH expression inhibited TRAF6, but not TRAF3-dependent, IFN-α production, suggesting that SH targets TRAF6 to inhibit TLR7-induced IFN production.

**CONCLUSIONS:** hMPV SH protein inhibits TLR7/MyD88/TRAF6 signaling leading to IFN gene transcription, identifying a novel mechanism by which hMPV SH protein modulates innate immune responses.

---

**Spirometry in the management of CVID**

Jack G. Ghably, MD, and Harry W. Schroeder, MD, PhD; University of Alabama at Birmingham, Birmingham, AL.

**RATIONALE:** Common Variable Immunodeficiency (CVID) is a primary disorder of the immune system characterized by an inadequate ability to produce antibodies predisposing patients to infections, predominantly within the respiratory tract. The mainstay of treatment is supplemental immune globulin. These patients are typically managed by following serial serum IgG levels and the dose of immunoglobulin adjusted to maintain a level within the normal range. However, this measurement does not precisely reflect the physiological demand for IgG replacement and patients may be underdosed predisposing them to serious infections and developing long term sequel.

**METHODS:** Adult patients seen in a specialty adult immune deficiency clinic between 1999-2016 were evaluated for underlying immune deficiency and placed on supplemental immunoglobulin if appropriate. These patients were tested with spirometry at first visit and every subsequent evaluation.

**RESULTS:** Analysis of records of these patients reveals that the FEV25-75 on spirometry correlates well with IgG levels and an increase in immunoglobulin dose corrects the FEV25-75 in predictable pattern.

**CONCLUSIONS:** The FEV25-75 is reduced in patients with untreated or insufficiently treated CVID. This is possibly a result of underlying small airway inflammation. Our research shows that this value may be reflective of underlying infectious inflammation in the patient with CVID and a better marker of disease activity and successful treatment. Patients whose immunoglobulin dose was adjusted to improve small airway inflammation yielded overall better clinical outcomes.
Snehal Patel, DO, Tara F. Carr, MD, FAAAAI, and Michael O. Daines, MD FAAAAI. Banner University Medical Center, Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, Tucson, AZ. University of Arizona, Tucson, AZ.

RATIONALE: Primary immunodeficiency-9 is an autosomal recessive disorder due to defects in the ORAI1 gene. ORAI1 encodes for calcium release-activated calcium (CRAC) channels which are essential for antigen induced gene expression for T cell activation and proliferation via the NFAT-driven pathway and T cell migration and homing to lymph nodes. Lymphocyte development is preserved while immune function is dramatically impaired. Patients with ORAI1 mutation are also at a higher risk of developing autoimmunity, ectodermal dysplasia, and muscular hypotonia. Here we present a child who presented with pneumocystis jiroveci pneumonia found to have ORAI1 missense mutation with a new variant not previously reported.

METHODS: SCID Comprehensive Panel by Massively Parallel Sequencing at Baylor Miraca Genetics Laboratories.

RESULTS: 8 month old girl presented with pneumocystis jiroveci pneumonia and rhizomucocutaneous infection of the right forearm. Absolute lymphocytes were elevated at 25,500 cells/µL (normal 4,000-13,500/µL). B and NK lymphocyte subset counts were normal. IgG 280 mg/dL (normal 203-934), IgA 215 mg/dL (normal 8-91) and IgM 70 mg/dL (normal 17-150). Low lymphocyte response to tetanus, PHA and Con A. Normal lymphocyte response to Pokeweed mitogen. Genome analysis revealed two heterozygous pathogenic variants (c.581T>C and c.802C>T) in the ORAI1 gene. Patient was treated with antimicrobials to resolution of infection and underwent successful cord blood transplant with matched unrelated donor.

CONCLUSIONS: There are only 6 other cases reported. C.581T>C variant has previously been reported, however, C.802C>T variant has not been reported with any disease process. Primary immunodeficiency-9 due to ORAI1 missense mutation should be considered in individuals with lymphocyte dysfunction.

Another Case of Interleukin-2 Receptor Alpha Chain (IL2RA) Deficiency

Danilo Gois Goncalves, MD, Larissa Prando Cau, MD, Pâmella Diogo Salles, MD, Paula Quadros Marques, MD, Mariele Morandin Lopes, MD, Claudia Leiko Yonekura Anagusko, MD, Leonardo Oliveira Mendonca, MD, and Myrthes Toledo Barros, MD; Clinical Immunology and Allergy Department, University of Sao Paulo, Sao Paulo, Brazil.

RATIONALE: IL2RA deficiency is an autosomal recessive complex disorder of immune dysregulation. Onset is usually during infancy and very few cases have been reported. Here we present a 17-year-old boy with IL2RA deficiency with rhinoconjunctivitis, asthma, celiac disease, and follicular bronchiolitis.

METHODS: Whole exome sequencing was performed.

RESULTS: This patient presented with recurrent pneumonia, furunculosis, rhinoconjunctivitis, asthma, and recurrent diarrhea since he was 9 years old. Low IgM titters (48 mg/dL), few NK cells (57 cells/mm³), a normal response to 5 of 7 pneumococcal serotypes after polysaccharide immunization and an absent response to cutaneous delayed-type hypersensitivity test (PPD, Candida albicans, Trychophyton spp., and group C Streptococcus) were found. IgA, IgG, CD19, CD3, CD4, and CD8 were normal. His diarrhea ended after gluten and lactose restrictions and he had positive anti-gliadin IgA titters and a normal duodenal biopsy after restrictions. His chest computerized tomography showed thickening of bronchial walls with mucoid impaction, cenotribular nodules and consolidation in lower right lobe. He was also submitted to open lung biopsy whose histopathology showed follicular bronchiolitis and organizing pneumonia. His whole exome sequencing confirmed IL2RA deficiency, position chr10: 6,067,953, variant C>T; consequence: p Ala34Thr CCDS7076.1, homozygosity (2 alleles). He responded well to prophylaxis with azithromycin, reducing the number of infections, and was administered intravenous immunoglobulin, which will be assessed afterwards.

CONCLUSIONS: We reported a rare case of IL2RA deficiency in a 17-year-old boy. He has some previously unreported manifestations of immune dysregulation. Each case report helps in identifying the best approach to IL2RA deficiency.

A Case of Delayed Diagnosis of Kostmann Syndrome in an Adolescent Boy

Daniel A. Rosloff, MD, and Jocelyn Celestin, MD, FAAAAI; Albany Medical College, Albany, NY.

RATIONALE: Kostmann Syndrome (KS) is a form of Severe Congenital Neutropenia with an estimated prevalence of 2.1 cases per million in the United States. KS is characterized by recurrent infections, stomatitis, isolated neutropenia, and early bone marrow promcytologic/myelocytic arrest. It is diagnosed by genetic and bone marrow studies with an Absolute Neutrophil Count (ANC) under 200.

METHODS: This is the case report of a 12-year-old male admitted for mastoiditis in August 2016 to a university-affiliated children’s hospital. He was seen in our service for a history of persistent neutropenia and recurrent infections.

RESULTS: The patient reported lifelong recurrent otitis media, severe stomatitis, and upper respiratory infections. He describes over 200 otitis media and URI events per year. His previously healthy biological mother died of H1N1 complications in 2009. She was reportedly neutropenic at that time. Our patient was initially discovered to have an ANC of 51 in June 2016 with normal serum immunoglobulins and an otherwise unremarkable Complete Blood Count (CBC). Evaluation and workup during this admission revealed a BMI below the 10th percentile, isolated neutropenia (ANC = 83) and Pseudomonas-positive middle ear effusion. KS was suspected and genetic studies (HAX-1, ELANE) were obtained, along with antineutrophil antibody screen. Bone marrow aspiration and biopsy are pending.

CONCLUSIONS: Our patient demonstrated signs of immunodeficiency from severe neutropenia potentially undiagnosed for years. A high index of suspicion should facilitate the early diagnosis of KS. Treatment with granulocyte-colony stimulating factors may decrease morbidity and improve the quality of life of affected patients.
58 Analyses of a Subset of Patients with Primary Immunodeficiency Diseases (PIDD) Who Switched Modes of Administration of Immunoglobulin (Ig) Therapy during Three Consecutive Studies

Richard L. Wasserman, MD, PhD, FAAAAI1, Sudhir Gupta, MD, PhD, MACP2, Mark R. Stein, MD, FAAAAI3, Isaac Reuven Melamed, MD4, Jennifer M. Pack, MD5, Werner Engl, PhD6, Heinz Leibl, PhD6, Christopher J. Rabbat, PhD2, and Leman Yel, MD, FAAAAI4, 1Allergy Partners of North Texas, Dallas, TX, 2University Of CA - Irvine, Irvine, CA, 3Allergy Associates of the Palm Beaches, North Palm Beach, FL, 4IMMUNOeHealth Centers, Centennial, CO, 5UCSF, San Francisco, CA, 6Shire, Vienna, Austria, 7Shire, Bannockburn, IL, 8Shire, Westlake Village, CA.

RATIONALE: Ig therapies for PIDD are available in different administration modes, characterized by their pharmacokinetics, infusion parameters, and tolerability. We report the efficacy and tolerability data for a subset of 31 patients with PIDD who switched modes of Ig therapy during three consecutive studies.

METHODS: In Study 1, patients received IVIG 10% every 3-4 weeks (>3 months), followed by weekly SCIG 10% (>2 weeks; mean 137% of IV dose); in Study 2, they were switched to recombinant hyaluronidase-facilitated SCIG 10% (IGHy) (mean 108% of IV dose) every 3-4 weeks for ~14-18 months; then, in Study 3 (extension of Study 2), they continued with the same IGHy dose for up to 48 weeks (exposure=122.5 patient-years).

RESULTS: Longitudinally across three consecutive studies, the annual rate of validated acute bacterial infections (VABIs) and all infections were low: IVIG (0.00/4.04), SCIG (0.09/3.93), and IGHy (0.04/2.4) (rate of VABIs/all infections, respectively). The rate of causally-related systemic AEs/patient-year was lowest for IVIG (0.13) (SCIG [0.90]; IGHy [1.56]). Median IgG trough levels (g/L) were similar for IVIG (10.4), SCIG (12.5 patient-months), and IGHy (13.1), and IGHy (9.9).

CONCLUSIONS: Long-term evaluation of the same patient cohort over three consecutive studies demonstrated that IGHy, compared to the other modes of Ig therapy patients received prior to initiating IGHy provided similar efficacy, and safety and tolerability profiles. IgG trough levels were maintained throughout the studies.

59 Two Brothers with Immunodeficiency: Mixed Clinical Findings with a Common Diagnosis

Deena Pourang, MD, and Shefali A. Samant, MD: Kaiser Permanente Los Angeles Medical Center, Los Angeles, CA.

RATIONALE: Activated phosphoinositide 3-kinase δ syndrome is novel autosomal-dominant primary immunodeficiency caused by a heterozygous gain-of-function mutation in the PIK3CD gene. We describe a case of two brothers with differing clinical presentations, both diagnosed with deleterious PIK3CD mutation.

METHODS: National Institutes of Health performed targeted capture of exons from a panel of immune related genes, followed by Sanger sequence of the suspect variant.

RESULTS: Two brothers, ages 12 and 19, presented for evaluation of immune deficiency. The younger brother had a more severe presentation with history of hypogammaglobulinemia, bilateral otitis media with tympanic membrane perforations, sinusitis, pneumonia, bronchiectasis and delayed gastric emptying—requiring immunoglobulin therapy for symptom resolution. He had persistent lymphadenopathy, status post resection with biopsy results revealing follicular, interfollicular and monocytoid hyperplasia, without evidence of malignancy. The older brother had normal immunoglobulin levels, bilateral otitis media, sinusitis, pneumonia and bronchiectasis—not requiring immunoglobulin therapy for symptom management. There was concern that familial inheritance may be underlying the brothers’ clinical phenotype. Genetic testing confirmed the brothers heterozygosity for a deleterious mutation in PIK3CD, c.3061G>A—causing p.E1021K, consistent with their clinical phenotype.

CONCLUSIONS: The younger brother is being considered for clinical trial with rapamycin therapy. The older brother is undergoing evaluation for mammalian target of rapamycin (mTOR) inhibitor trial. Their case illustrates the importance of identifying genetic conditions in familial immune deficiency, as the specific diagnosis has implications in therapeutic management beyond the supportive options of antibiotics and intravenous immunoglobulin. Individuals with PIK3CD mutation also warrant monitoring for development of autoimmunity and lymphoid malignancy.

60 An Atypical Severe Combined Immunodeficiency (SCID) Case Diagnosis Complicated by Alternative Care in the Era of Newborn Screening (NBS) for SCID

Taylor Alberdi, MD1, Johana B. Castro-Wagner, MD2, Bhumika Patel, MD3, Sonia Joychan, MD4, David Lindsey, MD5, Frederico R. Laham, MD, MS6, Kristzian Cosnos, PhD7, Boglarka Ujhazi1, Carla M. Duff, CPNP, MSN8, Jessica Trotter, MD, BS, CCRP, CRA1, Jack J. Blessing, MD, PhD2, Attila Kumanovics, MD9, Yenhu Chang, MD PhD9, Jamie H. Halle9, Panida Siraaron, MD, FAAAAI9, Greg Hale, MD9, Benjamin R. Oshrine, MD9, Luigi Notarangelo, MD10, Roshini S. Abraham, PhD, FAAAAI11, Anne Marie Corneau12, Aleksandra Petrovic, MD12, Jennifer W. Leiding, MD, FAAAAI12, and Joan E. Walter, MD, PhD13,14,15, 1University of South Florida Morsani College of Medicine, Tampa, FL, 2University of South Florida Morsani College of Medicine, Saint Petersburg, FL, 3University of South Florida Morsani College of Medicine, St. Petersburg, FL, 4Arnold Palmer Hospital, Orlando, FL, 5Massachusetts General Hospital, Boston, 6University of South Florida, St. Petersburg, FL, 7Cincinnati Children’s Hospital Medical Center, Cincinnati, OH, 8Department of Pathology, University of Utah, Salt Lake City, UT, 9John Hopkins All Children’s Hospital, St Petersburg, FL, 10UMass Medical School - New England Newborn Screening Program, boston, 11Children’s Hospital-Boston, boston, 12Mayo Clinic, Rochester, MN, 13UMass Medical School - New England Newborn Screening Program, Jamaica Plain, MA, 14University of South Florida, Tampa, FL, 15Johns Hopkins All Children’s Hospital, St Petersburg, FL.

RATIONALE: Most infants with severe combined immunodeficiency (SCID) can be identified early with TREC-based newborn screening (NBS). We present a case of an infant with atypical presentation of SCID resulting in a delayed diagnosis.

METHODS: Retrospective chart review.

RESULTS: A Florida (FL)-born infant from a midwife-attended home birth was referred for a specialist immunology consultation at 9 months of age after recurrent infections, failure to thrive and PJP pneumonitis. Immune phenotyping at 9 months revealed absence of naïve T cells with absent proliferation to mitogens and anti-CD3/IL-2. Extreme oligoclonal repertoire of CD3+ T cells (474 cells/mm³) supported a diagnosis of atypical SCID. Review of records showed that the infant’s only timely NBS sample was of insufficient quantity for the FL-NBS panel. A much later NBS specimen obtained at 8 months of age showed a normal TREC value. In light of the conflicting clinical/imunological presentation and 8-mo TREC result, extramural TREC analysis of the two NBS specimens (post-birth and 8-mo) was performed in Massachusetts. The post-birth specimen showed undetectable TREC however the 8-mo specimen was normal. At 11 months, a third NBS specimen was obtained; both FL and MA assays confirmed undetectable TREC. The patient developed HHV-6 viremia, which further delayed hematopoietic stem cell transplantation.

CONCLUSIONS: Early diagnosis of SCID requires multidisciplinary cooperation. Timely replacement of a poor quality specimen might have ensured an earlier diagnosis. Identity testing of the 8-mo specimen remains warranted. Clinical vigilance and awareness for late and/or leaky presentation of SCID should continue even in the era of SCID newborn screening.
A Case of Common Variable Immunodeficiency (CVID) and Antineutrophilic Cytoplasmic Antibody (ANCA)-Associated Vasculitits

Adeeb A. Bulkhi, MD1, Jennifer E. Ferguson, DO2, Mark C. Glaun, MD, PhD, FAAAAI1, and Richard F. Lockey, MD, FAAAAI1, 1Division of Allergy and Immunology, Department of Internal Medicine, Morsani College of Medicine, University of South Florida, Tampa, FL, 2University of South Florida Morsani College of Medicine, Tampa, FL.

RATIONALE: CVID is a primary humoral immunodeficiency characterized by recurrent sinopulmonary infections, hypogammaglobulinemia and poor polysaccharide antibody responses. More severe forms of CVID are associated with autoimmunity, granulomatous disease, and malignancy. An ANCA-associated vasculitis with CVID is presented.

METHODS: A complete history and physical examination, Past medical records, x-rays and laboratory tests reviewed.

RESULTS: A 21-year-old male diagnosed with CVID at age 13 presents with shortness of breath, hemoptysis, fever, chills and night sweats beginning 5 months ago, which worsened a week ago. He was tachypneic and hypoxic, and the lung examination revealed bilateral diffuse wheezes and ronchi. Laboratory tests indicated a leukocytosis, thrombocytopenia, and elevated ESR and CRP. He had undetectable serum IgA, low IgM, and marginally low IgG (on IVIG). CT chest revealed ground-glass opacities. Microbial tests for viral, bacterial and fungal infections were negative. An open lung biopsy demonstrated necrotizing capillaritis, diffuse alveolar hemorrhage and neutrophilic infiltrate with associated necrosis. The serological test revealed a positive proteinase-3 antibody (C-ANCA). He was treated with plasmapheresis, cyclophosphamide and prednisone and discharged on a tapered prednisone plus IVIG. A few weeks later, he exacerbated with lower extremity palpable purpura, elevated creatinine, proteinuria and RBCs casts. The CT of the kidneys was normal. Rituximab was started, the purpura resolved, hematurosis improved, and the ground-glass opacities on CT chest resolved.

CONCLUSIONS: This is the second case of CVID and ANCA-associated vasculitis reported. Vasculitides are potential autoimmune complications in a subpopulation of CVID subjects.

Autoimmune Cytopenias following Hematopoietic Stem Cell Transplant in Pediatric Patients with Primary Immunodeficiencies: A retrospective single center experience

Mirinda A. Gillespie, MD, ScM1, Jennifer W. Leiding, MD, FAAAAI2, Benjamin R. Oshrine, MD3, and Aleksandra Petrovic, MD1, 1Johns Hopkins All Children’s Hospital, St Petersburg, FL, 2University of South Florida Morsani College of Medicine, St Petersburg, FL, 3John Hopkins All Children’s Hospital, St Petersburg, FL.

RATIONALE: Autoimmune mediated cytopenias are a recognized complication post-hematopoietic stem cell transplant (HSCT) particularly among patients transplanted for non-malignant diseases. Definitive risk factors and the pathophysiology are not fully understood. No consensus guidelines regarding the treatment of post-HSCT autoimmunity exist.

METHODS: A retrospective chart review of patients with primary immunodeficiencies (PIDs) transplanted from 2005 to present at Johns Hopkins All Children’s Hospital was performed. n=29. Demographic and clinical data including age at HSCT, sex, ethnicity, DAT results, conditioning regimen, graft type and degree of match, and GVHD prophylaxis were collected on all patients. For patients diagnosed with autoimmune cytopenias, chimerism, use of immunosuppression, and treatment were characterized.

RESULTS: Out of 29 patients transplanted for PID, 4 (14%) developed autoimmune cytopenias following HSCT: 2 with Autoimmune Hemolytic Anemia (AIHA), 1 with Immune Thrombocytopenic Purpura (ITP), and 1 with both AIHA and ITP. HLH was the underlying pre-HSCT diagnosis in 3 of the 4 patients with autoimmune cytopenias. Autoimmune cytopenias occurred more frequently with reduced intensity conditioning regimens and were associated with mixed donor chimerism, notably in the T cell fraction. Common treatments included steroids, IVIG and immunosuppressant modification. Two patients also received treatment with rituximab with subsequent resolution of cytopenias.

CONCLUSIONS: Autoimmune cytopenias are a common complication in PID patients after HSCT. While the mechanism and risk factors are not well understood, conditioning regimen, graft source, and chimerism were associated with the development of post-HSCT autoimmune cytopenias in this cohort of PID patients. Treatment approaches may include modification of immunosuppression with or without rituximab.
IgA Monoclonal Gammopathy of Undetermined Significant (MGUS) in a Young Woman With Selective IgM Deficiency.

Sharon Julie Williams, MD,1 and Sudhir Gupta, MD, PhD. MACP1,2; 1University of California, Irvine, CA, 2Program in Primary Immunodeficiency and Aging, Division of Basic and Clinical Immunology, University of California School of Medicine, Irvine, CA.

**RATIONALE:** Selective IgM deficiency and IgA MGUS are rare disorders. IgA MGUS has not been described in selective IgM deficiency. A comprehensive immunological analysis in IgA monoclonal gammopathy has not been described. We present a comprehensive analysis of subsets of CD4+ and CD8+ T cells and B cells in the first case of IgA MGUS in a 21 year old woman with selective IgM deficiency that initially presented with recurrent urinary tract infections.

**METHODS:** IgA monoclonal gammopathy was diagnosed by immunoelectrophoresis and immunofixation. Patient has been followed 8 years for serum immunoglobulins by nephelometry and clinical features. Naïve, central memory, and effector memory subsets of CD4+ and CD8+ T cells, CD4 Treg, CD8 Treg, and naïve, transitional, marginal zone (MZ), germinal center (GC), regulatory B (Breg) cells, and plasmablasts (PB) were enumerated with specific monoclonal antibodies and isotype controls by multicolor flow cytometry.

**RESULTS:** During the last 8 years, IgA ranged between 602 mg/dl (current)-1090mg/dl (initial), and IgM between 35-45mg/dl. Immunoelectrophoresis and immunofixation revealed IgAκ monoclonal paraprotein. Analysis of B cell subsets revealed increased transitional B cells, GC, Breg, PB, and decreased MZ B cells. BAFF-R expression on memory B cells displayed two distinct peaks (normal and low expression). CD8 central memory and effector memory were decreased, whereas naive CD8+ T cells were increased.

**CONCLUSIONS:** IgA1A MGUS associated with selective IgM deficiency display abnormalities predominantly in various B cell subsets, including plasmablasts. These abnormalities may have a predictive value for progression to multiple myeloma.

The Timing of Infections in Patients with Primary Immune Deficiencies Treated with Intravenous Immunoglobulin (IVIg)

Winder Gill, MD, and Stephen D. Betschel, MD; University of Toronto, Toronto, ON, Canada.

**RATIONALE:** Patients with common variable immune deficiency and x-linked agammaglobulinemia are unable to produce their own antibodies thus leading to a higher incidence of recurrent infections, particularly those involving the sinuses and lungs. Treatment with intravenous immunoglobulin therapy aims to reduce the incidence of infections; however, as serum IgG approaches its trough during the third and fourth week after infusion, we hypothesized that the rate of infection would be higher during this time period.

**METHODS:** 23 patients with a diagnosis of either CVID or XLA treated with IVIg on a monthly basis were analyzed in a prospective cohort study with a median follow-up time of 11.3 months. Data was obtained as to the timing of infections after IVIg infusion was administered.

**RESULTS:** The mean number of days to infection after IVIg infusion was 16.7 in 23 patients analyzed, with the most common infections reported as sinusitis and upper respiratory tract infections.

**CONCLUSIONS:** We believe that this is the first reported prospective study to examine the timing of infections after intravenous immunoglobulin (IVIg) infusion in individuals with common variable immune deficiency and x-linked agammaglobulinemia. Further research is required into the comparison of infection rates in PID patients treated with IVIg versus subcutaneous immunoglobulin therapy, where serum IgG levels remain at steady state.

Hematological Malignancies Associated with Primary Immunodeficiencies

Lucy Yingying Duan1, and Eyal Grunebaum2; 1Department of Pediatrics, The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada, 2Division of Immunology and Allergy, Department of Pediatrics, The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada.

**RATIONALE:** Hematologic malignancies are increasingly recognized among patients with primary immunodeficiencies (PID), therefore a comprehensive review of this association is needed.

**METHODS:** A systemic search of the Ovid MEDLINE database was performed for all PID described in the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency classification system (IUIS 2014) for hematological malignancies. PID were categorized in accordance to the IUIS classification.

**RESULTS:** Reports of hematological malignancies were found in patients suffering from the following PIDs. (1) Combined immunodeficiencies: defects in gamma-c, coritin-1A, RAG1, AK2, Adenosine deaminase, Purine nucleoside phosphorylase, ZAP70, ITK, SH2D1A, RMRP, MAGT1, DOCK8, RHo-H, MST1, PIE3-delta, LRBA and CD27; (2) Combined immunodeficiencies with associated or syndromic features: Wiskott-Aldrich syndrome, Ataxia telangiectasia, Nijmegen breakage syndrome, Bloom syndrome, Immunodeficiency with centromeric instability and facial anomalies 1/2, PMS2 deficiency, DiGeorge anomaly, Schimke syndrome, Autosomal dominant Hyper-IgE syndrome and Dykeratosis congenita; (3) Predominantly antibody deficiencies: BTK deficiency, Common variable immunodeficiency, Warts, hypogamaglobulinemia, infections and myelokathexis syndrome, PRKC-delta deficiency, and selective IgA deficiency; (4) Diseases of immune dysregulation: Perfomin deficiency, STXBP2/Munc18-2 deficiency, Chediak-Higashi syndrome, Griscelli syndrome, Hermansky-Pudlak syndrome, IPEX, Autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy, Autoimmune lymphoproliferative syndrome and IL-10 receptor deficiency; (5) Congenital defects of phagocyte number, function, or both: Severe congenital neutropenia 1/3, Clericuzio syndrome, Leukocyte adhesion defect 1, Shwachman-Diamond syndrome, Glycogen storage disease 1b, X-linked neutropenia, Macrophage p91 phox deficiency and GATA2 deficiency; (6) Autoinflammatory disorders: Familial Mediterranean fever and Muckle-Wells syndrome.

**CONCLUSIONS:** Increased awareness for the possibility of malignancy is needed when caring for patients with PID.
67 Immune and Clinical Assessment in Pediatric Hispanic Vs. Non-Hispanic Patients with Partial DiGeorge Syndrome: An Institutional Review.

Hanady A. Caldenor, MD, Jose G. Calderon, MD, Zaimat Beiro, BS, and Vivian P. Hernandez-Trujillo, MD, FAAAAI, Nicklaus Children’s Hospital, Miami, FL.

RATIONALE: DiGeorge syndrome (DGS) is the result of microdeletions of chromosome 22q11.2, resulting in a highly variable phenotype. Since scarce information is available regarding possible racial differences, the purpose of this study was to characterize the immunologic status of a cohort of Hispanic vs. Non-Hispanic DGS patients.

METHODS: We studied 90 partial DGS patients by retrospective medical record review, and divided them into two comparison groups (Hispanic n=50 vs. Non-Hispanic n=40), 66.7% confirmed using FISH, ages 0–21 years old (48 females and 42 males, mean age of diagnosis 2.1 ± 1.5 years). Immune studies including lymphocyte subsets, mitogen proliferation, serum immunoglobulins and specific antibody response, and other clinical data were recorded.

RESULTS: Twenty seven patients (30.0%) had normal T and B lymphocyte numbers. Hispanic patients had significantly higher decreases in both T and B lymphocytes (26.0% vs. 7.5%, p=0.020). On the contrary, non-Hispanic patients had significantly higher decreases in both CD4+ and CD8+ T cells (42.5% vs. 22.0%, p=0.032). Twelve patients (13.3%) had decreased vaccine titers and seven patients (7.8%) had hypogammaglobulinemia, without significant differences among groups. Pre-diagnosis infections were found in 22.2% of patients and were significantly higher in Hispanics vs. non-Hispanics patients (32.0% vs. 10.0%, p<0.05). There was no difference in baseline titer levels between the two groups regarding serotypes 8, 9N, 12F, and 57. Cardiac malformations were common (85.6%). No significant differences were found regarding gastrointestinal, neurological or endocrine systems. Learning disabilities and speech delay were similar in both groups.

CONCLUSIONS: Hispanic patients with partial DGS exhibit some clinical and immunological differences when compared to non-Hispanic patients. Further studies are warranted to confirm these findings.

68 Pneumococcal Titer S in Patients Presenting for Evaluation of Immunodeficiency in an Allergy and Immunology Outpatient Clinic

Lachara Livingston, MD, and Wei Zhao, MD, PhD, Virginia Commonwealth University, Richmond, VA.

RATIONALE: Children under 24 months of age routinely receive 4 doses of pneumococcal conjugate vaccine 13-valent (PCV13) per the routine schedule. Part of the basic immunologic workup is to measure responses to vaccination. This study examines the pneumococcal titers at baseline and post-revaccination in patients presenting for immunodeficiency evaluation in our Allergy and Immunology Clinic.

METHODS: Patients ≥ 18 years seen in our clinic from July 1, 2015 to June 30, 2016 were reviewed. After baseline titers were obtained, pneumococcal polysaccharide vaccine 23-valent or PCV13 were administered with titers repeated in 4–6 weeks if indicated. Fifty-two patients aged 5 months to 18 years were included, 23 with protective titers at baseline and 29 required revaccination.

RESULTS: Baseline titer values of patients not requiring revaccination were statistically higher for 10 of 14 serotypes than baseline levels for those who received revaccination. Those include serotypes 1, 3, 4, 14, 19F, 23F, 26, 51, 56, and 68 (p<0.05). There was no difference in baseline titer levels between the two groups regarding serotypes 8, 9N, 12F, and 57. Serotype 12F was only protective at baseline for 5.8% of all patients and had the lowest rate of response following revaccination (58.6%). All other serotypes had adequate responses to revaccination, i.e. achieving protective levels in ≥ 79% of patients.

CONCLUSIONS: For patients presenting with a history of frequent infection, those who require revaccination tend to have low titers for serotypes 1, 3, 4, 14, 19F, 23F, 26, 51, 56, and 68. The titer of serotype 12F responds poorly after revaccination.

69 X-Linked Lymphoproliferative Syndrome (XLP1) Diagnosed after Rituximab

Anu Mallapaty, DO, MS, Shanmuganathan Chandrakasan, MD, and Kiran Patel, MD, MS, Emory, Atlanta, GA.

RATIONALE: Several case series and reports of prolonged hypogammaglobulinemia have been reported post Rituximab treatment. The etiology of this remains unclear but the question arises as to if those susceptible may have an unidentified primary immune deficiency.

METHODS: Case report

RESULTS: Our patient is a 7 year old male with history of abdominal Diffuse Large B cell lymphoma (DLBCL) diagnosed at the age of 4. He is currently in remission after receiving multiple chemotherapeutic agents including Rituximab. In the years following chemotherapy, this patient developed recurrent sinopulmonary infections and bronchiectasis. Chart review revealed normal immunoglobulin levels immediately prior to Rituximab treatment (IgG 615 mg/dL, IgM 115 mg/dL, IgA 153 mg/dL). However, recent re-evaluation revealed low IgG & IgA levels (IgG 59 mg/dL, IgM 306 mg/dL, IgA <8 mg/dL), along with absent class-switched memory B cells. Genetic testing identified a mutation (c.137+1G>A) in SH2D1A, consistent with prior reports of mutations causing XLP1.

CONCLUSIONS: Underlying primary immune deficiency may exist in patients presenting with hypogammaglobulinemia post Rituximab treatment. Specifically, screening for XLP1 with SLAM-associated protein (SAP) expression in male patients presenting with non-Hodgkin’s lymphoma such as DLBCL or Burkitt’s lymphoma should be considered at disease onset.

70 Beneficial Effects of Adalimumab Counteracted in Patient with Common Variable Immunodeficiency Disorder (CVID) Receiving IVIG: Case Report

Trisha Sharma, MD, and Marc A. Riedl, MD, MS, UCSD, San Diego, CA.

RATIONALE: Adalimumab is a monoclonal antibody (mAb) against TNF alpha used to treat rheumatoid arthritis (RA). Despite prevalence of autoimmune disease in CVID, there are no published cases of negative interactions between IVIG and adalimumab.

METHODS: We present a case of a patient with CVID and RA reporting diminished effect of adalimumab after receiving IVIG.

RESULTS: A 62 year old female with CVID, Crohn’s and RA presented to immunology clinic for follow up. She received weekly injections of adalimumab, which alleviated the joint pain and stiffness associated with RA, as well as Crohn’s-related chronic diarrhea. She expressed concern about an interaction between adalimumab and IVIG, stating that on the 1 week of the month when her adalimumab overlapped with her IVIG infusion she experienced diminished relief of severe joint pain, stiffness, and diarrhea. This occurred each month and resolved following her next dose of adalimumab. She had not experienced worsening autoimmune symptoms following IVIG therapy over the previous year prior to adalimumab therapy. The duration between administration of adalimumab and IVIG was increased; however, on follow up she reported no improvement and continues to struggle with symptom recurrence after receiving IVIG. IgG trough levels prior to IVIG transfusions remained at therapeutic levels of 900-1000.

CONCLUSIONS: We hypothesize that the co-administration of adalimumab with IVIG may result in reduced therapeutic effect from the mAb therapy due to anti-idiotypic antibodies within the supraphysiologic IgG levels immediately following IV Dosing. Understanding the mechanism of interaction will be increasingly important as mAb therapies are more widely administered.
SATURDAY

71 Combined immunodeficiency presenting as autoimmune hemolytic anemia

Aman Nasir, MD1, Jason W. Caldwell, DO, FAFAA1,2, Katharine Batt, MD3, and Talal I. Mousallem, MD4; 1Wake Forest University Baptist Medical Center, Winston Salem, NC, 2Pulmonary, Critical Care, Allergy, Wake Forest University Baptist Medical Center, Winston Salem, NC, 3Wake Forest University Baptist Medical Center, Winston Salem, NC, 4Internal Medicine, Wake Forest School of Medicine, Winston Salem, NC; Department of Pediatrics, Duke University Medical Center, Durham, NC.

RATIONALE: Combined immunodeficiency (CID) usually presents with recurrent infections. Mutations in some of the SCID causing genes can be associated with a broad spectrum of clinical phenotypes, ranging from severe combined immunodeficiency (SCID) to autoimmunity.

METHODS: The patient’s medical record was reviewed. We also reviewed the current literature on autoimmune cytopenias and primary immunodeficiency.

RESULTS: We report an 18 year old female with autoimmune hemolytic anemia referred to the Wake Forest Allergy and Immunology clinic for evaluation of hypogammaglobulinemia, noted after receiving rituximab. Workup was negative for viral infections (serology and PCR). She required RBC transfusions and was treated with prednisone and rituximab. Bone marrow biopsy showed a hypocellular marrow with myeloid hypoplasia. Lymphocyte enumeration showed an absolute lymphocyte count (ALC) of 100. The patient had no B cells. T cell count was 60 (CD4 10, CD8 50); NK cell count was 30. IgG 385 mg/dl, IgM 26 mg/dl; normal IgA and E levels. 100. The patient had no B cells. T cell count was 60 (CD4 10, CD8 50); NK cell count was 30. IgG 385 mg/dl, IgM 26 mg/dl; normal IgA and E levels. Erythrocyte ADA activity was normal. Mitogen and antigen-induced lymphocyte proliferation panel showed low/absent responses. Of note, the patient’s ALC was 400, six months prior to onset of anemia.

CONCLUSIONS: Rituximab may explain the patient’s hypogammaglobulinemia, but would not explain the profound T cell lymphopenia and low/absent mitogen and antigen lymphocyte responses. Her presentation is concerning for late onset CID. Extended genetic testing for SCID/CID was sent and the results are pending. Mutations in some of the genes associated with SCID such as RAG1/2 can be associated with a broad spectrum of clinical phenotypes, ranging from SCID to autoimmunity.

72 Common Variable Immunodeficiency with Angiosarcoma Associated with Hyperammonemia Secondary to High Dose IVIG Infusion

Li Yujie1, John A. Johnson, DO2, Chelsea Michaud, DO3, Haig Tcheurekdjian, MD4, and Robert Hostoffer, DO5; 1University Hospitals of Cleveland, Mayfield Heights, OH, 2University Hospitals Regional Medical Centers, Mayfield Heights, OH, 3UH Regional Hospitals - Richmond Campus, Richmond Heights, OH, 4Allergy/Immunology Associates, Inc., Mayfield Heights, OH, 5Allergy and Immunology Associates Inc., Mayfield Heights, OH.

RATIONALE: Common Variable Immunodeficiency (CVID) is the most common, symptomatic immunodeficiency, marked by humoral deficiency and recurrent respiratory tract infections. Its management may involve intravenous immune globulin (IVIG), which includes a spectrum of adverse effects ranging from headaches to anaphylaxis or stroke. We report a 78 year old patient diagnosed with CVID and a liver angiosarcoma who developed hyperammonemia secondary to high dose IVIG.

METHODS: Immunoglobulin levels were performed by Quest Diagnostics. Ammonia levels were performed by University Hospitals of Cleveland.

RESULTS: The patient is a 78 year old Caucasian male with CVID managed with biweekly high dose (1.1g/kg) IVIG treatment, who was admitted for generalized weakness secondary to a newly diagnosed hyperammonemic encephalopathy. At admission, his ammonia level was 87. A CT of his abdomen showed multiple nodules in the liver, and liver biopsy revealed angiosarcoma. His altered mental status delayed his discharge, as well as his scheduled IVIG infusion by 7 days; however, his total immunoglobulin level was found to be 1100, which is approximately his baseline. He received IVIG immediately following discharge. One week later, he was re-admitted for encephalopathy with an ammonia level of 81. No other etiologies of hyperammonemia were present.

CONCLUSIONS: Another case of hyperammonemia associated with high dose IVIG has been reported, however the patient was not diagnosed with an immunodeficiency. Additionally, no cases of hepatic angiosarcoma in an adult with CVID have been reported. We report the first case of an adult CVID patient with hepatic angiosarcoma associated with hyperammonemia secondary to high dose IVIG.

73 Late Presentation of Common Variable Immunodeficiency (CVID) in a Patient with Evans Syndrome

Wei An, MD1, Jennifer Monroy, MD1, and Nicholas L. Hartog, MD1,3; 1Washington University School of Medicine, Saint Louis, MO, 2Michigan State University College of Human Medicine, Grand Rapids, MI, 3Spectrum Health, Grand Rapids, MI.

RATIONALE: CVID is a common primary immunodeficiency (PID) with variable clinical presentation, but there is limited literature describing characteristics in the older population. We present a patient with late-onset CVID at age 70 whose initial presentation was Evans Syndrome, a rare disease defined by the presence of both autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP).

METHODS: We performed a retrospective chart review to present the relevant clinical and laboratory data.

RESULTS: A 70-year-old male with no infectious history was admitted for treatment of newly persistent AIHA and ITP consistent with Evans Syndrome. Prior treatment administered included IVIG, rituximab, and prednisone. Before initiating treatment, immunoglobulins were drawn and they were significant for undetectable IgA, IgM less than 38, and IgG less than 318. There was no evidence of protein-losing enteropathy. Chest CT exam showed ground glass opacities. His lymphocyte subpopulation was checked after Rituximab, and showed B cell lymphopenia with low absolute lymphocyte count of 200. No titers were checked before initiating IVIG. Workup for lymphoma and other malignancies were negative. During the admission, patient developed acute respiratory failure requiring intubation. Infectious workup was positive for CMV viremia along with parainfluenza and Moraxella respiratory infections. Family decided to withdraw care after continued deteriorating clinical status.

CONCLUSIONS: Care of elderly CVID patients present unique challenges due to lack of robust data characterizing their symptoms. Future clinical research that provides such information may potentially help guide their care.
AB23

SATURDAY

74 An Uncommon Condition in a Patient with Common Variable Immune Deficiency

Desha Jordan, MD, FAAP. Kelly Homlar, MD, Carolyn Lovell, MS, MAT, CGC, and Betty B. Wray, MD, FAAAAI; Medical College of Georgia at Augusta University, Augusta, GA.

RATIONALE: There is not a published case report describing a common variable immunodeficiency (CVID) patient presenting with pigmented villonodular synovitis (PVNS). Commonly, PVNS presents in the knee or hip. Presentation with ankle involvement is much rarer, with only a few such cases reported. Progression to bilateral ankle involvement appears to have not been previously documented.

METHODS: 27 year old female with CVID and clinical features of McCune-Albright Syndrome developed PVNS with bilateral ankle involvement. Physical examination showed café au lait spots, short stature and round facies. Fibrous dysplasia of the skull and long bones was notable on imaging. We explored the possibility of an immunologic connection between these disease states through a review of literature, laboratory results and imaging studies.

RESULTS: Routine karyotype and genetic testing of the GNAS locus were normal. Two chromosomal microarray analyses have showed a 743.8 kb interstitial gain at 12p13.33 gene locus. PHA lymphocyte stimulation testing was normal. B and T cell counts were normal at 500/mcL and 750/mcL respectively. NK cell count was low at 60/mcL with normal NK cell function. Serum immunoglobulins showed low IgA of 32 mg/dL, normal IgM of 43 mg/dL and IgG of 992 mg/dL on weekly subcutaneous immunoglobulin.

CONCLUSIONS: A defect at the 12p13.33 locus may cause the phenotype of CVID and McCune-Albright syndrome, with PVNS.

75 Good’s Syndrome: A Rare Adult-Onset Combined Immunodeficiency

Gargi Patel, Priyanka Batchu, and Amay Parikh; Rutgers Robert Wood Johnson, New Brunswick, NJ.

RATIONALE: Good’s Syndrome is a rare combined immunodeficiency seen in patients with thymoma and typically presents in fourth or fifth decade of life. We present a case of an opportunistic infection leading to a diagnosis of Good’s syndrome.

METHODS: A retrospective chart review of a 62 year old man with a history of thymoma and recurrent pneumonias for past six months who presented to the hospital with multifocal pneumonia.

RESULTS: Patient’s hospital course was complicated by pancytopenia and severe sepsis secondary to multidrug-resistant Klebsiella bacteremia and CMV viremia. After a prolonged hospital course with bloodstream infection with opportunistic organisms, immunologic workup was pursued which revealed low immunoglobulins, low T- Helper cells, reduced CD4/CD8 ratio, and no B cells. Immune work up and the history of thymoma were consistent with the diagnosis of Good’s Syndrome. Shortly after diagnosis, patient died from severe sepsis despite IVIG therapy.

CONCLUSIONS: Good’s syndrome is diagnosed in patients with thymoma with hypogammaglobulinemia, defective T-cell mediated immunity, and low or absent B cells. Good’s syndrome should be suspected in all adults who presents with recurrent infections from encapsulated organisms or opportunistic organisms concerning for adult onset immunodeficiency. Furthermore, immune workup should be performed in all patients with thymoma who present with sinopulmonary infections in order to start therapy with IVIG reduce risk of more severe infections.

76 Bacterial meningitis in pediatric patient with C2 deficiency

Ryan D. Buckley, MD1, Snehal Patel, DO2, and Michael O. Daines, MD, FAAAAI1, 2Banner University Medical Center, Department of Internal Medicine, Tucson, AZ, 3University of Arizona, Tucson, AZ.

RATIONALE: Homozygous C2 deficiency occurs in approximately 1 in 20,000 patients. Most patients with C2 deficiency remain asymptomatic; however, it is estimated 40% develop autoimmune diseases and 50% develop recurrent infections. It is associated with IgG deficiency and pyogenic infections with encapsulated bacteria - including Streptococcus pneumoniae, Haemophilus influenzae and Neisseria meningitides. Currently, there are no specific treatment guidelines for complement deficiencies. Here we present a case of a patient with C2 deficiency with a severe complication and our treatment of the disease.

METHODS: Immunoglobulin measurement performed by Sunquest Information Systems. Pneumococcal antibody measurement performed by Focus Diagnostics, Inc.

RESULTS: Ten-year-old Caucasian male with history of C2 complement deficiency (previously on subcutaneous Ig therapy) presented with fever and altered mental status. LP demonstrated milky CSF with significant pleocytosis (neutrophil predominant) with elevated protein and low glucose - concerning for bacterial meningitis. He was started on empiric Vancomycin and Ceftriaxone at meningitic dosing. CSF and blood cultures remained negative. HSV PCR and Coccioidioides immittis liters were negative. MRI brain revealed leptomeningeal enhancement. IgG on admission was 707mg/dL. Streptococcus pneumoniae antibody 14 serotypes within normal range. Patient clinically improved and completed 14 day course of Ceftriaxone. He received one dose of IVIG at 400mg/kg prior to discharge and resumed weekly subcutaneous immunoglobulin therapy thereafter.

CONCLUSIONS: This case outlines the disease presentation of C2 deficiency and treatment options with empiric antibiotics and IVIG.


Jack M. Mazurek, MD, MS, PhD, and Girija Syamlal, MBBS, MPH; National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Morgantown, WV.

RATIONALE: Work-related asthma includes new-onset asthma caused by factors related to work and preexisting or concurrent asthma worsened by factors related to work. As much as 51% of adult asthma may be related to work.

METHODS: To estimate the current asthma prevalence among U.S. workers, the 2009–2014 National Health Interview Survey data for currently employed adults aged >18 years were analyzed. Respondents with current asthma were those who have ever been told by a doctor or other health professional that they had asthma and still have asthma. Currently employed adults were those who reported being employed during the week prior to the interview; those on layoff or retired were excluded. Adjusted prevalence odds ratios (PORs) and confidence intervals were calculated.

RESULTS: Among an estimated 141 million employed adults, the current asthma prevalence was 6.5% (95% CI, 6.3 to 6.7%). Of the 21 industries, the highest asthma prevalence was in the health care and social assistance (8.8%). Of the 23 occupations, the highest asthma prevalence was in healthcare support (9.2%). The adjusted asthma PORs were significantly elevated among workers in the health care and social assistance (POR=1.17) and education services (1.12) industries, and in the education, training, and library (1.17) and protective service (1.30) occupations.

CONCLUSIONS: As many as 4.7 million working adults may have asthma related to work. Health care providers should ask workers with new or worsening asthma for occupational exposures and be alert to potential associations between workplace exposures and asthma symptoms.
AB24 Abstracts

**Impact of Titanium Dioxide Nanoparticles on Neuroinflammation in a Mouse Model of Asthma**

An-Soo Jang¹, K. J. M. Byung-Kon¹, Sun-Hye Lee², Pureun-Haneul Lee¹, and Junchyuck Lee³, ¹Soochunhyang University Bucheon Hospital, Bucheon, Korea, The Republic of, ²Soochunhyang University Bucheon Hospital, Bucheon, Korea, The Republic of, ³Soochunhyang University Bucheon Hospital, Bucheon, Korea, The Republic of.

**RATIONALE:** The interaction between chronic inflammation and neural dysfunction points to an involvement linking the nervous and the immune system in the airways. In particular, environmental exposure to nanoparticles has been associated with an enhanced risk of asthma. But the impact of nanoparticles on neurogenic mechanism remains to be determined. The aim of this study was to identify the impact of nanoparticles on neuro inflammation in a mouse model of allergic asthma.

**METHODS:** Using mice sensitized with ovalbumin (OVA) and OVA challenged (OVA sensitized/challenged mice) as well as mice treated with saline and challenged with air, and mice exposed to nanoparticles 200 µg/m³ on days 21-23. The effect of nanoparticles on P2X3, TRPV1, and neurotrophins was estimated using ELISA, immunoblotting, and immunohistochemical stain.

**RESULTS:** Nanoparticles exposure more in increased in airway inflammation, and airway obstruction in OVA mice, and those were augmented in nanoparticles exposed mice. TRPV1 protein increased and P2X3 protein decreased in OVA and nanoparticles exposed mice. Substance P, ATP, and CGRP increased in BAL fluid of OVA and nanoparticles exposed mice.

**CONCLUSIONS:** These results indicate that nanoparticles might be involved in the pathogenesis of bronchial asthma through neurogenic mechanism.

**Inflammatory cell response, functional and biochemical features of the airways of professional cleaning workers upon exposure in the workplace**

Cynthia F. Mafra Lima¹, Beatriz M. Saraiva², Jorge Kalil, MD³, Fabio M. Castro, MD⁴, and Clovis Eduardo S. Galvao, MD, PhD⁵, ¹University of Sao Paulo Medical School, Sao Paulo, Brazil, ²University of Sao Paulo Medical School, Sao Paulo, Brazil, ³Clinical Immunology and Allergy Department, University of Sao Paulo, Sao Paulo, Brazil, ⁴Clinical Immunology and Allergy Division of Sao Paulo University, Sao Paulo, Brazil, ⁵Univ Of Sao Paulo, School of Medicine, Sao Paulo, Brazil.

**RATIONALE:** There is consistent evidence from epidemiological studies that the cleaning professionals have a high risk of developing asthma. These workers are exposed to occupational agents of low and high molecular weight. It is important to produce evidence that this risk is related to work and not social conditions or other competitive factors, know the underlying pathological abnormality, and investigate possible agents. Thus, this study aims to assess if the work environment induces lung inflammation in asymptomatic workers, before the change of functional tests and the effectiveness of induced sputum and exhaled NO as early lung inflammation markers between professional cleaning workers.

**METHODS:** Workers were evaluated by comparing the sputum cytology, FeNO values, spirometry and PEF, during the work period and after the holidays.

**RESULTS:** In our study, we found a significant increase in FEV1 values after the vocational period, despite of being within the normal range in both periods. The average peak flow measurements also was higher during the vocational period compared to the period of work, although not statistically significant. We found a reduction of the exhaled measured values of NO after the holidays, reduction of eosinophils, lymphocytes and macrophages in induced sputum cytology, performed after the holiday period.

**CONCLUSIONS:** We demonstrate that the occupational environment to which professional cleaning non-domestic workers are exposed causes inflammation in the airways of asymptomatic workers. This inflammation can be measured by non-invasive methods such as induced sputum and FeNO, before the onset of changes in functional tests.

**Caddis Fly Allergy in a Hydroelectric Plant Worker, a Classic Association**

Caitlin M. G. McNulty, MD, and Rohit Dvekar, MBBS, PhD, Mayo Clinic, Rochester, MN.

**RATIONALE:** There are several historic case reports of allergy to caddisfly especially in setting of an occupational exposure. This healthy 39-year-old man presented with complaints of ocular itching and watery discharge, rhinorrhea, episodic wheezing temporally associated with his work especially in summer months. The work involved maintenance at hydroelectric plants in Illinois, USA. The patient was asymptomatic when away from work and on vacation. Previous management included wearing a dust mask, cetirizine, loratidine, lubricating eye drops and olopatadine eye drops with partial improvement.

**METHODS:** Based on his specific history, we performed percutaneous allergy testing to basic environmental panel (animal emanations: cat, dog, dust mite, and cockroach) along with caddisfly. *In-vitro* IgE allergen specific testing was performed for other arthropods and shellfish.

**RESULTS:** Percutaneous skin test was positive to caddisfly. Additional sensitization was noted to dust mite and cockroach. Serum specific IgE to shrimp was 0.37 kU/L and to moth was 1.69 kU/L. IgE to honeybee and yellow jacket venom was negative. Symptomatic management was preferred by the patient through a potential immunotherapy option exists.

**CONCLUSIONS:** This case serves to remind the clinician of allergic reactions to non-stinging insects which manifest as inhalant allergy. This can be measured by non-invasive methods such as induced sputum and exhaled NO as early lung inflammation markers between professional cleaning workers.

**Exposure to Tobacco Smoke and Childhood Rhinitis: A Population-Based Study**

Hui-Ju Tsai, MPH¹, Tsung-Chieh Yao, MD, PhD², Su-Wei Chang, PhD³, Wei-Chiao Chang, PhD³, and Jing-Long Huang, MD³, ¹National Health Research Institutes, Miaoli, Taiwan, ²Chang Gung Memorial Hospital, Taoyuan, Taiwan, ³Chang Gung University, Taoyuan, Taiwan, ⁴Taipei Medical University, Taipei, Taiwan.

**RATIONALE:** Previous studies have shown harmful effects of tobacco smoke exposure on respiratory health, whereas few population-based studies in this field using cotinine as a biomarker of tobacco smoke exposure, especially in non-white children. This study aimed to investigate the association between tobacco smoke exposure and childhood allergic diseases in a population setting.

**METHODS:** A population sample of Asian children aged 5-18 years (N=1,315) were evaluated using questionnaires, allergen-specific immunoglobulin E, and serum cotinine levels as an index of tobacco smoke exposure.

**RESULTS:** Serum cotinine levels were positively associated with rhinitis ever (adjusted odds ratio [AOR]=2.93; 95% confidence interval [CI]: 1.15-7.66) and current rhinitis (AOR=2.71; 95% CI: 1.07-6.89), while the association was marginally significant for physician-diagnosed rhinitis (AOR=2.26; 95% CI: 0.88-5.83). No association was observed for asthma or eczema. Stratified analyses showed that serum cotinine levels were positively associated with rhinitis ever (AOR=3.34; 95% CI: 1.05-10.61) and current rhinitis (AOR=4.23; 95% CI: 1.28-13.97) among teenagers but not in young children aged less than 10 years. Significant positive association of smoking cotinine levels with current rhinitis was found among children without allergic sensitization (AOR=6.76; 95% CI: 1.21-37.74), but not seen among those with allergic sensitization.

**CONCLUSIONS:** This Asian cohort demonstrates supportive evidence for positive association of tobacco smoke exposure with rhinitis, while the effect is mainly confined to non-allergic rhinitis and more pronounced in adolescents than in young children, highlighting the need for raising public health awareness about the harmful effects of tobacco smoke exposure on children’s respiratory health.
**Dog Ownership Is Associated with Uncontrolled Asthma**

Angela Tsuang, MD, MSc1, Jade Andrade1,2, Tricia D. Lee, MD1, and Supinda Bunyavanich2,3. 1Division of Allergy & Immunology, Department of Pediatrics, Icahn School of Medicine at Mount Sinai, New York, NY. 2Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY. 3Department of Pediatrics, Icahn School of Medicine at Mount Sinai, New York, NY.

**RATIONALE:** Contrasting effects of dog exposure on allergy outcomes have been reported. We sought to assess the relationship between dog ownership and asthma control.

**METHODS:** Detailed demographic data were collected and spirometry was performed on patients with persistent asthma recruited from the Mount Sinai Health System’s pediatric clinics (New York, NY). Persistent asthma was defined on the basis of bronchodilator response plus asthma symptoms ≥ twice weekly or asthma medication use (daily controller medication or short-acting beta agnost ≥ twice weekly). Asthma was considered uncontrolled if FEV1/FVC was <80% at enrollment. Statistical comparisons were performed using Fischer’s exact test, t-test, and multivariate logistic regression (STATA11).

**RESULTS:** Fifty-six patients with physician-diagnosed asthma participated in this study (mean age 12 years, standard deviation 4.5). 48% of patients had uncontrolled asthma (mean FEV1/FVC 70.8%, interquartile range (IQR) 68.0-77.0), and 52% had controlled asthma (mean FEV1/FVC 86.3%, IQR 82.0-89.0). 37% of patients reported that they had a dog at home. Dog ownership was associated with uncontrolled asthma (OR 3.4, CI 1.08-10.6). Age, race, geographic location of home, number of siblings, and asthma medication use (inhaled corticosteroids, combined long acting beta-agonist with inhaled corticosteroids, and/or montelukast) were not associated with asthma control. Parental history of allergy was significantly associated with dog ownership as well as with asthma control. After controlling for this confounder, dog ownership remained significantly associated with uncontrolled asthma (adjusted OR 4.9, CI 1.13-21.2).

**CONCLUSIONS:** Dog ownership is associated with increased odds of uncontrolled asthma.

**Longitudinal Trends in Asthma Emergency Department Visits, Pollutant and Pollen Levels, and Weather Variables in the Bronx from 2001-2008**

David Kordit1, Jennifer Toh, MD2, Tulsi Desai3, and Sunit P. Jariwala, MD1. 1Montefiore Medical Center, Bronx, NY, 2Montefiore Medical Center, New York, NY. 3Montefiore Medical Center, Bronx.

**RATIONALE:** To evaluate how asthma-related emergency department visits (AREDV), air pollutant levels, pollen counts, and weather variables changed from 2001 to 2008 in the Bronx (NY).

**METHODS:** We collected daily AREDV values (01/01/2001 to 12/31/2008) using our institution’s Clinical Looking Glass software. Daily values of temperature, humidity, carbon monoxide (CO), sulfur dioxide (SO2), ozone (O3), and nitrogen dioxide (NO2) were obtained from the National Climatic Data Center’s Bronx station. We obtained daily tree pollen counts from the Armonk counting station near the Bronx. We calculated median values for each variable, and used the Mann-Whitney test to compare 2001-2004 and 2005-2008 values. Due to seasonal variations of the variables, we considered each season separately regarding the 2001-2004 and 2005-2008 comparisons.

**RESULTS:** For AREDV, CO, SO2, and humidity, there were significant decreases for all seasons from 2001-2004 to 2005-2008 (all p<0.03), as well as for NO2 in the spring (2001-2004: 43 ppm; 2005-2008: 42 ppm; p=0.026) and winter (2001-2004: 41 ppm; 2005-2008: 39 ppm; p=0.005). Significant increases occurred for O3 levels in the spring, fall, and winter (all p<0.001), for temperature in the summer and winter (all p<0.05), and tree pollen in the spring (2001-2004: 102.5 grains/m3; 2005-2008: 155 grains/m3; p=0.017).

**CONCLUSIONS:** From 2001 to 2008, we observed significant: a) decreases in median AREDV, CO, SO2, and humidity for all seasons, and decreases in NO2 for the spring and winter; and b) increases in median O3 temperature, and spring tree pollen. Correlation and time-series analyses are necessary to further characterize our findings.
**Study of the Allergic Symptoms Prevalence and Some Relevant Factors Among School Children in Tehran**

Vahid Ghashadi Dana, MD. Fellow of Allergy and Clinical Immunology, Mohammad Reza Fazlollahi, Javid Morad Abbassi, Shahpar Haghighi, and Alireza Yousefzade; Asthma and Allergy Center, Tehran Medical Sciences branch of Academic Center for Education, Culture and Research (ACECR), Tehran, Iran (Islamic Republic of), 2Department of Allergy and Clinical Immunology, Rasoul Akram Hospital, Iran University of Medical Sciences, Tehran, Iran (Islamic Republic of), 3Immunology, Asthma and Allergy Research Institute, Tehran University of Medical Sciences, Tehran, Iran (Islamic Republic of), 4Epidemiology Department, School of Public Health, Shahid Beheshti University of Medical Sciences, Tehran, Iran (Islamic Republic of), 5Educational Department, Royan Research Institute, Academic Center for Education, Culture and Research (ACECR), Tehran, Iran (Islamic Republic of).

**RATIONALE:** Increasing of the childhood allergic diseases throughout the world and its heavy socioeconomic burden have posed an important health concern. Therefore, providing the updated relevant epidemiological information is robustly recommended.

We determined the prevalence of asthma, allergic rhinitis, and eczema symptoms in 6-7-year-old children of Tehran and ascertained the association between acetaminophen use, antibiotic consumption, as well as hospitalization for respiratory infection in early life and allergic symptoms.

**METHODS:** Data were gathered by using a modified questionnaire of the International Study of Asthma and Allergies in Childhood (ISAAC). Cluster sampling was used for random selection of primary schools. Then questionnaires (n = 4993) were completed by the parents of children.

**RESULTS:** The prevalence of current wheeze, wheeze ever, current itching rash, itchy rash ever, and rhinitis ever were found 19.64%, 27.49%, 8.95%, 8.28%, and 21.87%, respectively. Physician-diagnosed asthma, eczema and allergic rhinitis were reported in 4.32%, 7.29%, and 9.61% of children, respectively.

Univariate logistic regression analyses showed that acetaminophen and antibiotic use, and hospitalization for respiratory infection during the first year of life were all significantly associated (P < 0.04) with symptoms of allergic diseases. Also the strongest association (P < 0.03) was found between hospitalization due to respiratory infection in early life and allergic symptoms of children by multivariate analyses.

**CONCLUSIONS:** This study determined the rising pattern of allergic symptoms in 6-7-year-old children of Tehran. Moreover, acetaminophen and antibiotic use, and hospitalization due to respiratory infection in early life were detected as significant risk factors in the appearance of childhood allergic symptoms.

**Airborne Basidiospores: Are We Ignoring an Important Source of Aeroallergens?**

Estelle Levetin, PhD, FAAAAI, and Josh McLoud, MS; University of Tulsa, Tulsa, OK.

**RATIONALE:** During the 1980s and 1990s clinical and epidemiological studies showed that basidiospores were significant airborne allergens. However, little is known about the aerobiology of these ubiquitous spores. The current study examined airborne basidiospore levels in Tulsa over the past 15 years and the influence of meteorological conditions.

**METHODS:** The atmosphere in Tulsa, Oklahoma has been monitored with a Burkard spore trap using standard methods. Meteorological data were obtained from the Tulsa NOAA station. From 2001 to 2014 basidiospores were counted as undifferentiated basidiospores; however, in 2015 basidiospores were grouped into 4 categories: Ganoderma, Coprinus-type, other pigmented basidiospores, and hyaline basidiospores. Spore metrics were determined and analyzed for trends over time. For 2015 multiple regression analysis was used to examine the influence of meteorological parameters on the daily concentrations of the 4 basidiospore categories.

**RESULTS:** Basidiospores were registered in air samples on 98.4% of days and constituted 12.6% of the total air spora. The mean basidiospore concentration during this period was 739 spores/m³. Cumulative yearly basidiospore totals ranged from a low of 159,320 in 2011 to 542,988 in 2015. There was a significant increase in basidiospore levels during the 15 years (r = 0.638, p < 0.05). Although spore levels increased during years with higher rainfall, the trend was not significant. Multiple regression analysis showed that different meteorological parameters were significant predictors for the 4 spore categories with soil moisture significant in all models.

**CONCLUSIONS:** Airborne basidiospores are a major component of the air spora in Tulsa. More research is needed to determine their importance in other areas.
Mold Spore Release during Simulated Flooding and High Humidity

Peter Pityn, PhD1, and James J. Anderson, MLT2, 1OSHTECH Incorporated, London, ON, Canada, 2Environmental Allergy/OSHTECHINC, London, ON, Canada.

RATIONALE: Two one-month simulations were performed in a chamber to measure mold spore release from deteriorating building materials caused by flooding and excessive dampness.

METHODS: Penicillium chrysogenum was implanted on the backside of a typical wooden frame gypsum wall inside of an environmental chamber. The wall cavity was sealed. Water was fed slowly into the wall cavity, emulating a leaky foundation. One inch of water flooded the bottom of the chamber producing 100% RH continuously. Spore release inside the wall cavity and on the front side of the wall was measured and compared. Aspergillus fumigatus was implanted in the second study with conditions maintained at 75-85% RH and no flooding.

RESULTS: Many other molds produced heavy growth in equal or greater abundance. Sustained heavy growth during one month of flooding and later elimination of water did NOT release spores into air, until stripped by high velocity air. With sustained high humidity (no flooding) surface mold and spore releases within the wall cavity increased gradually, but not in front. Near the end, different spores were eventually released into the front airspace, but in far lesser amounts.

CONCLUSIONS: The wall is an effective barrier against molds released from the wall cavity. Spore release is inhibited by high humidity conditions. High air contamination does not necessarily accompany findings of extensive mold on building surfaces, as is often assumed or insinuated, until wall integrity is disrupted. The mold colonization process appears to be selective, modulated by environmental conditions.

Diversity of Viable Airborne Fungi in Tulsa, Oklahoma

Josh D. McLoud, and Estelle Levetin, PhD, FAAAAI; University of Tulsa, Tulsa, OK.

RATIONALE: The atmosphere contains a tremendous diversity of airborne fungal allergens; however, many unknown spores are commonly seen on our Burkard spore trap slides. To improve our understanding of the air spora viable air sampling has been on-going since February 2015 to identify both mycelial and yeast-like fungi.

METHODS: A single stage viable impaction sampler was used to collect weekly air samples on the University of Tulsa campus (Tulsa, Oklahoma) from February 2015 to August 2016. Air samples were incubated for three-days and mycelial colonies were identified by microscopy, while yeast-like colonies were identified using molecular methods. DNA was extracted from each yeast isolate and was used in a polymerase chain reaction to amplify ITS rDNA or ELO genes. The resulting amplicons were sequenced from each yeast isolate and was used in a polymerase chain reaction to identify findings of extensive mold on building surfaces, as is often assumed or insinuated, until wall integrity is disrupted. The mold colonization process appears to be selective, modulated by environmental conditions.

Comparison of Airborne Mold in the Mojave Desert and Las Vegas

Tanhiben Patel, MPH1, Alyssa Panning1, David Rivas1, Hongbin Jin, PhD, MPH, RN2, Mark Butner, PhD1, Dennis Bazylnski, PhD1, and Jarom S. Seggev, MD, FAACAI1, 1University of Nevada Las Vegas, Las Vegas, NV, 2UNLV, Las Vegas, NV.

RATIONALE: This study compared airborne mold concentrations in Las Vegas with the surrounding desert to determine seasonal variability between the urban and rural desert environments.

METHODS: Air samples were collected using a Burkard spore trap from January 1st to December 31st 2015, at a National Allergy Bureau (NAB) site in Las Vegas and a site in the Mojave Desert, located approximately 32 miles south of Las Vegas. Microscope slides were prepared and analyzed by light microscopy.

RESULTS: Las Vegas had an annual mean of 374±280 spores/m3 compared to 359±265 spores/m3 at the Mojave site (p<0.01). The peak concentrations occurred in June (1917 spores/m3) in Las Vegas and in March (1789 spores/m3) for the Mojave site. There were differences observed between Cladosporium and smut concentrations. At the Mojave site, the peak was in July with 1151 spores/m3, while the peak was in June for Las Vegas (696 spores/m3). The smut concentrations for both sites had the highest concentrations in June, with lower concentration is Las Vegas (599 grains/m3) compared to the Mojave desert (1439 grains/m3).

CONCLUSIONS: Mold concentrations in Las Vegas and the Mojave Desert show similar overall patterns. For both locations, Cladosporium and smuts had higher counts during the warmer months (March-September), which is consistent with expected trends for airborne molds. Although the Mojave location had a slightly lower mean concentration than Las Vegas, both Cladosporium and smut levels were higher in the Mojave site. Higher variation in the types of molds was observed at the Las Vegas site.

Study on the Clinical and Immunological Characteristics of Fungal Sensitive Asthma and Allergic Bronchopulmonary Aspergillosis

Peijian Zheng1,2, and Baoqing Sun1,2, 1State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China, 2Guangzhou Institute of Respiratory Disease, Guangzhou, China.

RATIONALE: The aim of this study was to investigate the clinical and immunologic characteristics of fungal-sensitive asthma (FA), non-fungal-sensitive asthma (NFA) and ABPA. We make an evaluation/reach patient and seek to further treatment.

METHODS: We recruited 56 subjects with asthma and 36 patients with ABPA. All asthmatic cases underwent detection of total IgE, eight types of fungal-specific immunoglobulin E (IgE) and IgE-M. Asthmatic patients with more than one type of fungal IgE≥0.35Ku/L were placed in the FA group(n=31), and those who did not fulfill this criterion were placed in the NFA group(n=25). Then, IgE-Af was detected in the FA group, whereas the ABPA group underwent detection of total IgE and IgE-Af. Asthmatic patients with more than one type of fungal IgE≥0.35Ku/L were placed in the FA group. IgE-Af was negatively and linearly correlated with FVC% predicted, FEV1% predicted, and FEF25-75% predicted.

CONCLUSIONS: There were different clinical and immunological features among NFA, FA and ABPA. The ABPA had worse function as well as higher percentage of bronchiectasis, and higher dose of oral corticosteroid. Besides, the sensitivity to aspergillus was more severe in ABPA. The level of IgE-Af was associated with the damage of lung function.

Abstracts AB27
AB28 Abstracts

92 Omalizumab Treatment in Patients with Cystic Fibrosis (CF) and Allergic Bronchopulmonary Aspergillosis (ABPA) as a Case Series

Johana B. Castro-Wagner, MD1, Chen Hsing Lin, MD2, Farnaz Tabatabaian, MD3, Nathan Tang, MD, FAAAAI4, and Panida Srichan, MD, FAAAAI4; 1University of South Florida Morsani College of Medicine, Saint Petersburg, FL; 2University of South Florida Morsani College of Medicine, Tampa, FL.

RATIONALE: ABPA occurs predominantly in individuals with asthma or CF. Standard treatment for ABPA includes oral corticosteroids and, occasionally, antifungal agents. It has been reported that omalizumab, a monoclonal anti-IgE antibody, can be an effective treatment for CF patients with ABPA.

METHODS: We performed a retrospective chart review on three adolescent CF patients who were diagnosed with ABPA and treated with omalizumab. Patients 1 and 2 presented with pulmonary exacerbations, diminishing FEV1, and abnormal chest radiographs. Pseudomonas aeruginosa and Aspergillus fumigatus were detected in bronchoalveolar lavage fluid from patient 1, and Mycobacterium spp. and A. fumigatus from patient 2. Patient 3 was previously diagnosed with ABPA at age 8 and received a trial of omalizumab treatment after unsatisfactory response to standard therapy. Symptoms improved and omalizumab was maintained for 3 years. Three years later, his lung function deteriorated. New infiltrates were noted on chest radiograph, and sputum cultures showed A. fumigatus.

RESULTS: Additional investigation revealed skin test positivity to A. fumigatus and presence of A. fumigatus-specific IgE and IgG in all 3 patients, suggesting ABPA diagnosis. Corticosteroids were withheld due to concomitant bacterial infection in patients 1 and 2, and history of corticosteroid-induced hypertension in patient 3. Treatment with omalizumab injection every 2 weeks was initiated and led to a substantial clinical improvement. After 3 months of therapy, FEV1 increased from baseline in all 3 patients.

CONCLUSIONS: Omalizumab may be an effective, alternative therapy for ABPA in CF patients who fail to respond to systemic corticosteroids or have contraindications to its use.

93 The sensitization of different fungus and correlation analysis of aspergillus fumigatus components sIgE level in patients with ABPA and aspergillus sensitized asthma

Wenting Luo1 and Baqing Sun2; 1First Affiliated Hospital of Guangzhou Medical University, Guangzhou Institute of Respiratory Diseases, State Key Laboratory of Respiratory Disease, National Clinical Research Center of Respiratory Disease, Guangzhou, China; 2State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China.

RATIONALE: Fungi allergens were the important inhaled allergens in the patients with respiratory allergic diseases. Aspergillus allergens was a risk factor for severe asthma, and important pathogenic factors for ABPA. The sensitizations of fungi allergens and aspergillus components of respiratory allergic disease were few reported in Asiatic countries. This paper focus on the sensitizations of fungi allergens and aspergillus components allergen in patients with respiratory allergic disease, explore the relationship between mold and respiratory allergic disease.

METHODS: 136 cases of fungal sensitization patients with respiratory allergic disease were included, using ImmunoCAP1000 system testing patients serum allergen extract sIgE, including penicillium notatum, branching cinerea, aspergillus fumigatus, candida albicans, alternaria and helminthosporium. After that patients with aspergillus sIgE ≥3.5kU/L, including 17 asthma and 12 ABPA, aspergillus components sIgE were further detected and analysis, including Asp f 1, 2, 3, 4 and Asp f 6.

RESULTS: 1. 84.6% patients were sensitized to 2 or more than 2 fungal allergens, aspergillus had the highest positive rate. There significant high correlation between the 6 fungal allergens extract sIgE (all r>0.80, P<0.01), 2. 44.4% patients were positive to all aspergillus components sIgE. There different degrees of correlations between components (all r>0.38, P<0.01). ABPA patients’ Asp f 1/2/6-sIgE were significant higher than patients with aspergillus sensitized asthma (P<0.05).

CONCLUSIONS: Aspergillus were the most important fungal allergen in China. There might be wide cross-react between fungal extract allergen. Asp f 1 and 2 were the main aspergillus components. Asp f 1/2/6 might helps identify diagnosis of ABPA and aspergillus sensitized asthma.
95 The Impact of Reported Penicillin Allergy on Patients with Streptococcus Bacteremia at an Urban Community Hospital

Sherry Tsai; Albert Einstein Medical Center, Philadelphia, PA.

RATIONALE: Intravenous penicillin is the antibiotic of choice for streptococcal bacteremia, which results in up to 48% mortality. The impact of reported penicillin allergy remains unclear in this patient population. Our study compares the clinical outcomes of streptococcal bacteremia in matched patients with (exposed) versus without (unexposed) reported penicillin allergy.

METHODS: Retrospective cohort study comparing exposed to unexposed adult patients admitted to Einstein Medical Center Philadelphia from 1/1/2014 to 12/31/2015.

RESULTS: In the cohort (n=331), the prevalence of reported penicillin allergy was 12%. We compared 15 exposed to 16 unexposed patients with matching demographics and clinical presentation. The exposed group more frequently reported allergy to other antibiotics than the unexposed group (33% vs 0%, p=0.02); were treated with more antibiotic classes (median of 3 versus 2 classes, p=0.05), had a shorter mean duration of antibiotic treatment (10 versus 20 days, p=0.04), developed more acute kidney injury (46.7% versus 31.3%, P > 0.05), and had more complications of infection (including endocarditis, metastatic infection, septic shock; 60% versus 43.8%; P > 0.05).

CONCLUSIONS: Our results suggest that patients who report penicillin allergy are more likely to report concurrent allergies to other drug(s) and receive more classes of antibiotics. The reduced duration of antibiotic treatment may indicate more cautious prescribing behavior in this group. The study is currently underpowered to detect differences in other clinical outcomes.

96 Impact of Hospital-Wide Guideline for Antimicrobial Stewardship in Patients with History of Beta-Lactam Allergy at an Academic Medical Center

Shayna Ravindran, MD1, Michael Beshir, PharmD2, Sheila Wang, PharmD2, Sindhu Bandi, MD1, Amy Hanson, PharmD2, Tristan O’Driscoll, PharmD, MPH2, and Mary C. Tobin, MD, FAAAAI1. 1Department of Immunology and Microbiology, Allergy/Immunology Section, Rush University Medical Center, Chicago, IL. 2Department of Pharmacy, Rush University Medical Center, Chicago, IL.

RATIONALE: Reported beta-lactam allergy leads to use of broad-spectrum antibiotics, resulting in increased costs, drug toxicity, suboptimal therapy, and infections such as Clostridium difficile, Methicillin-resistant-Staphylococcus-aureus (MRSA) and Vancomycin-resistant Enterococcus (VRE). A hospital-wide, multidisciplinary guideline was initiated to decrease the use of broad spectrum antibiotics in adults.

METHODS: The guideline, implemented in December 2014, helped providers recognize true beta-lactam allergy prevalence and cross-reactivity among beta-lactam agents, as well as assess allergy history. It encouraged use of penicillin skin testing and graded challenges when appropriate.

RESULTS: From June-December 2014 and 2015, we screened 3757 patients admitted with reported beta-lactam allergy. Of these, 200 patients were randomly selected from June-December 2014 (pre-guideline), as well as 200 patients from June-December 2015 (post-guideline). Retrospective chart review showed significantly more patients received vancomycin (39.5% to 26.5%, p <0.05) and aztreonam (6% to 4.5%, p <0.05) prior to guideline implementation. Significantly more patients received any beta-lactam agent (21.5% to 35%, p=0.003) and penicillin G (1.5% to 6%, p=0.03) after the guideline. There was also a trend towards increased 4th generation cephalosporin use (5% to 10.5%, p=0.06). The estimated cost of vancomycin and aztreonam use decreased from $25,298 to $17,836.

CONCLUSIONS: A beta-lactam allergy clinical guideline and algorithm decreased broad-spectrum antibiotic use, increased beta-lactam use and can decrease hospital costs. It is an effective tool that was implemented at our tertiary care center and could be expanded to others.
Aging with Penicillin Allergy. What Is Real?

Francisco Javier Iglesias-Souto, MD, PhD1, Fernando Rodríguez-Fernandez, MD, PhD2, and Victor Matheu, MD, PhD3; 1Hospiten Sur, Santa Cruz de Tenerife, Spain, 2Hospital Universitario Marques Valdecilla-IDIVAL, Santander, Spain, 3Hospital del Torax, Complejo Hospital Universitario Nuestra S. de Candelaria, Santa Cruz de Tenerife, Spain.

RATIONALE: Penicillin allergy remains the most common drug allergy. Epidemiological studies of penicillin allergy in outpatient populations is relatively scarce. There are a large number of patients labelled as allergic to drugs commonly used in clinical practice without having been studied. This creates a major health resource problem, having to use alternative antibiotics.

METHODS: A retrospective review of medical records was performed in patients over 60, studied by adverse reactions to penicillin for a period of 10 years. Diagnosis was supported by in vivo testing including skin test such as prick and intradermal test. Whether skin tests were negative a single-blind challenge or Drug Provocation Test was performed under medical surveillance to establish or exclude the diagnosis of penicillin allergy and, in selected cases, to provide alternative drugs for the patient in need. A total of 652 patients over 60 were studied for penicillin allergy, during a period of 10 years.

RESULTS: The results of the study show 90 positive cases (13.8%) of penicillin allergy. Most positive cases were detected by skin tests (n=67). Benzylpenicillins were the beta-lactam group most frequently involved in adverse reactions studied (34.7%, n=226), contrary to current consumption pattern.

CONCLUSIONS: The label of penicillin allergy is quite often erroneous. This involves using of more expensive and less effective therapeutic alternatives, which also facilitate the emergence of multi-resistant micro-organisms. Hence the importance of confirming the diagnosis of allergy.

Reflexive Penicillin Allergy Testing with In-Hospital Aztreonam Use

Justin R. Chen, MD1, Scott A. Tarver, PharmD2, Kristin S. Alvarez, PharmD3, Chi Nguyen2, and David A. Khan, MD, FAAAAI1; 1University of Texas Southwestern Medical Center, Dallas, TX, 2Parkland Health and Hospital System, Dallas, TX.

RATIONALE: Aztreonam is considered safe for administration in penicillin-allergic patients. However, most patients reporting penicillin allergies are in fact tolerant, leading to unnecessary use of this expensive broad-spectrum antibiotic. We present an initiative to reflexively bundle penicillin allergy testing with orders of aztreonam.

METHODS: An electronic panel was implemented linking penicillin allergy consultations with any aztreonam order. Individual providers could retain or remove the request (i.e. no penicillin allergy) at their discretion. Consults were reviewed on weekdays by an allergy-trained clinical pharmacist who performed inpatient penicillin skin testing and challenges. Patients with negative tests had their penicillin allergies removed from the record.

RESULTS: 30 consultations were placed over a 3 month period for aztreonam recipients reporting penicillin allergy. 11 (36%) were tested, all of whom were negative and subsequently cleared for penicillin. The median time from admission to test was 1.05 days [IQR 0.62-2.54], reduced from 3.69 days [IQR 1.39-6.95] for 22 patients receiving aztreonam in the 15 months prior (p=0.013). The most common reasons for not testing included antihistamine use (23%), discharge before being seen (20%), inability to consent (13%), and patient refusal (7%). Patients testing negative then accumulated 30.6 inpatient days of beta-lactam therapy with direct antibiotic costs of $326.47. In contrast, an identical duration of aztreonam 1-2g per dose costs $1,836.92 to $3,963.92, a projected savings of 82-92% or $137.31-$330.67 per patient.

CONCLUSIONS: Including allergy testing with orders of high-cost aztreonam facilitates early awareness and removal of inaccurate penicillin allergy diagnoses. This decreases superfluous antibiotic use and financially benefits healthcare institutions.
101 Re-Use of Penicillin after Annulation of Penicillin Allergy in Ambulatory Patients – Long Term Follow-up

Idit Lachover-Roth, MD1, Shoshan Sharon, BSc2, Yossi Rosman, MD1, Keren Meir-Shafir, MD3, Arnon Goldberg, MD3, and Ronit Confino-Cohen, MD4. 1Allergy and Clinical Immunology Unit, Meir Medical Center, Kfar-Saba, Israel, 2Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel, 3Allergy and Clinical Immunology Unit, Meir Medical Center, Kfar-Saba, Israel.

RATIONALE: Un-verified penicillin allergy is a growing public health problem associated with broad-spectrum antibiotics use, prolonged hospitalizations and higher costs of therapies. Negative skin test followed by an oral challenge test (OCT) is the current gold-standard used to annullet penicillin allergy.

METHODS: To assess the long term value of penicillin allergy annulation.

RESULTS: 778 patients with “Penicillin allergy” label underwent skin tests and OCT. In 570 (73%) the OCT was completed without adverse reactions. Antibiotic treatment was initiated in 316 patients (55%). Penicillin was used at least once in 261 of them (81%) and more than twice in 144 (45%). Only 53 patients (9%) used non penicillin antibiotics. In 292 (51%) the label “Penicillin allergy” still exists, however 169 (58%) twice in 144 (45%). Only 53 patients (9%) used non penicillin antibiotics. During the long follow up period most patients who needed antibiotics treatment used penicillin. However, it was less effective in erasing the limiting title from medical records.

102 Risk Stratification for Penicillin Desensitization in Allergic Pregnant Women with Syphilis

Juliana F. B. Garcia, Marcelo V. Aun, MD, Laila Sabino Garro, Jorge Kaiil, MD, Antonio Abilio Motta, and Pedro Giavina-Bianchi, MD, PhD, FAAACI; Clinical Immunology and Allergy Division of Sao Paulo University, Sao Paulo, Brazil.

RATIONALE: Penicillin is the only effective treatment of pregnant women with syphilis. The study assessed the safety and efficacy of risk stratification for guiding penicillin re-introduction in pregnant women with syphilis and penicillin-allergy history.

METHODS: Pregnant women with syphilis and history of immediate hypersensitivity reaction (HSR) to penicillin were enrolled. According to the risk stratification, patients were re-exposed to penicillin either through Rapid Drug Desensitization (RDD), provocation or regular administration. Patients with clinical history suggestive of penicillin-anaphylaxis, or positive serum specific IgE, or positive immediate skin test were considered at high risk and were desensitized.

RESULTS: We evaluated 18 pregnant women with latent syphilis and history of penicillin allergy. Ten patients (55.5%) had clinical history suggestive of immediate HSR and were desensitized. All patients presented negative serum specific IgE and prick test. Intradermal tests were positive in 3/10 (30%). Two of them were submitted to an oral protocol and reacted during RDD. The only patient that had positive intradermal test and didn’t react during RDD was submitted to an intravenous protocol. There was an association between positive intradermal tests and breakthrough reactions during RDD (p = 0.03). The remaining 7/10 (70%) patients that had negative intradermal test didn’t react during RDD. All patients completed the RDD. The other 8/18 (44.4%) patients considered of low risk did not present any HSR with penicillin full treatment.

CONCLUSIONS: Risk stratification and RDD were safe and effective. Intradermal skin testing identified patients with increased risk of reactions during RDD. Further studies are needed to compare intravenous and oral RDD protocols.

103 Analysis of Hypersensitivity Reactions to Betalactam Antibiotics during a 30 Year Period in a Drug Allergy Unit

Esther Barriqueno, MD, Phd1, Inmaculada Dona, MD, Phd2, Arturo Ruiz San Francisco, MD, Phd1, Maria Dolores Ruiz1, Tahia D. Fernandez, PhD2, Maria J. Monteale, PhD2, James R. Perkins, PhD2, Miguel Blanco, MD, Phd2, and Maria J. Torres, MD, Phd2. 1Allergy Unit, IBIMA-Regional University Hospital of Malaga, Malaga, Spain, 2Allergy Unit, IBIMA-Regional University Hospital of Malaga, Malaga, Spain, 3Malaga University Hospital-IBIMA, Malaga, Spain, 4Allergy Unit, IBIMA-Regional University Hospital of Malaga, Malaga, Spain, 5Research Laboratory, IBIMA, Regional University Hospital of Malaga, UMA, Malaga, Spain, 6Research Laboratory, IBIMA-Regional University Hospital of Malaga, Malaga, Spain, 7Allergy Unit, Infanta Leonor University Hospital, Madrid, Spain.

RATIONALE: Betalactams (BLs) are still the most frequent cause of hypersensitivity reaction to drugs mediated by specific immunological mechanism. The aim of this study was to analyse the pattern of sensitization to BLs during a 30-year period.

METHODS: Retrospective analysis of clinical records of 1257 patients with allergic reactions to BLs from 1985-2015 in the Allergy Unit of Malaga Regional University Hospital. The allergological study included: i) clinical history; ii) skin-prick and intradermal-tests with major (Benzylpenicilloyl-Poly-L-lysine, PPL) and minor determinants (MDM) of Benzylpenicillin, amoxicillin (AX), clavulanic acid (CLV) and cephalosporins; iii) Drug provocation test.

RESULTS: Clinical history: no significant differences in age, gender, immediate/non immediate reactions ratio, clinical symptoms, time interval between drug administration-symptoms and reaction-study. There were differences in the culprit BL with a decrease in AX (p < 0.0001) and an increase in AX-CLV (p < 0.0001) from 1985 to 2015. Skin-test: sensitivity varied over time from 70% (1985) to 40% (2005) and 60% (2013) (changes not significant). Analysing each skin-test agent we found a decrease in PPL/MDM sensitivity from 30% in 1985 to 10% in 2015 (p < 0.0001); and an increase in AX sensitivity from 30% in 1985 to 60% in 2001 followed by a decrease to 20% in 2015 (p = 0.003); and an increase in CLV sensitivity reaching 30% in 2015 (p < 0.001). Drug provocation test: this method was necessary for confirming the reaction from 26-41% of cases during the study period depending on skin-test sensitivity.

CONCLUSIONS: Skin test sensitivity varies over time, mainly reflecting changes in the BL involved in the reaction.
**104 Allergy to Betalactams Antibiotics at the End-of-Life Care**

F. Javier Fernandez, MD,1 Teodorike Jimenez-Rodriguez,2 Victor Soriano-Gomis,1 Jose Manuel Ramos-Rincón,1 Mariella Lindo-Gutiarra,1,2 and Luz Marina-Castellano,1 1UMH Alicante G.University Hospital - Allergy Sect., Alicante, Spain, 2ISABIAL-Alicante General University Hospital, Alicante, Spain.

**RATIONAL! E: Beta-lactam antibiotics are one of the most common cause of drug allergies. There are not enough evidence-based investigations at the end-of-life care. The aims of this study was mainly to determine the actual prevalence of allergy to beta-lactams in patients elderly than 80 years admitted to the Internal Medicine Service of Alicante University Hospital (AUH), Spain; and secondary to assess the cost of replacing betalactams with second-line antibiotics.

**METHODS: This cross-sectional study was initiated in December 2014.** Skin tests with BPO, MDM from Diater Spain, penicillin G, amoxicillin, cefuroxime and the responsible drug were performed. IgE to penicillin, amoxicillin and cefacar were carried out by CAP Thermofisher. Controlled challenge was done after negative allergic study. The protocol was approved by the Ethics Committee.

**RESULTS:** Until now 1723 patients were admitted, 106 of them (6.2%) reported allergy to betalactams and 70 of this (66%) agreed to participate in the study. Skin tests were performed on 63 of 70 patients (94%), and serum specific IgE to 53 of 70 patients (75.6%). But, only 2 (2.9%) were positive, 1 to amoxicillin and 1 to penicillin. 34 patients (48.6%) were under controlled challenge with no adverse reactions, and they followed penicillin treatment. The cost of patients treated versus non treated with betalactams during their stay at hospital was calculated.

**CONCLUSIONS:** Calculated prevalence of allergy to betalactam antibiotics was 2.86%. Betalactam allergy was ruled out in 48.6% of the patients. Treatment with beta-lactams is less expensive to treat uncomplicated infections.

**105 Antibiotic Selection in Children with Reported Beta-Lactam Allergy Admitted to a Pediatric Academic Medical Center**

Deepa Patadia, MD1,2, Megan E. Goebel, MD1,2, and David R. Stukus, MD, FAAAAI2; 1The Ohio State University Wexner Medical Center, Columbus, OH, 2Nationwide Children’s Hospital, Columbus, OH.

**RATIONAL! E: In adults, self-reported beta-lactam allergy has been correlated with increased use of alternative antibiotics and cost. Our aim was to determine if similar patterns occur among children with reported beta-lactam allergy.

**METHODS:** We performed a retrospective chart review for all inpatients (ages 6 months-18 years) who received at least one dose of antibiotic at our pediatric academic medical center between January 1-December 31, 2015.

**RESULTS:** Our study identified 9,691 inpatient admissions of which 925 (9.5%) had reported beta-lactam allergy. In this group, 17,980 antibiotics were administered. 1,742 (9.7%) given to patients with reported beta-lactam allergy. Patients with reported beta-lactam allergy were less likely to receive beta-lactam antibiotics (4.8% vs 22.5%; Relative Risk (RR) 0.21(0.17-0.26)), first generation cephalosporins (4.4% vs 11.6%; 0.38(0.31-0.48)), 2nd-4th generation cephalosporins (14% vs 16.9%; 0.83(0.73-0.93)), trimethoprim-sulfamethoxazole (3.3% vs 5.3%; 0.62(0.48-0.81)), or vancomycin (6.2% vs 8.8%; 0.71(0.59-0.86)), while they were more likely to receive clindamycin (13.6% vs 8.6%; 1.59(1.40-1.81)). At discharge, beta-lactam allergy patients received beta-lactam antibiotics and first generation cephalosporins less frequently. Unlike the inpatient setting, they received 2nd-4th generation cephalosporins (11.3% vs 4.7%; 2.38(1.87-3.02)), macrolides (13.6% vs 10.2%; 1.33(1.09-1.64)), fluoroquinolones (14.2% vs 10.6%; 1.34(1.10-1.64)), clindamycin (15.5% vs 10.4%; 1.49(1.24-1.81)), or a broad-spectrum antibiotic (2.8% vs 1.5%; 1.85(1.13-3.02)) more often.

**CONCLUSIONS:** Compared with those who do not report allergy, children with reported beta-lactam allergy receive a different selection of antibiotics, which may be less efficacious and more costly. Similar to adults, assessment of allergic status and/or application of antibiotic stewardship programs will likely benefit children with reported beta-lactam allergy.

**106 Amoxicillin Reuse after a Five-Day Challenge for the Evaluation of Delayed-Type Penicillin Allergy in Children**

Roxane Labrosse, MD1, Louis P. Paradis, MD, FAAAAI1, Kathryn Samaan, MD1, Jonathan Lacombe Barrios, MD1, Jean Paradis, MD, FAAAAI2, Philippe Begin, MD, FAAAAI1, and Anne M. Des Roches, MD, FAAAAI1; 1Centre Hospitalier Universitaire Sainte-Justine, Montreal, QC, Canada, 2CHUM, Hopital Notre-Dame, Montreal, QC, Canada.

**RATIONAL! E: Aminopenicillins are reputed for causing delayed-type rashes in children, particularly in the context of viral infections. Despite a negative allergy evaluation, a significant proportion of individuals continue to avoid penicillin class antibiotics (PCA) by fear of an allergic reaction. This study sought to evaluate PCA reuse amongst children with a negative five-day challenge, and assess subsequent amoxicillin re-sensitization.

**METHODS:** Patients with a history of a reaction to a PCA were prospectively recruited in the study. Double-blind skin prick testing and intradermal testing were performed so that all patients were subsequently challenged, independently of skin testing. Those with negative immediate challenges were sent home with a five-day challenge of amoxicillin to rule-out delayed reactions. Patients with negative challenges were called 2 years after their initial allergy evaluation to assess subsequent PCA use and tolerance.

**RESULTS:** 131 children with previous PCA reactions underwent a graded drug provocation test (DPT) to amoxicillin. 3 patients had a positive immediate challenge. The remaining 128 children continued amoxicillin for a total of 5 days; of those, 3 had a positive delayed challenge. Of the 125 patients with a negative challenge, 117 (94%) were reached at two-year follow-up: 78 had reused antibiotics, of which only 3 (3.8%) had refused PCA because of fear of an allergic reaction. Three out of the 68 (4.4%) that reused amoxicillin were re-sensitized.

**CONCLUSIONS:** Five-day challenge is a safe and effective way to rule out delayed-type PCA allergy in children, and it ensures a better compliance with future PCA use.
107 Beta-lactam Skin Testing Without Minor Determinant Mixture and a Two Step Oral Amoxicillin Provocation Test in Patients with a History of Beta-lactam Allergy: A Pilot Study

Keerthi Reddy, MD1, Jan J. Gutierrez-Serano, MD2, Sonia Alvarez-Lopez, MD, MS2, and Alexi Gonzalez-Estrada, MD3; 1East Tennessee State University, Johnson City, TN, 2Mexican Undersecretary of Health, Mexico City, Mexico, 3East Tennessee State University, Johnson City.

RATIONALE: Beta-lactam allergy accounts for approximately 10% of drug allergies in the US. This study aims to determine the safety of using penicillin G and penicilloyl-polylysine (PPL) without minor determinant mixture (MDM) to rule out penicillin allergy.

METHODS: A retrospective chart review of identified patients who presented with beta-lactam allergy at our Allergy Clinic from July 2015 to August 2016. All patients underwent immediate hypersensitivity skin testing with penicillin G and PPL followed by a commonly accepted oral provocation dose with 1/10 of amoxicillin (25 mg) with observation for 30 minutes, followed by a full dose of amoxicillin (250 mg) with observation for 60 minutes.

RESULTS: Of the 32 cases with a reported penicillin allergy, most were represented by women (75.0%). Mean age of evaluation was 59 (SD 16.8), and 90.6% of patients were Caucasian. Most common beta-lactam causing the allergic reaction was penicillin at 81.3%. Most reactions suspected were a Type 1 hypersensitivity reaction (67.9%), and approximately 50% of patients had atopy. The most common allergic reaction reported was urticaria (62.5%) followed by angioedema (25.0%). Of the 32 patients who underwent skin testing, 30 (93.8%) were negative, and 2 (6.3%) were positive. All cases that had a negative skin test completed an oral provocation test without adverse reactions (100%).

CONCLUSIONS: Skin testing with penicillin G and PPL without MDM followed by amoxicillin oral provocation test seems to be safe to rule out beta-lactam allergy.

108 The Incidence of Anaphylaxis Associated with Oral and Parenteral Penicillin-Class Antibiotic Exposures

Eric M. Macy, MD, FAAAAI1, and Lie H. Chen, PhD1; 1Kaiser Permanente Southern California Permanente Medical Group, San Diego, CA, 2Kaiser Permanente, Pasadena, CA.

RATIONALE: There is little accurate population-based data on the incidence of oral and parenteral penicillin-class antibiotic-associated anaphylaxis.

METHODS: All penicillin-class antibiotic use in Kaiser Permanente Southern California healthplan members seen between 1-1-2009 and 12-31-2015 was identified along with all episodes of anaphylaxis associated with the first exposure to each penicillin-class antibiotic course. Each case was then reviewed in detail to verify the episode was anaphylaxis and was penicillin-associated.

RESULTS: There were 5,201,036 unique healthplan members, mean age 35.6 ± 20.70 year and 52.5% females, who had at least one healthcare visit during the study interval. There were 1,840,830 individuals exposed to 3,837,003 courses of oral penicillins and 172,840 individuals exposed to 237,404 courses of parenteral penicillins. There were a total of 26,195,595 patient years of follow-up. The top oral penicillins used were amoxicillin 2,874,124 (74.89%), amoxicillin-clavulanate 556,781 (14.51%), and penicillin 347,090 (9.05%). The top parenteral penicillins used were piperacillin-tazobactam 103,832 (43.74%), penicillin 67,555 (28.46%), and amoxicillin 43,401 (18.28%). There were 18,122 (0.44%) new drug allergies in the US. This study aims to determine the safety of using penicillin G and penicilloyl-polylysine (PPL) without minor determinant mixture (MDM) to rule out penicillin allergy.

METHODS: A retrospective chart review of identified patients who presented with beta-lactam allergy at our Allergy Clinic from July 2015 to August 2016. All patients underwent immediate hypersensitivity skin testing with penicillin G and PPL followed by a commonly accepted oral provocation dose with 1/10 of amoxicillin (25 mg) with observation for 30 minutes, followed by a full dose of amoxicillin (250 mg) with observation for 60 minutes.

RESULTS: Of the 32 cases with a reported penicillin allergy, most were represented by women (75.0%). Mean age of evaluation was 59 (SD 16.8), and 90.6% of patients were Caucasian. Most common beta-lactam causing the allergic reaction was penicillin at 81.3%. Most reactions suspected were a Type 1 hypersensitivity reaction (67.9%), and approximately 50% of patients had atopy. The most common allergic reaction reported was urticaria (62.5%) followed by angioedema (25.0%). Of the 32 patients who underwent skin testing, 30 (93.8%) were negative, and 2 (6.3%) were positive. All cases that had a negative skin test completed an oral provocation test without adverse reactions (100%).

CONCLUSIONS: Skin testing with penicillin G and PPL without MDM followed by amoxicillin oral provocation test seems to be safe to rule out beta-lactam allergy.

109 Basophil Activation Test in Clavulanic Acid Selective Patients. Decrease of IgE Recognition over Time

Tahia D. Fernandez, PhD1, Maria Salas, MD, PhD2, Rubén Fernández3, Maria I. Montañéz, PhD4, Angela Martín-Serrano5, Nekane Barbero, PhD6, Ezequiel Perez-Inestrosa, PhD6, Cristobalina Mayorga, PhD7, and Maria J. Torres, MD, PhD7; 1Research Laboratory, IBIMA, Regional University Hospital of Malaga, UMA, Malaga, Spain, 2Allergy Unit, IBIMA, Regional University Hospital of Malaga, UMA, Malaga, Spain, 3IBIMA-Regional University Hospital of Malaga, Malaga, Spain, 4BIONAND-Andalusian Centre for Nanomedicine and Biotechnology, Malaga, Spain, 5IBIMA, Regional University Hospital of Malaga, Malaga, Spain.

RATIONALE: Amoxicillin-clavulanic acid (AX-CLV) combination is the most frequent cause of drug hypersensitivity reactions. The existence of selective reactions to CLV has been demonstrated in up to 40% of patients with immediate reactions to AX-CLV using the basophil activation test (BAT). This in vitro test is very useful for allergy diagnosis, although previously studies have shown that the time interval between reaction and study can affect its positivity. The aim of this study was to analyze the results of the test overtime in patients with selective reactions after AX-CLV intake.

METHODS: Patients with immediate reactions to AX-CLV were evaluated by skin test with penicillin G, AX, and CLV and drug provocation test when indicated. BAT was performed with AX and CLV at 2.5, 1.25, 0.25 and 0.05 mg/ml at different time points after the reaction.

RESULTS: After allergological workup, 16 patients were selective to AX and 17 selective to CLV, all of them with positive BAT to AX or CLV respectively. The median of negativization of BAT with AX was significantly lower (16 months (4-24)) compared to CLV (24 months (5-48)); (Gehan-Wilcoxon rank of 3.966; p = 0.0464). Regarding BAT with CLV, the median of negativization of the test was 4 months for anaphylactic shock, 16 months for anaphylaxis, and 12 months for urticaria.

CONCLUSIONS: Although the negativization of BAT with AX is faster than the BAT with CLV, in both cases the test must be performed in the first 12 months after the reaction occurrence, especially in those with more severe reactions (anaphylactic shock).

120 All abstracts are strictly embargoed until the date of presentation at the 2017 Annual Meeting.
SATURDAY

110 Use of Symptom and Quality of Life Questionnaires for Prediction of Reaction Severity during Aspirin Challenges in Patients with Aspirin Exacerbated Respiratory Disease

Naomi S. Schwartz, Teresa Pelletier, Golda Hudes, MD, PhD, David Rosenstreich, MD, and Elina Jerschow, MD, MSc; Albert Einstein College of Medicine/ Montefiore Medical Center, Bronx, NY.

RATIONALE: Aspirin challenges for treatment of aspirin exacerbated respiratory disease (AERD) result in bronchospasm. Finding predictors of reaction severity could be helpful in clinic.

METHODS: Baseline scores of the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), the mini Asthma Quality of Life Questionnaire (AQLQ), and the Sino-nasal Outcome Test (SNOT-22), and baseline forced expiratory volume in one second (FEV1) were recorded in 25 AERD patients before challenges. Changes in FEV1 during challenges and treatments required for reversal of hypersensitivity reactions were recorded.

RESULTS: The need for systemic corticosteroids was less in patients with higher AQLQ total and environmental subdomain scores: a median dose of 40 mg (IQR 0-60) prednisone was required for the treatment of patients with scores <5.5, while no prednisone was required in patients with scores ≥5.5 (p=0.03 for differences in total scores and p=0.04 for differences in environmental subdomain scores).

The need for racemic epinephrine treatment was less in patients with higher AQLQ total and symptom subdomain scores: 80% of patients with scores of <5.5 required epinephrine, while only 16% of patients with scores ≥5.5 required epinephrine (p=0.01 for both differences in total and symptom subdomain scores).

FEV1, RQLQ, and SNOT22 were not associated with reaction severity.

CONCLUSIONS: Baseline AQLQ scores may be helpful in predicting severity of reactions during aspirin challenges, as suggested by a more intense therapy of bronchospasm. While there was no significant difference in FEV1 decline, patients with lower AQLQ scores required more medications for treatment of their reactions.

111 Nasal Responses and Safety of L-ASA Nasal Provocation Test in a Large Series of Patients with NSAID-Exacerbated Respiratory Disease (NERD)

Paloma Campo, MD, PhD1, Innaculada Doña, MD, PhD2, Jesus Verge3, Tabia D. Fernandez, PhD4, Maria Dolores Cañamero5, Jose Antonio Cornejo, PhD5, Cristobalina Mayorga, PhD6, Carmen Rondon Segovia7, and Maria J. Torres, MD, PhD8. 1Allergy Unit, IBIMA-Regional University Hospital of Malaga, Malaga, Spain, 2Malaga, Spain, 3ENT Department, Regional Hospital of Málaga (Virgen de la Victoria)-IBIMA, Málaga-Spain, Malaga, Spain, 4Research Laboratory, IBIMA, Regional University Hospital of Malaga, UMA, Malaga, Spain, 5Malaga University Hospital-IBIMA, Malaga, Spain, 6Allergy Research Laboratory, Regional Hospital of Malaga-IBIMA, Malaga, Spain, 7IBIMA, Regional University Hospital of Malaga, Malaga, Spain.

RATIONALE: Nasal provocation test with lysine-aspirin (NPT-LASA) is a useful tool for the diagnosis of patients with NSAID-exacerbated respiratory disease (NERD). The aim was to evaluate the clinical characteristics, nasal/bronchial response and safety of the test in a large series of patients with NERD.

METHODS: Patients (referred from 2010-2015) with suspected NERD underwent a clinical evaluation. Later, NPT with saline and 29 mg of L-ASA was performed in both nostrils. Visual analogical scale (VAS) for nasal/bronchial, volume 2-6 by acoustic rhinometry (AR) and FEV1 measurements were performed at baseline and at 15, 60 and 120 min. Test was positive if an increase of ≥30% in VAS and ≥30% fall in vol 2-6 cm occurred.

RESULTS: One hundred and thirty seven patients participated (42.2±15.5 yrs, 64.2% women). Atopy was present in 70% of subjects, with asthma (61.3%) and rhinitis (77%). NPT-LASA was positive in 96 subjects (70.1%), with 35.8% of positive responses at 15 min, an additional 23.8% positive at 60 min and the remaining 40.4% at 120 min. Changes in VAS and vol 2-6 were significant between baseline and 15, 60 and 90 minutes for patients with positive NPT (p<0.001). No systemic reactions were observed. There were no significant differences between baseline FEV1 values and all other timepoints (p=0.176) in patients with positive NPT-LASA. Only 2 patients (1.45%) had a FEV1 fall >20% with mild symptoms that responded well to Terbutaline.

CONCLUSIONS: NPT-LASA is very well tolerated and can be safely used.

112 Hypersensitivity Reactions to Nsaids in Children.

Natalia Blanca-Lopez, MD, PhD1, Diana Pérez-Alzate, MD2, Jose Antonio Cornejo, PhD2, Natalia I. Perez-Sanchez, MD3, Maria Luisa Somoza, MD4, Francisco Javier Ruano, MD, PhD2, Elisa Haroun, MD5, Miguel Blanca, MD, PhD6, and Gabriela Canto, MD, PhD7. 1Allergy Unit, Infanta Leonor University Hospital, Madrid, Spain. 2Research Laboratory, Malaga Biomedical Research Institute (IBIMA), Malaga, Spain. 3Allergy Unit, Infanta leonor University Hospital, Madrid, Spain.

RATIONALE: NSAIDs hypersensitivity reactions can be cross-intolerant (CI) or selective according to the response to non chemically related drugs. Sufficient studies in children have not been carried out. We evaluated in our service children who developed reactions to NSAIDs.

METHODS: Subjects between 2-14 y.o. were evaluated. An allergy history plus skin test with inhalant allergens plus total IgE quantified by immunoassay were made. Incremental doses of ASA were administered adapted to body age/weight. If negative, we challenged with the culprit. Independent T test and Chi X2 was made.

RESULTS: We studied 113 children who experienced symptoms indicative of NSAID hypersensitivity. The 59% were males and the 41% females. Mean age 7,6 (0,5-14 y o). Atopic status occurred in the 46%. Drugs involved were: ibuprofen (81% of the episodes), paracetamol (10%), ASA (4.8%) and metamizol (1%). Cross intolerant were the 27%, selective immediate responders 1,7% and 74% had good tolerance. The clinical entities were urticaria/angioedema in 32% and isolated angioedema in 32%.

CONCLUSIONS: In children under 14 yo CI to NSAIDs with urticaria and/or angioedema is the most frequent group. Asthma accompanied with facial angioedema appeared in the 17.6%. Selective responders are uncommon. This contrast with previous studies undertaken in adults and adolescents as well as populations under 14 years.
113 Paracetamol and Ibuprofen Hypersensitivity in a Cohort of Paediatric Patients from the UK

Bogas Gador, MD, PhD1, Aikaterini Anagnostou, MD, MSc, PhD2, George Do Tsiot, MD, FAAAAI1, Immaculada Doña, MD, PhD1, and Maria J. Torres, MD, PhD3; 1Allergy Unit, IBIMA-Regional University Hospital of Malaga, Malaga, Spain, 2St Thomas’ Hospital, London, United Kingdom, 3Children’s Drug Allergy Clinic, Guy’s and St Thomas’ NHS Foundation Trust; King’s College London, King’s Health Partners, MRC & Asthma UK Centre in Allergic Mechanisms of Asthma, and the Department of Paediatric Allergy, London, United Kingdom, 4Allergy Unit, IBIMA-Regional University Hospital of Malaga, Malaga, Spain, 5Research Laboratory, IBIMA-Regional University Hospital of Malaga, Malaga, Spain.

RATIONALE: A few children with a clinical history of hypersensitivity reactions (HRs) to drugs can be confirmed hypersensitive and NSAIDs are the drugs most often reported, and involved in confirmed HRs. Although they are poorly studied in children, the clinical picture is similar to that of adults. Drug provocation test (DPT) is the gold standard needed to establish diagnosis and provide alternative choice of medication.

METHODS: We analysed a group of children with clinical history suggestive of HRs to NSAIDs, referred to the paediatric allergy team at St Thomas’ Hospital, between 2009-2015.

RESULTS: Regarding clinical history, almost a half of the children were atopic, being the sensitization similar to both grass pollen and house dust mite (HDM). We did not find any cofactor associated although 27% of them suffered from asthma, food allergy, and spontaneous chronic urticaria (SCU). From the total of patients, 63.6% referred immediate reactions. Facial angioedema was presented as the most common manifestation, and the mean number of episodes was 2. Using DPT, we could confirm HRs to NSAIDs in 81.8% of the children (56% to ibuprofen with a median cumulative dose of 362mg; 44% to paracetamol) using adenalin once. In the group of 8-16 years old, 50% developed angioedema.

CONCLUSIONS: The PPV of the clinical history was 73%. After DPT, confirmed as a safe approach, immediate angioedema was the most presenting symptoms, and the frequency increases progressively with age. Ibuprofen was the culprit confirmed drug most involved, probably due to their high consumption.

114 Comparison of NSAID Hypersensitivity Between Children and Adolescents.

Diana Pérez-Alzate, MD1, Natalia Blanca-Lopez, MD, PhD1, Jose Antonio Cornejo, PhD2, Maria Luisa Somoza, MD1, Francisco Javier Ruano, MD, PhD1, Elisa Haroun, MD2, Natalia I. Perez-Sanchez, MD1, Francisco Rivas4, Miguel Blanca, MD, PhD1, and Gabriela Canto, MD, PhD1; 1Allergy Unit, Infantia Leonor University Hospital, Madrid, Spain, 2Research Laboratory, Malaga Biomedical Research Institute (IBIMA), Malaga, Spain, 3Allergy Unit, Infantia Leonor University Hospital, Madrid, Spain, 4Research Unit, Marbella Hospital, Malaga, Spain.

RATIONALE: Although hypersensitivity reactions to NSAIDs are the most common cause of hypersensitivity drug reactions, no studies have been carried out focusing on populations stratified by age. Previous studies indicate that certain manifestations like facial angioedema are more frequently observed in children with asthma induced by NSAIDs being rather infrequent. Our aim was to compare a group of children with confirmed NSAIDs hypersensitivity versus a group of adolescents.

METHODS: Subjects with NSAIDs hypersensitivity were divided into two groups: A) those from 2 to 14 years and B) those from 15-20 years. Diagnosis was established by a clinical history and controlled challenge with ASA. Atopic status was verified with a detailed allergological study including skin testing to inhalant allergens. Clinical entities were classified in three categories: urticaria/angioedema, anaphylaxis and respiratory involvement (asthma and/or rhinitis).

RESULTS: We included in the group A 32 and in the group B 15 cases. No differences were observed in the atopic status between both groups. There were significant differences between males/females (p<0.05). When we compared the clinical entities there were more cutaneous manifestations, mainly angioedema, in the group A and more anaphylaxis in group B although there were no significant differences due to sample size.

CONCLUSIONS: Significant sex differences between hypersensitivity reactions to NSAID occurs with predominance of males in the first group (A). Although there are also a predominance of clinical entities, an increase number of cases is needed to establish significance. Studies on this direction are in progress.

115 Natural Evolution of NSAID-Induced Urticaria/ Angioedema over a 10-Year Follow-up

Immaculada Doña, MD, PhD1, Maria Salas, MD, PhD2, Esther Barrionuevo, MD, PhD1, Olivier Muñoz Daga3, Maria Isabel Sanchez-Rivas3, Maria Auxiliadora Guerrero3, Arturo Ruiz San Francisco, MD, PhD1, Paloma Campo, MD, PhD3, and Maria J. Torres, MD, PhD3; 1Allergy Unit, IBIMA-Regional University Hospital of Malaga, Malaga, Spain, 2Allergy Unit, IBIMA, Regional University Hospital of Malaga, UMA, Malaga, Spain, 3Allergy Unit, IBIMA-Regional University Hospital of Malaga, Malaga, Spain, 4Malaga Regional University Hospital-IBIMA, Malaga, Spain, 5Allergy Unit-Regional Hospital of Malaga-IBIMA, Malaga, Spain, 6Allergy Unit, IBIMA-Regional University Hospital of Malaga, Malaga, Spain, 7Malaga University Hospital-IBIMA, Malaga, Spain, 8Research Laboratory, IBIMA-Regional University Hospital of Malaga, Malaga, Spain.

RATIONALE: Non-steroidal anti-inflammatory drugs (NSAID) are the drugs most frequently involved in hypersensitivity reactions, being NSAID-induced urticaria/angioedema (NIUA) the most common phenotype. The perseverance of the sensitivity to NSAIDs in NIUA is unknown. Our aim was to verify the maintenance of hypersensitivity to NSAIDs in a well-characterized group of NIUA patients followed-up over a long period of time.

METHODS: Patients with confirmed NIUA during 2005-2014 (V1) were included (n=38). All subjects were prospectively re-evaluated by drug provocation test (DPT) with acetyl salicilic acid (ASA) and others NSAID at two different time points between 2013 and 2015 (V2 and V3).

RESULTS: The mean follow-up time for V2 was 54 months (IR: 36-72) after V1 and for V3 was 18 months (IR: 14-24) after V2. In V2, 24 patients (63.15%) tolerated ASA and other NSAIDs (Group A) and 14 (36.84%) experienced cutaneous symptoms in DPT with ASA (Group B). The number of previous episodes (p=0.005) and the percentage of reactions induced by ASA (p=0.039) and ibuprofen (p=0.006) were lower in Group A compared to Group B. Patients developed tolerance to NSAIDs 84 months (60-96) after the last reaction, being this interval shorter in non-atopic patients (p=0.003), those with immediate reactions (p=0.006) and when ibuprofen was not involved (p=0.005). In V3, all patients in Group A tolerated ASA and others NSAIDs and all patients in Group B had a positive DPT.

CONCLUSIONS: NIUA patients may develop tolerance to NSAIDs over time, probably influenced by atopy, type of reaction and drugs involved.
AB36 Abstracts

SUNDAY

116 Skin Testing Results and Induction of Tolerance Outcomes in Platinum-Sensitive Patients

Stephanie L. Mawhirt, DO1, Sonam Sani, MD2, Luz S. Fonacier, MD, FAAAAI1, Rosa Calixte, PhD1, Mark A. Davis-Lorton, MD, FAAAAI1, and Marcella Aquino, MD3, 1Winthrop-University Hospital, Mineola, NY, 2Winthrop-University Hospital, Mineola, 3Winthrop University Hospital, Allergy & Immunology, Mineola, NY.

RATIONALE: Skin tests (ST) are useful in identifying patients with immediate-type hypersensitivity to platinum chemotherapeutics. We investigated the outcomes of induction of tolerance (IOT) procedures in relation to platinum ST results.

METHODS: An IRB approved, seven year retrospective review of patients evaluated for platinum-based reactions was conducted. Data gathered for statistical analysis included index reaction details as well as ST results and IOT outcomes.

RESULTS: Platinum reactions were identified in 36 patients (88.9% female; age 63.6+10.1 years; n=34 carboplatinum, n=2 oxaliplatin) who underwent a total of 146 IOTs. Most index reactions (72.2%) were non-anaphylactic. Platinum ST (skin prick +/- intra-dermal) were performed (median 14 days) after the index reaction. The initial ST results (positive-negative-equivocal) comprised: (8-6-1) for completely IOT-tolerant patients (n=15) and (9-10-2) for patients who reacted during any IOT (n=21). Equivocal-ST patients were less likely to experience IOT reactions (OR=0.28, 95% CI:0.10-0.78; p=0.015). The conversion rate to positive was 63.6% (n=7/11; repeat ST 1—26 months after index reaction). All patients with index reactions of anaphylaxis or respiratory arrest converted to positive on repeat ST. IOT reaction rates were as follows: ST-non-converters (35.3%), ST-converters (31.7%), and initial positive-ST patients (29.9%). Of all patients, 24/36 displayed positive ST and 96.6% of all IOTs were completed.

CONCLUSIONS: Initial and repeat ST results did not predict IOT outcomes in our population. Initial equivocal-ST patients exhibited a decreased risk for IOT reaction and all patients with severe systemic reactions converted to positive on repeat ST. Nearly all IOTs were completed, allowing patients to receive additional platinum courses.

117 Assessment of Cellular Antigen Stimulation Test in Diagnosis of Drug Allergy

Maged Refaat, MD, FAAAAI. Rasha Shahin, MD, Eman Ahmed, MD, Aber Ab Elhameed, MD, Osama Ab MATIF, and Aya Elgandy, MSc; Allergy and Immunology unit, Ain Shams university, Cairo, Egypt.

RATIONALE: Diagnosis of the etiology of drug hypersensitivity is a vital step in therapy, which is mainly done through patient history, as skin testing is not always reliable and oral provocation testing is life-threatening. Cellular Antigen Stimulation Test (CAST) is a test, based on the determination of sulfideoleukotrienes produced by basophiles stimulated by allergens in vitro, has been proposed. Our objective was to evaluate the efficacy of Cellular Antigen Stimulation Test in diagnosis of patients with history of allergy to drugs and compare values with healthy controls.

METHODS: The study included 45 patients with drug allergy and 45 healthy persons as control group, both were subjected to full detailed allergic history to drugs and clinical examination, Skin prick test and Patch test to the particular drug were performed . Serum specific IgE of the drug. CAST by Enzyme Linked Immunosassay were also done.

RESULTS: The sensitivity of CAST in drug allergy was 48.9% and the specificity was 84.4%. Skin prick test, Patch test and specific IgE sensitivity in allergic patients were 51.1%, 33.3%, 62.2%, while their specificity were 91.1%, 91.1% and 73.3% respectively.

CONCLUSIONS: CAST has relatively higher specificity than sensitivity in diagnosing drug allergy. The value of this test is important specially when other in vitro or in vivo diagnostic tests are not reliable, as well as in non-IgE mediated hypersensitivity reactions.

118 A Novel Two Day Desensitization Protocol to Oral Mesalamine

Christine M. Panganiyan, MD, MS, Deena Pourang, MD, and Shafali A. Samant, MD; Kaiser Permanente Los Angeles Medical Center, Los Angeles, CA.

RATIONALE: Ulcerative proctosigmoiditis is a chronic inflammatory condition that is initially treated with mesalamine, a preferred treatment to steroids and immunomodulators. Hypersensitivity reactions to mesalamine have been reported and a limited number of desensitization protocols have been published taking between 3 days to weeks. We present a case of a patient with ulcerative proctosigmoiditis and aspirin allergy with adverse reactions to mesalamine who failed an oral mesalamine challenge. She subsequently underwent successful mesalamine desensitization with a rapid 2 day protocol.

METHODS: The desensitization took place in the intensive care unit. The starting dose of mesalamine was 1mg. On day 1, incremental doses were given every 30 minutes up to 500mg. On day 2, the patient received a total of 2.5 grams of mesalamine, which was her targeted daily dose.

RESULTS: The patient was successfully desensitized after 2 days with one hypersensitivity reaction. She developed mild shortness of breath with a drop in FEV1 from 450 to 350 on day 1 of the desensitization, which resolved with nebulized albuterol and fexofenadine. Since discharge from the hospital, she continued mesalamine 2.4 grams daily without adverse reactions.

CONCLUSIONS: This case demonstrates a patient with mesalamine hypersensitivity can be safely offered a rapid 2 day oral desensitization protocol, and maintained on the medication for long term management of ulcerative proctosigmoiditis.

119 Anaphylaxis to Botulinum Antitoxin: A Systematic Review

Edith Schussler, MD1, Joy Hsu, MD, MSC1, Patricia Yu, MPH2, Leslie C. Grammer, MD, FAAAAI3, and Anna H. Nowak-Wegrzyn, MD, PhD, FAAAAI1, 1Icahn School of Medicine at Mount Sinai, New York, NY, 2Centers for Disease Control and Prevention, Atlanta, GA, 3Division of Allergy-Immunology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL.

RATIONALE: Botulism is a rare but severe paralytic illness caused by neurotoxins. Equine-derived heptavalent botulinum antitoxin (BAT) is despecified and licensed for botulism treatment in the United States. Timely treatment reduces morbidity and mortality, but concerns about BAT-induced anaphylaxis exist. The risk of BAT-induced anaphylaxis and predictive value (PV) of skin testing (ST) before BAT administration have not been well-described. Also, how these values compare to those associated with botulinum antigens other than BAT is unclear.

METHODS: We conducted a systematic review of: (1) allergic reactions to botulinum antigens other than BAT and (2) the PV of ST before BAT administration, we searched 5 databases, hand-searched articles’ reference lists, and obtained BAT data from the manufacturer and the Centers for Disease Control and Prevention. Overall anaphylaxis incidence was determined for BAT and other botulinum antigens and compared using relative risk (RR). We calculated positive PV (PPV) and negative PV (NPV) of ST before BAT and other botulinum antigens.

RESULTS: Seven articles from 6 countries met the inclusion criteria. Anaphylaxis incidence was 1.64% (3/305 patients) for BAT and 1.16% (6/ 538 patients) for other botulinum antigens (RR=1.41, 95% confidence interval=0.47–4.27, p=0.5). PPV and NPV for BAT ST (33 patients) were both 100%. PPV and NPV of ST for other botulinum antigens (302 patients) were 0–56% and 50–100%, respectively.

CONCLUSIONS: Anaphylaxis incidence was similar between BAT and other botulinum antigens, and low for both. The PV of ST appears limited. The data do not support delaying BAT administration to perform ST.

120 A Systematic Review of Anaphylaxis to Botulinum Antitoxin

Seven articles from 6 countries met the inclusion criteria. Anaphylaxis incidence was 1.64% (3/305 patients) for BAT and 1.16% (6/538 patients) for other botulinum antigens (RR = 1.41, 95% confidence interval = 0.47–4.27, p = 0.5). PPV and NPV for BAT ST (33 patients) were both 100%. PPV and NPV of ST for other botulinum antigens (302 patients) were 0–56% and 50–100%, respectively.

CONCLUSIONS: Anaphylaxis incidence was similar between BAT and other botulinum antigens, and low for both. The PV of ST appears limited. The data do not support delaying BAT administration to perform ST.
120 Characterization of Patients with Allergic Reactions to Ibuprofen

Daniel Teitelbaum, Marcus Chiam, and Peter Vadas, MD, PhD; St. Michael’s Hospital, Toronto, ON, Canada.

RATIONALE: Allergic reactions to non-steroid anti-inflammatory drugs (NSAIDs) are amongst the most common causes of reactions to non-prescription medications. Ibuprofen is one of the most commonly used NSAIDs. Herein, we describe a cohort of patients who presented with allergy to ibuprofen.

METHODS: Consecutive patients were identified with ibuprofen allergy between 2008-2015 by retrospective chart review. These patients were characterized with respect to demographics, clinical characteristics of their reactions, number of ibuprofen reactions and anaphylaxis severity scores. This study was approved by the institutional REB.

RESULTS: 36 patients were identified with allergy to ibuprofen confirmed on history. Females were more commonly affected (25F:11M). The mean age at first reaction was 33 years (range: 5-65). Patients had a mean of 2.31 reactions (range: 1-8) prior to diagnosis. Mean time from to onset was 70.18 minutes (range: 2-540). The mean duration of symptoms was 174.09 minutes (range: 20-690). Most patients had cutaneous involvement (89%); whereas 42% had upper airway and 42% had lower airway involvement. Cardiovascular manifestations were documented in 36% of patients. Anaphylaxis severity scores were calculated. Reactions were mild (grade 1 in 17/36), moderate (grade 2 in 18/36) and severe (grade 3 in 1/36). Co-existent asthma was associated with moderate to severe anaphylaxis to ibuprofen.

CONCLUSIONS: Allergic reactions to ibuprofen are one of the most common causes of drug allergy. Patients most commonly affected are young females. Cutaneous involvement is almost always present, but many patients also report cardiopulmonary involvement. Most patients present with mild to moderate reactions, but reactions may be severe, especially in those with co-existent asthma.

121 Neuropsychiatric Associations with Drug Allergy

Nicholas L. Hartog, MD1, H. James Wedner, MD, FAAAI2, and Keerthi Karamched, MD3; 1Michigan State University College of Human Medicine, Grand Rapids, MI; Spectrum Health, Grand Rapids, MI, 2Washington University School of Medicine, St. Louis, MO, 3University of Michigan, Ann Arbor, MI.

RATIONALE: Drug allergy is commonly encountered and previous studies have evaluated various factors that are associated with drug allergy. We hypothesized that in our cohort certain neurological and psychiatric diagnoses would have higher rates of drug allergy/intolerance listed in their chart.

METHODS: We examined a cohort of 85 patients who were recruited for a separate study. Charts were reviewed for two years prior to enrollment. Neuropsychiatric diagnoses, drug allergy, and symptoms of drug allergy were based on the patient’s electronic medical record. SPSS was used for statistical analysis. Fisher’s exact test, independent T-test and Chi-squared were used where appropriate.

RESULTS: Positive correlation exists between number of psychiatric medications prescribed and number of medication allergies (R=0.468; p<0.001). Positive correlation exists between certain neuropsychiatric diagnoses (anxiety, chronic pain, depression, fibromyalgia) and number of medication allergies (R=0.381; p<0.001), with mean of 2.5 versus 1.1 allergies (p=0.001). Patients with a neuropsychiatric diagnosis were less likely to list an antimicrobial allergy (p=0.037) and more likely to list an anti-histamine allergy (p=0.047). Patients with a neuropsychiatric diagnosis were more likely to have “unknown” reaction listed (OR 3.86; 95% CI 1.6, 9.3; p=0.001), cutaneous reactions (1.5; 95% CI 1.03, 2.1; p=0.037), and have their reaction classified as a “possibly” IgE mediated (OR=1.5; 95% CI 1.03, 2.1; p=0.034).

CONCLUSIONS: A neuropsychiatric diagnosis is associated with an increased number of medication allergies/intolerances, less cutaneous symptoms, more “unknown symptoms”, and decreased likelihood of IgE mediated symptoms. This is a unique group of patients who should be further evaluated in a prospective study.

122 Adverse Reactions to Humanized Monoclonal Antibodies

Dasha Roa-Medellin, MD, Irene Garcia-Gutierrez, MD, Maria C. Lillo, MD, Marcos Sanchez-Dominguez, MD, Arantza Ais-Lariscogitia, Pharm, Maria L. Baeca, MD, PhD, and Pilar Tomero, MD; Hospital General Universitario Gregorio Maranon, Madrid, Spain.

RATIONALE: Humanized monoclonal antibodies (MoAbs) represent a new relevant and increasing therapy. The need to change the MoAb because of adverse reactions (AR) is unknown.

METHODS: Observational study including all patients that were treated with MoAb from Jan-2010 to Dec-2015 in a tertiary level hospital. Modifications of MoAb cycles because of AR were analyzed.

RESULTS: 7,363 MoAb were dispensed to 5,883 patients. 977 treatments were modified before they were concluded. AR were the cause in 119 cases (103 patients). Incidence: 12.2%. Patients’ age average: 45.9 ± 13.6y, 78.3% females, 4% atopics. 75% were rheumatologic conditions. The MoAb involved was: Infliximab 50%, Rituximab 23.5% and Adalimumab 10%. AR showed up in the 1st-2nd dose in 60.5%, 3rd-5th 20.17% and later: 19%. The main symptoms were cutaneous (64%), respiratory (30%), pharyngeal laryngeal (24%), cardiovascular (15.8%), neurological (14.1%). Only 10.8% had severe reactions. In 57 (45.6% moderate-severe) the drug was infused again with premedication (antihistamines/corticoids/NSAID). 89% tolerated the drug. In 38, (26.3% moderate-severe), it was changed by other MoAb. Twenty-four (62.5% moderate-severe) underwent an Allergy study Seven had a positive skin test (infliximab 2, rituximab 2, belimumab 1, ustekinumab 1, certolizumab 1). In these the treatment was changed. In other 5 (100% moderate-severe) a desensitization protocol was implemented, in which 80% had mild AR but tolerated the infusion.

CONCLUSIONS: The incidence of AR as causes of modification of MoAb treatment is low. Premedication seems a good initial option for AR. Desensitization is well tolerated, and may be considered the first option if no good alternative is available.
RATIONAL: Ibrutinib is an inhibitor of Bruton’s Tyrosine Kinase. Two types of dermatitis (late, or early) with ibrutinib are described. The former is usually asymptomatic. The latter is pruritic, may require discontinuation, steroids and antihistamines, and may be associated with other allergic manifestations. Re-challenge with full dose may result in rash recurrence and further delays in treatment. No oral rapid drug desensitization (ORDD) protocol to ibrutinib exists in the published literature.

METHODS: A 73yo with mantle cell lymphoma developed Stevens-Johnson reaction on lenalidomide, followed later by a pruritic rash on ibrutinib. We developed an ORDD strategy for ibrutinib based on Shone, et al, (JACI in Practice 2016). The therapeutic dose required was 566mg/day. Target dose on day 1 was 140mg. Initial 18-step ORDD up to 140mg was accomplished starting with 1ml of a 1:1,000,000 dilution and incrementally increasing dose every 20 minutes. This dose was maintained for one week, and then increased in one week intervals to 280mg, then 420mg, then full dose thereafter.

RESULTS: The patient tolerated the ORDD to ibrutinib and continues to do well on the medication for treatment of Stage IV mantle cell lymphoma.

CONCLUSIONS: Hypersensitivity reactions to ibrutinib may be difficult to differentiate from commonly encountered rashes associated with this drug. We present a successful outpatient ORDD to ibrutinib in a patient with Stage IV mantle cell lymphoma who developed grade 1 hypersensitivity, required steroids, and had recurrence of hypersensitivity reaction at resumption of therapy. This approach may help others better tolerate regimens containing ibrutinib.
**127 The Features of Drug Hypersensitivity in Japanese Children**

Yumiko Miyaji, MD, PhD, Masami Narita, MD, PhD, Tatsuki Fukue, MD, PhD, and Yukiko Ohy, MD, PhD; Division of Allergy, Department of Medical Specialties, National Center for Child Health and Development, Tokyo, Japan.

**RATIONALE:** Drug hypersensitivity (DH) is a common healthcare concern, but incidence of DH is low in children, resulting in few epidemiological data, especially in Japan. The aim of this study was to elucidate clinical features of DH in Japanese children.

**METHODS:** Study design is a retrospective chart survey based on the data extracted from electronic chart of patients who visited the allergy units of our hospital with referral of DH suspicion from April, 2005 to March, 2016.

**RESULTS:** The number of all patients extracted from electric database was 160 and their median age was 6.9 years old. Fifty five (34.4%) reacted to any drug within 1 hour after intake and 86 (53.8%) did within 2 hours. Fifty four patients (33.8%) were diagnosed as having DH, 52 (32.5%) as suspected DH and 46 (28.8%) as without DH. Drug provocation tests were performed in 35 children, and only 3 had positive reaction. Among 53 confirmed DH patients, the most common incriminated drug was antibiotics (29 ones and beta lactams was 77.4% of them), followed by, nonsteroidal anti-inflammatory drugs (NSAIDs) (7), vaccine (4), muscle relaxant (4), steroids (2), and anesthetic (1). The symptoms caused by antibiotics emerged within 1 hour in 18 patients (62.1%) and 11 (37.9%) showed anaphylaxis. Incidence of non-immediate type exanthema was higher in antibiotics DH (96.6%) than in NSAID DH (71.4%) (p<0.05).

**CONCLUSIONS:** Beta-lactam was the most common cause of childhood DH in Japan. Both of immediate and non-immediate reactions were commonly seen in most DH.

**128 Mast cell Tryptase and Carboxypeptidase A3 (CPA3) as Markers for Predicting Susceptibility to Severe Allergic Drug Reactions**

Rana Abadalkareem, MBBS, Laurie C. K. Lau, PhD, Ahmed Abdelmotteb, PhD, Naoising Zhou, PhD, Efrem Eren, MBBS, PhD, and Andrew F. Walls, PhD, FAFAAI; Immunopharmacology Group, University of Southampton, Southampton, United Kingdom, Changzhou University, Changzhou, China, Immunology Department, Southampton General Hospital, Southampton, United Kingdom.

**RATIONALE:** Allergic drug reactions can present with diverse symptoms ranging from a mild skin rash to a life-threatening systemic reaction. However, there is no means for predicting the severity of reactions. We have investigated both serum and salivary levels of markers of mast cell activation in patients with severe and less severe reactions to drugs.

**METHODS:** Subjects were attending for diagnostic drug challenge. Serum and saliva samples were collected before and two hours following challenge, and detailed histories taken. Sensitive enzyme linked immunosorbent assays (ELISA) were developed and validated, using specific antibodies to tryptase and CPA3 (lower limits of detection of 0.4 ng/ml and 0.2 ng/ml, respectively), and applied to serum and saliva samples.

**RESULTS:** At baseline, tryptase and CPA3 levels were higher in serum from patients who had previously suffered anaphylaxis than in that from those without a history of severe reactions. Similar findings were made for salivary levels. Serum concentrations of tryptase and CPA3 did not increase significantly following drug challenge, though the reactions provoked were in most cases restricted to mild skin reactions. There was only a weak association between levels of tryptase and CPA3, and there were cases with low levels of tryptase and high levels of CPA3 and vice versa.

**CONCLUSIONS:** Measurement of baseline levels of tryptase and CPA3 may be of value in identifying patients at greater risk of severe allergic reactions to drugs. The lack of a strong correlation between levels of these markers would argue for a need to measure both.

**129 Outcomes of Drug Provocation Test in Korean Children with Suspected Drug Hypersensitivity Reaction: A Single Center Experience**

Soo Ran Noh1, Hyun-ju Cho, MD2, Jisu Yoon3, Jinho Yu4, and Soo-Jong Hong, MD, FAAAAI5; 1Asan medical center, seoul, Seoul, Korea, The Republic of, 2Department of Pediatrics, Childhood Asthma Atepy Center, Research Center for Standardization of Allergic Diseases, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea, 3Asan medical center, Seoul, Korea, The Republic of, 4Department of Pediatrics, Childhood Asthma Atepy Center, Asian medical center, University of Ulsan College of Medicine, Seoul, Korea, The Republic of, 5Childhood Asthma Atepy Center, Department of Pediatrics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea.

**RATIONALE:** Drug provocation test (DPT) are the gold standard for confirming or excluding the diagnosis of DHR. However, there are little studies of DPT in children. The purpose of this study was to evaluate DPT results and safety as diagnostic methods of DHR in Korean children.

**METHODS:** We reviewed the medical records of 39 children under 19 years of age who attended our childhood asthma atopy center with a suspected drug hypersensitivity reaction and performed DPT between January 2010 and May 2016 at Asan Medical Center.

**RESULTS:** Total 111 DPT were performed in 39 children (20 boys and 19 girls) with a history of drug hypersensitivity reaction. Clinical presentation of drug allergy included skin rash (n=14), angioedema (n=19), and anaphylaxis (n=6). The median age at the time of drug provocation test was 9 years. Positive DPT were observed in 21 (53.8%) of 39 children and 28 (25.2%) of 111 cases. Drug causing positive reaction were acetaminophen in 6 (38%), NSAIDs in 10 (50%), cephalosporin in 1 (17%), TMP/SMX in 1 (50%), lidocaine in 1 (25%), and others (levodroprizine and idursulfase) in 2 (25%). There were no statistical differences between children who had positive and negative results regarding gender, age, personal and parenteral history of allergic disease, eosinophil count, and total IgE level. No one with positive drug provocation tests developed anaphylaxis during the DPT procedure.

**CONCLUSIONS:** Drug provocation test is safe for use in children with a history of drug hypersensitive reaction for definitive diagnosis of drug allergies.
Wat Mitthamsiri, MD, Panithan Pradubpongs, MD, Atik Sangapasavapilya, MD, and Tadech Boonpiyathad, MD; Division of Allergy and Clinical Immunology, Department of Medicine, Phramongkutklao Hospital and Phramongkutklao College of Medicine, Bangkok, Thailand.

**RATIONALE:** Drug provocation test (DPT) is the gold standard to diagnose analgesic drugs hypersensitivity reactions (HRs). The purpose of this study was to confirm the diagnosis in patients with NSAIDs and acetaminophen HRs and to find the safe alternatives.

**METHODS:** This is a retrospective study which enrolled adult participants with history of NSAIDs and acetaminophen-induced immediate drug HRs whose skin prick test results were negative. Their DPTs were single-blinded and placebo controlled. The analgesic drugs included acetaminophen, NSAIDs (aspirin, ibuprofen, diclofenac, mefenamic acid, and meloxicam), COX-2 inhibitor (etoricoxib) and tramadol. All participants were challenged with placebo and the analgesic drugs by ingestion of increasing dose every 60 minutes, started from 25%, 50%, 75% and then 100% of their targeted therapeutic dose.

**RESULTS:** Eighteen participants consented to DPTs. We performed 404 DPTs. Sixty-seven (16.58%) tests were positive with 2 of those were anaphylaxis. DPTs confirmed the diagnosis in all of 5 participants with the history of NSAIDs and acetaminophen HRs and 8 participants with the history of only NSAIDs HRs. DPTs were able to diagnose 50% of 4 participants with the history of acetaminophen HRs. Eleven participants had multiple NSAIDs positive results. DPTs with etoricoxib and tramadol were negative in 12 (66.66%) and 14 (77.78%) out of 18 participants, respectively. Six participants with etoricoxib positive DPTs had multiple NSAIDs positive DPTs too.

**CONCLUSIONS:** This study indicated the DPT was a good diagnostic test for analgesic drugs HRs. Etoricoxib and tramadol were tolerated in the majority but not all participants tested.

Lisa W. Fu, MD, Alexander Ho, MD, Jeffrey Zaltzman, MD, Lucy Chen, RPh, and Peter Vadas, MD, PhD; University of Toronto, Toronto, ON, Canada.

**RATIONALE:** Chlorhexidine is commonly used as an antimicrobial agent in the perioperative setting. Severe and life-threatening allergic reactions may occur sporadically in some patients, but there are no patient cohorts known to be at high risk. We describe a cohort of 8 patients with the history of NSAIDs and acetaminophen-induced immediate drug HRs whose skin prick test results were negative. Their DPTs were single-blinded and placebo controlled. The analgesic drugs included acetaminophen, NSAIDs (aspirin, ibuprofen, diclofenac, mefenamic acid, and meloxicam), COX-2 inhibitor (etoricoxib) and tramadol. All participants were challenged with placebo and the analgesic drugs by ingestion of increasing dose every 60 minutes, started from 25%, 50%, 75% and then 100% of their targeted therapeutic dose.

**METHODS:** This is a retrospective study which enrolled adult participants with history of NSAIDs and acetaminophen-induced immediate drug HRs whose skin prick test results were negative. Their DPTs were single-blinded and placebo controlled. The analgesic drugs included acetaminophen, NSAIDs (aspirin, ibuprofen, diclofenac, mefenamic acid, and meloxicam), COX-2 inhibitor (etoricoxib) and tramadol. All participants were challenged with placebo and the analgesic drugs by ingestion of increasing dose every 60 minutes, started from 25%, 50%, 75% and then 100% of their targeted therapeutic dose.

**RESULTS:** Eighteen participants consented to DPTs. We performed 404 DPTs. Sixty-seven (16.58%) tests were positive with 2 of those were anaphylaxis. DPTs confirmed the diagnosis in all of 5 participants with the history of NSAIDs and acetaminophen HRs and 8 participants with the history of only NSAIDs HRs. DPTs were able to diagnose 50% of 4 participants with the history of acetaminophen HRs. Eleven participants had multiple NSAIDs positive results. DPTs with etoricoxib and tramadol were negative in 12 (66.66%) and 14 (77.78%) out of 18 participants, respectively. Six participants with etoricoxib positive DPTs had multiple NSAIDs positive DPTs too.

**CONCLUSIONS:** This study indicated the DPT was a good diagnostic test for analgesic drugs HRs. Etoricoxib and tramadol were tolerated in the majority but not all participants tested.
133 Presentation and Management of Local Anesthetic Hypersensitivity in Ukraine

Igor Kaidash1, N. Digiari1, I. Mormol1, O. Demidenko1, G. Granovskaya1, M. Lornikivska1, V. Chopyak1, V. Lits1, V. Babadjian1, and Lawrence M. DuBuske2, MD, FAAAAI3, 1, Ukrainian Medical Stomatological Academy, Poltava, Ukraine, 2, Khmelnitzky Regional Hospital, Khmelnitzky, Ukraine, 3, Lviv National Medical University named after Daniila Galytzkogo, Lviv, Ukraine, 4, Shupyk National Medical Academy, Kyiv, Ukraine, 5, Kharkiv National Medical University, Kharkiv, Ukraine, 6, George Washington University School of Medicine, Washington, DC, 7, Immunology Research Institute of New England, Gardner, MA.

RATIONALE: The prevalence and management of local anesthetic reactions hypersensitivity reactions in Ukraine was surveyed.

METHODS: 272 physicians and dentists who provided local anesthesia were surveyed including 51.42% dentists, 16.17% surgeons, 20.58% trauma specialists and 11.02% anesthesiologists including 23.16% in universities; 38.9% regional hospitals; 28.3% city hospitals; and 8.08% private practices. The number local anesthetic procedures per week ranged from <1/5 (38.23%); 5 to 10 (10.29%); 10 to 15 (16.54%); 15 to 20 (14.7%); 20 to 25 (17.64%); 25 to 30 (10.66%) and >30 (9.55%).

RESULTS: Local anesthesia included regional (85.66%), infiltrative (85.29%), spinal (74.63%), surface (68.38%) and epidural (49.26%) employing articaine (229), lidocaine (195), procaine (146), bupivacaine (85.29%), spinal (74.63%), surface (68.38%) and epidural (49.26%)

CONCLUSIONS:

1. Prophylactic local anesthetic skin tests were done never by 8.82% and 5.88% in 50% of cases; and 8.82 % in 70% of cases while 1.1% never used

2. Epinephrine use for anaphylaxis varied from 8.45% in 10% of cases; 5.88% in 50% of cases; and 8.82 % in 70% of cases while 1.1% never used it.

3. Prophylactic local anesthetic skin tests were done never by 8.82% and 5.88% in 50% of cases; and 8.82 % in 70% of cases while 1.1% never used it.

4. Epinephrine use for anaphylaxis varied from 8.45% in 10% of cases; 5.88% in 50% of cases; and 8.82 % in 70% of cases while 1.1% never used it.

134 Oxaliplatin Induced Immune Thrombocytopenia in Patients with Oxaliplatin Hypersensitivity: Implications for Desensitization

Katherine Larabee Tuttle, MD1, Marlene Garcia-Neuer1, Nathan T. Connell, MD, MPH1, David I. Hong, MD, FAAAAI1, Mariana C. Castells, MD, PhD, FAAAAI1, and Paige G. Wickner, MD, FAAAAI1, 1, Division of Rheumatology, Allergy, and Immunology, Department of Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, 2, Division of Hematology, Brigham and Women’s Hospital, Boston, MA, 3, Division of Rheumatology, Allergy, and Immunology, Department of Medicine, Brigham and Women’s Hospital, Harvard Medical School, Chestnut Hill, MA.

RATIONALE: Oxaliplatin is a third-generation platinum-based chemotherapeutic employed in the treatment of colorectal cancer. There are seven case reports of thrombocytopenia in oxaliplatin treated patients secondary to drug-dependent neutralizing antibodies against platelet glycoproteins, defined as oxaliplatin-induced immune thrombocytopenia (OIIT). Here we report two cases of OIIT with concomitant oxaliplatin hypersensitivity in 2 months.

METHODS: Clinical history was obtained from retrospective chart analysis. Flow cytometry was performed at the Blood Center of Wisconsin for drug-dependent platelet antibodies on patient serum after exposure to oxaliplatin.

RESULTS: 2 of the 17 patients (11.7%) with oxaliplatin hypersensitivity and treated by desensitization at the BWH/DFCI Desensitization Center from August 2015 to August 2016 developed oxaliplatin induced immune thrombocytopenia. Both patients experienced grade II oxaliplatin hypersensitivity reactions after a mean 19 oxaliplatin cycles (SD 8.48). Patient 1 was noted to have oral and vaginal bleeding at the end of oxaliplatin desensitization #4 and required hospitalization for platelet transfusion. Platelet count decreased to 7x10^9/L post-infusion from a pre-infusion level of 135x10^9/L just prior to hospital admission. Patient 2 was noted to have persistent thrombocytopenia throughout desensitization: mean 78x10^9/L (SD 19x10^9/L) throughout oxaliplatin cycles but without mucosal bleeding. Both Patient 1 and 2 sera were positive for IgG anti-platelet antibodies only when exposed to oxaliplatin.

CONCLUSIONS: We report two confirmed cases of oxaliplatin-induced immune thrombocytopenia during desensitization over a two month time period. One patient experienced severe mucosal bleeding and thrombocytopenia necessitating hospital admission. Allergists performing oxaliplatin desensitization should be aware of this potentially life-threatening immune reaction.
Successful Management of Rituximab Infusion Reactions Using Desensitization

Sara Barmettler, MD1, and Aleena Banerji, MD1; 1Division of Rheumatology, Allergy and Immunology, Department of Medicine, Massachusetts General Hospital, Boston, MA. RATIONALE: Infusion reactions to rituximab are common in clinical practice. Given safety concerns regarding these reactions, patients are often switched to second-line agents or have delays in care, which has a negative impact on clinical outcomes.

METHODS: We evaluated all patients referred to the Allergy-Immunology clinic at a large, academic medical center for rituximab reactions during a one year period. Patient characteristics including indication for rituximab, severity of initial reaction, and need for ongoing rituximab treatment were reviewed. Patients subsequently underwent desensitization with modification for any further reactions, and outcomes were evaluated.

RESULTS: Between May 2015 and April 2016, seven patients with rituximab infusion reactions were evaluated. Mean age was 51±20 years and more than half were male (n=4, 57%). Rituximab treatment indications included lymphoma/leukemia (n=4), calcium-channel antibody-positive autonomic neuropathy (CCAPAN, n=1), paraneoplastic carcinoma-associated retinopathy (CAR, n=1), and GLILD (n=1). Initial reaction severity varied widely including grade 1 (n=2), grade 2 (n=3), grade 3 (n=1), and grade 4 (n=1) reactions. These seven patients completed 31 inpatient rituximab desensitizations. Six patients (86%) developed reactions during a one year period. Patient characteristics including indication for rituximab, severity of initial reaction, and need for ongoing rituximab treatment were reviewed. Patients subsequently underwent desensitization with modification for any further reactions, and outcomes were evaluated.

CONCLUSIONS: Desensitization is a safe and effective way to manage patients after rituximab reactions. Further research into risk stratification of rituximab reactions is needed to optimize care.

Oxaliplatin-Induced Thrombocytopenia and Hemolytic Anemia: Manifestation and Management

Johnson T. Wong, MD, FAAAAI1, Sarita U. Patil, MD1, Benjamin R. Slawski, NP2, and Aidan A. Long, MD, FAAAAI3; 1Division of Rheumatology, Allergy, and Immunology, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA. 2Massachusetts General Hospital, Boston, MA. 3Division of Rheumatology, Allergy and Immunology, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA. RATIONALE: Oxaliplatin-induced thrombocytopenia (OITP) and oxaliplatin-induced hemolytic anemia (OIHAn) can be severe and may limit the usage of oxaliplatin for cancer therapy. Knowing its presentation may help clinicians recognize the syndrome and provide an approach to their management.

METHODS: We reviewed all our cases of OITP and OIHAn among patients presented for desensitization for oxaliplatin hypersensitivity (OXS) for their clinical presentation, laboratory finding, and outcome during desensitizations.

RESULTS: We found 7 cases of OITP with all 7 also developed OIHAn either concurrently with onset of OITP (6) or subsequently (1). One developed OITP prior to the initial consultation whereas 6 developed OITP upon their first oxaliplatin desensitization (3) or subsequent desensitizations (3). The onset of OITP and OIHAn were often not recognized initially. Initial clinical symptoms range from asymptomatic to various combinations of fever, rigor, hypertension, abdominal pain, back pain, extremity pain, nausea/vomiting, and/or dark urine. All showed drop in platelet of >20k and and/or decrease Hct of >2.5% with desensitization. The drop in platelet was often less severe and delayed with desensitization but can still be severe. Additional laboratory finding include oxaliplatin-dependent anti-platelet IgG (4/4), iCoomb’s (2/4), and elevated LDH. Supplements were decreased in 1 and normal in 2. Most patients were switched to other drugs after 1-5 desensitizations but 1 continued due to lack of alternative treatment.

CONCLUSIONS: OITP and OIHAn may complicate oxaliplatin treatment/desensitization due to drug-dependent anti-platelet and anti-RBC antibodies with a characteristic pattern. Desensitization may help for those that have no alternative but the reactions may be severe.
139 Underlying Chronic Urticaria in Patients With Multiple Drug Allergies: A Call for Screening

Roxanne C. Oriel, MD1, Amanda Innamorato2, and Blanka M. Kaplan, MD. FAAAAI1, 1Division of Allergy and Immunology, Department of Pediatrics and Internal Medicine, Hofstra Northwell School of Medicine, Great Neck, NY, 2Cornell University, College of Human Ecology, Ithaca, NY.

RATIONALE: Among other triggers, medications and underlying infections may cause worsening of chronic urticaria (CU). We hypothesize that a significant proportion of patients labeled with multiple drug allergies have an underlying, undiagnosed chronic or recurrent urticaria ultimately leading to overdagnosis of drug hypersensitivity.

METHODS: A retrospective chart review was performed on drug allergic pediatric and adult outpatients evaluated by the division of Allergy & Immunology. Multiple drug allergies were defined as reaction to 2 or more chemically unrelated drugs. Demographics, drug allergy class, atopic conditions, and presence or absence of screening questions for urticaria were recorded.

RESULTS: Seventy charts from patients in the division of Allergy from 8/2013-7/2016 were reviewed. Forty-one patients met our definition of multiple drug allergies. 24.4% (10/41) of patients with multiple drug allergies had a concomitant diagnosis of CU. Of those patients, 90% were female and 90% had atopic disease. Antibiotics were the most common culprits (80%), with sulfonamides and beta-lactams comprising 87.5% and 62.5%, respectively. Notably, 65.9% (27/41) of the patients included in our study were not asked screening questions for chronic or recurrent urticaria.

CONCLUSIONS: Prevalence of reported drug allergy in CU patients is dramatically higher in comparison to that of the general population. With increasing importance on accuracy of drug allergies reported in medical records, it is prudent that patients with multiple drug allergies be screened for chronic or recurrent urticaria. Further studies are needed to evaluate if patients with CU have increased prevalence of drug hypersensitivity, or if underlying, untreated urticaria accounts for misdiagnosed drug allergy.

140 Neumuscular Blocking Agents Are an Important Etiology of Periprocedural Hypersensitivity Reactions

Melissa Iammatteo, MD1, Taha Keskin, MD2, and Elina Jerschow, MD, MSc3, 1Montefiore Medical Center/Albert Einstein College of Medicine, Bronx, NY, 2Montefiore Medical Center, Bronx, NY, 3Albert Einstein College of Medicine/ Montefiore Medical Center, Bronx, NY.

RATIONALE: Identifying the etiology of periprocedural hypersensitivity reactions (HSRs) remains challenging due to the multitude of medications involved. Recent American studies cited antibiotics as the most common identifiable etiology, while European studies identified neuromuscular blocking agents (NMBAs) as the most likely cause.

METHODS: We performed a retrospective chart review of all patients who underwent evaluation for periprocedural HSRs at an outpatient drug allergy clinic in Bronx, New York between December 2009 and June 2016. Patient demographics and description of historical HSR were obtained.

RESULTS: Skin testing to potential causative medications were reviewed along with subsequent drug challenges, when indicated. Tolerance of subsequent procedures was obtained through chart review and phone calls.

RESULTS: Thirty-five patients completed a comprehensive allergy evaluation. The majority of patients was female (74.3%, n=26) with a median age of 52 years (interquartile range [IQR] 40-62) and median of 16 weeks (IQR 5–52) between HSR and testing. An etiology was identified in 31 patients (88.5%) with multiple agents identified in 24 patients. NMBAs were the most commonly identified agent (n=24) followed by midazolam (n=15), ketamine (n=14), beta-lactams (n=11), local anesthetics (n=8), opiates (n=7), etomidate (n=4), and latex (n=4). Nineteen of the 23 patients reached for follow-up underwent subsequent procedures. Procedures were uneventful for all patients except for one, who experienced mild urticaria.

CONCLUSIONS: In our patient population, NMBAs are the most common cause of periprocedural HSRs. Unlike other studies, skin tests were positive to multiple agents in the majority of patients. Midazolam and ketamine are underrecognized potential etiologies.

141 Cytokine Release from Peripheral Blood Mononuclear Cells upon Stimulation with the Culprit Drugs during Acute Stage of Severe Cutaneous Adverse Reactions

Jettanong Klaewsongkram, MD1,2, Pattarawat Thantwiorasit, MSc1, Nithikan Suthumchai, MSc1, Pawinee Rerknimitr, MD2,3, Papapat Tuchinda, MD4, Leena Chularojanamonti, MD4, Ticha Rerkpattanaapit, MD5, Kummutnart Chanprapaph, MD6, Wareeporn Disphanurat, MD7, Panlop Chakkavitumrong, MD7, Napatra Tovanaabutra, MD8, Chutika Srisuttiyakorn, MD9, Chonlaphat Sukasem, B. Pharm, PhD10, and Yuttana Srinoulprasert, PhD, MD11, 1Division of Allergy and Clinical Immunology, Allergy and Clinical Immunology Research Group, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, 2King Chulalongkorn Memorial Hospital, The Thai Red Cross Society, Bangkok, Thailand, 3Division of Dermatology, Allergy and Clinical Immunology Research Group, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, 4Department of Dermatology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, 5Allergy Immunology and Rheumatology Division, Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand, 6Division of Dermatology, Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand, 7Division of Dermatology, Department of Medicine, Faculty of Medicine, Thammasat University, Pathumthani, Thailand, 8Dermatologic Division, Department of Internal Medicine, Chiang Mai University, Chiang Mai, Thailand, 9Division of Dermatology, Department of Medicine, Phramongkutklao Hospital, Phramongkutklao College of Medicine, Bangkok, Thailand, 10Division of Pharmacogenomics and Personalized Medicine, Department of Pathology, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand, 11Department of Immunology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.

RATIONALE: In vitro drug allergy diagnosis is not recommended during acute stage of severe cutaneous adverse reactions (SCARs). Programmed death ligand 1 (PD-L1) could negatively regulate drug-specific T cell response. This study was to explore a panel of cytokines suitable for the identification of culprit drugs during acute SCAR period and whether anti-PD-L1 supplementation could increase sensitivity of the test.

METHODS: Peripheral blood mononuclear cells (PBMCs) collected during acute stage in 15 SCAR patients (5 acute generalized exanthematous pustulosis-AGEP, 5 drug reaction with eosinophilia and systemic symptoms-DRESS, and 5 Stevens-Johnson syndrome/toxic epidermal necrolysis-SJS/TEN) were stimulated with the culprit drugs or non-allergic control drugs for 72 hours. Twenty-two cytokines released in culture media were then analyzed with multiplex immunoassays. P values < 0.05 were considered significant.

RESULTS: Granzyme B, perforin, and granulysin levels were significantly higher in DRESS (8.02, 6.60, 7.72 vs 2.79, 3.71, 2.85 ng/ml) and IL-12p70 levels were higher in AGEP (0.55 vs 0.23 pg/ml) after PBMC stimulation with the culprit drugs compared to control drugs. In the presence of anti-PD-L1, IFN-γ levels were 2.5 folds higher in SCAR patients in general while IL-17A levels were 5.8 folds higher in AGEP upon stimulation with the culprit drugs compared to those stimulated with control drugs. IL-27 levels seemed increased in SJS/TEN.

CONCLUSIONS: The measurement of cytokine released from PBMCs upon stimulation with the suspected drugs could be a useful tool to identify the culprit drugs in SCAR, especially in DRESS and AGEP, even in the acute stage. More researches are needed to confirm diagnostic value.
Drug-Induced Anaphylaxis Visits: A 4-Year Follow-up Study in Two Emergency Departments in Montreal

Sofianne Gabrielli, MD, Ann E. Clarke, MD, MSc, FRCP, Harley Eisman, MD, Judy Morris, MD, MSc, Lawrence Joseph, PhD, Sebastien LaVieille, MD, MSc, Peter Small, MD, and Moshe Ben-Shoshan, MD, MSc. 1 Division of Pediatric Allergy and Clinical Immunology, Department of Pediatrics, McGill University Health Center, Montreal, Quebec, Canada, 2 Division of Rheumatology, Department of Medicine, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada. 3 Department of Emergency Medicine, Montreal Children’s Hospital, McGill University Health Center, Montreal, Quebec, Canada, 4 Department of Emergency Medicine, Sacre-Coeur Hospital, Montreal, QC, Canada, 5 Division of Allergy and Clinical Immunology, Jewish General Hospital, McGill University, Montreal, Quebec, Canada, 6 Division of Pediatric Allergy and Clinical Immunology, Department of Pediatrics, Montreal Children’s Hospital, Montreal, Quebec, Canada.

RATIONALE: Data is sparse on drug-induced anaphylaxis (DIA). We aimed to assess the percentage and diagnosis of DIA cases among all visits due to anaphylaxis in a pediatric and an adult emergency room (ER).

METHODS: Children presenting to the Montreal Children’s Hospital (MCH) and adults presenting to Hôpital du Sacré-Coeur (HSC) with anaphylaxis were recruited as part of the Cross-Canada Anaphylaxis Registry. A standardized data form documenting the reaction was collected and patients were followed annually to determine assessment by allergist.

RESULTS: From June 2012 to May 2016, 45 children and 65 adults presented to the ER with DIA. Despite an increasing percentage of anaphylaxis at the MCH of 0.21% (95%CI, 0.15, 0.27) over 4 years, there was no conclusive change in percentage of DIA due to wide confidence intervals (-2.8% [95%CI, -7.3%, 1.7%]). Results at HSC for the percentage change of both anaphylaxis and DIA from 2012 to 2016 were also inconclusive (-0.0062% [95%CI, -0.048, 0.036] and -1.2% [95%CI, -14.7%, 12.3%], respectively). Consent for follow up was provided for all pediatric cases and half of adults. Among these, 61.9% (95%CI, 46.6%, 77.2%) of children and 32.4% (95%CI, 15.8%, 48.9%) of adults had seen an allergist after the ER visit. Drug allergy was confirmed by either skin test or oral challenge in 36.4% (95%CI, 2.5%, 70.3%) of children and 87.5% (95%CI, 77.2%, 100%) of adults. Among these, 61.9% (95%CI, 46.6%, 77.2%) of children and 32.4% (95%CI, 15.8%, 48.9%) of adults had seen an allergist after the ER visit. Drug allergy was confirmed by either skin test or oral challenge in 36.4% (95%CI, 2.5%, 70.3%) of children and 87.5% (95%CI, 77.2%, 100%) of adults.

CONCLUSIONS: Only a small number of patients with suspected DIA are subsequently assessed and confirmed. It is crucial to assess all DIA by an allergist to avoid mislabeling patients.
Clinical Characterization of a Large Population of Subjects with Respiratory Vs Cutaneous Non-Steroidal Anti-Inflammatory Drugs (NSAID) Hypersensitivity Reactions

Jesus Verge1, Inmaculada DoNa, MD, PhD2, Ibon Egiluz Gracia3, Ana Prieto del Prado4, Luisa Galindo5, Francisca Gomez, MD, PhD6, Jose Antonio Cornejo, PhD7, Carmen Rondon Segovia8, and Paloma Campo, MD, PhD9; 1ENT Department, Regional Hospital of Malaga (Virgen de la Victoria)-IBIMA, Malaga-Spain, Malaga, Spain, 2Allergy Unit, IBIMA-Regional University Hospital of Malaga, Malaga, Spain, 3Allergy Research Laboratory-Malaga Regional University Hospital-IBIMA, Malaga, Spain, 4Pediatric Area, Health Center Don JosA^f/A,A,A© Molina DA/A/A,A.Az. AlhaurA^f/A,A.An de la Torre., Malaga, Spain, 3Allergy Department, Regional Hospital of Malaga-IBIMA, Malaga-Spain, Malaga, Spain, 5Allergy Unit, IBIMA-Regional University Hospital of Malaga, Malaga, Malaga, Spain, 6Allergy Research Laboratory, Regional Hospital of Malaga-IBIMA, Malaga, Spain, 7Malaga Regional University Hospital-IBIMA, Malaga, Spain, 8Allergy Unit, IBIMA-Regional University Hospital of Malaga, Malaga, Spain.

RATIONALE: Non-steroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (NERD) is an entity well differentiated from NSAID-induced urticaria/angioedema (NIUA). Our aim was to perform a comparative study of a large series of patients with NIUA and NERD.

METHODS: Patients referred between 2005-2015 with history of NERD and NIUA. Diagnosis was performed by clinical history and drug provocation test (DPT) (nasal: NERD, oral: NIUA) when indicated. DPT was also performed to test tolerance to alternative NSAID.

RESULTS: Nine hundred and three patients included (NERD n=250, NIUA n=743). Most reactions were attributed to ibuprofen (60.8% NERD vs 56.4% NIUA, p=0.24), followed by aspirin (59.2% NERD vs 44% NIUA) (p=n.s.) and others (NERD 28.8% metamizol, NIUA 20.9% paracetamol). In NERD, reactions after taking NSAID were asthma (83%) and rhinitis (44%), whereas in NIUA were urticaria (73.7%) and angioedema (72.1%). Atoy was similar in both groups (NERD 57.9% vs NIUA 62.7%, p=0.23), with similar allergen distribution (NERD: D.pteronyssinus 36.2%, Olea 26.7%; NIUA: D. pteronyssinus 32%, Olea 28.9%). Nasal provocation test with lysine aspin (NERD n=137) was positive in 69.4%. Paracetamol (1gr) was the most tolerated NSAID (NERD 81.9%, NIUA 73.7%). Celecoxib was the most tolerated selective COX-2 inhibitor (NERD 100%, NIUA 88.9%). Occurrence of reaction after NSAID intake was earlier in NERD vs. NIUA: aspirin (47 vs 80.9 min), ibuprofen (40.7 vs 161.6 min) and paracetamol (57.4 vs 165 min).

CONCLUSIONS: NERD and NIUA share some characteristics despite being clinically different. More studies are needed to establish if those groups share or not a common causative mechanism.

Desensitization for Platinum Hypersensitivity

Hye-Ryun Kang1,2, Jisu Shim3, Soo Jie Chung1, Sung-Yoon Kang2, Kyoungh-Hee Sohn2, Woo-Jung Song2, Heung-Woo Park2, and Sang-Heon Cho1,2; 1Drug Safety Monitoring Center, Seoul National University Hospital, Seoul, Korea, The Republic of, 2Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea, The Republic of.

RATIONALE: Desensitization is a safe alternative for patients with drug hypersensitivity reactions. Although desensitization protocols with multiple serial dilutions are widely used currently, they involve laborious technical work for pharmacists and nurses. The incidence of breakthrough reaction (BTR) during desensitization with platinum chemotherapeutic agents was reported from 32% to 56% in previous studies. Here we newly present a simple easy desensitization protocol without dilution process for platinum hypersensitivity.

METHODS: We performed an observational study of 21 platinum hypersensitive patients who underwent a new 1 bag desensitization protocol. Platinum-based chemotherapeutic agents were reconstituted with 150-200 mL of dextrose water or 0.9% saline and gradually administered in 12 steps without dilution from a rate of 0.1 mL/hr to 150 mL/hr (for oxaliplatin and carboplatin) or 450 mL/hr (cisplatin) by doubling of infusion rate. Outcomes and safety profiles were assessed.

RESULTS: All 80 desensitization cases completed infusion of culprit agents: 64 (80%) cases had no BTR at all and 16 (20%) cases showed BTR. Most of those BTRs were mild reactions (CTCAE grade 1 or 2) (12, 75%) and no anaphylactic reaction was encountered during desensitization. BTRs occurred most frequently during the first desensitization cycle (5, 31.3%). Occurrence of BTRs were significantly related with more severe initial HSRS. Otherwise, no significant difference was observed according to premedication, age, accumulated number of previous exposures for the development of BTRs.

CONCLUSIONS: Our new non-dilution desensitization protocol is not only more efficient but also safer than previous multiple serial dilution protocols.

A Survey on Primary Care Providers’ Awareness of Penicillin Allergy in a VA Medical Center

Chongwei Cui, MD, PhD, and Joseph S. Yusin, MD, FAAAAI; VA Greater Los Angeles Health Care System, Los Angeles, CA.

RATIONALE: Penicillin allergy (PA) is reported by approximately 10% of the U.S. population; however, fewer than 10% were truly IgE-mediated hypersensitivity. We investigated how knowledgeable primary care providers (PCPs) are on key facts of PA in our VA medical center.

METHODS: We sent out a survey to 73 PCPs at our medical center. The questions focus on key facts that PCPs should master, including the percentage of true PA among reported cases, the percentage of patients who reported PA in the past remaining positive on skin testing, and the potential savings by performing skin testing over choosing alternative antibiotics. The survey concluded with the question asking readiness to refer PA patients for skin testing.

RESULTS: Among 20 responses, none referred patients to allergy clinic during the past 12 months. 59% are aware that less than 10% of reported PA is truly allergic. 53% are unaware that less than 20% of patients with a remote PA history over 15 years ago remain positive on skin testing. 71% are unaware that antibiotic costs are 63% higher for patients reporting PA than for those who do not. 65% are unaware that performing skin testing can save up to 90% costs per patient encounter. 77% conclude that they will refer patients with PA history and multiple comorbidities for skin testing in the future.

CONCLUSIONS: Education of PCPs on key facts of penicillin allergy is crucial in their decision making in regards to referring patients with reported PA for skin testing.
All abstracts are strictly embargoed until the date of presentation at the 2017 Annual Meeting.

**147 Study of Protein Haptenation By Biotinylated Clavulanic Acid: Usefulness in Studies on Allergy Towards Betalactams**

Angela Martin-Serrano, PhD1,2, Necane Barbero, PhD1,3, Adriana Ariza, PhD2,3, D. Fernandez, PhD2, Ezequiel Perez-Inestrosa, PhD1,3, Maria Salas, MD, PhD4, Cristobalina Mayorga, PhD1,4, Dolores Perez-Sala, PhD5, Maria J. Torres, MD, PhD6, and Maria I. Montaño, PhD1,2,1 BIONAND-Andalusian Centre for Nanomedicine and Biotechnology, Malaga, Spain, 2Research Laboratory, IBIMA, Regional University Hospital of Malaga, UMA, Malaga, Spain, 3Department of Organic Chemistry, University of Malaga, Malaga, Spain, 4Allergy Unit, IBIMA, Regional University Hospital of Malaga, UMA, Malaga, Spain, 5Department of Chemical and Physical Biology, Centro de Investigaciones Biologicas, C.S.I.C., Madrid, Spain, 6Research Laboratory, IBIMA-Regional University Hospital of Malaga, Malaga, Spain.

**RATIONALE:** Clavulanic acid (CLV) is a betalactam which inhibits betalactamases activity and is frequently administered combined with amoxicillin. Lately, immediate allergic reactions to CLV have been reported in 30% of patients allergic to Amoxicillin-CLV. Since protein haptenation with betalactams is known to be necessary to activate the immune system, the objective was to study haptenation and develop tools to identify CLV target proteins.

**METHODS:** Human serum albumin (HSA) was incubated with increasing concentrations of CLV. Conjugates were purified by filtration and characterized by MALDI-TOF-MS. Biotinylated CLV (CLV-B) was synthesized introducing an oxygenated linker between CLV and a biotin moiety, for studying haptenation of human serum proteins. HSA and serum modifications were identified as modified proteins.

**RESULTS:** Both CLV and CLV-B modified HSA (Δm=279.8 and Δm=543.0 respectively, compared with HSA control). Modification was proportional to the amount of CLV or CLV-B used during incubation. CLV-B was used as a sensitive tool to find out serum proteins target of haptenation. HSA, transferrin and heavy and light chains of immunoglobulins were identified as modified proteins.

**CONCLUSIONS:** Our results show that CLV-B is a valuable tool for the identification of CLV targets with high sensitivity. The elucidation and comparison of CLV and CLV-B reactivity during conjugation deserve further study to finally understand the activation of the immune system by CLV.

**148 Value of Synthetic Antigenic Determinants of Clavulanic Acid in Basophil Activation Test for Evaluating Immediate Reactions to Clavulanic Acid**

Maria I. Montaño, PhD1,2, Necane Barbero, PhD2,3, D. Fernandez, PhD2, Angela Martin-Serrano, PhD1,2, Gador Bogas, MD, PhD4, Adriana Ariza, PhD2, Cristobalina Mayorga, PhD1,4, Ezequiel Perez-Inestrosa, PhD2,3, and Maria J. Torres, MD, PhD6.

**RATIONALE:** Clavulanic acid (CLV) is nowadays frequently administered in combination with amoxicillin. Selective reactions to CLV account for around 30% of allergic reactions to amoxicillin-CLV combination. Recently, basophil activation test (BAT) using CLV has demonstrated specific recognition of the drug, and usefulness for diagnosing patients with immediate allergic reactions to amoxicillin-CLV combination. The aim of this study was to design synthetic CLV determinants and assess their value in BAT for the diagnosis of immediate allergic reactions to CLV.

**METHODS:** Five well-defined synthetic determinants were designed considering the generation of either aldehyde- or amine-functionalized molecules after different chemical fragmentations of CLV. The study included 20 patients with a selective immediate hypersensitivity reaction to CLV plus 15 non-atopic controls tolerating CLV. BAT was performed with CLV and five synthetic determinants presenting different functionalities: aldehyde (Clav1, Clav2 and Clav3) or amine (Clav4 and Clav5). To confirm IgE-mediated basophil activation, the phosphatidylinositol 3-kinase (PI3-K) inhibitor wortmannin (WTM) was used in the BAT.

**RESULTS:** BAT results in patients were positive only with CLV (43%) and two of the synthetic determinants, Clav2 (85%) and Clav3 (71%). We confirmed that positive BAT results were an IgE-mediated response by using the WTM. Healthy controls showed negative BAT to CLV and all synthetic determinants, except to Clav3 (28%).

**CONCLUSIONS:** Aldehyde-functionalized determinants (Clav2 and Clav5) activate basophils by a specific IgE mechanism from patients selective to CLV. The additional use of synthetic determinants, besides the parent drug, increases significantly BAT sensitivity, thus improving and refining the BAT-based diagnosis of immediate reactions to CLV.

**149 Searching for the Culprit Agents for Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis from a Nationwide Claim Database in Korea**

Min-Suk Yang, MD, PhD1,2, Jin Yong Lee3, Jayeon Kim4, Byung-Keun Kim5, Ju-Young Kim6, Heung-Woo Park7, Sang-Heon Cho8, Kyung-Up Min9, and Hye-Ryun Kang8; 1SMG-SNU Boramae Medical Center, Seoul, South Korea, 2Department of Internal Medicine, Seoul National University College of Medicine, Seoul, South Korea, 3SMG-SNU Boramae Medical Center, Seoul, Korea, The Republic of, 4Institute of Health and Environment, Seoul National University, Seoul, Korea, The Republic of, 5Seoul National University Bundang Hospital, Seongnam-si, Korea, The Republic of, 6Gyeongsang National University Hospital, Jinju-si, Korea, The Republic of, 7Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea, The Republic of, 8Drug Safety Monitoring Center, Seoul National University Hospital, Seoul, Korea, The Republic of.

**RATIONALE:** There can be ethnic difference in the culprit agents for Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). The incidence of SJS and TEN (ALDEN) score. The distribution of ALDEN score for 29 TEN cases was as following; 14 with score 6, 11 with score 5 and 4 with score 4. The most frequent culprit agents for both SJS and TEN were allopurinol (18/133), carbamazepine (15/133) and lamotrigine (11/133). Methazolamide showed the highest incidence of SJS and TEN (25.97 cases/1,000,000 prescription) considering the amount of nationwide prescription rate.

**CONCLUSIONS:** Allopurinol, carbamazepine, lamotrigine and carbonic anhydrase inhibitors were the most frequent cause of SJS and TEN in Korea.
Diagnostic Value of Allergy Testing in Children Undergoing Four-Food Elimination Diet for Eosinophilic Esophagitis

Melanie M. Makhija, MD, MS1,2, Joshua B. Wechsler, MD3,4, Carla M. Davis, MD, FAAAI5, Anthony P. Olive, MD6, Seth Marcus, MD, MSCH7, Mirna Chehade, MD, MPH8,9, Barry K. Wershil, MD8,10, and Amir F. Kagalwalla, MD3,4; 1Division of Allergy & Immunology, Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, IL, 2Ann and Robert H. Lurie Children’s Hospital of Chicago, Chicago, IL. 3Ann and Robert H Lurie Children’s Hospital of Chicago, Chicago, IL, 4Northwestern University Feinberg School of Medicine, Chicago, IL, 5Baylor College of Medicine and Texas Children’s Hospital, Department of Pediatrics, Section of Immunology, Allergy and Rheumatology, Houston, TX, 6Texas Children’s Hospital, Houston, TX, 7GI Care for Kids, Atlanta, GA, 8Department of Pediatrics, Icahn School of Medicine at Mount Sinai, New York, NY, 9Mount Sinai Center for Eosinophilic Disorders, Icahn School of Medicine at Mount Sinai, New York, NY, 10Ann and Robert H Lurie Children’s Hospital of Chicago, Chicago.

RATIONALE: Empiric six-food elimination diet is standard of care therapy for eosinophilic esophagitis (EoE). The efficacy of allergy testing in predicting dietary triggers of eosinophilia remains unclear.

METHODS: We assessed the diagnostic accuracy of food-specific IgE (sIgE) and skin prick testing (SPT) for identifying specific EoE triggers. A multi-center prospective study of four-food elimination diet (FFED) was performed in children with EoE. Serum IgE and SPT to milk, wheat, egg and soy were analyzed in 35/50 (70%) FFED responders who underwent food reintroduction.

RESULTS: 78 children underwent FFED (68% male, median age 8.4 years, 84% white, 83% atopic). Histologic remission occurred in 50 patients (64%). Cow’s milk was a food trigger in 85%, wheat in 31%, egg in 13% and soy in 8%. Of the responders 17% were SPT positive to milk, 20% to egg, 14.7% to wheat and 26.5% to soy. Specific IgE was >0.35 in 40% to milk (median sIgE 0.85kU/L), 22.9% to egg (median 1.45kU/L); 20% to wheat (median 0.88kU/L) and 23.5% to soy (median 0.72kU/L). The diagnostic odds ratios were poor for both SPT and sIgE for all foods (range 0-1.9 for SPT and 0-12.8 for sIgEs). The accuracy of testing (both SPT and sIgE) was highest for egg (62.1% SPT, 80% sIgE), followed by soy (64.5% SPT, 75.9% sIgE) and wheat (57.8% SPT, 57.1% sIgE) and lowest to milk (15.8% SPT, 27.8% sIgE).

CONCLUSIONS: Skin prick and sIgE testing were not accurate diagnostic predictors of food triggers in EoE patients on FFED based on assessment of esophageal histology.
151 The diagnostic utility of serum assays for total IgG4 and specific IgG4 antibodies to cow’s milk proteins in children with eosinophilic esophagitis: Comparison with an unselected birth cohort

Alexander J. Schuyler, BS, BA1, Elizabeth A. Erwin, MD2, Emily Oken, MD, MPH1, Sheryl Rifas-Shiman, MPH2, Jonas Lidholm, PhD2, Jeffrey Wilson, MD, PhD2, Anubha Tripathi, MD3, Lisa J. Workman, BA1, Diane R. Gold, MD3, and Thomas A. E. Platts-Mills, MD, MPH 4, Sheryl Rifas-Shiman, MPH 3, Jonas Lidholm, PhD 2, Jeffrey Wilson, MD, PhD 2, Anubha Tripathi, MD 3, Lisa J. Workman, BA 1, Diane R. Gold, MD 3, and Thomas A. E. Platts-Mills, MD, MPH 4, 1University of Virginia, Charlottesville, VA, 2Nationwide Children’s Hospital, Columbus, OH, 3Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, 4Thermo Fisher Scientific, Uppsala, Sweden, 5Harvard T.H. Chan School of Public Health, Boston, MA.

RATIONALE: Eosinophilic esophagitis (EoE) is associated with specific IgG4 antibodies (sIgG4) to common foods, especially cow’s milk (CM). Little is known regarding the epidemiology of sIgG4 to CM or other foods in the general population. Thus, the diagnostic utility of IgG4 assays is unclear.

METHODS: We studied 67 children (median age = 11 years) diagnosed with EoE by esophageal biopsy at The University of Virginia (Charlottesville, VA) or Nationwide Children’s Hospital (Columbus, OH): 101 controls (median age = 12.8 years) from a birth cohort unselected for any disease (Project Viva); and 40 unrelated non-allergic controls (median age = 12 years) without specific IgE antibodies (sIgE) to foods. Sera were assayed for sIgE and sIgG4 to CM proteins (alpha-lactalbumin, beta-lactoglobulin, caseins) and total IgG4 (tIgG4) by ImmunoCAP.

RESULTS: The prevalence of CM sensitization (sIgE ≥0.10 IU/mL) among the pediatric EoE patients and unselected controls was 79% (n = 53/67) and 22% (n = 22/101), respectively. The titers of tIgG4 to the CM proteins were higher in EoE patients than in unselected controls (p < 0.001). Elevated tIgG4 based on laboratory values (p < 0.01) and sIgG4 to alpha-lactalbumin and caseins (p < 0.001) were more common in EoE patients compared to unselected controls. Furthermore, the mean sIgG4 to CM (all three proteins) as a percentage of tIgG4 was higher in EoE patients than in unselected controls (p < 0.001). Similar serological differences between EoE patients and non-allergic controls were also observed.

CONCLUSIONS: Among children with EoE, sIgG4 to CM can significantly contribute to tIgG4. The results suggest that titer of sIgG4 to CM proteins could be incorporated into a diagnostic algorithm for EoE.

152 Asthma Phenotypes in Children with Eosinophilic Esophagitis

Tarina Quraishi; University of Cincinnati, Cincinnati.

RATIONALE: The association between asthma and Eosinophilic Esophagitis (EoE) is not well characterized. Multiple small studies have estimated that rates of asthma in children with EoE range between 38-66%, and the severity of asthma phenotypes associated with EoE is not well understood. We hypothesized that children with a diagnosis of asthma would have a higher prevalence of EoE than the general pediatric population, and that children with both asthma and EoE would have more severe persistent asthma than children without EoE.

METHODS: The Cincinnati Children’s Hospital Medical Center Asthma Center identified 70 patients with a physician diagnosis of asthma and endoscopy-proven diagnosis of EoE for a retrospective cohort study. Systematic chart review characterized patients’ asthma severity in the year prior to EoE diagnosis, defined as intermittent asthma (absence of inhaled corticosteroid therapy), mild/moderate persistent asthma (low dose inhaled corticosteroid), or severe persistent asthma (high dose inhaled corticosteroid).

RESULTS: Children with a diagnosis of asthma had a higher prevalence of EoE (n = 3,071, 2.27%) than the general pediatric population. Children with both asthma and EoE have more severe persistent asthma (n = 41, 31.7% severe) than children without EoE.

CONCLUSIONS: Asthma diagnosis is associated with a higher prevalence of EoE, and EoE diagnosis is associated with more severe persistent asthma, among children followed at an urban asthma center.
154 Dietary Intake, Inflammation And Mucosal Integrity In Adult Patients With Eosinophilic Esophagitis

Berber Vlieg-Boerstra, RD, PhD1, Marlou de Kroon, MD, PhD2, Marijn Warners, MD3, Marleen Van Ampting, PhD4, Lucien Harthoorn, PhD5, Simone Eussen, PhD6, and Arjan Breedenoord, MD, PhD7, 1Department of Pediatrics, Onze Lieve Vrouwe Gasthuis (OLVG), Amsterdam, Netherlands, 2Department of Health Sciences, University Medical Center Groningen, Groningen, Netherlands, 3Department of Gastroenterology & Hepatology, Academic Medical Center, Amsterdam, Netherlands, 4Nutricia Research, Nutricia Advanced Medical Nutrition, Utrecht, Netherlands.

RATIONALE: In Eosinophilic Esophagitis (EoE) we hypothesized that, besides the fact that food allergy may play a role, also nutrients/foods may exert direct (protective) effects on the inflammation and mucosal integrity of the esophagus. Aims: To explore the relationship between diet and a) inflammation and b) mucosal integrity/permeability in adult EoE patients.

METHODS: In adult patients previously diagnosed with EoE, who participated in other studies (Triallregister.nl:NTR4502 and NTR4892) at baseline three-day food diaries were analyzed for nutrients and foods and were studied for their relationships with log-transformed values of eosinophil counts, Trans Epithelial Resistance (TER) (mucosal integrity) and Transepithelial Fluorescein Flux (FLUOR) (permeability) by means of multiple regression analyses corrected for age, gender and energy intake.

RESULTS: Thirty-four patients were included. The amount of fiber (β = -0.132; p=.044), iron (β = -0.327;p=.001, pasta/rice (β = -0.014;p=.028) and soy products (β = -0.010;p=.007) were inversely related to eosinophil counts. Patients in spontaneous disease remission (<15 Eosinophils per High Power Field (n=5)) consumed significantly more fiber (p = .012), magnesium (p = .024), vegetables (p = .029), yoghurt (p = .045) and less vitamin B12 (p=.006) and meat (p = .034) than patients with active disease (≥15) (n=29) (Mann-Whitney test).

Mucosal integrity/permeability: Consumption of oil rich in linoleic acid was inversely related to mucosal integrity (TER, β = -0.083;p=.019). Consumption of cooking fat was positively related (FLUOR, β = 0.228; p = .0012), whereas buttermilk/low fat yoghurt with LGG was inversely related to permeability (FLUOR, β = -0.036;p = .002).

CONCLUSIONS: These results support our hypothesis that in adults with EoE individual nutrients/foods may positively or negatively impact inflammation and mucosal integrity of the esophagus.

155 Application of Clinical Scoring System to Distinguish Eosinophilic Esophagitis vs. Proton Pump Inhibitor-Responsive Esophageal Eosinophilia

Charmi Patel, MD1, and Punita Ponda, MD, FAAAAI2; 1Hofstra Northwell School of Medicine, Hempstead; North Shore-Long Island Jewish Medical Center, Great Neck, NY, 2Division of Allergy and Immunology, Northwell Health, Great Neck, NY.

RATIONALE: Diagnosis of Eosinophilic Esophagitis (EoE) is evident with biopsy, but differentiating between EoE and proton-pump inhibitor-responsive esophageal eosinophilia (PPI-REE) using clinical history continues to pose difficulty. We use a clinical score that aims to discriminate the two entities.

METHODS: The scoring system by Mulder et al. was applied to fourteen patients with known esophageal biopsy of ≥15 eosinophils per high-power field (hpf). The scoring system uses clinical and endoscopic features at initial presentation to determine a odds ratio. This odds ratio accuracy was then assessed based off histological findings after treatment with a PPI.

RESULTS: Of the fourteen patients, eleven had scores ≥100 with a 0.85 relative odds of EoE. Three patients had a score of ≥100 of which two had a score of 26 and 93 with a 0.21 and 0.80 relative odds of EoE respectively. Both had PPI-REE. One patient had a score of 0 and <0.21 relative odds with EoE. The remainder of the eleven patients had >15 eosinophils/hpf on repeat endoscopy after PPI trial with a diagnosis of EoE.

CONCLUSIONS: This scoring system correctly identified eleven out of twelve patients with EoE and one out of two patients with PPI-REE. A large number of more evenly distributed PPI-REE and EoE patient populations are needed to validate this scoring system. However, this has the potential to be applied to suspected EoE patients on initial evaluation to expedite management (performance of skin tests) prior to histologically assessing PPI-responsiveness in patients with higher likelihood of having EoE.

156 Effectiveness of Targeted Food Elimination Diet in Management of Pediatric Eosinophilic Esophagitis (EoE): A Retrospective Review.

Shalini Thiru, BS1, Stephanie L. Vakaljian, BS2, Mary E. Sherlock, MD, FRCP(C)3, Mary Zachos, MD, FRCP(C)4, Elyanne Ratcliffe, MD, FRCP(C)5, Robert Issenman, MD, FRCP(C)2, Nikhil Pai, MD, FRCP(C)2, and Jason A. Ohayon, MD, FRCP(C)1, Hamilton Allergy, Hamilton, ON, Canada, 2Dept of Ped Gastroenterology, McMaster University, Hamilton, ON, Canada, 3Dept of Ped, McMaster University, Hamilton, ON, Canada.

RATIONALE: Management of Eosinophilic Esophagitis (EoE) consists of targeted food elimination (TFE), six food elimination (SFED) and/or topical steroid (TS) therapy. Compliance remains a challenge with SFED. The role of TFE with initial TS therapy and subsequent TS weaning was reviewed in a retrospective analysis in pediatric EoE.

METHODS: This study was conducted between 2010 and 2016 in a pediatric allergy clinic from patients referred by Pediatric Gastroenterology. Patients selected had endoscopic evaluation and confirmation of EoE with subsequent post allergy assessment and intervention biopsy. Allergy assessments included traditional allergy testing (AT) and food patch testing (FT). Follow up assessments were based on clinical assessments and repeat biopsy analysis.

RESULTS: A total of 52 pediatric biopsy-proven EoE patients were identified over 6 years. Thirteen of 15 (87%) showed significant improvement on TFE and/or TS. Ten of 13 (77%) displayed a significant reduction of the pre-treatment biopsy Eosinophils (Eos) level from an average of 105 Eos/hpf to normal post treatment values (i.e. 0-15 Eos/hpf). Two of 15 (13%) showed an increase in Eos but with clinical improvement. Four of 15 (27%) children were managed successfully with TFE alone, 8/15 (53%) with combined TFE and initial TS and 1/15 (7%) were TS dependent. None of the 15 required SFED.

CONCLUSIONS: In a group of children with EoE, where biopsies were available post allergy intervention, the majority of children improved both clinically and endoscopically by TFE with and without initial TS therapy. The challenges of maintaining a SFED was not required in these children.
157 Serum IgG4 to food proteins, but not to the barrier function proteins desmoglein 1 or 3, are increased in eosinophilic esophagitis

Jeffrey Wilson, MD, PhD1, Alexander J. Schuyler, BS, BA, Amitha Tripathi, MD, Scott P. Commans, MD, PhD2, Elizabeth A. Erwin, MD3, and Thomas A. E. Platts-Mills, MD, PhD, FAAAAI, FRSA1; 1University of Virginia, Charlottesville, VA, 2University of North Carolina, Chapel Hill, NC, 3National Children’s Hospital, Columbus, OH.

RATIONALE: Food allergy, impaired mucosal barrier function and abundant local IgG4 production have all been described in eosinophilic esophagitis (EoE). We investigated IgG4 to multiple food antigens that are implicated in EoE, as well as desmoglein 1 and 3 based on their role in the mucosal barrier function and as established IgG4 targets in variants of pemphigus.

METHODS: We assessed IgG4 levels to relevant food antigens from sera banked at the University of Virginia in selected pediatric and adult patients with biopsy-diagnosed EoE and relevant controls. IgG4 and IgE were measured by ImmunoCAP using commercial assays or biotinylated antigen coupled to streptavidin immunosorbent. For desmoglein 1 and 3, we screened sera from 10 adult and 10 pediatric EoE patients using a modified commercially available ELISA.

RESULTS: IgG4 geometric mean levels to multiple food antigens represented in the six-food elimination diet were significantly higher in EoE patients as compared to relevant allergic and non-allergic controls. The milk proteins alpha-lactalbumin, beta-lgactoglobulin and caseins were the most pronounced. Significant, but less strong results were obtained for IgG4 to egg proteins ovalbumin and ovomucoid. IgG4 to galactose-alpha-1,3-galactose was undetectable or <1% of the total IgG4 in EoE patients and controls. IgG4 signatures were similar in both pediatric and adult cohorts. There was no evidence of serum IgG4 to desmoglein 1 or 3.

CONCLUSIONS: IgG4 to milk proteins are elevated in EoE compared to non-allergic controls and traditional IgE-mediated food allergies. Desmoglein down-regulation has been described in EoE but we saw no evidence that the mechanism involves IgG4 autoantibodies.

158 Changes in Biomarker Nasal Nitric Oxide in Children with Eosinophilic Esophagitis after Treatment

Miguel J. Lanz, MD, FAAAAI1, Mirna M. Gonzalez, BA1, Erick Hernandez, MD,2, Ruben Gonzalez-Vallina, MD2, 1AAADRS Clinical Research Center, Coral Gables, FL, 2Nicklaus Children’s Hospital, Miami, FL.

RATIONALE: In eosinophilic esophagitis (EoE), repeated esophageal biopsies are required to verify treatment-response, but a noninvasive biomarker that can anticipate improvements prior to post-treatment biopsies has not been found. Nasal nitric oxide (nNO) has been shown to measure eosinophils and obstruction of the upper airways. Since the epithelium of the nasal cavity and esophagus are similar, we propose to measure changes of nNO to predict treatment response in EoE.

METHODS: Children, aged 6-17 years, with EoE by biopsy had exhaled NO (FeNO) and nNO measured prior to any dietary and/or swallowed steroids initiation. After three months of treatment, NO was measured prior to unblinding of biopsy results. For nNO, subjects performed a breathhold for at least 20 seconds while a nasal olive with aspiration (5ml/sec; NIOX MINO nasal) was placed at the nostril. Subjects with upper airway abnormalities, including sinusitis, and those taking nasal steroids or leukotriene modifiers were excluded. Subjects with allergic rhinitis without EoE served as controls with same medications excluded.

RESULTS: Thirteen of 15 EoE children improved their eosinophil counts on biopsy from mean of 50/hpf to 4/hpf post-treatment. A significant change in nNO was found at EoE improvement of 216ppb (*p<0.01); from mean nNO 442ppb to 658ppb. A weak inverse correlation (r = -0.496) was found for increasing nNO with decreasing eosinophils on biopsies. No significant changes were found with FeNO over this treatment course. Allergic rhinitis controls had no significant changes in nNO.

CONCLUSIONS: Increases in nNO after EoE treatment should be further studied to predict timing for esophageal biopsies.

159 Characterization of Eosinophilic Esophagitis in Dust Mite Sensitized Children

Erving Arroyo-Flores, MD1, Wilfredo Cosme-Blanco, MD, PhD1, Carmen Pimentel, MD1, Rita M. Diaz, MD, FAAAAI1, and Sylvette Nazario, MD2; 1UPR Recinto de Ciencias Medicas, San Juan, PR, 2Division of Allergy and Immunology, University of Puerto Rico Medical Sciences Campus, San Juan, Puerto Rico.

RATIONALE: Eosinophilic esophagitis (EoE) associated with dust mite sensitization has been described in a few case reports. Improvement of EoE has been observed in patients with allergic rhinitis treated with dust mite immunotherapy. The current study intends to characterize a population of pediatric patients with EoE and mite sensitization.

METHODS: Retrospective chart reviews of 42 Puerto Rican pediatric patients with confirmed EoE. Data collected included demographics, atopic history, skin prick test (SPT) to aeroallergens and foods, patch test for foods, number of eosinophils in endoscopic biopsy, total IgE and serum eosinophil count. Patients were divided into two groups based on positive or negative SPT result to dust mite extract.

RESULTS: The dust mite sensitized group showed a trend towards a higher level of eosinophils per high power field in esophageal biopsies in comparison to the dust mite negative group with EoE, 32 vs 22 (P=.07) respectively. Furthermore, sensitization to foods, as tested by SPT, was more common in the dust mite group than in the negative dust mite group, 71% vs 22% (P=.003) respectively. No difference was found between the groups with respect to proportion of positive food patch test (P=.497).

CONCLUSIONS: EoE is a mixed IgE and T-cell mediated disease. However, in our sample, the dust mite sensitized group exhibited a higher frequency of IgE-mediated sensitization to food, in the absence of food patch test differences. This suggests that IgE might play a stronger role than the T-cell mediated mechanism, in the pathogenesis of EoE in dust mite sensitized patients.
160 Simultaneous Assessment of Eosinophil Biomarkers in Eosinophilic Esophagitis Patients

Evelyn L. Angulo, MD1; Mats W. Johansson, PhD2; Elizabeth A. Schwantes, MS3; Paul S. Fichtinger, BS4; Shelly M. Cook, MD5; Eric A. Gaumitz, MD1; and Sameer K. Mathur, MD, PhD6, FAAAAI7.; 1Department of Medicine, Division of Allergy, Pulmonary and Critical Care Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI, 2Department of Biomolecular Chemistry, University of Wisconsin School of Medicine and Public Health, Madison, WI, 3Department of Medicine, Division of Allergy, Pulmonary and Critical Care Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI, 4Department of Pathology and Laboratory Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI, 5Department of Medicine, Division of Gastroenterology and Hepatology, University of Wisconsin School of Medicine and Public Health, Madison, WI.

RATIONALE: Monitoring disease activity in eosinophilic esophagitis is challenging as there is a lack of validated tools to replace invasive procedure-based endoscopy and pathology evaluation. We aim to identify a profile of eosinophil surface biomarkers that will correlate with eosinophil activation and disease activity in eosinophilic esophagitis. Previous studies have demonstrated that expression of eotaxin in esophageal tissue is a prominent mediator for the recruitment and activation of eosinophils in eosinophilic esophagitis.

METHODS: Peripheral blood eosinophils purified by density centrifugation and negative selection using AutoMACS were stimulated with eotaxin. In an effort to identify biomarkers that correlate with EoE disease activity, previously identified eosinophil surface proteins associated with activation or allergic diseases were selected for analysis by flow cytometry. This pilot experiment was designed to concurrently examine biomarkers including: alphaL, alphaM, beta1, and beta2 integrins, activated beta1 integrin (monitored by mAb N29), CCR3, CD40, CD44, CD66b, CRTH2, and P-selectin glycoprotein ligand-1 (PSGL-1) on eosinophils, as well as alphaL, alphaM, beta1, and beta2 integrins, activated beta1 integrin (monitored by mAb N29), CCR3, CD40, CD44, CD66b, CRTH2, and P-selectin glycoprotein ligand-1 (PSGL-1) on eosinophils, as well as alphaL, alphaM, beta1, and beta2 integrins, activated beta1 integrin (monitored by mAb N29), CCR3, CD40, CD44, CD66b, CRTH2, and P-selectin glycoprotein ligand-1 (PSGL-1) on eosinophils.

RESULTS: Eotaxin stimulation of purified eosinophils upregulated surface protein expression of beta2, alphaM and alphaL integrins, and CD66b, while downregulating CRTH2, CCR3, and N29 signals. No major changes in the expression of the other biomarkers were observed. Eotaxin stimulation of eosinophils results in the upregulation or downregulation of several surface biomarkers. We expect that the modulation of the surface expression of these biomarkers will be observed and will correspond to changes in eosinophilic esophagitis disease activity.

161 Effectiveness of Elimination Diets in Treating Eosinophilic Gastroenteritis

Miiori Sato, MD, Akio Yoshida, MD, Motoko Mitsui, MD, Miyuki Ohta, MD, Yumiko Miyaji, MD, PhD, Shinichiro Inagaki, MD, PhD, Tatsuki Fukute, MD, PhD, Masami Narita, MD, PhD, Katsuhiko Arai, MD, PhD, Kenji Matsutomo, MD, PhD, Yukihito Ohya, MD, PhD, and Ichiro Nomura, MD, PhD. National Center for Child Health and Development, Tokyo, Japan.

RATIONALE: Elimination diets have been shown to be effective for eosinophilic esophagitis (EoE), but not for eosinophilic gastroenteritis (EGE). The aim of this study was to explore the effectiveness of dietary therapy by identifying the causative foods in EGE.

METHODS: This is a case series study of 12 EGE patients (7 girls), all of whom were age 6 years or over when diagnosed with EGE by GI histology, from April 2007 to August 2016, in our hospital. The patients’ characteristics were extracted from the electronic data in the medical records. Food elimination and later reintroduction (2-3 weeks’ daily ingestion of a food) were performed for 10 patients to identify the offending foods.

RESULTS: The median age at diagnosis was 11 years, and 11 patients had a history of allergic diseases. Histologically, 5 patients were diagnosed with eosinophilic gastritis, 4 with eosinophilic colitis, and 3 with eosinophil infiltration in the entire GI tracts. Dietary elimination therapy (n = 10) was effective for 9 (90%), who entered remission. One patient (10%) responded well to avoidance of pollen, but not to food elimination. Offending foods were identified as pork (43%), beef (29%), shrimp (29%), rice (29%) and others. In positive challenge tests, blood eosinophils (P = 0.02) and CCL17 (P = 0.04) were markedly increased in 75% of tests. None of the 10 patients we followed needed long-term administration of steroids.

CONCLUSIONS: An appropriate elimination diet can lead to remission of EGE, without use of oral steroids.

162 Resolution of Protein-Losing Enteropathy (PLE) Secondary to Eosinophilic Gastrointestinal Disease (EGID) with Targeted Food Elimination Diet in a Toddler

Hannah Duffey, MD1; Jacob Robson, MD2; and Rafael Firszt, MD3; 1University of Utah, Department of Pediatrics, Division of Allergy and Immunology, Salt Lake City, UT, 2University of Utah Department of Pediatrics, Division of Gastroenterology, Salt Lake City, UT.

RATIONALE: Eosinophilic gastrointestinal diseases (EGIDs) are inflammatory disorders distinguished by eosinophilic infiltration of the stomach, small bowel and colon. Protein-losing enteropathy (PLE) from EGID is uncommon but reported. Treatments range from food elimination diets to immunosuppression; however, in the few cases reported, patients required either a significantly restricted diet or steroids for resolution of symptoms. We present a toddler with severe PLE and gastrointestinal blood loss from EGID, whose symptoms resolved and laboratory findings improved after food elimination diet alone.

METHODS: Skin prick testing was positive for cow’s milk, egg and wheat. Accordingly, a targeted food elimination diet was pursued, and serial exams and lab testing were performed.

RESULTS: A 29-month-old female with alpha-thalassemia minor presented with over one year of edema and severe anemia requiring multiple admissions and transfusions. Endoscopy and colonoscopy with biopsies were significant for marked eosinophilia in her stomach, small and large intestines. Her labs were remarkable for peripheral eosinophilia, hypoalbuminemia, anemia, positive fecal hemoccult, and elevated stool alpha-1 antitrypsin and fecal calprotectin at 1180mcg/g. Within 2 months of therapy with elimination diet, her edema, anemia, and peripheral eosinophilia resolved. Additionally, her fecal calprotectin markedly decreased.

CONCLUSIONS: To our knowledge this is the first report of a toddler with PLE secondary to EGID who was successfully treated with a targeted elimination diet based on skin prick testing. Further, we document that fecal calprotectin, a marker of neutrophilic inflammation, can be elevated in patients with EGID with blood and protein gastrointestinal losses, and corrects with treatment.
Tolerance of baked-milk in milk-triggered children with eosinophilic esophagitis (EoE)

Megan Patterson, MD1, Sarah Beckwith, BS2, Malik Rettiganti, PhD3, Chunqiao Luo, MS4, Peggy Chandler, APRN5, Rebecca Levy, MD6, Helen Casteel, MD7, Maryelle Vonlanthen, MD5, Stephen Fiedorek, MD8, Amy M. Scurlock, MD7, Stacie M. Jones1, and Robbie Pesek, MD9; 1Division of Allergy/Immunology, Department of Pediatrics, University of Arkansas for Medical Sciences and Arkansas Children’s Hospital, Little Rock, AR, 2Division of Allergy/Immunology, Department of Pediatrics, University of Arkansas for Medical Sciences and Arkansas Children’s Hospital, Little Rock, AR, 3Division of Biostatistics, Department of Pediatrics, University of Arkansas for Medical Sciences and Arkansas Children’s Hospital, Little Rock, AR, 4Division of Biostatistics, Department of Pediatrics, University of Arkansas for Medical Sciences and Arkansas Children’s Hospital, Little Rock, AR, 5Department of Pathology, University of Arkansas for Medical Sciences and Arkansas Children’s Hospital, Little Rock, AR, 6Pediatric Gastroenterology Associates, Little Rock, AR, 7The Pediatric Clinic, North Little Rock, AR, 8Department of Pediatrics, University of Arkansas for Medical Sciences and Arkansas Children’s Hospital, Little Rock, AR.

RATIONALE: Foods are the most common trigger in children with EoE. Elimination of the culprit food leads to resolution of clinical symptoms and eosinophilic inflammation in the majority of individuals. However, elimination diets can be difficult to implement and may be associated with decreased quality of life. The authors sought to determine the tolerability of baked milk in children with EoE triggered by cow’s milk.

METHODS: Subjects 2-18 years of age with peak eosphageal eosinophil count > 15 eos/hpf after 8 weeks of PPI treatment were enrolled in a prospective database. Disease management was chosen based upon provider/subject preference. Subjects that were placed on a milk-elimination diet for 10-12 weeks were considered responders if the peak eosphageal eosinophil count decreased to < 15 eos/hpf on follow-up endoscopy. In milk-responders, baked milk was introduced into the diet for at least 10-12 weeks before repeat endoscopy was performed with evaluation of change in peak eosinophil count. Milk sensitization was analyzed in each subject by skin/serum IgE testing.

RESULTS: A total of 188 subjects were evaluated. Forty-seven subjects were placed on a milk elimination diet; 20 subjects were responders and subsequently added baked milk into their diet. Seven subjects (35%) showed no increase in symptoms or eosphageal eosinophils on follow-up endoscopy, indicating baked milk tolerance. There were no significant differences in milk sensitization in those that tolerated baked milk versus those that were non-tolerant.

CONCLUSIONS: Introduction of baked milk should be considered in subjects with milk-triggered EoE. Larger, controlled studies are needed.
Development of IgE-mediated Immediate Hypersensitivity to a Previously Tolerated Food Following its Avoidance for Eosinophilic Gastrointestinal Diseases (EGID): a Case Series

Hsi-en Ho, MD, and Mirna Chehade, MD, MPH; 1Icahn School of Medicine at Mount Sinai, New York, NY. 2Mount Sinai Center for Eosinophilic Disorders, Icahn School of Medicine at Mount Sinai, New York, NY.

Rationale: There is a rare risk of increasing degree of IgE-mediated sensitization to a previously tolerated food following its avoidance. The existence of this phenomenon in EGID is not well established.

Methods: Longitudinal follow-up of EGID patients between 2007-2016 was performed. Clinical history, skin prick testing, and food-specific IgE were reviewed.

Results: We report two children with eosinophilic esophagitis and one with eosinophilic gastritis who were diagnosed at a mean age of 6.9 (range 1.7-12.5) years. All patients were regularly consuming cow’s milk (CM) and had negative skin prick testing to CM (0 mm wheal size). Empiric dietary elimination therapy, including strict CM avoidance, was instituted with induction of clinical and histological disease remission. At mean 22.4 (range 15.9-33.4) months after CM elimination, all patients developed evidence of IgE-mediated hypersensitivity to CM. Repeat CM skin prick testing showed mean wheal size of 10.7 (range 7-14) mm. Pre- and post-therapy CM-IgE (kIU/L) were undetectable and 1.79 in patient 1, 4.11 and 13.30 in patient 2, respectively. Patient 3 had post-therapy CM-IgE of 9.48 kIU/L and demonstrated clinical immediate hypersensitivity (urticaria, facial edema) after accidental ingestion of CM.

Conclusions: We believe this is the first reported series of de novo IgE-mediated immediate hypersensitivity or increasing IgE sensitization to a previously tolerated food, following dietary elimination therapy in children with EGID. Its prevalence and underlying pathogenesis in relation to EGID warrant further investigation, as it may have significant implications on management decisions.

Clinical characteristics of chronic FPIES in infants

Albana Harizaj, Research assistant1, Fallon Schultz, MSW, LCSW, CAM2, and Anna H. Nowak-Wegrzyn, MD, PhD, FAAAAI3; 1Icahn School of Medicine at Mount Sinai, New York, New York, 2International FPIES Association (I-FPIES), Point Pleasant, New Jersey, 3Icahn School of Medicine at Mount Sinai, New York, NY.

Rationale: FPIES is a non-IgE-mediated food allergic disorder with usual onset in infancy that may manifest as acute or chronic symptoms. Chronic-FPIES is not well characterized. We sought to describe the phenotype of chronic-FPIES and compare it to acute-FPIES.

Methods: Caregivers of children with FPIES were surveyed using an anonymous Qualtrics survey on www.fpies.org. Results were analyzed using t-Test, Excel Data Analysis Package.

Results: Among 151 completed surveys, parents reported 47.7% acute-FPIES, 44.4% both acute and chronic-FPIES, 7.9% chronic-FPIES. Diagnosis of FPIES was confirmed by a physician in 78% of the cases. Milk was the most common trigger for chronic-FPIES 58.3%, followed by soy 50%, rice 33.3%, and oat 16.7%. Milk was the most common trigger for acute-FPIES 52.7%, followed by oat 44.4%, milk 37.5%, and soy 13.8%. Symptoms during breastfeeding were reported in 66.7% chronic-FPIES and 40.3% acute-FPIES. Most common symptoms during breastfeeding in patients with chronic-FPIES were: gastroesophageal reflux 66.7%, diarrhea 58.3%, poor weight gain 41.6%, and vomiting 33.3%. Most common symptoms during breastfeeding in patients with acute-FPIES were: gastroesophageal reflux 26.4%, diarrhea 16.7%, vomiting 15.3%, and poor weight gain 12.5%. Anti-reflux medications were prescribed in the first year of life for 50% children with chronic-FPIES and 34.7% with acute-FPIES.

Conclusions: Parents reported various chronic symptoms in the majority of infants with FPIES. Symptoms during breastfeeding were reported more often than previously appreciated, especially in chronic-FPIES. These parental reports warrant further investigation.
Stool Edn Levels in Different Clusters of Non-IgE-Mediated Gastrointestinal Food Allergy

Kanami Orihara, PhD1,2, Ichiro Nomura, MD, PhD2, Tetsuo Shoda, MD, PhD3, Hiroko Suzuki, MD, PhD3, Hideaki Morita, MD, PhD3, Akio Matsuda, PhD2, Hirohisa Saito, MD, PhD1, and Kenji Matsumoto, MD, PhD2, 1Waseda Institute for Advanced Study, Waseda University, Tokyo, Japan, 2Department of Allergy and Clinical Immunology, National Research Institute for Child Health and Development, Tokyo, Japan, 3Department of Allergy and Immunology, National Research Institute for Child Health and Development, Tokyo, Japan.

RATIONALE: Because of its non-specific symptoms and lack of useful biomarkers, non-IgE-mediated gastrointestinal food allergy (GI allergy) is not easily diagnosed. Recent studies showed that stool eosinophil-derived neurotoxin (EDN) levels are higher in young children with food protein-induced enterocolitis syndrome (FPIES), one phenotype of GI allergy. In the present study, we investigated whether stool EDN is also useful for diagnosing other types of GI allergy.

METHODS: The study subjects were 65 GI allergy patients (age 1 day to 1.5 years) and 99 non-allergic controls (age 7 days to 30 days). We divided the GI allergy patients into 4 clusters according to the presence/absence of vomiting and bloody stool, as we reported previously (Cluster 1 (vomiting and bloody stool), 12; Cluster 2 (vomiting but no bloody stool), 18; Cluster 3 (no vomiting or bloody stool), 15; Cluster 4 (No vomiting but bloody stool), 20). Stool EDN levels were measured with an ELISA kit.

RESULTS: Compared with the non-allergic controls, stool EDN levels were significantly higher in patients in Cluster 1 and Cluster 4, followed by those in Cluster 2. ROC curve analysis revealed that AUC \( \geq 0.8 \) in these 3 clusters. However, stool EDN levels in Cluster 3 were similar to that in the controls.

CONCLUSIONS: Measurement of stool EDN levels may help us diagnose patients with GI allergy, except for the type with no vomiting or bloody stool (Cluster 3).

Increase in FPIES Cases Seen in an Upstate New York University-Based Allergy Practice

Kiranjit K. Khalsa, MD, MPH1, Daniel Rosloff, MD, Britta Sundquist, MD1, Karsi M. Jarvinen-Seppo, MD, PhD, FAAPA1, and Muhammad A. Pasha, MD, FAAPA1; 1Albany Medical College, Albany, NY, 2University of Rochester School of Medicine and Dentistry, Rochester, NY.

RATIONALE: Food Protein-Induced Enterocolitis Syndrome (FPIES), is a non-IgE mediated allergy affecting the gastrointestinal tract, resulting in vomiting, diarrhea and dehydration. Previously considered a rare disorder, FPIES incidence and number of rare triggers appear to be increasing. METHODS: This study is a retrospective case series of fifteen patients, allocated by diagnosis code, with FPIES. Patients were gathered from 2009-2016 at a University-based Allergy & Immunology practice in Upstate New York.

RESULTS: Fifteen patients, eight boys and seven girls (mean age at diagnosis: 8.8 months) diagnosed with acute FPIES were included in this study. There were no cases found between 2009-2013. The first case was diagnosed in 2013. Since then cases increased every year. Symptoms reported by parents included non-bilious vomiting (80%), lethargy (66.7%), skin color changes (20%), diarrhea (20%), bilious vomiting (13.3%) and poor tone (13.3%). The mean onset of symptoms occurred 2.3 hours after ingestion. Foods triggering symptoms included rice (7), oats (5), milk (4) and egg, sweet potato, banana, apple, pear, squash, mango, and avocado (1 each). Thirteen patients had negative allergy skin testing. Patient with FPIES to egg had a negative challenge, whereas two with milk triggered had positive follow-up oral challenges.

CONCLUSIONS: Our study indicates an increasing prevalence of FPIES (especially solid food FPIES) in Upstate New York, with uncommon food triggers emerging, such as avocado and mango. It is not clear whether this is due to increase prevalence or awareness. Regardless, heightened recognition of FPIES among clinicians is crucial in order to promptly initiate management and improve patient care.

Clinical Characteristics of Adults Presenting with Non-IgE Mediated

Jennifer Du, and Peter Vadas, MD; PhD; St Michael’s Hospital, Toronto, ON, Canada.

RATIONALE: Several recent studies have described adult patients with non-IgE mediated symptoms triggered by foods. Symptoms are typically gastrointestinal, including vomiting, abdominal pain and diarrhea. Herein, we describe a cohort of 49 adults with non-IgE mediated, gastrointestinal symptoms to specific foods.

METHODS: A retrospective chart review was undertaken of patients seen in an academic allergy practice from 2008-2015. Demographic and clinical information was extracted from electronic records of eligible patients. The results were compared to the phenotypes reported in previous studies.

RESULTS: Forty-nine patients were identified 88% of whom were female. The median age of onset was 34 years (mean 36.9; range: 14 to 71) with a median delay of 2 years from the onset of symptoms to assessment. The median time from ingestion to symptom onset was 1.5 hours (mean 2.62 hours; range: 15 minutes to 7 hours). Duration of symptoms lasted a median of 3 hours (mean 12.63 hours; range: 40 minutes to 120 hours). The most common gastrointestinal symptoms reported were abdominal pain (41/49; 84%), diarrhea (31/49; 63%) and vomiting (22/49; 45%). The most common symptom-inducing foods were seafood (reported in 43% of patients) followed by dairy products and wheat (each reported in 20% of patients) and egg (reported in 16% of patients). Allergy skin tests and ImmunoCAP tests for food-specific IgE were negative in all patients.

CONCLUSIONS: Non-IgE mediated abdominal pain, vomiting and diarrhea are most commonly triggered by a small number of foods. Treatment is avoidance of the specific foods and reassurance that these patients are not at risk for anaphylaxis.

Avocado-Induced Food Protein-Induced Enterocolitis Syndrome (FPIES): Case Series of a Previously Unreported Trigger

Sheeba Kunnel, MD1,2, Kathryn Neupert, MD1,2, and Pooja Varshney, MD1,2; UT at Austin Dell Medical School, Pediatric Residency Program, Austin, TX. 2Dell Children’s Medical Center of Central Texas, Austin, TX.

RATIONALE: Acute FPIES is an increasingly recognized non-IgE mediated gastrointestinal food hypersensitivity characterized by profuse vomiting and diarrhea leading to dehydration and lethargy. Food specific serum IgE and skin prick tests (SPT) are often negative, potentially making diagnosis a challenge. Common triggers are milk, soy, grains, poultry, and legumes. Avocado has not been previously reported as a trigger of solid-food FPIES.

METHODS: Retrospective chart review of 5 patients with clinically diagnosed FPIES at a children’s hospital-based Allergy/Immunology outpatient clinic in Austin, TX.

RESULTS: Five patients (A-E) with avocado-induced FPIES were identified. All had repetitive vomiting and dehydration following avocado ingestion between the ages of 5 to 9 months. Four had previously been diagnosed with FPIES to common triggers such as milk, oat, and rice. Patients A, B, D, and E had negative SPT to avocado; Patient C had a weakly positive SPT. Patient A had a positive avocado serum IgE. All patients were managed with avocado avoidance with resolution of symptoms. Patient B passed an oral food challenge (OFC) to avocado at 24 months of age. Patients A, C, D, and E await future OFC’s.

CONCLUSIONS: To our knowledge, avocado-induced FPIES has never been reported in the literature. Geography and prevalence of avocado in the diet of our population may explain our observations. Infants with solid-food FPIES may react to multiple triggers, making it prudent for providers to consider less-recognized foods as triggers of FPIES to avoid delayed diagnoses.
173 Adherence to Asthma Guidelines at a Tertiary Center

Lori P. Banka, DO1,2, Sophia Giang3, Cindy Xi, MD1, Salima A. Thobani, MD3, Lyne G. Scott, MD, FA-AAAI2, Marilyn Li, MD, FA-AAAI4, and Kenny Kwong, MD2, 1LAC-USC Medical Center, Los Angeles, CA, 2LAC-USC Medical Center, Los Angeles, CA, 3Keck School of Medicine, Los Angeles, 4University of Southern California, Los Angeles, 5University of Southern California, Los Angeles, CA, 6LAC-USC Medical Center, Los Angeles.

RATIONALE: Asthma related hospitalizations remain the single most common reason for admissions among children despite the availability and dissemination of guidelines for diagnosis and treatment of asthma. The objective of this study is to evaluate patients admitted to a pediatric tertiary care center for asthma exacerbation who received care according to the National Heart Lung and Blood Institute Expert Panel Review 3 (NHLBI-EPR 3) asthma guidelines after hospitalization.

METHODS: Retrospective analysis of 108 pediatric patients who were hospitalized at LAC-USC Medical Center (LUMC) for asthma exacerbations during a two year period from May 1, 2013 to May 1, 2015. Inclusion criteria comprised of patients with a primary diagnosis of asthma, admission to LUMC and ages 3-21. Patients outside this age, with a co-diagnosis of bronchitis, congenital heart disease, cystic fibrosis, renal disease and immunodeficiency were excluded from the study. 102 patients met these criteria.

RESULTS: 85.3 % (87/102) of patients received appropriate guideline based care and 26.5% (27/102) of these patients were seen by an asthma specialist. Guideline based care was defined as patients who received the appropriate dose and controller medications 85.3% (87/102), asthma education 86% (88/102), asthma action plan 87.3% (89/102) and follow up appointment 86.2% (88/102).

CONCLUSIONS: Results demonstrated significant adherence to asthma guidelines in treatment of asthmatic children at LUMC. Possible factors contributing to adherence to guidelines include, allergy specialists attending on pediatric wards, allergy consultants and house-staff allergy rotations. Understanding and applying the factors that contributed to provider success may overall increase provider adherence to guidelines at other institutions.

174 Does Carrying a Rescue Inhaler Correlate With Better Asthma Control?

Sima J. Patel, DO1, Shreya N. Patel, MD2, Chandler Sy1, Mark C. Siracusa1, and Alan H. Wolff, MD3,4, 1Rutgers New Jersey Medical School, Newark, NJ, 2Rutgers-New Jersey Medical School, Newark, NJ, 3Rutgers New Jersey Medical Center, Newark, NJ, 4Medical Service (111) Department of Veteran’s Affairs, East Orange, NJ.

RATIONALE: We wanted to evaluate the adherence of inner-city asthmatics in our Allergy clinic. We hypothesized that carrying a rescue inhaler may be a measure of adherence and studied if it correlated with higher asthma control test (ACT) scores.

METHODS: After obtaining IRB approval, 20 asthmatics between 18-50 years old were recruited. We determined if they were carrying their rescue inhaler to the visit and if they used it correctly. An ACT score was calculated for each patient. The data was analyzed using an unpaired 2-tailed t-test.

RESULTS: There was no significant difference in ACT scores between patients who brought their inhalers and those that did not bring their inhalers to their visit (p=0.67). Further all subjects except one, who did not have their rescue inhaler, demonstrated proper inhaler technique.

CONCLUSIONS: Our study did not show any correlation between carrying a rescue inhaler and ACT scores. This suggests carrying a rescue inhaler is not a measure of adherence. The lack of correlation was not due to poor inhaler technique. This study is limited by the small sample size and only obtaining the data on a single visit. Studying a larger group for a longer time period may result in a different finding.

175 Value Stream Analysis of an Allergy Clinic in an Urban Academic Medical Center

Maggie M. Barnthouse, MD1, Jennifer M. Bjelich, MHA, FACHE, SSGBB, Minalini Gakdari, MD, MHSA1, and Mamta Reddy, MD, MBOE2, 1Children’s Mercy Hospital/UMKC, Kansas City, MO, 2Children’s Mercy Hospital, Kansas City, MO, 3Ohio State University/Fisher College of Business, Columbus, OH.

RATIONALE: A Value Stream Map (VSM) reflects workflow as the patient experiences it, from referral until bill. The purpose was to create a process map and apply “lean math” to identify waste, improve flow, and optimize value to patients, our customers.

METHODS: A clinical and administrative team was convened. Training was conducted on Shingo’s “Seven Forms of Waste.” A time study delineated “value added” (VA) and “non-value added” (NVA) tasks and minutes spent in and between each step. The process was mapped; takt time (“cadence”) was calculated (total time divided by demand); and a time-ladder captured waiting, NVA, VA and total lead times. Line balance charts and “opportunity bursts” were analyzed to propose countermeasures and a future state map. The Office of Research Integrity designated this as NHS research.

RESULTS: System takt time was 20 minutes per patient. Process time was reflected as VA (42 minutes) and NVA (49 minutes) time. Total waiting time was 49 minutes. Total lead time for current state visit was 91 minutes, with 46% of overall visit being VA. After analyzing line balance charts and “opportunity bursts,” the future state map revealed the potential to reduce overall wait time to 5 minutes and decrease total lead time to 45 minutes, which increased overall VA time for the future state visit to 88%.

CONCLUSIONS: The workforce is the greatest reservoir of expertise in improving the efficiency of the local system. The VSM activity engages the team in eliminating waste, thereby optimizing value for the patient.

176 Rate of follow-up with allergy/immunology and maintenance of active epinephrine prescriptions in patients with anaphylaxis to venom

Christine Muglia1, Alan H. Wolff, MD2, and Mark E. Weinstein, MD1, 1Rutgers New Jersey Medical School, Newark, NJ, 2Medical Service (111) Department of Veteran’s Affairs, East Orange, NJ, 3Hudson-Essex Allergy, LLC, Belleville, NJ.

RATIONALE: Since insect stings occur randomly, venom allergy may not be an active issue addressed regularly during routine office visits. We studied veterans with anaphylaxis to venom to evaluate their rate of follow-up with the Allergy/Immunology Service and assess our ability to maintain current epinephrine prescriptions.

METHODS: A retrospective study of veterans with venom anaphylaxis diagnosed by Allergy/Immunology was performed. We recorded the presence of current epinephrine prescription, prescribing service, date of last follow up with Allergy/Immunology, and whether they had subsequent visits with other services at the VA after their loss to follow up with Allergy/Immunology.

RESULTS: Thirty one patients with a documented venom allergy in our medical records had anaphylaxis diagnosed by Allergy/Immunology. Of these 31 patients, 23 continue to receive medical care in our VA. Surprisingly, 83%(19/23) of the active patients no longer follow with Allergy/Immunology Service and only 35% (8/23) have current prescriptions on file. Primary care physicians filled 63% (5/8) of the epinephrine prescriptions.

CONCLUSIONS: Very few patients with venom anaphylaxis follow-up with Allergy/Immunology and have current epinephrine prescriptions. The majority of patients with current epinephrine prescriptions no longer follow with Allergy/Immunology, however receive their prescriptions from their primary care provider. Patients with venom anaphylaxis are possibly lost to follow-up because insect stings occur rarely and patients forget about the allergy. Patients may also be unaware that epinephrine expires. We feel it should be stressed to each patient that their epinephrine prescriptions need to remain active/unexpired and that it can be re-filled by any physician.
AB56 Abstracts

FEBRUARY 2017

177 Many Children Referred to a Tertiary Care Pediatric Allergy Clinic Do Not Have an Allergy

Victoria E. Cook, MD1, Jordan Yeo1, Christopher Mill, MSc1, Kyla Hildebrand, MD2, Elodie Portales-Casamar, PhD3, and Edmond S. Chan, MD, FAAAAI1. Division of Allergy & Immunology, Department of Pediatrics, Faculty of Medicine, University of British Columbia, BC Children’s Hospital, Vancouver, BC, Canada, 2Division of Allergy & Immunology, Department of Pediatrics, Faculty of Medicine, University of British Columbia, BC Children’s Hospital, Vancouver, British Columbia, Vancouver, BC, Canada.

RATIONALE: The prevalence of allergic disease is increasing, and wait times for allergy consultation are concerning. Existing reports of referral patterns focus primarily on adults, and do not report final diagnoses. This is the first study comparing reasons for referral with final diagnoses from a pediatric allergy clinic.

METHODS: Among 1075 new referrals made to BC Children’s Hospital Allergy Clinic in 2014, 500 were randomly selected. Data on demographics, referring physician, reason for referral, symptoms, and final diagnosis were recorded. Descriptive statistics were used to characterize reasons for referral and final diagnoses.

RESULTS: Among 401 referrals reviewed to date, 60% were from general practitioners. Median age was 4 years (Interquartile Range, IQR =6); 41% were female. Most had a single reason for referral (59%). Reasons for referral included food allergy (48%), allergic rhinoconjunctivitis (22%), urticaria (14%), eczema (13%), asthma (11%), family history (7%), parent request (7%), and drug allergy (7%). Nearly half (45%) of referred patients did not receive a diagnosis of allergy. Among patients diagnosed with allergy (219/401), 33% received multiple diagnoses. The most common final diagnoses were food allergy (53%), allergic rhinoconjunctivitis (40%), atopic dermatitis (14%), and asthma (11%). Of 194 patients referred for possible food allergy, 109 (56%) were diagnosed with food allergy by the consultant allergist.

CONCLUSIONS: We report a higher proportion of referrals for food allergy (48%) than described previously. About half of referred patients were diagnosed with allergy, suggesting many may not have required referral. Greater efforts to educate parents and referring physicians about when to truly suspect allergy and the pitfalls of over-testing are warranted.

178 Improved Management For Children With Asthma And Anaphylaxis Via A Web-based Quality Improvement Project

Irum Noor, DO1, Randy Alevi, DO1, Jennifer Theriot, MD1, Ratika Gupta, MD1, Mark A. Davis-Lorton, MD, FAAAAI2, Marcella Aquino, MD2, Luz S. Fonacier, MD, FAAAAI2, David R. Stukus, MD, FAAAAI2, and Ruth Gubernick, MPH1. 1Winthrop University Hospital, Mineola, NY, 2Winthrop University Hospital, Mineola, NY, 3Winthrop University Hospital, Allergy & Immunology, Mineola, NY, Nationwide Children’s Hospital, Columbus, OH, 4AAP-NJ Chapter, Hamilton, NJ.

RATIONALE: Studies demonstrate a gap in implementation of evidence based asthma and anaphylaxis care despite significant morbidity. A web-based quality improvement (QI) project was utilized to enhance care for patients with asthma and anaphylaxis.

METHODS: A prospective QI study, part of the Medical Home Chapter Champions Program on Asthma, Allergy, and Anaphylaxis, was performed at our pediatric (peds) and allergy/immunology (A/I) offices from January-July 2016 using a web-based learning initiative. Monthly measures included asthma action plans (AsAP), inhaler technique (InT), spirometry, appropriate epinephrine prescription (EPI), allergy/anaphylaxis action plans (AnAP), self-injectable epinephrine technique (EPI-T), and patient engagement (PE). Our interventions involved educational webinars, physician lectures, and updates in the electronic medical record.

RESULTS: All measures demonstrated improvement with 142 patients in the peds office and 50 patients in the A/I office. AsAP improved from 4.2% to 8.3% in peds and 0% to 100% in A/I. InT from 29.2% to 50% in peds and 66.7% to 100% in A/I, and spirometry from 5.6% to 16.7% in peds and 33.3% to 100% in A/I. Appropriate EPI improved from 77.8% to 84% in peds and stayed at 100% in A/I. AnAP rose from 0% to 4% in peds and 14.3% to 100% in A/I, and self-injectable EPI-T rose from 16.7% to 76% in peds and 85.7% to 100% in A/I. PE improved from 11.9% to 59.5% in peds and 7.7% to 100% in A/I.

CONCLUSIONS: Pediatricians and allergists working with a web-based educational program can improve quality of care for patients with asthma and anaphylaxis and identify specific areas for improvement.

179 Allergic diseases affect the subjective sense of well-being in Korean Adolescents

Kyung Suk Lee, MD1, Sun Hee Choi, MD, PhD2, Hye Mi Jee, MD3, and Yeong-Ho Rha, MD, PhD3. 1Department of Pediatrics, CHA University Bundang Medical Center, Seongnam, South Korea, 2Kyung Hee University Hospital at Gangdong, Seoul, South Korea, 3CHA University Bundang Medical Center, Seongnam, Korea, The Republic of. “Kyung Hee University Hospital, Seoul, South Korea.

RATIONALE: Allergic diseases affect school activities, mood and life of quality in adolescents. We aimed to evaluate the relationship between allergic diseases and subjective sense of well-being in Korean adolescents.

METHODS: In this study, 68,043 Korean adolescents aged 12 to 18 years who participated in the 2015 Korea Youth Risk Behavior Web-Based Survey (KYRBWS, 2015) were used as sample. Multivariate regression analysis was performed to find relationship between allergic diseases and subjective sense of well-being. In addition, we also analyzed the relationship between allergic diseases and recognition of the subjective status of health.

RESULTS: The prevalence of asthma (BA), allergic rhinitis (AR) and atopic dermatitis (AD) were 8.8%, 33.2% and 24.2% in Korean adolescents, respectively. After adjusting, subjective sense of well-being was associated with allergic diseases (BA: adjusted odd ratio (aOR) 1.519, p = 0.001; AR: aOR 1.407, p = 0.000; and AD: aOR 1.292, p = 0.004). Worst recognition of the subjective status of health was also revealed as a risk factor of allergic diseases (BA: aOR 1.922, p = 0.002; AR: aOR 1.832, p = 0.000; and AD: aOR 1.714, p = 0.000) compared with excellent recognition of the subjective status of health.

CONCLUSIONS: We found that allergic diseases could affect subjective sense of well-being, and recognition of the subjective status of health in Korean adolescents from this study. These provide evidence that control of allergic diseases is important for improving the quality of life of Korean adolescents.
180 Determinants of Quality of Life (QoL) Among Children Undergoing Oral Food Challenge (OFC) in Canada

Lianne Soller, PhD1, Christopher Mill, MSc2, Tiffany Wong, MD1, Ingrid Buerg1, Tracy Gonzalez3, Timothy Teoh1, Kyla Hildebrand, MD2, and Edmond S. Chan, MD, FAAAAI3; 1BC Children’s Hospital, Vancouver, BC, Canada, 2Division of Allergy & Immunology, Department of Pediatrics, Faculty of Medicine, University of British Columbia, BC Children’s Hospital, Vancouver, BC, Canada, 3Division of Allergy & Immunology, Department of Pediatrics, Faculty of Medicine, University of British Columbia, BC Children’s Hospital, Vancouver, British Columbia, Vancouver, BC, Canada.

RATIONALE: To describe QoL of children undergoing OFC in Canada and explore association between QoL, demographic/clinical characteristics, and parental confidence in recognizing anaphylaxis and using an autoinjector.

METHODS: The FAQLQ-PF (higher score=poorer QoL; range=0-6) was used to calculate QOL among children (n=166) undergoing OFC at the BC Children’s Hospital Allergy clinic between Jan’14 and Oct’15. Linear regression was used to assess the relationship between QoL, demographic/clinical characteristics, and several confidence domains.

RESULTS: Mean QOL score was 1.95 (95%CI: 1.71, 2.17) overall. Linear regression showed no significant difference between HC and WC children, but higher (p<0.002) and PsS (p=0.009) for tree nut allergy, likely due to egg being harder to avoid. We found no association between QOL and several confidence domains, suggesting confidence with recognizing anaphylaxis and using an autoinjector may be more worry about risks. Tree nut allergy resulted in better QOL than egg allergy, likely due to egg being harder to avoid. We found no association between QOL and several confidence domains, suggesting confidence with recognizing anaphylaxis and using an autoinjector is insufficient for improving QOL.

CONCLUSIONS: Health professionals are likely more aware of risks of food allergy, negatively affecting their child’s QOL. Similarly, older children, those who’ve experienced severe reactions, and those who’ve used an autoinjector may be more worried about risks. Tree nut allergy resulted in better QOL than egg allergy, likely due to egg being harder to avoid. We found no association between QOL and several confidence domains, suggesting confidence with recognizing anaphylaxis and using an autoinjector is insufficient for improving QOL.

181 Impact of Asthma Control on Health Related Quality Of Life of Affected Children and their Caregivers

Shajitha Melethil, MD, Karen E. Smith, PhD, Vibha S. Acharya, BS, Heidi Spratt, PhD, Sandra Ho, MD, and Randall M. Goldblum, MD; University of Texas Medical Branch, Galveston, TX.

RATIONALE: Asthma is a chronic disease that can negatively affect the health-related quality of life (HRQoL) of children and their primary caregivers. Caregiver mental health and perception of HRQoL burden directly influences asthma control in children. Current studies have not compared the impairment of HRQoL of children and caregivers whose asthma is well-controlled (WC) versus not well-controlled (NWC) to healthy children (HC).

METHODS: Children between 5-17 years of age were stratified into three groups: WC (n=25), NWC (n=6), and HC (n=10). Caregivers completed Child Health Questionnaire Parent Form (CHQPF-28) constituting 14 concepts, combined to derive physical (PhS) and psychosocial (PsS) summary measures of HRQoL in children. They also completed the Pediatric Asthma Caregiver’s Quality of Life Questionnaire (PACQLQ) which evaluates activity limitations and emotional functioning of caregivers.

RESULTS: Non-parametric tests were used for analysis of non-normally distributed data. Kruskal-Wallis test showed significant differences among the groups for PhS (p<0.002) and PsS (p=0.02). Pairwise comparisons showed no significant difference between HC and WC children, but higher psychosocial functioning and fewer physical limitations when compared to NWC. Wilcoxon rank test on PACQLQ indicated that caregivers of children with WC asthma reported superior emotional functioning and fewer activity limitations versus NWC (p=0.015).

CONCLUSIONS: HRQoL is significantly higher in children with WC asthma when compared to NWC, supporting the parental perception that caring for children with WC asthma is similar to caring for HC. This finding adds further impetus for attaining optimal control of asthma in order to improve the well-being of these children and their families.

182 Genome-wide gene-environment interaction study to identify potential genes for respiratory syncytial virus infection in asthmatic children

Ching-Hui Tsai, and Yungling Lee; National Taiwan University, Taipei, Taiwan.

RATIONALE: Respiratory syncytial virus (RSV) is the most common cause of hospitalization and mortality in children, and RSV induced lower respiratory infections increased risks of childhood asthma. In our previous study, children with current RSV infection were found to have increased risks of severe asthma. However, not all children exposed to RSV developed asthmatic symptoms. Host genetic background may contribute factors of causes of severe asthma exacerbations. Therefore, the purpose of this study is to perform gene-RSV interactions to identify genes related to severe asthma exacerbations in children.

METHODS: Taiwanese Consortium of Childhood Asthma Study (TCCAS) is a consortium-based study coordinated by several pediatric study groups in Taiwan. Asthmatic children, diagnosed by pediatric asthma specialists under Global Initiative for Asthma guidelines, were recruited from hospitals and clinics. We examined the whole genome genotyping and expression from peripheral blood mononuclear cells. Current RSV infection status was confirmed by ELISA kits to assess the units of IgM antibodies to RSV.

RESULTS: We used in silico analysis to investigate differentially expressed genes (DEGs) of RSV infection from GEO datasets. In addition, genome-wide SNP-based association study for RSV infection were also examined in TCCAS. Expression quantitative trait loci (eQTL) analysis was applied to investigate the targeted genetic polymorphisms and DEGs. Finally, we performed gene-RSV interaction study to investigate the association between all targeted SNPs and RSV infection on severe asthma exacerbations. We will further validate our genetic targets by genome-wide SNP-based gene-RSV interaction.

CONCLUSIONS: Host genetic polymorphisms would modify the level of RSV-induced asthma exacerbations in children.
Clinical Burden Among Patients With Severe Asthma in a Specialty Care Setting

Brian D. Stone, MD1, Jill R. Davis, MS2, Kathleen M. Fox, PhD3, Bradd Schiffman4, David A. Brown, MD, FAACAP1, and Frank J. Trudo, MD, MBA5.
1Allergy Partners of San Diego, San Diego, CA, 2Astrazeneca, Wilmington, DE, 3Strategic Healthcare Solutions, LLC, Alen, SC, 4Allergy Partners, Asheville, NC, 5Allergy Partners of Western North Carolina, Skyland, NC.

RATIONALE: The study objective was to describe the clinical burden of severe asthma among patients treated in the US community setting to understand unmet needs.

METHODS: This retrospective cohort study utilized electronic health record data from patients aged ≥12 years treated at a large US allergy practice network. Patients with severe asthma (i.e., receiving GINA Step 4 or 5 treatment) between 1/1/2010-4/30/2016 were characterized by lung function (FEV1 and FEV1/FVC % predicted) and symptom control (Asthma Control Test [ACT]) at baseline and 12 and 24 months post-index date.

RESULTS: Of 120,116 asthma patients, 12,922 (10.8%) had severe asthma; mean age was 44.4 years, 67% were female, 78% were White, 77% had blood eosinophilia (≥400 cells/μL), 21% had concomitant rhinitis, 21% had sinusitis, and 44% had allergic sensitivities. Mean FeNO was 36.2 ppb. Eosinophil counts were >200 cells/μL for 41% of patients with recorded eosinophil counts (2.3% of study population). Mean baseline ACT score was 17.0. Among patients with ACT scores at 12 months and 24 months (0.07 and 0.04 liters, respectively). Low (<19) or high (≥24) ACT scores were associated with reduced lung function and symptom control.

CONCLUSIONS: A considerable proportion of patients receiving GINA Step 4 or 5 therapies for severe asthma exhibit eosinophilic airway inflammation and uncontrolled asthma. Additional therapies may be required to reduce the clinical burden for these patients.

Patient Characteristics and Factors Associated with Persistent High Costs in Asthma

Jianbin Mao1, Xiao Xu2, Jeffrey T. McPheeters3, Jill R. Davis, MS2, and Trung N. Tran2.
1Optum, Eden Prairie, MN, 2AstraZeneca, Gaithersburg, MD, 3Strategic Healthcare Solutions, LLC, Wilmington, DE.

RATIONALE: Asthma patients may continue incurring high costs for several years, and primary drivers of these costs are unknown.

METHODS: This retrospective study used claims data from a commercial and Medicare Advantage health plan. Patients aged ≥12 years met Healthcare Effectiveness Data and Information Set persistent asthma criteria for 2 consecutive years during 2007–2012. Index date was January 1 of third year. Only patients with high annual asthma-related costs (≥85th percentile) at baseline (1-year pre-index) were included. Patients were grouped by follow-up asthma-related costs (1-year post-index): persistent high (≥85th percentile) or non-persistent (≥85th percentile).

RESULTS: PH and NP groups had 11,998 (61%) and 7,716 patients respectively. Compared with NP patients, PH patients were significantly older (47.0 vs. 41.3 years), and were more likely to have been on GINA Step 4/5 care (66.2% vs. 51.2%). As evidenced by having received high-dose inhaled corticosteroids (ICS) plus long-term β2 agonists (LABA) (26.3% vs. 19.5%) and ≥2 ICS/LABA canisters (50.6% vs. 33.4%) or long-acting muscarinic antagonists (4.7% vs. 2.4%) at baseline. PH patients were more likely to have had excessive (≥7 canisters) short-acting β2 agonist use, and had ≥25% baseline days with oral corticosteroids but fewer exacerbations at baseline. Logistic-regression analysis confirmed older age, high number of ICS/LABA fills, and high GINA step care were among major differentiators of PH vs NP groups.

CONCLUSIONS: Despite frequent medium- and high-dose ICS/LABA treatment, the majority of patients with high costs continued to incur high asthma-related costs in subsequent years, which calls for better disease management.

The Cost-Effectiveness of a Chlamydia Trachomatis Vaccination Program in Young Women in the United States

Jared Diktowski, MD Candidate, Afsana Rahman, MD Candidate, Margaret Hammerschlag, MD, Stephan Kohlihoff, MD, and Tamar A. Smith-Norowitz, PhD; SUNY Downstate Dept of Pediatrics, Brooklyn, NY.

RATIONALE: C. trachomatis is a major public health concern with >1.4 million cases in the United States (U.S.) reported to the Centers for Disease Control and Prevention in 2012 and >500 million 2013 USD spent in lifetime costs. Current screening programs for the control of this infection may not be affordable; vaccine development may be necessary for controlling infection with C. trachomatis. Thus, we examined the impact of a potential chlamydia vaccination program by creating a decision analysis model to estimate the effect of vaccination on chlamydia-associated costs, morbidity and mortality.

METHODS: We developed a Markov Model (TreeAge Software) which considered a cohort of US women, >9 y, in the population. The morbidity, mortality and health-care costs associated with chlamydial infection of mothers and fetus/neonates was calculated over a 17-year time frame. We developed two major comparison arms: 1) Chlamydial Vaccination Program Scenario 2) No Chlamydial Vaccination Program. Base case analysis vaccine efficacy and coverage were set to those of HPV in the US, with efficacy and coverage, as well as other variables in the model, ranged in sensitivity analyses.

RESULTS: The model estimates a program would cost $661 million for a cohort of 2,009,200 women over a 17-year period, an increase of $39 million over no vaccination program ($622 million). A vaccination program would prevent 31 thousand cases of chlamydia, and avert 21 spontaneous abortions as a result of chlamydial infection.

CONCLUSIONS: A chlamydia vaccination program results in increased cost to the healthcare system, but averts significant chlamydia-associated morbidity and mortality.
**Health Care Resource Utilization and Work Impairment for Asthma Patients Adherent to Medium- or High-Dosage ICS/LABA Fixed Combination Treatment: Findings From a US Real World Survey**

Jill R. Davis, MS¹, Mark Small², Frank J. Trudo, MD, MBA², James Siddall², and James Pike²; ¹AstraZeneca, Wilmington, DE, ²Adelphi Real World, Bollington, United Kingdom.

**RATIONALE:** Uncontrolled asthma can impact healthcare resource utilization and work productivity. Asthma control may not be achieved for all patients adherent to treatment. This study describes the health care and work productivity burden of patients adherent to medium- or high-dosage inhaled corticosteroid/long-acting beta2-agonist (ICS/LABA) treatment.

**METHODS:** Cross-sectional data from 3 US Adelphi asthma surveys, conducted during 2013–2016, were analysed in diagnosed asthma patients, prescribed medium- or high-dose ICS/LABA, and self-reported medium to high treatment adherence (Morisky Medication Adherence Scale). 629 physicians completed patient record forms for 5 asthma patients each, recording health care resource utilization (HCRU) and treatment information. These patients were invited to complete a questionnaire, including the Work Productivity and Activity Impairment (WPAI) questionnaire. Descriptive statistics were reported.

**RESULTS:** 428 patients (mean age 44 years; 62% female; 70% employed) met inclusion criteria. Mean numbers of primary care and specialist visits for asthma in the last 12 months were 1.9 and 3.4, respectively. Mean numbers of asthma exacerbations in the past 12 months was 1.28, of which 15.1% were treated in the ER or through hospitalization. 153/422 patients (36.3%) had ≥2 asthma exacerbations during the last 12 months. Mean percentage overall work impairment due to asthma was 19.6% (n=263).

**CONCLUSIONS:** Despite adherence to medium- or high-dosage ICS/LABA therapy, patients had considerable health care resource utilization and work impairment due to asthma which suggests an unmet need in asthma management.

**Clinical and Economic Burden of Hospitalizations with Registry of Penicillin Allergy**

Bernardo Sousa-Pinto¹², António Fernandes³, Luís Araújo¹, João Almeida Fonseca²³, Alberto Freitas²³, and Luis Delgado, MD, PhD, FAAAAI¹³, ¹Immunology Laboratory, Basic and Clinical Immunology, Faculty of Medicine, University of Porto, Portugal, Porto, Portugal, ²Department of Health Information and Decision Sciences (CIDES), Faculty of Medicine, University of Porto, Porto, Portugal, ³Center for Health Technology and Services Research (CINTESIS), Faculty of Medicine, University of Porto, Porto, Portugal.

**RATIONALE:** Overdiagnosis of penicillin allergy appears to be a public health concern, as previous studies have shown that this diagnosis is associated with an increased risk of infection by multi-resistant agents. Therefore, we aimed to compare hospitalizations with and without registry of penicillin allergy concerning their clinical and economic burden.

**METHODS:** We analyzed a database containing all hospitalizations occurred in Portuguese public hospitals from 2000 to 2014. We identified all episodes with reported penicillin allergy and compared them with an equal number of hospitalizations without such registry regarding patients’ demographic characteristics and comorbidities (assessed by the Charlson comorbidity index), length of stay, estimated hospitalizations costs, and frequency of drug-resistant and Clostridium difficile infections.

**RESULTS:** There were 104,165 hospitalizations with registry of penicillin allergy. Patients’ mean age was similar among episodes with and without reported penicillin allergy. Compared to non-allergy cases, episodes with registry of penicillin allergy were associated with increased mean hospitalizations costs ($3,450.09 versus 3,225.48 US Dollars; p<0.001) and with a higher average Charlson comorbidity index (0.90 versus 0.79; p<0.001). The median length of stay was similar (4 days) among both groups. Hospitalizations with registry of penicillin allergy were associated with a higher frequency of infections by penicillin-resistant agents (0.03% versus 0.01%; p=0.043), methicillin-resistant Staphylococcus aureus (0.32% versus 0.16%; p<0.001) and Clostridium difficile (0.12% versus 0.08%; p=0.010).

**CONCLUSIONS:** A registry of penicillin allergy is associated with higher hospitalizations costs, increased comorbidities and higher frequency of drug-resistant agents. Therefore, performing a correct diagnosis of penicillin allergy is of the highest importance.

**A Cost-Effectiveness Analysis of Probiotic with Peanut Oral Immunotherapy (PPOIT) in Children**

Marcus S. Shaker, MD, MS, FAAAAI; Dartmouth-Hitchcock Medical Center, Lebanon, NH.

**RATIONALE:** PPOIT may decrease accidental systemic reactions and improve quality of life (QOL), but reactions from therapy itself are frequent. The study aimed to characterize the cost-effectiveness of PPOIT when compared with avoidance alone.

**METHODS:** Markov cohort simulations of 2,000 subjects evaluated PPOIT for children with peanut allergy. Long term survival was modeled using age-adjusted mortality and the risk of food allergy fatality. Model assumptions were based on costs of peanut allergy, PPOIT, and treatments for reactions, as well as probabilities of therapeutic response, inadvertent accidental exposures, allergic reactions, fatalities, and QOL improvements.

**RESULTS:** Cost-effectiveness in quality-adjusted life-years (QALY) was dominated by PPOIT. Mean costs were $39,623 (95% CI $39,050 - $40,197) vs $41,685 (95% CI, $41,033 - $42,337) with effectiveness differences of 18.26 QALY (95% CI, 18.17-18.35) vs 17.11 (95% CI, 17.03-17.23), for PPOIT vs avoidance groups. A mean number of 12.3 (95% CI, 12.0-12.5) and 2.0 (95% CI, 1.9-2.1) allergic reactions occurred per subject in the PPOIT and avoidance groups over 20 years of simulation, with 2.3 (95% CI, 2.2-2.3) episodes of anaphylaxis per subject in the PPOIT group and 1.1 (95% CI, 1.0-1.2) episodes in the avoidance group.

**CONCLUSIONS:** In this computer simulation subjects treated with PPOIT actually experienced a greater rate of peanut associated allergic reactions and anaphylaxis; however, associated improvements in QOL may still make this strategy favorable for some patients. This analysis illustrates possible challenges of using OIT in practice because although QOL improves, the number of total and severe reactions may actually increase.
SATURDAY

190 Consistent Efficacy and Safety of 12 SQ House Dust Mite Sublingual Immunotherapy Tablet Among Subgroups with Allergic Rhinoconjunctivitis

Jose A. Bardeles, MD, FAAAAI1, David I. Bernstein, MD, FAAAAI2,3, Harold S. Nelson, MD, FAAAAI4, Joerg R. Kleine-Tebbe, MD, FAAAAI4, Gordon L. Sassman, MD, FAAAAI4, Dorte Seitzberg, PhD5, Dorte Rehm1, Armanjo Kar, PhD5, Ziliang Li, PhD5, Susan Lu, PharmD5, and Hendrik Nolte, MD, PhD5, 1Allergy and Asthma Center of North Carolina, High Point, NC, 2Bernstein Clinical Research Center, LLC, Cincinnati, OH, 3University of Cincinnati College of Medicine, Cincinnati, OH, 4National Jewish Health, Denver, CO, 5Allergy and Asthma Center Westend, Berlin, Germany.

RATIONAL: Efficacy and safety of 12 SQ house dust mite (HDM) sublingual immunotherapy (SLIT)-tablet (MK-8237; Merck/ALK) has been demonstrated in clinical trials. This analysis examined the consistency of efficacy and safety across subgroups of interest in subjects with HDM allergic rhinitis with/without conjunctivitis (ARC).

METHODS: Two double-blinded, multicenter trials (NCT01700192, NCT01454544) were conducted in which subjects (aged ≥12 years) with HDM ARC with or without asthma were randomized to daily 12 SQ-HDM or placebo for up to 52 weeks (N=2,138). Primary endpoint in both trials was average total combined rhinitis score (TCRS; rhinitis daily symptom plus medication score) during the last 8 weeks of treatment. TCRS data were pooled for subgroup analysis based on age, gender, race, baseline asthma status, and allergen sensitization. Safety data were pooled from the four phase 2/3 North American and EU trials that evaluated 12 SQ-HDM safety.

RESULTS: In the two individual trials, treatment with 12 SQ-HDM improved TCRS 17% and 18% vs placebo. Across the subgroups there were consistent trends of significant (based on 95% CIs) numeric superiority with 12 SQ-HDM vs placebo. The lowest observed TCRS improvement was 15% in subjects without asthma, and the greatest improvement was 25% in subjects aged 12-17 years. The AE profile was generally similar within subgroups, although the incidence of drug-related adverse events in the 12 SQ-HDM and placebo-treated groups appeared numerically higher in subjects aged 12-17 years vs 18-49 years.

CONCLUSIONS: The 12 SQ-HDM SLIT-tablet consistently improved symptoms and was well tolerated in relevant subgroups of subjects with HDM ARC.

191 Long-Term Treatment with 300IR 5-Grass Pollen Sublingual Tablet in Grass Pollen Allergic Subjects: Safety Outcome Year after Year

David B. K. Golden, MD, FAAAAI1, John M. Fahrenholz, MD, FAAAAI1, Kevin E. Renahan, MSc1, Sandrine Khairallah, MSc2, and Kathy Abiteboul, PharmD3, 1Medstar Franklin Square Medical Center, Baltimore, MD, 2Vanderbilt University Medical Center, Nashville, TN, 3Stallergenes Greer, Cambridge, MA, 4Stallergenes Greer, Antony, France.

RATIONAL: To investigate the safety outcomes in subjects with grass pollen-induced allergic rhinoconjunctivitis (ARC) receiving 300IR 5-grass pollen sublingual tablet who presented with adverse reactions (ADRs) during the first season of treatment and continued over a second and/or third treatment season.

METHODS: In a double-blind, randomized Phase III study, adults (18-50 years) with medically confirmed grass pollen ARC for at least 2 years received placebo or a 300IR tablet pre-seasonally [4 months (4M) or 2 months (2M) before] and co-seasonally for 3 consecutive years, and were followed for 2 years post-treatment. ADRs were analyzed descriptively year after year in the subjects treated for at least 2 seasons.

RESULTS: During Year 1, 633 adults (300IR 4M=207, 300IR 2M=207, placebo=219) received at least one dose of treatment and 71% (300IR 4M), 57% (300IR 2M) and 25% (placebo) reported at least one ADR. From those who continued the study, ≥62% (300IR 4M/2M) and 27% (placebo) in Year 2, ≥51% (300IR 4M/2M) and 8% (placebo) in Year 3 presented with ADRs. Each year, the most frequent ADRs were application-site reactions (i.e., oral pruritus, throat irritation, mouth edema and ear pruritus) which mostly occurred within the first week of treatment initiation. Their incidences decreased over the years studied. The most frequent ADRs were generally of mild severity and lasted for one to four months.

CONCLUSIONS: During long-term immunotherapy with 300IR 5-grass pollen sublingual tablet, the most frequent ADRs, generally mild, were reported with decreasing incidences over the years studied and could persist for up to four months during treatment.

192 Duration and Recurrence of Local Site Reactions Associated with 12 SQ House Dust Mite Sublingual Immunotherapy Tablet Treatment

David I. Bernstein, MD, FAAAAI1,2, Harold S. Nelson, MD, FAAAAI3, Joerg R. Kleine-Tebbe, MD, FAAAAI4, Qing Li, PhD5, Hanne H. Villesen6, and Hendrik Nolte, MD, PhD5, 1Bernstein Clinical Research Center, LLC, Cincinnati, OH, 2University of Cincinnati College of Medicine, Cincinnati, OH, 3National Jewish Health, Denver, CO, 4Allergy & Asthma Center Westend, Berlin, Germany, 5Merck & Co., Inc., Kenilworth, NJ, 6ALK, Horsholm, Denmark.

RATIONAL: Local site reactions to sublingual immunotherapy (SLIT) are expected since the high-dose allergen elicits an IgE-mediated response. Information regarding the duration and recurrence of these local events may improve patient acceptability and adherence to SLIT treatment.

METHODS: The duration and recurrence of the most common local site reactions associated with 12 SQ house dust mite (HDM) SLIT-tablet treatment were evaluated. Adverse event (AE) data were collected from four phase 2 and phase 3 clinical trials of SQ HDM SLIT-tablet. Data on AE duration and recurrence were pooled for 1,383 subjects treated with the 12 SQ-HDM dose.

RESULTS: The most common local site reactions with 12 SQ-HDM were throat irritation, oral pruritus, ear pruritus, and lip swelling. Approximately 95% of the local site reactions were assessed as mild-to-moderate in severity. The median duration on the first day of treatment was 42 minutes (range =1-870) for throat irritation, 30 minutes (range =1-826) for oral pruritus, 30 minutes (range =1-624) for ear pruritus, and 60 minutes (range =10-864) for lip swelling. The median recurrence was 12 days (range =1-377) for throat irritation, 12 days (range =1-532) for oral pruritus, 10 days (range =1-376) for ear pruritus, and 3 days (range =1-379) for lip swelling.

CONCLUSIONS: The duration of the most common local site reactions associated with 12 SQ-HDM was 30 to 60 minutes, and the recurrence was less than 2 weeks. These data should reassure patients that local site reactions to SQ HDM SLIT-tablet are typically mild-to-moderate, often transient, and that most decrease with continued treatment.
193 Sublingual Peanut Immunotherapy: Role of Duration and Dose.

Ahmad Hamad, MD; Edwin Kim, MD; Deanna Hamilton, RN; Pamela H. Stephens, MSN, CPNP; AE-C; Sarah Bennick, RN, MSN, CPNP; Lauren Herthly, RN, MSN, CPNP; Elizabeth Pitkin, RN, BSN; A. Wesley Burks, MD; University of North Carolina, Chapel Hill, NC; University of North Carolina at Chapel Hill, Chapel Hill, NC.

Rationale: Desensitization has been shown with sublingual immunotherapy (SLIT) in children with peanut allergy with a median reaction threshold of 1710 mg of peanut protein after 12 months of therapy using a 2 mg maintenance dose. We aimed to study if higher doses and longer duration of treatment could provide a more robust response.

Methods: Fifty-five subjects ages 1-11 years with peanut allergy were enrolled in an open-label study of peanut SLIT. After an entry oral food challenge (OFC), subjects were built up to a maintenance dose of 4 mg of peanut protein and continued on therapy for a total of 48 months. An exit OFC was then performed to a cumulative dose of 5000 mg of peanut protein to assess for desensitization.

Results: We report interim results for the first 14 subjects to undergo the OFC after 48 months of peanut SLIT therapy. The median cumulative dose of peanut protein tolerated was 0 mg (0-425 mg) prior to treatment while it was 2900 mg (800-5000 mg) after 48 months of peanut SLIT.

Conclusions: Peanut SLIT demonstrated desensitization to a significantly higher level than would be expected of an accidental ingestion of peanut (~100 mg). The longer duration of treatment and higher daily maintenance dose resulted in more effective desensitization to peanut than previously published. Further investigation is needed to evaluate the effectiveness of this dose on the induction of sustained unresponsiveness.

194 Safety of Year-Round Initiation with SQ House Dust Mite Sublingual Immunotherapy Tablet

Hendrik Nolte, MD, PhD; David I. Bernstein, MD, FAAAAI; Joerg R. Kleine-Tebbe, MD, FAAAAI; Peter A. Fejerskov, MD; Qin Li, PhD; Susan Lu, PharmD; Megan McGrattan, MD; and Harold S. Nelson, MD, FAAAAI; 1Merck & Co., Inc., Kenilworth, NJ; 2Bernstein Clinical Research Center, LLC, Cincinnati, OH; 3University of Cincinnati College of Medicine, Cincinnati, OH; 4Allergy and Asthma Center Westend, Berlin, Germany; 5ALK, Horsholm, Denmark; National Jewish Health, Denver, CO.

Rationale: In polysensitized subjects, seasonal pollen exposure could impact the safety of treatment initiation with house dust mite (HDM) sublingual immunotherapy (SLIT)-tablets. The safety of year-round initiation of SQ HDM SLIT-tablet (6 and 12 SQ-HDM doses) was evaluated.

Methods: Adverse event (AE) data were collected from five phase 2/3 North American and European trials of 6 and 12 SQ-HDM (total N=3,731). Data on subjects with any AE, treatment-related AEs, local site reactions, and asthma-related AEs were pooled and evaluated comparing the season when treatment was initiated with the season during which the AE started (up to 2 years after initiation). Seasons were winter (December-February), spring (March-May), summer (June-August), and fall (September-November).

Results: Overall, 72% of subjects were polysensitized. The highest reported frequencies of any AEs, treatment-related AEs, and local site reactions were consistently reported in the same season in which SLIT-tablet treatment was initiated, and decreased with treatment. Regardless of the season treatment was initiated, the placebo-subtracted frequencies of treatment-related AEs were generally similar and ranged from 33% to 45% during the initiating season. For polysensitized and monosensitized subjects initiating in spring and summer (pollen seasons), placebo-subtracted frequencies of treatment-related AEs in spring were 46% and 44%, respectively, and in summer were 44% and 49%. Asthma-related AE frequency was similar across seasons.

Conclusions: The highest AE frequency occurred within the same season in which treatment was initiated, and AEs did not appear to increase in polysensitized subjects who initiated during pollen seasons. The frequency of asthma-related AEs was not affected by the initiation season.

195 Long-Lasting Effect of Allergen-Specific Sublingual Immunotherapy in a Murine Model of Japanese Cedar Pollinosis

Soichi Tsuchiji, Kazufumi Katayama, Yoshiyuki Nakano, Satoru Iida, Minako Tajii, Junji Tsuicaida, Makoto Kodama, Hiroki Tajji, Kota Kawachi, Michitaka Shichijo, and Hidekazu Tanaka; Shionogi & CO., LTD., Toyonaka-shi, Japan.

Rationale: Sublingual immunotherapy (SLIT) is considered a potentially curative treatment for allergic diseases, but the mechanism remains to be elucidated. Japanese cedar (JC) pollen, which is dispersed in early spring, is a major cause of allergic rhinitis in Japan. We established a murine model of JC pollinosis and evaluated the effect of JC pollen extract SLIT.

Methods: BALB/c mice were intranasally sensitized to JC pollen, then administered four courses of nasal allergen challenge at 5-week intervals, mimicking seasonal JC pollen exposure. Between allergen challenges, mice were treated sublingually with two doses (low or high) of JC pollen extract. Mice received no SLIT treatment between the third and fourth challenges to allow assessment of long-term effects. Nasal symptoms, T-cell response, antibodies, and histological changes in nasal mucosa were examined.

Results: JC-SLIT significantly reduced the JC pollen-induced nasal symptoms, both during and approximately 2 months after SLIT treatment. While the magnitude of the effect at the end of SLIT was similar in the low- and high-dose groups, the high-dose group showed a greater effect in the off-treatment period, suggesting more potent lasting effects with higher SLIT doses. Th2 cytokine production in submandibular lymph nodes, nasal mucosa hyperplasia, and JC-specific IgE were reduced in the JC-SLIT-treated groups.

Conclusions: We have developed a JC pollinosis mouse model that may be useful for studying SLIT mechanisms and biomarkers. Our results also demonstrate that SLIT induces long-lasting effects, which occur in a dose-dependent manner.

196 The SQ HDM Slit-Tablet Reduces Symptoms of House Dust Mite Allergic Rhinitis in Adolescents; A Subgroup Analysis of Results from a Dbpcc Phase III Trial (TO-203-3-2)

Kaare Lund, PhD; Kazuhiro Okamya; Keisuke Masuyama; and Bente Riis; 1,2 ALK, Horsholm, Denmark; 3Torii Pharmaceutical Co., Ltd., Chuo-ku, Tokyo, Japan; 4Department of Otohinolaryngology-Head and Neck Surgery, Interdisciplinary Graduate School of Medicine and Engineering, University of Yamanashi, Yamanashi, Japan.

Rationale: The SQ house dust mite (HDM) SLIT-tablet is an allergy immunotherapy tablet approved in Europe (treatment of HDM allergic rhinitis and asthma in adults; ACARIZAX, ALK) and Japan (treatment of HDM allergic rhinitis in adults and adolescents; Miticure, TORII). HDM allergy is frequent among children and adolescents and allergen immunotherapy a relevant treatment option.

Methods: This was a randomized DBPC trial in Japan (JapicCTI no. 121848) including 946 subjects; 278 were adolescents (12-17 years of age). Subjects were randomized 1:1:1 to daily treatment with the HDM SLIT-tablet 6 SQ-HDM (in Japan: 10.000 JAU) (dose 1), 12 SQ-HDM/20.000 JAU (dose 2) or placebo. In a post hoc analysis, the efficacy in adolescents was investigated. The primary endpoint was the total combined rhinitis score (TCRS), counting 4 rhinitis symptoms and the rhinitis medication score.

Results: At the end of trial after 1 year of treatment, the TCRS was 4.0 with dose 1, 4.1 with dose 2 and 5.1 with placebo, implying absolute differences of 1.1 (95%CI [0.2; 2.0], p=0.020) and 1.0 (95% CI [0.1; 1.9], p=0.037) between the active groups and placebo among the adolescents. The adjusted mean rhinitis, conjunctivitis, rhinoconjunctivitis, and quality of life scores in adolescent subjects were also in favor of active treatment and similar to those in adult subjects (18 to 64 years old).

Treatment was well tolerated.

Conclusions: HDM SLIT-tablets were efficacious in adolescents (12-17 years old) with HDM allergic rhinitis. Efficacy in adolescents and adults were similar. There were no signals of differential safety profiles between adults and adolescents.
197
Intracellular Th2 Cytokine Profile after Two Years Sublingual Immunotherapy in Respiratory Allergy Patients

Ludmila Maslova1, Leonid Titov2, and Lawrence M. DuBuske, MD, FAAAAI1; 1Belarusian Medical Academy of Post-Graduate Education, Minsk, Belarus, 2Republican Research and Practical Center for Epidemiology and Microbiology, Minsk, Belarus, 3George Washington University School of Medicine, Washington, DC; Immunology Research Institute of New England, Gardner, MA.

RATIONALE: Intracellular cytokine profiles may be impacted by sublingual immunotherapy (SLIT).

METHODS: 60 allergic rhinoconjunctivitis with or without asthma from 19 to 46 years old received SLIT (drop formulations) for 2 years (Sevapharma, Czech Republic). Group 1- 30 patients with allergic rhinitis with asthma (6) and without asthma (24) were treated with monotherapy with grasses or Artemisia. Group 2 - 30 patients with allergic rhinitis with asthma (9) patients or without asthma (21), were treated with grasses or Artemisia and also dust mites or indoor molds. 30 healthy subjects were controls. CD4+ T-cells were assessed for intracellular IL-4, IL-5, IL-13 after stimulation for 6 hours with PMA plus ionomycin before SLIT and after 2 years of SLIT.

RESULTS: SLIT was effective reducing overall symptom scores and rescue medication in Group 1 and in Group 2 (p<0.0001). CD4+ T-cells including IL-4+ cells, IL-5+ cells, IL-13+ cells were significantly increased before SLIT compared to controls. CD4+ T-cells positive for inflammatory cytokines were reduced after 2 years of SLIT including CD4+ cells with IL-4+ reduced from 0.91 to 0.30 (p=0.001) in Group 1 and from 0.75 to 0.28 in Group 2 (p=0.001); IL-5+ reduced from 4.71 to 2.05 in Group 1 (p=0.001) and from 6.11 to 1.88 in Group 2 (p=0.001); and IL-13 + reduced from 4.90 to 1.58 (p=0.001) in Group 1 and from 4.95 to 2.06 in Group 2 (p=0.001).

CONCLUSIONS: Reduction of IL-4+, IL-5+ and IL-13+ CD4+cells demonstrated that SLIT can modulate allergen-specific T-cell immune responses.

198
Impact of Solicitation of Adverse Events on the Safety Profile of 12 SQ House Dust Mite Sublingual Immunotherapy Tablet

Susan Lu, PharmD1, David I. Bernstein, MD, FAAAAI2,3, Gordon L. Sussman, MD, FAAAAI4, Peter A. Fejerskov5, Ziliang Li, PhD1, Harold S. Nelson, MD, FAAAAI6, and Hendrik Nolte, MD, PhD5; 1Merck & Co., Inc., Kenilworth, NJ, 2Bernstein Clinical Research Center, LLC, Cincinnati, OH, 3University of Cincinnati College of Medicine, Cincinnati, OH, 4University of Toronto, Toronto, ON, Canada, 5ALK, Horsholm, Denmark, 6National Jewish Health, Denver, CO.

RATIONALE: Local site reactions are the most common treatment-related adverse events (AEs) associated with sublingual immunotherapy (SLIT). The objective of this analysis was to describe the safety profile of SQ house dust mite (HDM) SLIT-tablet (12 SQ-HDM dose) when the presence or absence of local site reactions was solicited vs unsolicited.

METHODS: Four double-blinded, multicenter trials were conducted in which subjects were randomized to daily 12 SQ-HDM SLIT-tablet or placebo for up to 52 weeks. In the North American trial (NCT01700192; N=1,272), subjects documented daily the presence or absence of 15 local site reactions using a questionnaire of closed-ended questions (solicited AEs). In the other three trials, AEs were spontaneously reported (unsolicited) and the data were pooled (N=1,287). The current analysis was limited to adults aged 18-65 years.

RESULTS: The most common AEs (≥2%) that led to study discontinuation in subjects treated with 12 SQ-HDM were throat irritation, oral pruritus, ear pruritus, and mouth swelling. Approximately 95% of treatment-related AEs were mild-to-moderate. The placebo-subtracted frequencies of local site reactions associated with 12 SQ-HDM treatment were notably higher when solicited vs unsolicited (i.e., throat irritation, 46% vs 13%, respectively; oral pruritus, 47% vs 17%; ear pruritus, 40% vs 4%; mouth swelling, 8% vs 2%; tongue ulceration, 10% vs 0%; mouth ulceration, 7% vs <1%).

CONCLUSIONS: Qualitatively, the safety profile of 12 SQ-HDM was similar when AEs were solicited vs unsolicited. Active solicitation is a likely cause of the higher frequency of local site reactions in the North American trial versus the other three trials.

199
Effect of Adjuvanted and Standard Sublingual Immunotherapy on Respiratory Function in Pure Rhinitis Due to House Dust Mite over a 5-Year Period

Maurizio Marogna, MD; Azienda Opesdaliere Fondazione Macchi, Porto Ceresio, Italy.

RATIONALE: In this study we assessed disease modifying effect (changes in respiratory function, onset of bronchial hyperreactivity, onset of new sensitizations) in patients monosensitized to dust mites and with pure allergic rhinitis over 5-years receiving SLIT.

METHODS: The study was observational, open, prospective. Patients with pure mite-induced allergic rhinitis were followed-up, receiving adjuvanted SLIT (aSLIT), standard SLIT (sSLIT) or drug treatment alone, according to their preference. Onset of asthma, changes in pulmonary-function and bronchial hyperreactivity (BHR) were assessed over 5-years. Onset of new sensitizations and symptoms- medication score (SMS) were evaluated.

RESULTS: 124 patients had 5-year evaluation (8-57yr, 69 male). After 5 years of treatment, new sensitizations appeared differentially among treatments with 58.1% of new sensitizations in drug treatment group, 13.2% in sSLIT patients, and 8.1% in aSLIT patients. At the end of 5 years, SMS significantly changed in all groups, with a negative trend for controls, as compared to SLIT treatments. SMS decreased in both SLIT groups at 5 years, with no change in patients on drugs alone. Use of salbutamol (absent at baseline), showed an overall increase only in non-SLIT group drugs with significant difference at 5 years. There was a difference among treatments in PD20 after 5 years: control group had a lower PD20. No significant difference in PD20 was detected between sSLIT and aSLIT. FEV1 significantly decreased in controls, with no change in sSLIT group and a significant increase in aSLIT.

CONCLUSIONS: aSLIT and sSLIT reduced onset of new sensitizations and maintained intact pulmonary function, as compared to patients receiving drug treatment alone.
Role of Endogenous Protease Inhibitor in Airway Epithelial Cells in the Pathogenesis of Eosinophilic Chronic Rhinosinusitis

Hideaki Kouzaki1, Ichiro Tojima2, Tomohisa Kato3, Koji Matsumoto3, Shino Shimizu1, Takeshi Shimizu1, and Hirohito Kita, MD4; 1Shiga University of medical science, Otsu, Japan, 2Shiga University of medical science, Otsu, SHiga, Japan, 3Shiga University of medical science, Otsu, Shiga, Japan, 4Mayo Clinic, Rochester, MN.

RATIONALE: Chronic rhinosinusitis (CRS) is a heterogeneous disease with different etiologies and pathogenesis. Cystatin A and SPINK5 are endogenous protease inhibitors (EPIs), which may play important roles in epithelial barrier function. The purpose of this study is to investigate the role of EPIs in the pathogenesis of CRS.

METHODS: We examined the expression of Cystatin A and SPINK5 in nasal epithelial cells of CRS patients by ELISA, RT-PCR and immunofluorescence staining. We then examined the effects of recombinant EPIs in allergen-induced production of epithelial-derived cytokines, IL-25, IL-33 and TSLP from cultured normal human bronchial epithelial (NHBE) cells.

RESULTS: The protein and mRNA expressions of cystatin A and SPINK5 were significantly low in nasal epithelium of patients with eosinophilic CRS (ECRS) as compared to those with non-eosinophilic CRS and control individuals. Immunofluorescence staining demonstrated that the expression levels of cystatin A and SPINK5 were decreased in nasal epithelium of ECRS patients. Allergen-induced production of IL-25, IL-33 and TSLP were inhibited in NHBE cells by treating with recombinant cystatin A or SPINK5. In contrast, allergens-induced secretion of IL-25, IL-33 and TSLP were significantly increased by infecting NHBE cells with small interfering RNA for SPINK5 or Cystatin A.

CONCLUSIONS: These results indicate that cystatin A and SPINK5 play an important role in protecting airway epithelium from exogenous proteases, and that the decreased expression of EPIs may be involved in the pathogenesis of intractable eosinophilic CRS.
**201 Expression Of Surfactant Protein A In Human Nasal Epithelial Cells After Infection With Rhinovirus C In The Presence of Histamine**

Georgios T. Noutsios, PhD1, Erin Romero, BS1, Amanda L. Willis, MS2, Jaeden T. Calsonstudent1, Julie G. Ledford, PhD1, and Eugene H. Chang, MD1, 2Department of Otolaryngology, University of Arizona, Tucson, AZ, 3University of Arizona, Tucson, AZ, 4University of Arizona - Department of Otolaryngology, Tucson, AZ.

**RATIONALE:** The nasal airway is the first barrier for inhaled pathogens. Rhinovirus is the commonest infection, and RV-C is the most virulent strain. Surfactant protein A (SP-A) is a critical innate immune molecule for the lower airway, but its function in the upper airway is not well characterized. We hypothesized that: 1) RV-C binding to sinonasal epithelia (SNEC) is enhanced with histamine, 2) SP-A is expressed in SNEC, 3) SP-A levels are upregulated after RV-C infection.

**METHODS:** SP-A humanized transgenic (hTG) mice or knockouts were used to investigate expression of SP-A in mouse sinonasal tissues, SNEC isolated from chronic rhinosinusitis (CRS) patients, cultured in air-liquid interface (ALI), and infected apically (4, 24 and 48h) with GFP-RVC or vehicle in presence or absence of basolateral histamine. RVC binding and replication were assessed with fluorescence microscopy and qRT-PCR. SP-A mRNA and protein measured by qRT-PCR and western blot (WB).

**RESULTS:** SP-A protein and mRNA were expressed in nasal tissues from CRS patients, differentiated ALI SNEC and in nasal tissues of SP-A hTG mice. RVC binding and replication was enhanced when histamine was present compared to basal conditions. SP-A mRNA and protein increased during RVC binding at 4h but decreased 48h post infection.

**CONCLUSIONS:** RV-C binding was increased after SNEC exposure to histamine, suggesting that allergic disorders may enhance RV-C infection in vivo. SP-A was expressed and upregulated after 4 hrs of infections, but decreased at 48 hrs suggesting a novel role in the sinonasal innate immune response to rhinovirus infections.

**202 Dexpramipexole effectively lowers blood and tissue eosinophils in subjects with chronic rhinosinusitis with nasal polyps**

Calman Prussin, MD, FAAAAI1, Tanya M. Laidlaw, MD, FAAAAI2, Reynold A. Panettieri, MD3, Berrylin J. Ferguson, MD4, Nithin D. Adappa, MD5, Andrew P. Lane, MD6, Stella Lee, MD7, Mary Sullivan7, Don Archibald, MPhil 7, Steven I. Dworetzky, PhD7, Greg Hebrank, MD7, and Michael E. Bozik, MD7; 1Knopp Biosciences, LLC, Pittsburgh, PA, 2Brigham and Women’s Hospital, Division of Rheumatology, Immunology, and Allergy, Boston, MA, 3Rutgers Institute for Translational Medicine and Science, New Brunswick, NJ, 4University of Pittsburgh, Pittsburgh, PA, 5Department of Otolaryngology–Head and Neck Surgery, University of Pennsylvania, Philadelphia, PA, 6Johns Hopkins Dept of Otolaryngology, Baltimore, MD, 7Knopp Biosciences, LLC, Pittsburgh, PA.

**RATIONALE:** Dexpramipexole is an oral investigational drug serendipitously noted to lower blood eosinophils in prior clinical studies in amyotrophic lateral sclerosis.

**METHODS:** An open-label study of dexpramipexole 300 mg/day was undertaken in subjects with chronic rhinosinusitis with nasal polyps (CRSwNP) with a baseline blood absolute eosinophil count (AEC) ≥ 0.3 x 10⁹/L and polypl eosinophilia. The primary endpoint examined was change in AEC from baseline to end of study. Change in nasal eosinophils from baseline to end of study was an exploratory endpoint. Data are shown from this ongoing study.

**RESULTS:** Baseline AEC was 0.524 x 10⁹/L in the 11 subjects studied to date. AEC at month 6 was 0.034 x 10⁹/L, a 93% reduction (p=0.001). Seven of the 11 subjects had eosinophil counts reduced to 0.020 x 10⁹/L or less at month 6. In the 10 subjects who had biopsies, polyp tissue eosinophilia was reduced from 190 to 11 eosinophils per high-powered field, a 94% reduction from baseline (p=0.004). Dexpramipexole was well tolerated with no drug-related serious adverse events. Five subjects elected to continue on a long-term extension study.

**CONCLUSIONS:** In sum, dexpramipexole is a well-tolerated orally-available drug with robust blood and tissue eosinophil-lowering activity. Given that eosinophil lowering by dexpramipexole is greater than or equal to that of current biologics, its clinical activity in asthma and other eosinophil-associated diseases is of great interest. Based on its oral administration, safety profile, and convenience, dexpramipexole has the potential for use by a broader segment of asthma patients than is currently indicated with approved biologics, including both moderate and severe asthmatics.
204 Role of IL-25 in Extracellular Matrix and Collagen Production in Nasal Fibroblast

Yong Min Kim, Soo Kyong Park, Jun Xu, and Sun Hee Yeon; Chungnam National University School of Medicine, Daejeon, Korea, The Republic of

RATIONALE: Interleukin(IL)-25 has been shown to play important roles in the pathogenesis of chronic rhinosinusitis with nasal polyps. Nasal polyps are associated with chronic inflammation of the mucous membranes in the paranasal sinuses and involved in extracellular matrix (ECM) accumulation. The aim of this study was to evaluate the effect of IL-25 on myofibroblast differentiation and extracellular matrix production in nasal polyp-derived fibroblasts and to determine the underlying molecular mechanism of these processes.

METHODS: Nasal polyp-derived fibroblasts were stimulated with IL-25. Cytotoxicity was evaluated by MTT assay. IL-25 receptor mRNA levels were measured by RT-PCR. α-SMA, fibronectin and collage type \( \gamma^2 \) expression levels were measured by using RT-PCR, western blot, collagen assay, and immunofluorescence staining. Fibroblast migration was evaluated with scratch assay. Mitogen-activated protein kinase (MAPK) and NF-κB activated were determined by using western blot analysis. The total collagen amount was analyzed with Sircol collagen assay.

RESULTS: IL-25 had no significant cytotoxic effects on nasal polyp-derived fibroblast. IL-25 significantly induced the expression levels of α-SMA, fibronectin, and collagen type \( \gamma^2 \) production in dose dependent manner. The collagen migration and invasion were also significantly induced by IL-25 exposure in nasal fibroblasts. IL-25 increased MAPKs and the specific inhibitors significantly decreased IL-25 induced of α-SMA and fibronectin and collagen type \( \gamma^2 \).

CONCLUSIONS: IL-25 has stimulatory effect on ECM production via α-SMA and fibronectin and collagen type \( \gamma^2 \).

205 Clinical Factors Associated with Acute Exacerbations of Chronic Rhinosinusitis

Jason Kwah, MD\(^1\), Whitney W. Stevens, MD, PhD\(^1\), Robert C. Kern, MD\(^2\), Stephanie S. Smith, MD\(^2\), Kevin C. Welch, MD\(^2\), David B. Conley, MD\(^2\), Bruce K. Tan, MD, MS\(^2\), Leslie C. Grammer, MD, FAAAAI\(^1\), Amy Yang, MS\(^1\), Robert P. Schleimer, PhD, FAAAAI\(^1\), and Anju T. Peters, MD, FAAAAI\(^1\); 1Department of Medicine, Division of Allergy-Immunology, Northwestern University Feinberg School of Medicine, Chicago, IL, 2Department of Otolaryngology, Northwestern University Feinberg School of Medicine, Chicago, IL.

RATIONALE: Chronic rhinosinusitis (CRS) can be complicated by frequent acute exacerbations leading to significant morbidity and healthcare burden. Our objective was to identify clinical factors associated with frequent acute exacerbations in patients with CRS.

METHODS: This is a case-control study of patients treated for CRS from January 2014 to December 2015 at a single tertiary care center. Frequent exacerbators were defined as patients who were prescribed ≥2 antibiotics, and infrequent exacerbators were defined as patients prescribed 0-2 antibiotics over the study period for acute CRS exacerbations. Various clinical factors were examined in those with frequent versus infrequent exacerbations. Multivariable logistic regression analyses were performed while controlling for race and gender for three variables of interest: allergic rhinitis, asthma, and peripheral eosinophilia.

RESULTS: Of the 3109 CRS patients identified, 1464 were frequent exacerbators and 1645 were infrequent exacerbators. On univariate analyses, female gender, non-white race, higher BMI, any drug allergy, allergic rhinitis, peripheral eosinophilia, asthma, lower FEV1, previous sinus surgery, severe sinus inflammation on CT, ≥1 steroid prescription, and presence of autoimmune disease were factors significantly associated with frequent acute exacerbations compared to infrequent exacerbations. In multivariable analyses, after adjusting for race and gender, allergic rhinitis (OR 1.6, 95% CI 1.3-1.8), peripheral eosinophilia (OR 1.2, 95% CI 1.0-1.5), and asthma (OR 1.8, 95% CI 1.5-2.1) remained significantly associated with frequent CRS exacerbations.

CONCLUSIONS: There are clinical factors that are associated with frequent acute exacerbations of CRS. In particular, allergic rhinitis, peripheral eosinophilia, and asthma are independently associated with frequent antibiotic treatment of acute CRS exacerbations.

206 New Exhalation Delivery Systems (EDS) Enhance Topical Steroid Delivery in Chronic Rhinosinusitis With Nasal Polyps

Per G. Djupesland, MD, PhD\(^1\), John Messina, Jr, PharmD\(^2\), and Ramy Mahmoud, MD, MPH\(^2\); \(^1\)OptiNose, Oslo, Norway, \(^2\)OptiNose, Yardley, PA.

RATIONALE: Nasal polyps typically originate in the middle or superior meatus. Natural properties of nasal anatomy and aerodynamics seriously limit the ability of conventional nasal sprays to effectively deliver medication to superior/posterior nasal regions. Administering topical steroid (fluticasone) using a promising new delivery mechanism, an Exhalation Delivery System (EDS), has been found to produce significant polyp reduction, even elimination, in chronic rhinosinusitis with nasal polyps (CRSwNP) suggesting this limitation can be overcome.

METHODS: Devices utilizing the EDS delivery mechanism dynamically seals the soft palate, expand nasal passages, and propel medication superiorly/posteriorly beyond the nasal valve. Nasal geometry in CRSwNP-patients was assessed using CT and acoustic rhinometry. Deposition patterns using EDS devices were assessed endoscopically after colored dye delivery and by gamma-scintigraphy in five CRSwNP patients. Comparisons of EDS and traditional spray delivery were also made using dye and color-changing gel in anatomically correct casts (CT-validated).

RESULTS: In patients, the presence, location and degree of polyp obstruction was documented by CT, AR and endoscopy. Endoscopic and scintigraphic images after delivery of colored dye and radiolabeled saline, respectively, demonstrate deep and extensive medication deposition on the polyp surfaces and regions in CRSwNP patients using an EDS. Photos of deposition patterns in anatomically correct casts visually illustrate that the liquid EDS delivers considerably more medication to the middle and superior meatuses than conventional nasal spray.

CONCLUSIONS: EDS delivery reaches the polyp surfaces in CRSwNP patients and cast studies show improved deposition in regions of the nasal cavity (middle and upper meatus) where sinuses drain and polyps originate.
EXHANCE-3: A Phase 3, Three-Month Study of Safety and Efficacy of Fluticasone Propionate Exhalation Delivery System (FLU-EDS) in Patients with Chronic Rhinosinusitis with (CRSwNP) and without Nasal Polyps (CRSsNP)

Mandel R. Sher, MD, FAAAAI,1 Eric A. Mair, MD, FAAP, FACS,2 John Messina, Jr, PharmD,3 Jennifer Carothers, ScD, MBA,1 Ramy Mahmoud, MD, MPH,1 and Per G. Djupesland, MD, PhD;4 Center for Cough, Largo, FL,2 Charlotte Eye, Ear, Nose and Throat Associates, Charlotte, NC,3 OptiNose, Yardley, PA,4 OptiNose, Oslo, Norway.

**RATIONALE:** EDS have been shown to deliver drug deeper and more broadly in the nasal cavity (particularly superiorly and posteriorly), with less loss to drip-out and swallowing, than conventional nasal sprays. FLU-EDS uses an EDS to improve fluticasone delivery, including to the ostialomeatal complex where sinus ostia drain/ventilate and polyps originate.

**METHODS:** Multicenter, 12-week, open-label study of FLU-EDS 372µg BID in CRSw/sNP. Lund-Mackay scores, polyp grade, surgical eligibility, and local adverse events were evaluated via nasoendoscopy before, during, and after treatment. Sino-Nasal Outcome Test-22 (SNOT-22), Patient Global Impression of Change (PGIC), and other outcomes were also assessed.

**RESULTS:** 706 patients were enrolled, 102 CRSwNP and 603 CRSsNP, with baseline SNOT-22 scores 43.8 and 43.2, respectively. Prior use of conventional intranasal steroids was common (92.3%) as was surgery (27.5%). Among patients with baseline Lund-Mackay edema scores >0, 33.3% CRSwNP and 54.8% CRSsNP had complete resolution. FLU-EDS scores improved dramatically in CRSwNP (-23.7) and CRSsNP (-24.4). More than 90% of patients reported improvement as assessed by PGIC, with >70% reporting ‘much’ or ‘very much’ improvement. At last visit nasoendoscopy, 48% CRSwNP had polyp elimination in at least 1 nostril, 63% had >1-point improvement in polyp grade, mean bilateral nasal polyp score dropped from 2.9 to 1.6 and surgical eligibility was reduced by 57%. FLU-EDS was well-tolerated with a safety profile similar to traditional intranasal steroids.

**CONCLUSIONS:** FLU-EDS 372µg BID was well-tolerated, and significant improvements across a broad range of objective and subjective measures were measured in CRS patients with and without polypos.

NAVIGATE I: A Randomized Double-Blind Trial of a Fluticasone Proprionate Exhalation Delivery System (FLU-EDS) for Treatment of Chronic Rhinosinusitis with Nasal Polyps (CRSsNP)

Daniel F. Soteres, MD, FAAAAI,1 John Messina, Jr, PharmD,2 Jennifer Carothers, ScD, MBA,2 Ramy Mahmoud, MD, MPH,1 and Per G. Djupesland, MD, PhD;1 Asthma and Allergy Associates, P. C., Colorado Springs, CO,3 OptiNose, Yardley, PA,4 OptiNose, Oslo, Norway.

**RATIONALE:** Deeper and broader distribution, especially to the ostialomeatal complex where sinus ostia drain/ventilate and polyps typically originate, may optimize efficacy in CRS.

**METHODS:** Patients diagnosed with CRSwNP and moderate-severe congestion were randomized to FLU-EDS (93µg, 186µg, or 372µg BID) or placebo EDS for 24-weeks (16 double-blind and 8 open-label). All received FLU-EDS 372µg BID during the 8-week extension. Multiple endpoints, including all core CRS symptoms, were measured. Change in congestion score (0-3) at week 4 and summed bilateral polyp grade (0-6) at week 16 were co-primary endpoints. Change in Sino-Nasal Outcome Test-22 (SNOT-22) was a pre-specified alpha-controlled key secondary endpoint.

**RESULTS:** 323 patients enrolled (mean age=45, baseline SNOT-22=51, prior conventional intranasal steroid use=94%, prior surgery=35%). All FLU-EDS doses produced significantly greater improvement in both co-primary endpoints compared with placebo (polyp grade: placebo -0.45; FLU-EDS -0.96 to -1.06, p<0.05 all comparisons; congestion scores: placebo -0.24; FLU-EDS -0.49 to -0.62, p<0.05 all comparisons). FLU-EDS also significantly improved all 4 cardinal CRS symptoms, including anosmia/hyposmia, facial pain/pressure, rhinorrhea, and congestion/obstruction (p<0.05, all comparisons). Polyp grade continued to improve through 24 weeks. Changes in SNOT-22 score and Patient Global Impression of Change were superior in all FLU-EDS groups versus placebo (p<0.05, all comparisons). Surgical eligibility decreased from 36-9% to 23.2%. The safety profile was similar to conventional intranasal steroid nasal sprays.

**CONCLUSIONS:** FLU-EDS produced clinically and statistically significant improvement, as measured by a wide range of objective and subjective outcomes including all core symptoms and polyp grade.

Significant Cognitive Function Impairment in Association with Sleep Disruption in Patients with Chronic Rhinosinusitis (CRS)

Ferry Gunawan, MD,1 Jessica W. Hui, MD,2 Arpita Mehta, MD,2 Mary C. Tobin, MD, FAAAAA,2 Sindhu Bandi, MD,2 Pete S. Batra, MD,3 Phillip S. LoSavio, MD,7, and Mahboobeh Mahdavinia, MD, PhD;2 Department of Internal Medicine and Pediatrics, Rush University Medical Center, Chicago, IL,3 Department of Immunology and Microbiology, Allergy/Immunology Section, Rush University Medical Center, Chicago, IL,7 Department of Otorhinolaryngology-Head and Neck Surgery, Rush University Medical Center, Chicago, IL,2 Department of Immunology and Microbiology, Allergy and Immunology Section, Rush University Medical Center, Chicago, IL.

**RATIONALE:** It has been previously shown that CRS patients suffer from sleep disruption. However, little is known about the functional outcome of sleep disturbance and cognitive function in CRS. This study aimed to identify how sleep disruption in CRS patients contributes to cognitive function.

**METHODS:** We performed a prospective cohort study of 115 patients with confirmed diagnostic criteria for CRS. We used a standard questionnaire to evaluate three cognition predictors: 1)memory loss, 2)lack of concentration and 3)decreased productivity. We tested these in association with sleep disruption (lack of good night sleep, night-time-awakening and waking-up-tired) measured by a visual scale test. We further assessed the correlation of cognition predictors with SNOT-22 and CRS comorbidities. Pearson correlation was used to evaluate the link between variables.

**RESULTS:** We found a significant positive correlation between memory loss and sleep questions; lack of good night sleep(r=0.68,p<0.01), night-time-awakening(r=0.61,p<0.012) and waking-up-tired(r=0.77,p<0.0001). Difficulty concentration was correlated with lack of good night sleep(r=0.48,p<0.05) and waking-up-tired(r=0.55,p=0.02). Decreased productivity was also correlated with lack of good night sleep(r=0.72,p<0.0001), night-time-awakening(r=0.72,p<0.0001) and waking-up-tired(r=0.64,p<0.0001). All three cognition variables were positively correlated with higher SNOT-22 scores. Decreased productivity was lower in CRS cases with allergic rhinitis.

**CONCLUSIONS:** Sleep disruption in CRS is significantly associated with memory loss, lack of concentration and decreased productivity indicative of its link to cognitive function impairment in CRS. Cognitive function predictors were correlated with subjective severity scores of CRS (SNOT-22) and allergic rhinitis. Therefore addressing sleep disruption in CRS is of utmost importance.
All abstracts are strictly embargoed until the date of presentation at the 2017 Annual Meeting.

### 210 Associations of Community and Environmental Factors with 6-month Transition States of Chronic Rhinosinusitis

Agnes S. Sundaresan, MD, MPH,1 Annemarie G. Hirsch, PhD, MPH,1 Cara M. Nordberg, MPH,1 and Brian S. Schwartz, MD, MS1,2, Gesingter Health System, Danville, PA, 2Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD.

**RATIONALE:** Chronic rhinosinusitis (CRS) is a burdensome and prevalent inflammatory disease of upper airways whose pathophysiology is driven by host-environment interaction. However, associations of community and environmental factors with CRS transition states have not been previously examined.

**METHODS:** We mailed a CRS symptom questionnaire to 23,700 primary care patients in Pennsylvania and 6-month follow-up questionnaire to 7801 responders. We defined CRS based on European Position Paper on Rhinosinusitis (EPOS) epidemiologic criteria. We characterized transition states of CRS: persistent CRS if met EPOS criteria for CRS at both time points and non-persistent CRS if met criteria only at baseline; incident CRS if had no history at baseline but met criteria at follow-up and never CRS if never met criteria. We evaluated associations of distance to minor and major roadways (in quartiles), residential greenness index, community type and urbanicity. We performed multivariate survey logistic regression controlling for age, sex, race/ethnicity, Medical Assistance and tobacco use.

**RESULTS:** There were 4966 responders at follow-up; 558 had persistent CRS, and 83 incident CRS. The fourth quartile of distance to minor roads was associated with reduced odds of persistent CRS compared to non-persistent CRS, OR = 0.38; 95% CI = 0.17-0.81 and there was a trend of decreasing odds across all four quartiles (p < 0.01). Similar association was seen for incident CRS versus never CRS for the third quartile of distance.

**CONCLUSIONS:** Patients residing the farthest from minor roads had a reduced risk of persistent CRS. Residential greenness, major roadways, and urbanicity were not associated with transitions.

### 211 Sleep Disruption in Chronic Rhinosinusitis: Risk Factors Predictive of Worse Sleep Quality

Jessica W. Hui, MD,1 Ferry Gunawan, MD,2 Jason Ong, PhD3, Helen J. Burgess, PhD4, Shahram Sarrafi, MD,2 James J. Herdegen, MD5, Christopher D. Codispoti, MD, PhD3, Mary C. Tobin, MD, FAAAAI6, Robert P. Schleimer, PhD, FAAAAI6, Pete S. Batra, MD,6 Phillip S. LoSavio, MD,6 Ali Keshavarzian, MD6, and Mahboobeh Mahdavinia, MD, PhD6, 1Department of Internal Medicine and Pediatrics, Rush University Medical Center, Chicago, IL, 2Department of Immunology and Microbiology, Allergy/Immunology Section, Rush University Medical Center, Chicago, IL, 3Department of Neurology, Sleep Medicine Section, Northwestern University Feinberg School of Medicine, Chicago, IL, 4Department of Behavioral Sciences, Biological Rhythms Research Laboratory, Rush University Medical Center, Chicago, IL, 5Department of Sleep Disorders Service and Research Center, Rush University Medical Center, Chicago, IL, 6Department of Medicine, Division of Allergy-Immunology, Northwestern University Feinberg School of Medicine, Chicago, IL, 7Department of Otorhinolaryngology-Head and Neck Surgery, Rush University Medical Center, Chicago, IL, 8Department of Internal Medicine, Division of Digestive Diseases and Nutrition, Rush University Medical Center, Chicago, IL, 9Department of Immunology and Microbiology, Allergy and Immunology Section, Rush University Medical Center, Chicago, IL.

**RATIONALE:** Recently, anti-IgE monoclonal antibody has emerged as a potential therapy for CRS. However, evidence for its efficacy in this patient population is sparse. The purpose of this study was to evaluate the clinical effect of omalizumab therapy on patient symptoms of recurrent CRS.

**METHODS:** A non-concurrent prospective cohort study with 25 patients diagnosed with CRS having failed surgical and/or medical therapy on omalizumab and five control patients who met omalizumab therapy indications but could not access coverage. Data extraction targeted demographic details, asthma, environmental allergy and CRS specific disease related data. Change in overall and each of the major symptoms of CRS were rated on a 10 cm visual analogue scale (VAS). The Mann-Whitney test was used to compare symptom improvement between groups.

**RESULTS:** Mean treatment duration was 19 months. 76% of omalizumab treated patients had CRS with polyps, 33% had AERD. Omalizumab therapy provided a mean overall symptom improvement of 69.5% (individually: facial pain 78.5%, nasal obstruction 69.8%, rhinitis 56.2%, and olfaction 55.8%). For the control group, mean overall symptom improvement since omalizumab screening was 16.8%: nasal obstruction 15.2%, rhinitis 16.4%; there was no improvement in olfaction or facial pain. Symptom improvement was significantly higher for omalizumab treated patients in every category (p <0.05).

**CONCLUSIONS:** Omalizumab treatment provided significant improvement in every major clinical symptom of CRS in the treated cohort of patients with severe recurrent CRS in comparison to the control cohort. A well-designed randomised clinical trial is needed to further assess the efficacy and safety of omalizumab treatment for CRS.
Evidence for circadian rhythm disruption in chronic rhinosinusitis

Mahboobeh Mahdavinia, MD, PhD1, Helen J. Burgess, PhD2, Jason Ong, PhD3, Pete S. Batra, MD4, Robert P. Schleimer, PhD, FAAAAI2, and Ali Keshavarzian, MD5. 1Department of Immunology and Microbiology, Allergy and Immunology Section, Rush University Medical Center, Chicago, IL; 2Department of Behavioral Sciences, Biological Sciences Research Laboratory, Rush University Medical Center, Chicago, IL; 3Department of Neurology, Sleep Medicine Section, Northwestern University Feinberg School of Medicine, Chicago, IL; 4Department of Otorhinolaryngology-Head and Neck Surgery, Rush University Medical Center, Chicago, IL; 5Department of Medicine, Division of Allergy-Immunology, Northwestern University Feinberg School of Medicine, Chicago, IL. 6Department of Internal Medicine, Division of Digestive Diseases and Nutrition, Rush University Medical Center, Chicago, IL.

RATIONALE: Circadian rhythms are the physiological processes of the human body that cycle every 24 hours. They are controlled by multiple endogenous and exogenous factors. When disrupted, they have significant metabolic, psychologic and sleep-related consequences. Patients with chronic rhinosinusitis(CRS) have increased sleep disruption; however circadian rhythms have never been investigated in this condition.

METHODS: We did a prospective case-control study of 142 CRS patients and 40 controls. All were interviewed about their weekly sleep and activity through standard questionnaires: 1) Munich ChronoType Questionnaire, which investigates circadian rhythms and social jet-lag (>2 h shift in the sleep-wake cycle between work-days and free-days); 2) OwL-and-Lark (O&L) that measures chronotype. Chronotype is the individual’s tendency to sleep and wake-up at a particular time during a 24-h period and a behavioral manifestation of the circadian rhythms. Electronic charts were also reviewed for demographics and medical history. Logistic or linear regression analyses were done to correct for BMI, age and gender. Cases on medications that affected sleep were excluded.

RESULTS: CRS cases shifted their sleep times by 0.94 ± 0.83h (mean ± SD) between weekend and week-day wake-up times; controls shifted 0.51 ± 0.52h; (p < 0.05). Social jetlag was seen in 15.8% of CRS and 3.2% of controls. Total O&L scores were lower in CRS than controls (56.09 ± 8.702 vs. 61.27 ± 1.950, respectively; p < 0.05) indicating their tendency towards a later chronotype.

CONCLUSIONS: Patients with CRS have increased circadian disruption and a significant shift in their circadian rhythms towards a later chronotype. This disruption could affect other physiological systems and their metabolism, and calls for future studies investigating its underlying mechanism.

Unsupervised network modeling of specific odors in patients referred for rhinitis-sinusitis

Meredith Haskins, MD1, and Rohit Divekar, MBBS, PhD2. 1Hennepin County Medical Center, Minneapolis, MN; 2Mayo Clinic, Rochester, MN.

RATIONALE: Partial or complete secondary anosmia is an important symptom in chronic rhinosinusitis (CRS). We wished to perform unsupervised modeling of odorant perception in sinus disease for quantitative and qualitative assessment of smell loss.

METHODS: This was a retrospective review of 222 patients who underwent olfactory testing (2011-2015) at the Mayo Clinic. Olfactory testing was done with ‘brief smell identification test’ (Sensonics®). Respiratory diagnoses were physician assigned: asthma (19%), chronic rhinosinusitis with nasal polyps (CRSwNP, 24%) and without nasal polyps (CRSsNP, 27%). Atopy (47%) was defined as presence of a positive skin or in-vitro test. Laboratory data CBC, eosinophil count and total IgE were collected where available. Unsupervised bipartite (odorant – subject) network model was generated to assess qualitative and quantitative relationships between degree and nature of secondary hyposmia.

RESULTS: There were no gender differences in odorant perception (P = 0.66). Hyposmia defined as abnormal score < 9 was reported by 13.5% of total cohort. Univariately CRSwNP or asthma were associated with hyposmia (P < 0.001). CRSsNPs or atopy were not associated with hyposmia (P > 0.05). Degree of hyposmia correlated inversely with total IgE and blood eosinophil count (P < 0.05). Unsupervised network validated poorer smell perception with CRSwNP and comorbid asthma. Inability to smell specific scents showed trend towards spatial co-localization. A number of non-chronic sinusitis controls were unable to perceive gasoline.

CONCLUSIONS: Quantitative and qualitative assessment of secondary hyposmia showed association with CRSwNP and comorbid asthma. Clustering of specific odors was not seen, however larger studies with expanded odorant panels are needed to further clarify the findings.
IgG4 Sinusitis in Association with Aspirin Exacerbated Respiratory Disease

Kirit J. Johal, MD1, Kevin C. Welch, MD2, and Anju T. Peters, MD, FAAAAI3. Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL. 2Department of Otolaryngology, Northwestern University Feinberg School of Medicine, Chicago, IL.

RATIONALE: IgG4-related disease (IgG4-RD) is an emerging systemic inflammatory disease, now recognized in numerous organs. Aspirin Exacerbated Respiratory Disease (AERD) is defined as asthma, chronic rhinosinusitis with nasal polyposis and hypersensitivity to cyclooxygenase-1 inhibitors. A type II inflammatory mechanism has been suggested as the underlying defect in both AERD and IgG4-RD. We report the first case of IgG4-RD of the sinuses in an individual with co-existing AERD.

METHODS: Serum samples were obtained. H&E stains and IgG immunohistochemical stains were performed on sinonasal biopsy specimens.

RESULTS: A non-smoking male with history of AERD presented with left eye proptosis and epiphora worsening over one year, as well as chronic nasal symptoms. CT sinus demonstrated asymmetric enlargement of the left orbit extraocular muscles and bony expansion of the pterygopalatine fossa with erosions. Serum IgG level was within normal limits, however, the serum IgG4 subclass was elevated. Endoscopic sinus surgery was performed. Biopsy of the left pterygopalatine mass demonstrated sinonasal mucosa with dense lymphoplasmacytic infiltrate, increased IgG4+ plasma cells, and associated focally increased fibrosis. Right sinonasal mucosa showed similar findings. In conjunction with surgical intervention, our patient responded well to prednisone therapy.

CONCLUSIONS: We report a case of IgG4-RD occurring concurrently with AERD. While thought to be rare, IgG4-RD is increasingly being recognized as affecting many organ systems. Healthcare workers who treat patients with AERD should be aware that IgG4-RD and AERD may present concurrently in the sinonasal cavity.

The Impact of Chronic Sinusitis on Subjects Suffering from Persistent Cough

Hiroko Nogami, Chie Oshikawa, Satoshi Honjo, and Tomoaki Iwanaga; National Hospital Organization Fukuoka Hospital, Fukuoka, Japan.

RATIONALE: Upper respiratory diseases have been linked with lower respiratory diseases. However, it has not been fully evaluated that the impact of chronic sinusitis on the subjects with persistent cough. We investigated the impact of chronic sinusitis to the subjects with persistent cough.

METHODS: One hundred fifty subjects (84 females, 66 males, mean age 50.8 ± 15.6 years) suffering from cough over three weeks were included. Their chest X-ray and auscultation were normal. They underwent para-nasal sinus X-ray. If any one of the following findings including mucosal thickening, opacity, and air-fluid level was observed in the X-ray, the subject was considered as having comorbid sinusitis. Cough duration, ventilatory function using spirometer, CBC, IgE and the final diagnosis were ascertained with medical records. We compared those data according to the presence of comorbid sinusitis.

RESULTS: Among the 150 subjects, 60 subjects (40%) had radiologic evidence of sinusitis. The final diagnosis of 60 subjects were cough variant asthma (n = 27), asthma (n = 4), post nasal drip syndrome (3), sinus bronical syndrome (4), post infectious cough (4), and unknown (3). Subjects with chronic sinusitis had significantly lower forced expiratory volume % in one second (FEV1/FVC%), %V50 and %V25 than those without chronic sinusitis. The number of eosinophils / white blood cells (%) of subjects with sinusitis had significantly higher than those without sinusitis

CONCLUSIONS: Chronic sinusitis was complicated in 40.0% of the subjects who had persistent cough over three weeks. The presence of comorbid sinusitis was suggested to be in conjunction with obstructive ventilation disorder.

IgG4 Sinusitis with Intracranial Extension – A Case Series

Meera Mehta1, and Jennifer A. Shih, MD2. 1Emory University School of Medicine, Atlanta, GA. 2Emory University, Atlanta, GA. Children’s Healthcare of Atlanta, Atlanta, GA.

RATIONALE: Allergic fungal rhinosinusitis (AFRS) is a localized allergic reaction to noninvasive fungal growth in an immunocompetent host. Criteria for diagnosis include: 1) nasal symptoms that persist for 12 weeks or longer, 2) presence of eosinophilic mucin in a sinus cavity, 3) immunocompetence, 4) characteristic radiography, 5) systemic fungal allergy. AFRS has been described in adults, but rarely in children.

METHODS: Hospital charts of 7 children diagnosed with AFRS via previously published criteria were reviewed. Demographics, clinical presentation, lab evaluations, radiographs, pathology, treatment course, and outcomes after a 6-year follow-up period were recorded.

RESULTS: Seven patients (mean age 13yr ± 1.87yr, male 3/7 (43%), female 4/7 (57%)) presented with the following symptoms: proptosis (n = 2), asthma (n = 2), nasal congestion (n = 2), polyps (n = 5), and intracranial extension (n = 2). The racial distribution was African American 4/7 (57%), and Asian 3/7 (43%). All were diagnosed in the SE United States between June 2008 and June 2010. All had radiographic evidence of sinusitis and specific IgE to fungal organisms. All fit defining criteria. The most common fungus identified was Bipolaris species (57%). Post surgical treatment included antifungals and immunotherapy. One patient presented during her first recurrence. At follow-up, 1/6 (17%) had recurrence of disease. One patient was lost to follow-up.

CONCLUSIONS: This case series of pediatric patients with allergic fungal rhinosinusitis had significantly lower recurrence rate over an 8 year study period compared to historic recurrence rates of 90%. Interesting observations of this cohort include the rate of intracranial extension 2/7 (28%) and an exclusively minority racial distribution.

Surgery Vs. Medical Treatment in Patients with Chronic Rhinosinusitis

Aimi Thakor Philipp, MD1, Frederick Yoo, MD2, Marilene Wang, MD3, and Joseph S. Yusin, MD, FAAAAI4. 1VA Greater Los Angeles Health Care System, Los Angeles, CA. 2VA Greater Los Angeles Healthcare System, Los Angeles, CA.

RATIONALE: Chronic Rhinosinusitis (CRS) is an inflammatory disease of the nasal and paranasal sinus mucosa that is present for longer than three months. Some patients opt for sinus surgery as treatment and it would be helpful to predict which patients would do best with surgical intervention versus medical treatment. Our study assesses clinical differences between nonsurgical patients and surgical patients suffering from CRS over a two year period and whether CT staging can predict outcome.

METHODS: Our study compared two patient groups diagnosed with CRS: surgical patients vs. non-surgical patients. Both groups received conventional medical management. Associations were investigated using preoperative Lund staging for sinus CT results and comparing the Sino-Nasal Outcome Test (SNOT-22) among participants periodically over two years.

RESULTS: Seventeen patients were followed for two years and administered the SNOT-22 every three to six months. There was no significant difference in SNOT-22 scores between the surgical and non-surgical patients (P = 0.877). The Lund score based on the original sinus CT scan did not predict outcome between these two populations of patients using the SNOT-22 scores. Both groups showed various stages of improvement and exacerbations over the two year period.

CONCLUSIONS: This study emphasizes the difficulty of treating patients suffering from chronic sinusitis. Larger studies are needed to determine if there truly is a difference in clinical outcomes between the two groups and if this can be determined by use of CT staging.
Alveolar Macrophages from House Dust Mite-Tolerant Mice Induce Foxp3+ Regulatory T Cells in an IL-10-Independent Manner

Sonali J. Bracken, Alexander J. Adami, Linda A. Guernsey, Robert R. Clark, Evan R. Jellison, Craig R. Schramm, and Roger S. Thrall; University of Connecticut Health, Farmington, CT.

RATIONALE: Alveolar macrophages (AMs) are critical for maintaining immune tolerance in the lung. Previous studies have shown that naïve AMs can induce Foxp3+ regulatory T cells (Tregs) but lose this ability when initially exposed to inhaled allergens, thereby promoting the development of asthma.

The purpose of this study was to determine whether long-term exposure to inhaled house dust mite (HDM) improves the ability of AMs to induce Tregs.

METHODS: We have previously established that short-term (2 wk) HDM exposure induces allergic airway disease (AAD) whereas long-term (11 wk) exposure promotes tolerance to HDM (i.e. suppression of allergic inflammation with increases in pulmonary Tregs and IL-10+ AMs). AMs were sorted from the lungs of HDM-AAD (2 wk) and HDM-tolerant (11 wk) C57BL/6 mice and co-cultured with naïve CD4+Foxp3 T cells in the presence or absence of exogenous TGF-β and IL-10/IL-10R blockade for 72 hours. The percentage of induced Foxp3+ Tregs was then examined.

RESULTS: AMs from HDM-tolerant mice induced significantly more Tregs than HDM-AAD mice (31% vs 14%, p = 0.0001), suggesting that AMs adopt regulatory functions following long-term allergen exposure. This effect was dependent upon the addition of exogenous TGF-β and was not reversed following IL-10/IL-10R blockade (p = 0.15).

CONCLUSIONS: These findings suggest that the generation of regulatory AMs following long-term HDM exposure may play an important role in the suppression of HDM-induced asthma through induction of Tregs. RNA sequencing studies are currently underway to determine the players involved in regulatory AM-mediated Treg induction, as these cells are a promising immunotherapeutic target for asthma.

Airway Exposure to Staphylococcus Aureus Particles Promotes Development of Antigen-Specific Th2-Type Immunity to Inhaled Antigens through Production of Interleukin-1 Alpha (IL-1 alpha)

Kenichiro Hara; Gunma University Graduate School of Medicine, Department of Respiratory Medicine, Maebashi, Japan.

RATIONALE: We have already reported that airway exposure to Staphylococcus aureus (S. aureus) particles promotes development of ovalbumin (OVA)-specific Th2-type immunity to inhaled antigens through production of thymic stromal lymphopoietin (TSLP) in mice model of chronic bronchial allergic inflammation. In early phase, airway administration of S. aureus increased bronchoulveolar lavage (BAL) levels of IL-10a and IL-1β. Therefore, we tested the hypothesis that airway exposure to S. aureus facilitates Th2-type immune responses through IL-1α in the airway.

METHODS: S. aureus particles or recombinant IL-1α were administered intranasally (i.n.) to naive BALB/c mice or IL-1 receptor-1 knockout mice (IL-1R1KO). Alternatively, S. aureus particles or IL-1α were administered together with endotoxin-free OVA (i.e. chronic exposure) on days 0 and 7, and mice were then exposed to OVA alone i.n. on days 21,22 and 23.

RESULTS: Airway administration of S. aureus particles to naïve mice increased BAL levels of IL-1α, and then did them of TSLP in early phase. In the chronic model, airway exposure to OVA alone did not sensitize naïve mice. In contrast, naïve mice treated with both IL-1α and OVA developed OVA-specific Th2-type immune responses in a TSLP-dependent manner, when exposed to OVA alone, they developed airway eosinophilia, peribronchial hypertrophy, and increased BAL levels of IL-5 and IL-13. Moreover, airway Th2 response to OVA was significantly inhibited in IL-1R1KO mice.

CONCLUSIONS: Airway exposure to S. aureus promotes development of Th2-type immune responses to inhaled antigens through production of IL-α. Inhibition of IL-1α may be effective in the treatment of patients with allergic asthma.

Tr1 Cell Identification and Phenotype in Children with and without Food Allergy

Jenna R. Bergerson, MD, MPH; Kristin Erickson, MD, and Anne Marie Singh, MD; 1Northwestern University, Division of Allergy and Immunology, Chicago, IL; Division of Allergy-Immunology, Department of Pediatrics, Ann & Robert H. Lurie Children’s Hospital of Chicago, Chicago, IL; 2Northwestern University Feinberg School of Medicine, Chicago, IL; 3Division of Allergy & Immunology, Department of Pediatrics, Ann & Robert H. Lurie Children’s Hospital of Chicago, Northwestern University Feinberg School of Medicine, Chicago, IL; Northwestern Feinberg School of Medicine, Chicago, IL.

RATIONALE: Tr1 cells are a subtype of peripherally induced regulatory T cells and are thought to be pivotal in promoting and maintaining oral tolerance. As early life is a critical period for establishing oral tolerance, we sought to investigate the role of food allergy diagnosis and age on Tr1 cells in children with and without FA.

METHODS: Peripheral blood mononuclear cells were isolated from 30 pediatric patients and analyzed using flow cytometry. Populations of Tr1 cells (CD4+CD45RA-Lag3+CD49b+) were determined in children with and without FA, and compared by Mann-Whitney test.

RESULTS: Overall, the percentages of Tr1 were significantly higher (0.57 ± 0.39, p = 0.023) in healthy children compared to food allergic children. When examining the effect of age, percentages of Tr1 cells were significantly higher (0.55 ± 0.18, p = 0.038) in young healthy children <6 years old compared to food allergic children <6 years old. In addition, healthy children <6 years old had significantly more CD4+CD45RA-Lag3+CD49b+ cells that express the putative gut homing marker CCR6+ than their peers with FA (0.28 ± 0.08, p = 0.0041).

CONCLUSIONS: Overall, children without FA have a higher percentage of Tr1 cells than food allergic children, and younger control children have significantly more Tr1 cells. Furthermore, gut-homing Tr1 cells in younger children may be important in the development of oral tolerance. These data suggest that Tr1 cells are important in oral tolerance, particularly in younger children.

Follicular Helper T (Thh) Cells Mediate Peanut Allergy

Takao Kobayashi, PhD; Joseph J. Dolence, PhD2; Koji Iijima, PhD2, and Hirohito Kita, MD; 1Mayo Clinic Rochester, Rochester, MN, 2Mayo Clinic, Rochester, MN.

RATIONALE: While peanut allergy is a major medical problem, the immunologic mechanisms of the disease have not been fully understood. Follicular helper T (Thh) cells are specialized in supporting B cell maturation and antibody production. The goal of this study was to investigate the roles for Thh cells in the development of peanut allergy by using mouse models.

METHODS: To induce peanut allergy, naïve BALB/c mice were exposed intranasally (i.n.) to peanut flour for 4 weeks. FACS analyses, in vitro cell culture and gene-deficient mice were used to dissect the immunologic mechanisms.

RESULTS: When naïve mice were exposed i.n. to peanut flour, they developed peanut-specific IgE antibody in 2 weeks, which continued to rise for 4 weeks. Intraperitoneal challenge of these mice with peanut extract induced clinical signs of systemic anaphylaxis, including itching, reduced motility, and hypothermia. In IL-4 reporter mice, a large number of IL-4-competent Thh cells and a smaller number of Th2 cells were identified in the draining lymph nodes. Thh cells produced large quantities of IL-4 and IL-21 in vitro. Furthermore, TCRβ-deficient mice transfused with Thh cells produced >25x higher titers of peanut-specific IgE as compared to those transfused with Th2 cells. Finally, CD4-specific Bcl6 conditional knockout mice that are deficient in Thh cells (but Th2-cell compartment is intact) were totally protected from developing peanut-specific IgE antibody and anaphylactic responses.

CONCLUSIONS: Thh cells, but unlikely Th2 cells, mediate production of specific IgE antibody in peanut allergy. Thh cells may serve as a potential therapeutic target for food allergy.
**224** Age Difference in the Immune Response to Endotoxin (LPS) Shapes Th2-Mediated Airway Inflammation and Development of Asthma.

Beatriz León, PhD, and Andre Ballesteros-Tato; University of Alabama at Birmingham, Birmingham, AL.

**RATIONALE:** In addition to genetic factors, environmental exposures is also of primary importance for the development of asthma and allergy disorders in children, as demonstrated by epidemiological data showing children growing up in traditional farms seem to develop asthma less often than children growing up in urban areas. According to the hygiene hypothesis, this is due to increased exposure to endotoxin (LPS) and other farm-related microorganism-derived compounds. However little is known about how early-life contact to microbial compounds influence the development of asthma.

**METHODS:** Adult (8 weeks-old) and infant (3 weeks-old) mice were intranasally (i.n.) sensitized with 25μg of house dust mite (HDM) allergen extract in the presence of different doses of LPS, for 3 consecutive days. 3 weeks later, mice were i.n. challenged with 25μg of HDM extract for 3 consecutive days.

**RESULTS:** HDM allergen sensitization in adult mice induced T-helper type 2 (Th2)-driven airway inflammation, i.e., influx of Th2 cells into the airways, airway eosinophilic inflammation and increased IgE-producing plasmablasts. In contrast, HDM allergen sensitization with low-dose LPS (10 μg) abrogated HDM-driven Th2-mediated allergic airway inflammation without increasing Th1 cell trafficking into the airways. Unlike adults, infant mice exposed to HDM with low-dose LPS (10 μg) developed Th2 responses allergic airway inflammation and required allergen sensitization with high-dose LPS (100 μg) to effectively suppress allergen-specific Th2 responses and allergic inflammation.

**CONCLUSIONS:** These results show that airway exposure levels of endotoxin provide different protection against asthma and allergies in adults and infants.

**225** Peanut Specific-CD4+ T Cells Responses in Peanut Allergic and Peanut Sensitized but Tolerant Subjects

William W. Kwok, PhD1, Mary L. Farrington, MD2, Elizabeth Whalen, PhD3, Erik R. Wambre, PhD, MBE1, Kari Nadeau, MD, PhD4, and Amedee Renand, PhD5; 1Benaroya Research Institute at Virginia Mason, Seattle, WA, 2Virginia Mason Medical Center, Seattle, WA, 3Benaroya Research Institute, Seattle, WA, 4Pediatric Allergy Immunology, Stanford University School Medicine, Stanford, CA, 5Benaroya Research Institute at Virginia Mason, Seattle.

**RATIONALE:** The immunogenicity of different Ara h components in eliciting specific CD4 T cell responses in both peanut allergic and peanut sensitized but tolerant subjects (i.e. presence of peanut specific IgE but non-reactive to peanut food challenge) remains unclear.

**METHODS:** Fourteen allergic and six tolerance subjects were recruited. T cell responses toward Ara h 1, 2, 3, 6 and 8 were evaluated by CD154 up-regulation assays. T cell responses towards Ara h 2 were also evaluated by tetramer staining assay.

**RESULTS:** T cell responses against Ara h 1, 2, 3 and 6 were significantly stronger compared to response against Ara h 8 in allergic subjects. Phenotypes of Ara h 2- and Ara h 1, 3, 6-specific T cells were heterogeneous and could be CCR4+CD27-CRT1H2+, CCR4+CD27+CCR6+ or CCR4+CD27+CCR6-+ Experiments with both CD154 up-regulation and tetramers staining assay in evaluating Ara h 2 responses gave similar outcomes. Peanut-sensitized but tolerance subjects had significantly lower frequencies of Ara h 2 and Ara h 1, 3, 6-specific T cells compared to allergic subjects. Ara h 8-specific responses in most subjects of this group were very weak or absent.

**CONCLUSIONS:** Specific memory CD4 T cell response with a predominant TH2 phenotype against Ara h 1, 2, 3 and 6, but not against Ara h 8, was related to an allergic response. Conversely, a weak or an absence of a specific memory CD4 T cell response against Ara h 1, 2, 3 and 6 was related to an absence of a clinical response in peanut sensitized but tolerant subjects.
**227 Analysis of Peanut-specific T Cells as a Tool to Monitor State of Disease**

Veronique Schulten, PhD1, Carla Oseroff2, Victoria Trippe2, Kari C. Nadeau, MD, PhD, FAAAAI1, Monali Manohar1, Alessandro Sette, PhD3, and Bjorn Peters5; 1La Jolla Institute for Allergy and Immunology, La Jolla, CA, 2La Jolla Institute for Allergy & Immunology, La Jolla, CA, 3Stanford University, Stanford, CA, 4Stanford University School of Medicine, Stanford, CA, 5La Jolla Institute for Allergy & Immunology, La Jolla, CA.6La Jolla Institute for Allergy and Immunology, San Diego, CA.

**RATIONALE:** Peanuts are among the most severe triggers for food allergy. Peanut allergy prevalence is increasing worldwide and only about 20 percent of affected individuals outgrow it later in life. CD4+ T cells play a major role in the pathophysiology of peanut allergy as well as tolerance induction by administration of desensitization regimens such as oral immunotherapy.

**METHODS:** To improve our understanding of the peanut-specific T cell response, we mapped T cell epitopes for three major peanut allergens, Ara h 1, 2 and 3 using cytokine production in PBMC from peanut-allergic children as measured by ELISPOT as a read-out.

**RESULTS:** In total, 83 peptides from 39 different regions were identified (32 from Ara h 1, 17 from Ara h 2 and 44 from Ara h 3), of which 61 peptides elicited responses in 3 or more donors. A pool containing the 19 most immunodominant peptides, accounting for 46% of the total response, was further validated as a diagnostic tool to discriminate T cell responses from allergic vs non-allergic individuals more effectively compared to peanut extract. Finally, HLA class II restrictions were determined and used for production of tetramer reagents. Tetramer staining allowed detailed phenotypic characterization of peanut-specific T cells by flow cytometric analysis from peanut sensitized individuals, who exhibit severe symptoms compared to those unresponsive to peanut despite comparable peanut-specific IgE titers and T cell reactivity to peanut extract.

**CONCLUSIONS:** Our results demonstrate that the peanut-specific T cell response can be used as a biomarker to distinguish peanut allergic cohorts with different disease severity.

**228 ILC2 Are Activated By Macrophages through Pla2g5-Dependent Generation of Linoleic Acid and Oleic Acid**

Munehiro Yamaguchi1, Jannatul Firdous2, Joshua A. Boyce, MD, FAAAAI1, and Barbara Balestrieri, MD3; 1Showa University, Tokyo, Japan, 2Brigham and Women’s Hospital, Boston, MA, 3Brigham and Women’s Hospital, Division of Rheumatology, Immunology, and Allergy, Boston, MA.4Brigham and Women’s Hospital/ Harvard Medical School, Boston, MA.

**RATIONALE:** Group V phospholipase A2 (Pla2g5) is a lipid-generating enzyme necessary for development of M2 macrophages and their effector functions in allergic lung inflammation. We hypothesized that free fatty acids (FFAs) produced by Pla2g5-expressing macrophages contribute to ILC2 activation.

**METHODS:** C57BL/6 Wt and Pla2g5-null mice were exposed Alternaria alternata or recombinant (r)-IL-33 intranasally for 10 days. Innate lymphoid cells (ILCs), CD45+ Lin- (CD3, CD19, Ly6g, CD11c, CD11b, Nk1.1, FceR1), Thy1.2+ and eosinophils were measured by FACs. Lung IL-33 was measured by western blots. Pla2g5-null and Wt mice received Wt bone marrow (BM)-macrophages intratracheally at day 2, followed by Alternaria intranasally at day 3, 6 and 9 or only Alternaria. FFAs were measured by mass spectrometry in Wt and Pla2g5-null BM macrophages.

**RESULTS:** Alternaria-treated Wt mice had significantly increased numbers of eosinophils and activated ILC2s expressing Sca-1, CD25, ST2, IL-13 and IL-5, and increased amounts of IL-33 protein in the lung, compared to Alternaria-treated Pla2g5-null mice. Exogenous administration of r-IL-33 did not restore eosinophilia and ILC2 activation in Pla2g5-null mice. However, the number of eosinophils and activated ILC2s was significantly increased in Alternaria-treated Pla2g5-null mice receiving Wt BM-macrophages compared to Alternaria-treated Pla2g5-null mice. Pla2g5-null BM-macrophages produced less medium-long chain FFAs, including linoleic acid (LA) and oleic acid (OA). Furthermore, intranasal administration of LA and OA increased eosinophilia and the number of IL-5+ILC2 in a Pla2g5-dependent manner.

**CONCLUSIONS:** Macrophages activate ILC2 through Pla2g5-dependent generation of LA and OA.

**229 A New Approach Identifies a Previously Unrecognized and Dominant Population of Human Type-2 Innate Lymphoid Cells (ILC2s)**

Mukesh Verma, Sucai Liu, PhD, Lidia Michalec, PhD, Anand Sripada, Donald Rollins, MD, James Good, MD, Magdalena M. Gorska, MD, PhD, and Rafeul Alam, MD, PhD, FAAAAI; National Jewish Health, Denver, CO.

**RATIONALE:** The CRTH2+ ILCs are widely referred to as human ILC2s. The extent of type-2 cytokine production by non-CRTH2 ILCs is not well recognized.

**METHODS:** We studied ILCs from blood and lung obtained from asthmatic patients and disease controls, and from transplant-rejected lung donors. We characterized ILCs by RNA-seq, flow cytometry and ELISA.

**RESULTS:** CRTH2 and other cell surface-markers (IL7Ra, CD161, and KLRG1) of ILC2s were highly plastic and underwent up- and down-regulation when cultured at different cell densities or with cytokines/mediators. Consequently, no single combination of the surface-markers captured all IL5+, IL13+ or GATA3+ ILC2s. The use of additional GATA3-inducible surface-markers (IL25R, IL33R, TSLPR, ICOS, CCR4, CD30, and CD200R1) failed to capture all type-2 cytokine+ ILC2s. The median frequency of IL5+ cells in CRTH2+ and IL7Rx+ populations was 0.9% and 0.8% of BAL cells (N=32 asthma patients). In contrast, CRTH2- and IL7Rx+ populations, and from transplant-rejected lung donors. We characterized ILCs by RNA-seq, flow cytometry and ELISA.

**CONCLUSIONS:** CRTH2+ and other cell surface-markers (IL7Ra, CD161, and KLRG1) of ILC2s were highly plastic and underwent up- and down-regulation when cultured at different cell densities or with cytokines/mediators. Consequently, no single combination of the surface-markers captured all IL5+, IL13+ or GATA3+ ILC2s. The use of additional GATA3-inducible surface-markers (IL25R, IL33R, TSLPR, ICOS, CCR4, CD30, and CD200R1) failed to capture all type-2 cytokine+ ILC2s. The median frequency of IL5+ cells in CRTH2+ and IL7Rx+ populations was 0.9% and 0.8% of BAL cells (N=32 asthma patients). In contrast, the frequency of IL5+ cells in the CRTH2+IL7Rx- (DN)double negative but CD25+ population was 2-fold higher (0.2%. P=0.03). Similarly, the blood DN population contained 2-3 fold higher number of IL5+ cells (median 0.07% vs 0.02% and 0.03% of PBMC in the CRTH2+ and IL7Rx+ populations, respectively). Adoptive transfer of human lung ILC2 subpopulations to Rag1-/-:c/- mice and followed by Alternaria challenge showed that CRTH2+, IL7Rx+ and DN ILC2s were equipotent in inducing airway hyperreactivity.

**CONCLUSIONS:** Quantification of ILC2s through the detection of type-2 cytokine+ cells in the lineage- cell population provides the most accurate count of ILC2s in biological samples and avoids underestimation that results from the use of cell surface-markers (e.g. CRTH2).
230 Characterization of Myeloid and Plasmacytoid Dendritic Cells in Microbes, Allergy, Asthma and Pets (MAAP) Birth Cohort Infants

Stacey M. Bellemore1, Alexandra Sitark1, Suzanne L. Havstad1, Erik T. Mann1, Albert M. Levin2, Susan V. Lynch, PhD2, Dennis R. Owosky3, Christine C. Johnson1, Nicholas W. Lukacs4, Edward M. Zoratti5, Kimberly J. Woodcroft6, and Kevin R. Bobbitt3, 1Henry Ford Health System, Detroit, MI, 2University of California, San Francisco, San Francisco, CA, 3Medical College of Georgia at Augusta University, Augusta, GA, 4University of Michigan, Ann Arbor, MI.

RATIONALE: Dendritic cells (DCs) are essential for the induction and regulation of immune responses; however, little is known about the characteristics of DCs in very early life. The purpose of this study was to prospectively characterize selected DC functional markers, which are associated with inducing a Th1 or Th2 immune response, from birth through 6 months of age.

METHODS: Peripheral blood mononuclear cells from 47 infants with both cord and venous blood at 6 months were isolated and cultured, in vitro, with medium alone or PHA, CpG or LPS for 48 hours, then analyzed by flow cytometry. DCs (Lin–Class II+) were classified as either myeloid (mDCs, CD11c+) or plasmacytoid (pDCs, CD123+) and analyzed for additional markers (OX40L, CD86, TLR4) expressed as percent of mDC or pDC. Paired t-tests were used to assess change over time.

RESULTS: In general, mDCs exhibited higher percentages of cells expressing activation markers than pDCs. The mean percentage of OX40L+ mDCs in unstimulated cells significantly decreased over time (cord=26.6%, 6-month=12.9%, p=0.007). In unstimulated cells and following LPS stimulation, fewer mDCs at 6 months were TLR4+ than at birth (unstimulated: cord=37.0%, 6-month=18.7%, p=0.009; LPS-stimulated: cord=39.1%, 6-month=19.6%, p=0.009). In contrast, CD86+ pDCs marginally increased from cord to 6-months of age following CpG stimulation (cord 40.7%, 6-month 51.4%, p=0.12).

CONCLUSIONS: This study provides novel information regarding very early life changes in functional marker expression in stimulated and unstimulated mDCs and pDCs. Patterns of early life DC functional marker expression may be linked to regulation of Th2 inflammation and the risk of allergy.

231 Testosterone attenuates group 2 innate lymphoid cell cytokine expression and innate immune-mediated airway inflammation

Jacqueline Cephus1, Matt T. Stier2, Hubaida Fuseini3, Shinji Toki, PhD4, Melissa H. Bloodworth2, Weisong Zhou, PhD3, Kasia Goleniewska5, Jian Zhang6, Kelli L. Boyd2, Stokes Peebles, MD, FAAAAI4, and Dawn C. Newcomb, PhD5, 1Vanderbilt University, Clarksville, TN, 2Department of Pathology, Microbiology, and Immunology, Vanderbilt University, Nashville, TN, 3Department of Pathology, Microbiology, and Immunology, Vanderbilt University, Nashville, TN, 4Vanderbilt University School of Medicine, Nashville, TN, 5Division of Allergy, Pulmonary and Critical Care Medicine, Vanderbilt University School of Medicine, Nashville, TN, 6Division of Allergy, Pulmonary, and Critical Care Medicine, Vanderbilt University, Nashville, TN.

RATIONALE: Sex hormones are important in asthma pathogenesis, as women have an increased prevalence of asthma compared to men. Group 2 innate lymphoid cells (ILC2) help establish airway inflammation in asthma, but the role of sex hormones in regulating ILC2-mediated airway inflammation remains unknown. We hypothesize that testosterone and its derivative, 5a-dihydrotestosterone (DHT), negatively regulate ILC2 cytokine expression and ILC2-mediated airway inflammation.

METHODS: In vitro, sorted lung ILC2 were stimulated with IL-2 and IL-33 plus 5a-DHT (0-3nM) or vehicle (n=5). After 6 days, IL-5 and IL-13 production was measured by flow cytometry and mRNA expression of ILC2 transcription factors, RORalpha, Gata3, and Id2, were measured by qPCR. For in vivo studies, sham-operated or gonadectomized female and male BALB/c mice were intranasally challenged with 5μg of Alternaria extract (Alt Ext) or vehicle for 4 consecutive days (n=6-9). Lungs and bronchoalveolar lavage (BAL) fluid were harvested on day 5 for analysis of IL-5 and IL-13 production and infiltration of inflammatory cells.

RESULTS: In cultured ILC2, 5a-DHT decreased CD25 expression, a component of the IL-2 receptor required for ILC proliferation, as well as IL-5 and IL-13 production (p<0.05). 5a-DHT also decreased mRNA expression of RORalpha, but not Gata3 or Id2, in cultured ILC2. In vivo, testosterone decreased IL-5 and IL-13 production from ILC2 as well as eosinophil infiltration into the BAL fluid (p<0.05).

CONCLUSIONS: Testosterone and 5a-DHT negatively regulate ILC2-mediated airway inflammation by decreasing ILC2 cytokine production. These data provide a potential mechanism for the increased asthma prevalence in women compared to men.

232 A Phase 1 Study of ANB020, an anti-IL-33 monoclonal Antibody in Healthy Volunteers

Marco Londei, Brian Kenney, Gerrit Los, and Margaret H. Marino; AnaptysBio, San Diego, CA.

RATIONALE: IL-33 is a gatekeeper of atopic responses via activation of ILC2 leading to rapid Th2 cytokines release and by directly influencing pathogenic allergen specific T cells and mast cells activation. Therefore IL-33 inhibition may provide a therapeutic benefit to atopic patients. ANB020 is a humanized IgG1 antibody specific for human IL-33. ANB020 has high affinity against IL-33 and inhibits IL-33 activity in preclinical models.

METHODS: In this SAD and MAD Phase 1 study safety, tolerability and pharmacokinetic (PK) profiles were explored in healthy volunteers who received either single or multiple doses of ANB020 and pharmacodynamic (PD) profiles were explored in whole blood ex vivo assays. ANB020 was dosed over a range of 10 to 750 mg IV or SC. Subjects were randomized (3:1) to receive ANB020 or placebo. Dose escalation decisions were based on safety, tolerability and pre-specified adverse events (AEs) intensity and frequency. Safety and tolerability, PK, ex vivo PD were assessed over a period of 85 days.

RESULTS: ANB020 showed a good tolerability and safety profile with an equal AE representation in ANB020 and placebo dosed subjects. PK was linear at all doses tested for both IV and SC route of administration. Ex vivo PD activity was observed after single administration for over 43 days at the tested doses.

CONCLUSIONS: In this Phase 1 healthy volunteer study, the PK and PD results were shown to be compatible with a monthly dosing regimen. The results of this phase 1 study support the advancement of ANB020 into clinical studies for patients with atopic diseases.
233 Allergenicity and Immunomodulatory Effect of a Depigmented-Polymerized Peanut Extract Tested in a Mouse Model of Peanut Allergy

Philine A. Eigenmann, MD, FAAAAI1, Christophe Frossard1, Mayte Gallego2, Maria Morales Esteban2, and Jeronimo Carnes2. 1Geneva University Hospitals, Geneva, Switzerland, 2R&D Department, Laboratoryo LETI S.L., Madrid, Spain.

RATIONALE: The availability of animal models has allowed the investigation of different forms of immunotherapy. This study aims to investigate the allergenicity of a depigmented-polymerized peanut allergen extract in a mouse model of peanut allergy.

METHODS: Four-week-old CH3/HeOUJ female mice were divided in four groups of eight mice. Mice were orally sensitized with native extract (NE) (10 mg) or depigmented-polymerized extract (PE) (10 mg), 9 times at weekly intervals. At week 9 animals were orally challenged (100 mg of NE or 100 mg of PE). Serum samples were collected at 0, 30, and 45 days. Rectal temperature was measured every 10 minutes after challenge and the clinical score recorded.

• Group 1: sensitized with NE and challenged with NE
• Group 2: sensitized with NE and challenged with PE
• Group 3: sensitized with PE and challenged with NE
• Group 4: sensitized with PE and challenged with PE

RESULTS: Mice sensitized with NE showed high titers of peanut-specific IgE and IgG after sensitizations, significantly higher (p<0.05) than in mice sensitized with PE. After antigen challenges, Group 1 developed severe reactions while in Group 2, anaphylactic reactions were largely less severe than in Group 1. Group 3 developed severe anaphylactic reactions while in Group 4, 75% of animals did have significant symptoms. The body temperature correlated with the symptom score.

CONCLUSIONS: Sensitization with PE induced lower levels of antigen-specific antibodies. Moreover, mice challenged with PE experienced less clinical symptoms than NE indicating that depigmented-polymerized extracts are significantly less allergenic.

234 Antigen Absorption is Correlated With Allergic Reaction Severity Upon Oral Peanut Challenge in Mice

Kelly Orgel. Michael D. Kulis, PhD, Martin T. Ferris, Ping Ye, PhD, Rishu Guo, PhD, Darla R. Miller, Fernando Pardo-Manuel de Villena, and A. Wesley Burks, MD; University of North Carolina at Chapel Hill, Chapel Hill, NC.

RATIONALE: Current murine models of peanut allergy react on intraperitoneal challenge but fail to react on oral challenge, making them less physiologically relevant. However, a recently identified inbred mouse strain from the Collaborative Cross (CC) experiences a severe, systemic reaction on oral challenge. Differences between common lab strains and CC mice were characterized to determine which feature makes CC mice reactive.

METHODS: C3H/HeJ, C57BL/6J, and CC females were sensitized intragastrically at 4-6 weeks of age with peanut extract and cholera toxin for 4 weeks and then challenged intragastrically with peanut extract. Mice were bled one week post-sensitization and 60 minutes after challenge. Serumology and Ara h 2 (Ah2) absorption were compared between strains.

RESULTS: Within 15 minutes of challenge a significant decrease in body temperature was observed in CC mice, (n=12; mean: -2.8°C, range: 0.7-5.3°C) with no change in C3H/HeJ or C57BL/6J. Peanut-specific IgE (PNSIgE) and PNSIgG1 were significantly higher in CC mice compared to C3H/HeJ (p<0.05) but no different from C57BL/6J. PNSIgE did not correlate with reaction severity in CC mice. The major peanut component, Ah2 was detectable in the serum of CC and C57BL/6J, but not C3H/HeJ mice after challenge. However, serum quantities of Ah2 were significantly greater in CC mice compared to C57BL/6J (p<0.05), and serum Ah2 levels correlated with reaction severity (r²=0.5217, p=0.0011) in CC mice.

CONCLUSIONS: CC mice are an improved animal model of peanut allergy. Ah2 absorption into the circulation is correlated with systemic reactions in mice, and could be an important factor in humans experiencing severe reactions.

235 Murine Model of Food-Induced Anaphylaxis after Epicutaneous Sensitization

Masato Tamariki MD,1,2 Hideaki Morita, MD, PhD,1, Sumika Toyama1,3, Kenichiro Motomura, MD,1, Ken Arae, PhD1,4, Susumu Nakae, PhD,5 Hiroshi Saito, MD, PhD6, and Kenji Matsumoto, MD, PhD2. 1Department of Allergy and Clinical Immunology, National Research Institute for Child Health and Development, Tokyo, Japan, 2Department of Pediatrics, The Jikei University School of Medicine, Tokyo, Japan, 3Tokyo Medical and Dentistry Graduate School, Japan, Tokyo, Japan, 4Department of Immunology, Faculty of Health Science, Kyorin University, Tokyo, Japan, 5Laboratory of Systems Biology, Center for Experimental Medicine and Systems Biology, The Institute of Medical Science, The University of Tokyo, Tokyo, Japan, 6Department of Allergy and Immunology, National Research Institute for Child Health and Development, Tokyo, Japan.

RATIONALE: Food-induced anaphylaxis is reportedly most common in young children, but the precise reason for that remains unclear. In order to study the mechanisms of this phenomenon, we tried to establish a murine model of anaphylaxis to OVA through epicutaneous sensitization.

METHODS: BALB/c female mice, 1-4 weeks old, were epicutaneously sensitized with 400 mg OVA in a Finn Chamber on tape-stripped dorsal skin for 3 days/week for 3 weeks. After sensitization, each mouse received 5 mg OVA intragastrically, and the rectal temperature was measured. Serum OVA-specific IgE titers were measured by ELISA.

RESULTS: A significantly marked body temperature decrease was observed in younger mice compared with older mice. However, OVA-specific IgE titers were significantly lower in younger mice than older mice.

CONCLUSIONS: We successfully established a murine model of food-induced anaphylaxis after epicutaneous sensitization in which younger mice develop more severe anaphylaxis. Because that more severe anaphylaxis could not be explained on the basis of the serum antigen-specific IgE titer, some other mechanisms must underlie this phenomenon.

236 Effect of Proparacaine in a Mouse Model of Allergic Rhinitis

Hyun Hee Kim,1 Hwan Soo Kim,2 Yoon Hong Chun,1 Jong-seo Yoon1, and Jin Tack Kim1. 1Department of Pediatrics, College of Medicine, The Catholic University of Korea, Seoul, Korea, The Republic of, 2Bucheon St. Mary’s Hospital Department of Pediatrics College of medicine The Catholic University of Korea, Seoul, Korea, The Republic of.

RATIONALE: Lidocaine, a local anesthetic is a treatment option in uncontrolled asthma due to its immunomodulatory effects. In the present study, proparacaine, a derivative of lidocaine was evaluated for its therapeutic application in a mouse model of allergic rhinitis.

METHODS: The mice were divided into 4 groups: control group, allergic rhinitis (AR) group, ciclesonide (CIC) group, and proparacaine (PPC) group. Allergic symptom scores, eosinophil counts, goblet cell counts, and mast cells counts were measured. Serum OVA-specific IgE, OVA-specific IgG1, OVA-specific IgG2a, and cortisol levels were measured.

RESULTS: Intranasal administration of PPC significantly decreased allergic symptoms, infiltration of eosinophils, goblet cells, and mast cells in the nasal mucosa. Serum OVA-specific IgE, OVA-specific IgG1, OVA-specific IgG2a was significantly higher in the AR compared with the control group. Serum cortisol levels were not significantly different among the 4 groups.

CONCLUSIONS: PPC appears to be effective in treatment of mouse model of allergic rhinitis. This finding suggests that PPC might have a role in the treatment of allergic rhinitis.
**237 Pulmonary Immune Response Following Subchronic Stachybotrys chartarum Exposure**

Tara L. Crosston, PhD, 1 Ajay P. Nayak, PhD, 1 Angela R. Lemons, MS, 1 W. Travis Goldsmith, BS, 2 Dori M. Germolec, PhD, 1 Donald H. Beezhold, PhD, FAACAI, 1 and Brett J. Green, PhD, FAACAI; 1 Health Effects Laboratory Division, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Morgantown, WV, 2Toxicology Branch, Division of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.

**RATIONALE:** Exposures to fungal bioaerosols have been associated with respiratory morbidities. The mechanisms that underlie the pulmonary immune response to *Stachybotrys chartarum* requires further characterization. Here we examine the murine pulmonary microRNA (miRNA), mRNA, and proteomic profiles following *S. chartarum* subchronic inhalation exposure.

**METHODS:** Female B6CF1/N mice (n = 5-7) repeatedly inhaled viable *S chartarum* conidia (3.5*10^5* total) or HEPA-filtered air twice a week for 4 and 13 weeks. Lung tissue and bronchoalveolar lavage fluid (BALF) were collected at 24 and 48 hours following final exposure and processed for RNA, proteomic, and flow cytometry analyses.

**RESULTS:** Proteomic analysis showed a significant increase in chitinase-like proteins known to be associated with asthma. BALF cellularity revealed a Th2 response dominated by increased CD4+ T cells, IL-4, and IL-13 at 4 weeks that shifted to an IFN-γ Th1 dominant response after 13 weeks. Macrophages were elevated after 4 and 13 weeks of exposure, along with increased arg1, retinol and il13 expression, indicating ongoing inflammation. Eosinophil levels were dramatically increased after 4 weeks but were decreasing by 13 weeks, potentially attributed to increased Il5 expression in male and female mice compared to vehicle and HDM challenged mice. We identified genes showing consistent expression changes between subchronic inhalational exposure to *S chartarum* conidia.

**CONCLUSIONS:** Our results showed males had attenuated HDM induced airway inflammation compared to females, but the mechanism remains unknown. Understanding the effect of sex hormones on airway inflammation associate with severe asthma will potentially help in the development of new therapeutics.

**238 Female Mice Have Increased House Dust Mite Induced Airway Inflammation Compared to Male Mice**

Hubaida Fuseini 1,2, Jacqueline Cephus 3, Jeffry Yung 1, Jian Zhang 4, Kasia Goleniewska 5, Stokes Peebles, MD, FFACAI, 1 and Dawn C. Newcomb, PhD 1,5; 1Vanderbilt University, Nashville, TN, 2Department of Pathology, Microbiology and Immunology, Vanderbilt University, Nashville, TN, 3Department of Pathology, Microbiology and Immunology, Vanderbilt University, Nashville, TN, 4Vanderbilt University, Clarksville, TN, 5Division of Allergy, Pulmonary, and Critical Care Medicine, Vanderbilt University, Nashville, TN. 

**RATIONALE:** Starting around puberty, severe asthma prevalence is increased in women compared to men. This dichotomy is maintained until women reach menopause. Patients with severe asthma have increased airway inflammation that is mediated by increased expression of IL-5, IL-13, IL-4 by CD4+ Th2 cells and other type 2 cells, and/or increased IL-17A from CD4+ Th2 cells and γδ T cells. We hypothesize that male sex hormones decrease type 2 and IL-17A mediated airway inflammation.

**METHODS:** Twenty-five ug of house dust mite (HDM) or vehicle was intranasally administered to WT BALB/c male and female mice 4 times a week for 3 weeks. Bronchoalveolar lavage (BAL) fluid and lungs were harvested 24 hours after last challenge. Cytokine levels were determined by ELISA and infiltration of inflammatory cells by cell differential analysis.

**RESULTS:** HDM increased BAL and lung IL-5, IL-13 and IL-17A protein expression compared to HDM challenged male mice (n=3-5, p<0.05). HDM challenged female mice also had increased eosinophils and neutrophils in the airways compared to male mice (n=3-5, p<0.05).

**CONCLUSIONS:** Our results showed males had attenuated HDM induced airway inflammation compared to females, but the mechanism remains unknown. Understanding the effect of sex hormones on airway inflammation associate with severe asthma will potentially help in the development of new therapeutics.

**239 Gene expression profiling of a Pru p 3-induced anaphylaxis model**

James R. Perkins, PhD, 1 Maria Jose Rodriguez 1, Maria Francisca Palomares, PhD 1, Francisca Gomez 3, MD, PhD 3, 2 Ana Molina 1, Miguel Gonzalez 2, Maria J. Torres, MD, PhD 3, 3 and Cristobalina Mayorga, PhD 2, 3; 1Research Laboratory, IBIMA-Regional University Hospital of Malaga, Malaga, Spain, 2Allergy Unit, IBIMA-Regional University Hospital of Malaga, Malaga, Spain, 3Allergy Unit, IBIMA, Regional University Hospital of Malaga, UMA, Malaga, Spain.

**RATIONALE:** The lipid transfer protein, Pru p 3, is a key peach allergen that can induce anaphylaxis. The underlying mechanisms are not fully understood, however antigen-presenting cells such as dendritic cells (DCs) are known to play a critical role. We performed RNA-sequencing (RNA-seq) expression profiling of DCs in a mouse model of anaphylaxis induced by Pru p 3.

**METHODS:** We used Illumina RNA-seq to profile transcriptional changes in DCs taken from lymph nodes of mice during the acute phase of Pru p 3 induced anaphylaxis. Mice were intranasally sensitized for 5 weeks using Pru p 3 with LPS as an adjuvant. Following sensitisation, anaphylaxis was induced by intraperitoneal Pru p 3 administration. Gene expression levels were compared with littermates to identify differentially expressed genes. RNA-seq sequences were aligned with TopHat; DESeq2 was used to compare gene expression.

**RESULTS:** A total of 222 genes showed significant expression changes. The most differentially expressed genes included cytokines and their receptors and genes related to NF-kB functioning. Gene ontology annotation analysis found enrichment for immune and inflammatory responses; pathway analysis using KEGG enrichment for cytokine interactions and NOD-like receptor signalling.

**CONCLUSIONS:** We identified genes showing consistent expression changes between DCs from anaphylactic mice and controls. Future work will measure expression for the most significant genes in sensitised but not anaphylactic mice that received Pru p 3 but not LPS. We will also investigate the expression in anaphylactic mice that received Pru p 3 immunotherapy in order to investigate the molecular mechanisms underlying the induction of tolerance.

**J ALLERGY CLIN IMMUNOL**  VOLUME 139, NUMBER 2
AB76 Abstracts

240 Inhibition of IL-6 Release in Vitro by in Vivo Administration of an IKK Inhibitor in Mice with Lung Fibrosis Induced by Poly I:C

Karry Anne Karin Belanger, Bing Tian, PhD, Allan R. Brasier, MD, and Bill T. Ameredes, PhD; University of Texas Medical Branch, Galveston, TX.

RATIONALE: Interleukin (IL)-6 is known to act as a growth factor that promotes epithelial-to-mesenchymal transition (EMT) and fibrosis, and is upregulated in acute animal models of airway injury with Polyinosinic-polycytidylic acid (Poly I:C), a viral mRNA analog. Previously, we demonstrated that Poly (I:C) results in leukocyte priming for IL-6 release that is maintained beyond the early and late phases of chronic airway inflammation. To establish mechanism, we investigated the relevance of the NF-κB pathway in this response, by in vivo treatment with an IKK inhibitor.

METHODS: C57Bl6 mice were administered intranasal Poly (I:C) (500 mcg; n=5/group) daily, over 21 days. A subset was pre-treated with an IKK inhibitor BMS345541 (BMS; 10mg/kg body weight, i.p.) 1 day before each poly (I:C) challenge. One week after last challenge, bronchoalveolar lavage (BAL) fluid and leukocytes were collected, and cells were cultured (72 hr), with and without LPS (1000 ng/ml). IL-6 in the culture media was measured by ELISA; data were compared by t-tests.

RESULTS: As compared to PBS-treated controls, BAL total cell counts (in 10^4 cells/ml) were slightly elevated with Poly (I:C) (4.5 vs. 3.1; P<0.05), and not different with Poly (I:C)+BMS (3.3, n.s.). Spontaneous IL-6 release from cultured leukocytes was unaffected, whereas with LPS stimulation, it was significantly increased with Poly (I:C) (495 pg/ml, P<0.05), and significantly reduced with BMS (27 pg/ml), to levels not different from PBS controls (13 pg/ml).

CONCLUSIONS: We conclude that the NF-κB pathway is essential in the Poly (I:C)-dependent priming response of airway leukocytes to produce and release IL-6 within the airway.

241 Matrix Metalloproteinase 7: Role in Epithelial Integrity and Ciliogenesis in Pulmonary Fibrosis in a Mouse Model

Emma Westermann-Clark, MD1,2, Jutaro Fukumoto, MD, PhD1, Ramani Soundararajan, PhD1,2,3,4, Richard F. Lockey, MD,4,5, FAAAAI1-3, and Narasiah Kolliputi, PhD1,2; University of South Florida, Tampa, FL, 1Moffitt Cancer Center, Tampa, FL, 1James A Haley Veterans Hospital, Tampa, FL.

RATIONALE: Matrix metalloproteinase 7 (MMP7) is a potential preclinical serum biomarker for idiopathic pulmonary fibrosis (IPF). The role of MMP7 in IPF is examined using the novel Atp8b1 mutant mouse, which spontaneously develops lung fibrosis. This is a good mouse model to study the role of MMP7 in epithelial integrity and ciliogenesis in IPF.

METHODS: Morphological alterations in mouse lung epithelium were explored using electron microscopy. Quantitative real time (qRT-PCR) was used to investigate MMP7 and related transcripts in wild type (WT) and mutant mice. Expression of MMP7 was confirmed by Western blot. Immunohistochemistry (IHC) localized MMP7 expression.

RESULTS: Atp8b1 mutant mice spontaneously develop lung fibrosis at 14 months, confirmed by H&E/trichrome/toluidine blue staining. Electron microscopy reveals decreased and truncated cilia in lung epithelium. MMP7 is significantly upregulated 4.3 fold by ΔΔCq method (p=0.018, n=12). Western blot of lung lysate and bronchoalveolar lavage fluid verified this result. IHC labeling localized MMP7 to bronchiolar epithelial cells. Ingenuity pathway analysis of Affymetrix microarray data identified Rho-GTPases as a key pathway perturbed in mutant mice. MMP7 cleaves E-cadherin, releasing a component of the adherens junction, p120, which is known to modulate the activity of Rho-GTPases. Rho-GTPases RhoA, and Cdc42 were significantly elevated more than 2-fold in mutant vs WT mice.

CONCLUSIONS: MMP7 is upregulated in this novel Atp8b1 mutant mouse which spontaneously develops lung fibrosis. This is a good mouse model to study the role of MMP7 in epithelial integrity and ciliogenesis in IPF.

242 Clinical Features of the Asthmatic Frequent-Users of the Emergency Department in a Tertiary Hospital

Beatriz Pola Bibian, Gemma Vilá-Nadal, MD, Javier Domínguez Ortega, Nataly Cancelleri Fernandez, Pilar Barranco Sanz, and Santiago Quirce Gancedo; La Paz Hospital, MADRID, Spain.

RATIONALE: Exacerbations are the major cause of morbidity and mortality of asthma, worsening disease control. Some patients may require in the same episode successive visits to the emergency department (ED). Identifying factors that justify this profile could guide us in treatment decisions in order to reduce future risk.

METHODS: From a retrospective study performed in 2014, including 831 patients who suffered an asthma exacerbation and needed medical care at the ED in a tertiary hospital, we collected demographic and clinical data of patients who returned again at least one more time in the next 15 days.

RESULTS: 52 patients suffered a relapse (a new visit to the ED in less than 15 days from the first episode). The average age was 58 and 73.1% were women. >20% had comorbidities associated. 44.2% had no previous diagnosis of asthma. Of previous known asthmatics, 46.3% were uncontrolled and 12% did not have any treatment. 26% had a sudden onset. 31.3% had >400 eosinophils/mm^3 in blood. 70.3% were mild crisis and just 16% required hospitalization. The months with more episodes were May and June (30.3%).

CONCLUSIONS: A high percentage of patients need to come back to the ED repeatedly after an exacerbation. They are mostly poorly controlled or underdiagnosed asthmatics and have high percentage of sudden onset crisis than other asthmatic patients. Crisis are less severe and with a lower rate of hospitalization. Comorbidities are frequently associated, probably related with difficulty to achieve control. Other causes apart from respiratory infections might be relevant in these patients.
**243 Successful Treatment with Candida Immunotherapy in a Woman with Recurrent Vulvovaginal Candidiasis.**

Immaculada Sanchez-Machin, MD, PhD1, Victor Matheu, MD, PhD2, Paloma Pozo-Guedes, MD, PhD3, Ruperto Gonzalez-Perez, MD, PhD4, and Fernando Rodriguez-Fernandez, MD, PhD5; 1Hospital Universitario Marques Valdecilla-IDIV AL, Santander, Spain. 2Hospital Universitario Nuestra S. de Candelaria, Santa Cruz de Tenerife, Spain. 3Hospital Universitario Marques Valdecilla-IDIV AL, Santander, Spain.

**RATIONALE:** Recurrent vulvovaginal candidiaris (RVVC) is defined as four or more episodes over a one year period, and affect a 5-8% of adult women. No effective long term cure has been found.

**METHODS:** Caucasian 37-years woman assisting to an outpatient clinic refer that her major medical problem was a RVVC. She could not stand sitting more than a few minutes, because she had continuous burning in genital area. Painful coitus was the most limiting symptom: she can’t have a normal sexual life and her greatest wish to get pregnant was being truncated. RVVC was diagnosed by recurrent vaginal culture and treated with topical and systemic antifungal treatments over the past six years by gynecologist and GP.

**RESULTS:** Skin prick tests (SPT) to common aerollergens were positive (D. pteronyssinus and farinae). SPT with C. albicans (Bial-Aristegui SA) was negative. Intradermal test was similar to negative control. Total IgE 321: U/L; specific IgE to C. albicans: <0,35kU/L.

Patient was looking for a possible treatment for her RVVC and a C albicans subcutaneous immunotherapy (Immunotek SL) was offered as ex-juvanti-bus treatment. She gave her written informed consent.

An initiation cluster schedule was started, and then monthly. After 3 months of treatment, her symptoms were only previous to menstruation. At 14th month she became pregnant. Currently, she is on third year of successful immunotherapy. No systemic adverse events with immuno-therapy had been experienced.

**CONCLUSIONS:** The diagnosis of sensitization to molds can be difficult. An ex juvantis treatment in RVVC was successfully offered with Candida immunotherapy.

**244 Childhood Asthma Mortality In Minas Gerais, Brazil.**

Raquel Reis Pitchon, Medical research1, Henrique Pitchon Magalhães Ribeiro, Medical research2, Adriana Pitchon Reis, Medical research3, Cristina Alvim, Medical research1, and Claudia Andrade, Medical research1; 1UFMG - Federal University of Minas Gerais, Belo Horizonte, Brazil. 2FCMMG - Faculdade Ciencias Medicas de Minas Gerais, Belo Hori- zonte, Brazil.

**RATIONALE:** The objective of the study was to measure asthma mortality in the state of Minas Gerais, Brazil, occurred in the age group under 19 years old, during the period of 1996 to 2013.

**METHODS:** This is an ecological study of asthma mortality rates using the National Mortality Database (Ministry of Health of Brasil). The main variable studied was the coefficient of asthma mortality multiplied by the National Mortality Database (Ministry of Health of Brasil). The main factors such as parental smoking.

**RESULTS:** In the period studied there were 438 deaths. Of these deaths, 73% (321 records) were of children under 5 years old. The coefficients of asthma mortality in the period and in each of the four studied groups show that the decline in mortality rate was more pronounced in the age group of 0 to 4 years old. In this group, the average annual reduction of mortality rate for asthma was 0.086; in the group of 5 to 9 years old, it was 0.007; in the group 10 to 14 years old, it was 0.002 and in the group of 15 to 19 years old, was 0.010.

**CONCLUSIONS:** It is possible to assume that the decline of the mortality rate in those groups are related to the improvement of processes in health services. However, the eradication of deaths from asthma requires major efforts including written plans of action for the treatment of acute asthma crisis, improving prophylactic treatment and education and reducing risk factors such as parental smoking.

**245 Pediatric Patient With Convincing History of P-Tert-Butylphenol Formaldehyde Resin Contact Dermatitis.**

Amanda S. Troger, BSN, RN1, and Burcin Uygungil, MD2; 1Children’s National Medical Center, Rockville, MD. 2Children’s National Health Sys- tems, Department of Allergy and Immunology, Washington, DC.

**RATIONALE:** Exposure to the chemical p-tert-butylphenol formalde- hyde resin (PTBP FR) causes dermatitis in allergic patients. Many general market products and medical devices contain PTB FR. A child presented to the allergy clinic with complaints of rash after using pool attire.

**METHODS:** Patient’s primary nurse and physician took a detailed history, reviewed pertinent literature and discussed patch testing with the family.

**RESULTS:** Five-year-old boy presented with complaints of red, itchy rash after swimming in the pool on multiple occasions. The rash occurred where the neoprene life vest, goggles and floaties touched his skin. A similar rash appeared on his feet when his shoes got wet. The rash also presented where probes were adhered when the patient received an electrocardiogram. Prior serum latex IgE testing resulted negative by parent report. Based on the history, the rash was consistent with contact dermatitis (CD). A review of literature indicated the chemical causing the CD was most likely p-tert-butylphenol formaldehyde resin (PTBP FR). This is a chemical compound derived from glues and adhesives present in many every day and medical products, including skin guards, wet suits, electrocardiograph monitoring elec- trodes and sneaker adhesives, that when wet releases resin and causes CD. The family and medical team decided that patch testing was not necessary at this time given the likelihood of the culprit allergen, however, they will consider patch testing in the future which is the gold standard in diagnosis of CD.

**CONCLUSIONS:** The patient received documentation on avoidance measures for the PTBP FR and treatment options if contact reactions occur.

**246 Acyclovir Induced Bullous Drug Reaction Mimicking As Bullous Pemphigoid in a 65 Year Old Filipino Male: A Case Report.**

Dan Karlo D. Esquera, Jomari R. Biias, and Christopher Rey G De Guzman; Iloilo Mission Hospital, Iloilo City, Philippines.

**RATIONALE:** Bullous pemphigoid(BP) is a rare skin condition that causes large, fluid-filled blisters. It is a autoimmune subepidermal blistering disease. The Pathogenesis has not yet been fully elucidated, but it is widely accepted that a strong correlation with various medications may exists. In reality, more than 50 different drugs have been associated with BP. There have been no reports yet on the association between acyclovir and BP up to date. We report a rare case of 65 year old male with recent intake of acyclovir presented with bullous lesions.

**METHODS:** Skin Biopsy.

**RESULTS:** A case of a 65 year old filipino male with history of acyclovir treatment for herpes zoster. The onset of bullous lesions manifested on 10th day of said medication which prompted admission. Physical examination revealed large fluid-filled blisters affecting the neck and extremities. Patient was referred to Dermatologist for Skin Biopsy and was started with Hydrocortisone. Bullous lesions were aspirated and potassium permanganate application was done. Skin Biopsy revealed subepidermal blistering with fibrin, plasma and eosinophils; edema of papillary dermis and dense perivascular and interstitial infiltrate of lymphocytes, histio- cytes and mostly eosinophils. Due to clinical presentation and the tempo- ral relationship between the administration of acyclovir and bullous formation with skin biopsy, the diagnosis of acyclovir induced BP became more likely.

**CONCLUSIONS:** We believe this is the first reported case of acyclovir induced BP in our locality. It could raise awareness among medical practitioners of a drug that could precipitate a BP reaction.
**247 Reduction of Indoor Aeroallergen and Overall Particle Count Using AHPCO and Plasma Hybrid Technology for Air Purification**

Nabarun Ghosh, PhD1, Constantine Saadeh, MD, FICF2, Nelofar Sherali, BS3, Jeff Bennett, PhD3, Chandini Revanna, MPH, CHI, MS4, Jon Bennett, BS5, and Denny Mullay, BS3, 1West Texas A&M University, Canyon, TX, 2Allergy ARTS, Amarillo, Amarillo, TX, 3Air Oasis, Amarillo, TX, 4Texas Tech University, Lubbock, TX.

Rationale: The allergy and asthma cases have doubled since 2007. We have analyzed the aeroallergen data of the Texas Panhandle using a Burkard Spore Trap for 17 years that showed a steady increase in aeroallergen counts. We developed an air purification system implementing a hybrid AHPCO or Advanced Hydrated Photocatalytic Oxidation and Plasma Nanotechnology that can reduce the indoor aeroallergens efficiently.

Methods: Using the Burkard Spore Trap, Digital, Fluorescence and Scanning Electron Microscopy we analyzed the aeroallergen data for 17 years. We developed and assessed AHPCO and Plasma Nanotechnology to improve the filter-less air purification system further for net reduction of indoor aeroallergens. Particle counts were recorded to assess the capacity of sterilization. In a fiberglass chamber we used a Dylos Air Quality Monitor to detect and compare the particle counts on running the air purifier for 24, 72, and 120 hours of exposures.

Results: A shift in flowering seasons and increased aeroallergen indices in Texas Panhandle, all resulted in increased allergy and asthma cases. The air purification system with novel AHPCO and Plasma technology reduced the indoor particulate matters gradually with varied time interval.

Conclusions: The incidence of allergy among the residents of Texas Panhandle is just doubled to the rate of the State of Texas. Strong wind current, local feedlots, a gradual shift in flowering season contributed to a high incidence of allergy and asthma. We implemented an air purification system using a hybrid AHPCO and Plasma Nanotechnology that reduced the indoor particulate matters including all forms of aeroallergen.

**248 Is There a Time-Dependent Association Between Cat Dander Sampling Time and Feld1 Levels?**

Jennifer Marcelo1, Rachel Harrison1, Suzanne M. Kelly, PhD2, Ammir Al-Housan2, Nate Stepner3, Jimmy Yang4, Jacob Karsh4, and William H. Yang, MD, FAAAAI5. 1Red Maple Trials Inc., Ottawa, ON, Canada, 2Royal College of Surgeons Ireland, Dublin, Ireland.

Rationale: Live cats in a challenge chamber generate Feld1 levels that cause symptoms in allergic subjects. However, Feld1 levels can vary over time and the delay in completing the Feld1 ELISA assay means that actual allergen levels are not known after the fact. Our purpose is to determine whether it is possible to assess cat dander levels using light microscopy and correlate these levels to Feld1 measured by ELISA. This would allow more rapid measurements and tighter control on allergen levels.

Methods: Cat dander was collected using three sampling pumps with Millipore glass fiber filters. Two filters were stained with 1:1 Parker’s ink / saline and examined at 20x magnification using a light microscope. Filters were divided into 4 virtual quadrants and 1, 2, or 3 random fields per quadrant were counted. To differentiate from other particulate matter, translucent irregularly shaped particles between 5-20 μm were considered as dander and counted. Feld1 on the third filter was measured by ELISA. Samples were obtained after 15, 30, 45 and 60 minutes.

Results: There was no time dependent or spatial relationship observed between sampling time (15 vs 60 min) and Feld1 (2.38ng to 1.05ng, respectively) or dander levels counting 1 field per quadrant (5425, 9657 particles/filter, respectively) or 3 fields per quadrant (849, 9928 particles/filter, respectively).

Conclusions: Staining with Parker’s ink did not prove to be a successful method to accurately count regardless of the number of fields counted. Further testing will be conducted in hopes to improve dander staining and counting.

**249 Tree Pollen Levels during Two “Very Strong” El Niño Events**

James J. Anderson, MLT1, and Peter Pityn, PhD2. 1Environmental Allergy Assays, London, ON, Canada, 2OSITECH Incorporated, London, ON, Canada.

Rationale: We anticipated that the very strong el Niño of 2016 would be a factor in boosting local tree pollen levels as recorded during el Niño1998.

Methods: Daily 24 hour Burkard spore trap samples from mid-March to mid-June of 1998 to 2016 were analyzed for tree pollen content. Meteorological factors were examined to explain the large difference between the 1998 & 2016 tree pollen counts.

Results: (1) Total tree pollen levels in 1998 were the highest recorded in SW Ontario, while the 2016 levels were the lowest. (2) We did not find a correlation between weather factors (rainfall & growing degree days) and the two “very strong” El Niño events. (3) Local tree pollen levels have dropped substantially after a peak in 2010.

Conclusions: El Niño is a recurring global climatic phenomenon resulting from changes in oceanic surface temperatures that affect weather. Very strong El Niño events occur approximately every 15-20 years. In 1998, local pollen production was elevated for almost all the deciduous trees with very high levels of Juniper/Cedar. The literature indicates that annual pollen production is primed by precipitation in the previous year and the season is initiated by temperature (growing degree days). We found such relationships inconsistent and did not explain the two El Niño “seasons” or the recent drop-off in recorded tree pollen production.

**250 Pneumococcal Vaccination Coverage Among Adults with Work-Related Asthma, Asthma Call-Back Survey, 29 States, 2012–2013**

Katelynn Dodd, MPH1, and Jacek M. Mazurek, MD, MS, PhD2. 1NIOSH/CDC, Morgantown, WV, 2National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Morgantown, WV.

Rationale: Pneumococcal vaccination is recommended for all adults with asthma and a Healthy People 2020 goal aims to increase coverage among adults with asthma to 60%. Adults with work-related asthma (WRA) have more severe disease than those with non-WRA and would likely benefit from receiving a pneumococcal vaccine. This study aimed to assess pneumococcal vaccination coverage and identify groups who were less likely to have received a pneumococcal vaccine among ever-employed adults with WRA.

Methods: Data from 2012–2013 Behavioral Risk Factor Surveillance System Asthma Call-back Survey for ever-employed adults (18–64 years) with current asthma from 29 states were assessed. Adults with WRA had ever been told by a physician their asthma was work-related. Pneumococcal vaccine recipients had ever received a pneumococcal vaccine. Logistic regression was used to calculate adjusted prevalence ratios (PR) and associated 95% confidence intervals (CIs).

Results: Among an estimated 12 million ever-employed adults with current asthma in 29 states, 42.0% received a pneumococcal vaccine.

Pneumococcal vaccination coverage among adults with WRA was 53.7% compared with 35.0% for adults with non-WRA (PR=1.56, 95% CI=1.17–1.98). Among adults with WRA, coverage was c≤5% for those 18–44 years (41.8%), Hispanics (36.2%), uninsured (38.5%) and differed significantly across age, employment status, health insurance status, asthma control, and a history of routine checkup for asthma in the last year.

Conclusions: Pneumococcal vaccination coverage among adults with WRA and non-WRA is below the Healthy People 2020 target level. These results can help target successful vaccination interventions to certain adults with asthma to improve coverage.
Antibiotic Prescribing Practices amongst Internists in Penicillin Allergic Patients

Sharzad J. Alagheband, MD1, Mark A. Davis-Lorton, MD, FAAAAI2, Luz S. Fonacier, MD, FAAAAI2, and Marcella Aquino, MD2; 1Winthrop University Hospital, Mineola, 2Winthrop University Hospital, Allergy & Immunology, Mineola, NY.

RATIONALE: Approximately 10% of patients report a history of penicillin (PCN) allergy. In cases of antibiotic prescribing, labeled PCN-allergic patients often receive non-beta-lactam antibiotics, such as quinolones, vancomycin, cephalosporins and macrolides to avoid allergic reactions. These alternatives maybe less effective, more toxic (aminoglycosides), more expensive and broader spectrum agents are often associated with increased risk of c-difficile diarrhea (clindamycin, fluoroquinolones) as well. We sought to determine the prescribing patterns of internists in the outpatient setting in PCN-allergic labeled patients.

METHODS: We performed a three-month retrospective, IRB approved matched cohort study of patients with and without a documented PCN allergy in our Internal Medicine (IM) clinic. We recorded the prescribing patterns of IM physicians for patients with a history of PCN allergy (cases). This was compared to the antibiotic selection in sex-matched, age-matched control subjects without a history of PCN allergy (controls).

RESULTS: PCN allergy was documented in 518 charts. Macrolides and quinolones were the most common class of antibiotics prescribed in both groups. Macrolides were given to 260(50.2%) cases and 112(21.6%) controls (p=0.696). Fluoroquinolones were given to 150(29%) cases and 109(21%) controls (p=0.803). There were only 10(1.9%) cases prescribed cephalosporins compared to 53(10.2%) of controls (p=0.451). Ceftriaxone and vancomycin were not prescribed in either group.

CONCLUSIONS: The data suggests that there are many factors that influence a patient’s compliance in completing the full course of AIT. Health care providers should be aware of these factors when discussing AIT with patients.

Factors Influencing Compliance with Allergen Immunotherapy

Nicolle Cascone, RN1, Andrej Petrov, MD1, Stacy L. Rosenberg, MD1, and Merritt L. Fajt, MD, FAAAAI2; 1University of Pittsburgh Medical Center, Division of Pulmonary, Allergy and Critical Care Medicine, Pittsburgh, PA, 2The University of Pittsburgh Asthma Institute at UPMC and the University of Pittsburgh School of Medicine, Department of Pulmonary, Allergy and Critical Care Medicine, Pittsburgh, PA.

RATIONALE: Allergen immunotherapy (AIT) is currently recommen- ded for a continuous treatment period of 3-5 years [AAAAI practice parameters]. There are likely multiple factors that affect patient compli- ance in completing the full course of AIT once started.

METHODS: We conducted a retrospective chart review of 430 adult patients started on AIT for treatment of allergic rhinoconjunctivitis from June 15, 2004 through June 15, 2014. We compared demographic features, co-morbidities and features specific to environmental allergies between the patients who completed the full course of AIT vs. those who stopped AIT pre-maturely (< 3 years after starting AIT). Data was analyzed non-parametrically.

RESULTS: In 430 patients started on AIT for environmental allergies, several demographic factors were found in association with non-compliance. Younger age associated with an increased rate of non-compliance (p=0.00019). Gender is a also a risk factor, with a tendency for a greater percentage of females to pre-maturely discontinue AIT vs. males (54% vs. 44%, p=0.06). In terms of co-morbidities, vocal cord dysfunction diagnosis associated with a greater rate of pre-mature discontinuation (72% vs. 49%, p=0.0008). Although a prior history of any anaphylaxis associated with AIT non-compliance (p=0.01), systemic reaction to AIT did not impact compliance. The presence of mold in AIT extract was also associated with pre-mature AIT discontinuation (p=0.037).

CONCLUSIONS: The data suggests that there are many factors that influence a patient’s compliance in completing the full course of AIT. Health care providers should be aware of these factors when discussing AIT with patients.
**ABSTRACTS**

**254 Insight into Rhinovirus-Induced Asthma Exacerbation Using High-Throughput Immunosequencing of B-Cell Repertoires**

Yu-Chang Bryan Wu, PhD1,2, Aaron M. Rosenfeld3, Nadine Upton, PhD4,5, Jaideep Dhariwal2,5, Uri Hershberg1, David Kipling6, Sebastian L. Johnston, MD, PhD5, and Hannah J. Gould1,2,1 King’s College London, London, United Kingdom, 2MRC & Asthma UK Centre in Allergic Mechanisms of Asthma, London, United Kingdom, 3Drexel University, Philadelphia, PA, 4Kings College London, London, United Kingdom, 5Imperial College London, London, United Kingdom, 6Cardiff University, Cardiff, United Kingdom.

**RATIONALE:** Viral infections, particularly by the common cold rhinovirus (RV), increase risk and severity of asthma exacerbations. We hypothesize that RV infections affect the IgE repertoire and intensify IgE-mediated allergic reactions in asthmatic patients.

**METHODS:** Fifteen healthy and 16 moderate asthmatic subjects were experimentally infected with RV-16. Total B cells bronchial biopsies and bronchoalveolar lavage and 5 B-cell populations (naïve cells, three memory subsets, and plasmablasts distinguished by CD27, IgD, CD38 expression using flow cytometry) in the blood were collected at baseline (day -14) and post-RV infection (day +3 and day +8). The immunoglobulin (Ig) heavy-chain genes in a total of 152 samples were sequenced on the Illumina 2x300 MiSeq system. Multiple bioinformatics tools were employed to analyze Ig repertoires including IMGT/HighV-QUEST and other tailored Ig repertoire analysis software (e.g., BASELINE).

**RESULTS:** Over 6 million unique productive sequences (IgA, IgG, IgE, and IgM) were included after stringent quality-control filtering. Baseline IgE clones in asthmatics were distinguished from those in healthy subjects with different Ig gene usage, more selection and higher hypermutations (p < 0.0001). Post-infection IgE sequences with higher hypermutations and clonal relatives to baseline IgE repertoire were observed in asthmatic but not in healthy subjects. Temporal dynamics and compartmental connections of B-cell clones, differing between asthmatic and healthy subjects, suggests a significant involvement of IgG clones in IgE-mediated immune responses in asthmatic patients.

**CONCLUSIONS:** Our high-throughput immunosequencing of B-cell repertoires revealed that RV infection exacerbated IgE responses in asthmatic patients, leading to higher serum IgE levels associated with their clinical symptoms.

**255 Preliminary Evaluation of a Food Allergy Outreach Clinic for Underserved Populations in Washington DC**

Maria F. Fortiz; Children’s National Medical Center, Hyattsville, MD.

**RATIONALE:** A major concern regarding food allergies (FA) is the risk of food-induced anaphylaxis. The DC CARES project was developed to address the FA needs of an underserved population in Washington, DC. This project’s objective is to evaluate initial enrollment in the DC CARES program.

**METHODS:** Patients seen in the emergency department (ED) at Children’s National Medical Center (CNMC) for food-induced anaphylaxis were contacted after their admission and scheduled for a DC CARES appointment. Patients met with an allergist and a DC CARES team member to receive comprehensive education about FA management, anaphylaxis, and a personalized FA emergency care plan.

**RESULTS:** In 6 months, 146 patients were seen at the ED for food-induced anaphylaxis and attempted to be contacted. During screening calls, 24 patients (17%) were not eligible for the program because they were already followed by a CNMC allergist (N=12) or an outside allergist (N=12). Eighty-two patients were not interested in participating or could not be reached (56%). Forty patients (28% of participants who could be reached or were eligible) agreed to be scheduled for a DC CARES appointment; 26 (18%) attended and 14 (10%) did not show for the appointment.

**CONCLUSIONS:** Most patients seen in the CNMC ED for food-induced anaphylaxis do not follow up for FA diagnostic and preventative care after discharge, even with hospital outreach and the availability of a comprehensive program. Additional community advocacy may be required to target this population more effectively.

**256 IL-33 Promotes Egress of Group 2 Innate Lymphocytes (ILC2) from the Bone Marrow**

Matthew T. Stier1, Kasia Golenska2, Jian Zhang2, and Stokes Peebles, MD, FAAAAI1,2, 1Department of Pathology, Microbiology, and Immunology, Vanderbilt University, Nashville, TN, 2Division of Allergy, Pulmonary, and Critical Care Medicine, Vanderbilt University, Nashville, TN.

**RATIONALE:** Group 2 innate lymphocytes (ILC2) are mucosally embedded effector cells that promote type 2 immune responses to allergens, viruses, and other environmental insults. In peripheral tissues, ILC2 robustly proliferate and express cytokines in response to the alarmin IL-33. However, the role of IL-33 on ILC2 development and egress from the bone marrow remains unclear.

**METHODS:** We assessed the frequencies and functional capacities of ILC2 in the bone marrow, lung, skin, and mesenteric lymph nodes of WT, IL-33-deficient, and/or ST2-deficient mice by flow cytometry.

**RESULTS:** We identified that deficiency in IL-33 signaling lead to an accumulation of ILC2 in the bone marrow and a decrease in ILC2 in the lungs, skin, and mesenteric lymph nodes compared to wild type mice. These bone marrow and peripheral tissue ILC2 frequencies were established by an ILC2 cell-intrinsic mechanism. Absent IL-33 signaling did not appreciably affect the capacity of bone marrow ILC2 to proliferate or secrete canonical ILC2-associated cytokines. However, lack of IL-33 signaling significantly altered the chemokine receptor profile on bone marrow ILC2, with ST2-deficient ILC2 overexpressing Cxcr1, Ccr7, Ccr9, Cxcr4, and Ptgr2 compared to wild type ILC2. Treatment of wild type ILC2 with IL-33 ex vivodecreased the expression of CXCR4, a major chemotactic signal for the retention of cells in the bone marrow. Moreover, pharmacologic blockade of CXCR4 induced mobilization of ILC2 from the bone marrow of ST2-deficient mice.

**CONCLUSIONS:** These data suggest a mechanism by which IL-33 negatively regulates CXCR4 expression on developing ILC2 leading to efficient egress of these cells from the bone marrow.
IL-33 Signaling Contributes to Diesel Exhaust Particles (DEP)-Induced Asthma Exacerbations and Recall Responses

Eric B. Brandt, PhD, FAAAAI, Paige Bolcas, B.S., Brandy Ruff, A.S., and Gurjit K. Khurana Hershey, MD, PhD, FAAAAI; Cincinnati Children’s Hospital Medical Center, Cincinnati, OH.

RATIONALE: Exposure to traffic pollution, notably diesel exhaust particles (DEP), increases risk for asthma and asthma exacerbations. The contribution of IL-33, an alarmin generated by stressed lung epithelial cells, remains poorly understood. Our main objective is to determine the importance of IL-33 signalling through its receptor ST2 in DEP-induced asthma exacerbations in a well characterized murine model.

METHODS: ST2 deficient and Balb/c control mice were exposed nine times over a 3-week period to house dust mite (HDM) ± DEP. Seven weeks later, some mice received a single HDM challenge to assess memory responses. Airway hyper-responsiveness (AHR), BALF inflammation and lung T-cell subsets were assessed after primary and recall responses.

RESULTS: DEP co-exposure with HDM resulted in a mixed Th2/Th17 response in the lungs of exposed mice. After 7 weeks of rest, a single exposure to HDM induced AHR more strongly in mice previously exposed to both HDM and DEP versus HDM alone. AHR was significantly lower in ST2 deficient mice compared to wild type controls after both the primary HDM±DEP exposures and the HDM recall. Interestingly, Th17 rather than Th2 lung cell levels were primarily decreased in ST2 deficient mice, most notably IL5/IL13/IL17A producing CD4+ T-cells.

CONCLUSIONS: IL-33 contributes to DEP-induced asthma exacerbations and the accumulation of pathogenic Th2/Th17 cells in the lungs of HDM and DEP co-exposed mice.

Glucagon-like Peptide 1 Receptor (GLP-1R) Signaling Inhibits Aeroallergen-Induced IL-33 Release and Reduces Group 2 Innate Lymphoid Cell (ILC2) Activation In Vivo

Shinji Toki, PhD, Kasia Goleniewska, Sara Reiss, Jian Zhang, Melissa H. Bloodworth, Matt T. Stier, Weisong Zhou, PhD, Dawn C. Newcomb, PhD, Kelli L. Boyd, Kevin D. Niswender, and Stokes Peebles, MD, FAAAAI; Division of Allergy, Pulmonary, and Critical Care Medicine, Vanderbilt University, Nashville, TN; Department of Pathology, Microbiology, and Immunology, Vanderbilt University, Nashville, TN; Department of Molecular Physiology and Biophysics, Vanderbilt University, Nashville, TN; Division of Diabetes, Endocrinology, and Metabolism Vanderbilt University, Nashville, TN.

RATIONALE: Glucagon-like-peptide-1 receptor (GLP-1R) signaling has inhibited inflammation in mouse models of autoimmunity and other disease states. However, the effects of GLP-1R signaling on aeroallergen-induced type-2 innate airway inflammation are unknown. We hypothesized that GLP-1R signaling reduces Alternaria extract-induced early innate type-2 airway inflammation by blocking of group 2 innate lymphoid cell (ILC2) activation.

METHODS: BALB/c mice were challenged intranasally with Alternaria extract or PBS for 4 consecutive days following GLP-1R agonist (liraglutide) or vehicle treatment. Bronchoalveolar lavage (BAL) fluid and lungs were harvested 1 hour after the first challenge or 24 hours after the last challenge.

RESULTS: GLP-1R agonist treatment significantly decreased IL-33 release in the BAL fluid 1 hour after the first Alternaria extract-challenge, and reduced IL-33 expression in lung epithelial cells 24 hours after the last Alternaria extract-challenge compared to vehicle treatment. Further, GLP-1R agonist treatment significantly decreased the number of IL-5 and IL-13 expressing ILC2 in the lungs challenged with Alternaria extract compared to vehicle treatment. In addition, GLP-1R agonist treatment significantly decreased IL-5, IL-13, CCL11, CCL17, CCL22 and CCL24 protein expression in the BAL fluid and lung homogenates, the number of macrophages, eosinophils and lymphocytes in the BAL fluid, perivascular eosinophil accumulation in the lung, mucus production in the bronchial epithelium, and airway responsiveness (AR) induced by Alternaria extract-challenge for 4 consecutive days.

CONCLUSIONS: These results reveal that GLP-1R signaling reduces IL-33 release, consequent ILC2 activation, and the early type-2 innate immune responses to an inhaled protease-containing aeroallergen.

Dynamic Binding to Chromatin Regulates the Extracellular Release of Interleukin-33 (IL-33)

Jared Travers, Cora E. Miracle, Mark Rochman, PhD, and Marc E. Rothenberg, MD, PhD, FAAAAI; Cincinnati Children’s Hospital Medical Center, Cincinnati, OH.

RATIONALE: Interleukin-33 (IL-33) is a pro-atopy, epithelial-derived cytokine released following necrosis. Before extracellular release, IL-33 is retained within the nucleus bound to chromatin, but the role of this binding remains largely understudied. Herein, we examined the molecular characteristics of IL-33 binding to chromatin in esophageal epithelial cells and its functional significance in regulating IL-33 extracellular release.

METHODS: Immunofluorescence (IF) was performed on esophageal biopsies from patients with eosinophilic esophagitis or control individuals. Biochemical fractionation, IF, fluorescence recovery after photobleaching (FRAP), and enzyme-linked immunosorbent assay (ELISA) were performed on an esophageal epithelial cell line (TE-7) overexpressing IL-33 via lentiviral transduction.

RESULTS: IF for IL-33 revealed only nuclear staining in esophageal epithelial cells in vitro and during allergic inflammation in vivo. Biochemical fractionation demonstrated IL-33 enrichment in the chromatin fraction compared with heat shock protein 90. Assessment of nuclear mobility by FRAP demonstrated that GFP-tagged full-length IL-33 had a 70% recovery time of 29 seconds compared to 3 seconds for IL-1 alpha. A truncated form of IL-33 (IL-33112-270) which lacks the chromatin binding domain was highly mobile within the nucleus similar to the GFP-alone control. Functionally, IL-33112-270 demonstrated increased extracellular release following induction of necrosis with calcium ionophore or hydrogen peroxide (8 to 20-fold, p < 0.0001) compared with chromatin-bound full-length IL-33.

CONCLUSIONS: In summary, herein we have demonstrated that IL-33 binding to chromatin is dynamic and regulates its availability for release during necrosis. We propose that intracellular retention of IL-33 during necrosis may serve as a mechanism to curtail inflammatory responses in allergic disease.
All abstracts are strictly embargoed until the date of presentation at the 2017 Annual Meeting.

**260** Sex Differences in the Localization and Activation of Type 2 Innate Lymphoid Cells in Experimental Asthma

**Kristi J. Warren, PhD** 1, John D. Dickinson, MD, PhD1, Joseph H. Sisson, MD1, Todd A. Wyatt, PhD1, and Jill A. Poole, MD, FAAAAI2; 1University of Nebraska Medicine, Omaha, NE, 2Univ of Nebraska, Omaha.

**Rationale:** The prevalence of asthma in humans is increased in females compared to males after puberty, but the reasons for this remain unclear. The rare type 2 innate lymphoid cells (ILC2) have been recently implicated as drivers of allergic asthma. The objective of this study was to investigate sex differences in an experimental murine model with a focus on sex-specific ILC2 effects.

**Methods:** Male and female BALB/c mice were sensitized and subsequently challenged with aerosolized ovalbumin (OVA) on days 17-21 for serum, bronchoalveolar lavage fluid (BALF), and lung tissue collection, and challenged for an additional 5 days for airway hyper-responsiveness (AHR).

**Results:** As compared to saline, OVA challenged mice demonstrated increased serum OVA-IgE, AHR, levels of type 2 cytokines (IL-4, IL-5, IL-13), and cellular influx of eosinophils, B cells, dendritic cells, T cells, and ILC2. Sex differences were demonstrated such that female mice had increased serum OVA-specific IgE, lung nitric oxide levels, and AHR as compared to males. As compared to male mice, dendritic cells were decreased in BALF and B cells were increased in the BALF and lung tissues of OVA challenged females. Female OVA challenged mice also demonstrated lower frequency of ILC2 in BALF, yet increased frequency compared to males. As compared to male mice, dendritic cells were decreased in BALF and B cells were increased in the BALF and lung tissues of OVA challenged females. Female OVA challenged mice also demonstrated lower frequency of ILC2 in BALF, yet increased frequency in whole lung tissue. There was a significant increase in the levels of IL-5 and IL-13 produced ex vivo by IL-33 stimulated, isolated lung ILC2 from female saline and OVA challenged mice as compared to males.

**Conclusions:** Taken together, the study highlights a potential sex-specific difference in ILC2 localization and activation in experimental allergic asthma.

---

**261** Caregiver report of child’s asthma control predicts future acute visits, independent of guideline-based measures of asthma control

**Suzanne L. Rossi, MD** 1, Torie L. Grant, MD1, Jean Curtin-Brosnan, MA1, and Elizabeth Matsui, MD, MHS1,2, 1Johns Hopkins School of Medicine, Baltimore, MD, 2Division of Pediatric Allergy/Immunology, Johns Hopkins School of Medicine, Baltimore, MD.

**Rationale:** It is unknown whether caregiver perception of a child’s asthma control, independent of National Asthma Educational and Prevention Program (NAEPP) control measures, is a predictor of future acute visits.

**Methods:** 150 Baltimore children (5-17y) with persistent asthma were enrolled in a prospective cohort study. Questionnaires administered at baseline, 3, 6, 9, and 12 months captured symptoms, rescue medication use, asthma-related acute visits in the previous 3 months, and caregiver-reported asthma control. Controlled, uncontrolled, and poorly controlled asthma were defined based on days of symptoms, activity limitation, albuterol use, and nighttime awakenings in the past two weeks and FEV1/FVC. Relationships between caregiver-reported control and acute visits in the subsequent 3 months were analyzed using generalized estimating equations with a logit link function and a lagged caregiver-reported asthma control variable.

**Results:** 43.3% were female, 91.3% black, and 85.3% had public insurance. At baseline, 80% met NAEPP criteria for uncontrolled asthma, 20% had caregiver-reported uncontrolled asthma and 27.5% had an acute visit within the subsequent 3 months. In unadjusted models, caregiver-reported uncontrolled asthma was a predictor of an acute visit in the subsequent 3 months (OR [95% CI]: 2.4 [1.4-4.1], p = 0.001) and remained a predictor after adjusting for age, gender, insurance, NAEPP-based asthma control, and rhinitis (OR [95% CI]: 2.1 [1.2-3.6] p = 0.01).

**Conclusions:** Caregiver-reported asthma control is a predictor of future acute asthma visits, independent of NAEPP guideline asthma control measures, suggesting that eliciting caregivers’ report of asthma control may be important in identifying children at high risk for future acute visits.
All abstracts are strictly embargoed until the date of presentation at the 2017 Annual Meeting.

**263 Maternal Vitamin E Plasma Isoform Concentrations and Association with Child Wheezing and Asthma Outcomes**

Cosby A. Stone, MD, MPH, Joan A. Cook-Mills, PhD, Tebeb Gebretsadik, MPH, Emma K. Larkin, PhD, Christian Rosas-Salazar, MD, MPH, Alexandra Connolly, BS, Theresa Rogers, BS, Zhouwen Liu, MS, Kaitlin Costello, BA, and Tina V. Hertert, MD, MPH; Vanderbilt University Medical Center, Nashville, TN. 1Northwestern University, Chicago, IL. 2Department of Biostatistics, Vanderbilt University School of Medicine, Nashville, TN. 3Vanderbilt University Center for Asthma Research, Nashville, TN.

**RATIONALE:** Isoforms of vitamin E (specifically alpha- and gamma-tocopherol) have shown differential effects on *in vivo* mouse models of allergic inflammation and adult-onset asthma in humans. We hypothesized that maternal postpartum vitamin E isoforms would show differential associations with early life childhood respiratory outcomes.

**METHODS:** We conducted a prospective nested study of the INSPIRE birth cohort of 651 children with maternal postpartum plasma vitamin E isoforms measured at study enrollment. We ascertained the outcome of recurrent wheezing requiring asthma medication at two years of life using validated questionnaires. We evaluated for association with, and for interaction between, alpha- and gamma-tocopherol concentrations and recurrent wheezing, while adjusting for covariates.

**RESULTS:** Median age of the children at time of maternal sample collection was 50 days [IQR 16, 81]; 47% were female and 61% were white. Children with two-year wheezing (N = 174; 27%) had mothers with significantly lower postpartum concentrations of plasma alpha-tocopherol (68 μmol/L [IQR: 42, 96]) compared to those who did not (75 μmol/L [IQR: 50, 106]), p = 0.021. In multivariable regression analysis for interaction, the relationship of alpha-tocopherol with wheezing was modified by gamma-tocopherol concentration in tertiles (main effect of alpha tocopherol p = 0.014, interaction p = 0.006). At the highest tertile of gamma tocopherol, the protective association of alpha tocopherol on child wheezing was modified.

**CONCLUSIONS:** In this cohort, increasing maternal postpartum plasma alpha-tocopherol isoform concentration was associated with decreased likelihood of wheezing requiring asthma medications at two years. This protective association appeared to be attenuated at high concentrations of gamma-tocopherol.

**264 Baseline Blood Eosinophils and Reduction of Asthma Exacerbations By Omalizumab in Children with Moderate-to-Severe Allergic Asthma**

Stanley J. Szefler, MD, FAAAAI, Thomas B. Casale, MD, FAAAAI, Karin Rosén, MD, PhD, Benjamin L. Trzaskoma, MS, TMirah Haselkorn, PhD, Benjamin Ortiz, MD, and William Busse, MD; Children’s Hospital Colorado and University of Colorado School of Medicine, Aurora, CO. 2Division of Allergy and Immunology, University of South Florida, Tampa, FL. 3Genentech, Inc., South San Francisco, CA. 4Novartis Pharmaceuticals Corporation, East Hanover, NJ. 5School of Medicine and Public Health, University of Wisconsin, Madison, WI.

**RATIONALE:** Since eosinophils may predict response to omalizumab therapy, we evaluated blood eosinophil count as a predictive biomarker for response to omalizumab in children. During the 24-week inhaled steroid dose-stable phase of a double-blind, randomized, controlled trial in children ≥6 to <12 years old with inadequately controlled, moderate-to-severe, allergic asthma, clinically significant asthma exacerbation rates were reduced by 31% (p = 0.007) with omalizumab (75-375 mg every 2 or 4 weeks) versus placebo.

**METHODS:** This posthoc exploratory Poisson regression analysis examined exacerbation rate reductions with omalizumab versus placebo at Week 24, stratified by baseline blood eosinophil subgroups: < 300/μL (n = 146), ≥300/μL (n = 429), < 400/μL (n = 223), and ≥ 400/μL (n = 352). Clinically significant exacerbations were defined as those requiring either systemic corticosteroid therapy or a doubling of baseline inhaled corticosteroid dose for ≥3 days.

**RESULTS:** Baseline demographic and clinical characteristics were similar between treatment groups and within eosinophil strata. Mean (SD) age ranged from 8.2 (1.8) to 8.8 (1.8) years. Baseline mean (SD) percentage predicted prebronchodilator forced expiratory volume in 1 second (FEV₁) ranged from 83.6 (20.4) to 91.6 (13.2). Exacerbation rates were reduced by the following percentages (95% CI) with omalizumab versus placebo: <300/μL, 5% (-48%, 41%; p = 0.83); ≥300/μL, 39% (15%, 56%; p = 0.004); <400/μL, 15% (-30%, 44%; p = 0.46); and ≥400/μL, 41% (15%, 59%; p = 0.005).

**CONCLUSIONS:** Omalizumab significantly reduces exacerbations in children with moderate-to-severe allergic asthma. In children with elevated baseline eosinophil counts (≥300/μL), a significantly greater response to omalizumab was observed for asthma exacerbation reduction compared with placebo; children with lower baseline eosinophil had nonsignificant reductions in exacerbation rates.

**265 Changing High Risk Asthma in Memphis through Partnership (CHAMP): A Healthcare Delivery Innovation Program for Pediatric Asthma**

Christie F. Michael, MD,1,2 Christina M. Underhill, PhD,3 Errin Newman, MD,1 David A. Petty, DO,1 Susan Steppe, LAPS,2 and Dennis Stokes, MD, MPH,1 University of Tennessee Division of Clinical Immunology, Memphis, TN. 2Le Bonheur Children’s Hospital, Memphis, TN. 3Cook Children’s Physician Network, Fort Worth, TX. 4Idaho Allergy and Asthma, Idaho Falls, ID. 5University of Tennessee Health Science Center, Memphis, TN.

**RATIONALE:** The Changing High Risk Asthma in Memphis through Partnership (CHAMP) program is a healthcare delivery innovation to treat pediatric asthma, which accounts for 40% of admissions to our children’s hospital. The aim of CHAMP is to reduce hospital admissions and ED utilization for asthma exacerbations.

**METHODS:** Children on government insurance with poorly controlled asthma (ED/hospital utilization) qualified for the program. CHAMP program components address weaknesses in the current healthcare delivery system, which include fragmented care, poor sharing of information across points of care, and inadequate access to care. A high-risk asthma registry was developed to house insurance claims data and enhance data sharing across points of care. A community-based care coordination team brings support services into the home and school and makes providers more accessible at the time of need. A 24-hour asthma call line ensures patients access to sick/after hours care. We measured outcomes of calls to our 24-hour call line, as well as reductions in emergency room visits and hospitalizations. Data compares 12 months prior to 12 months post enrollment for each patient.

**RESULTS:** 479 children were enrolled. We report a 55% reduction in ED visits from pre to post CHAMP (mean±SD: 1.53±1.32 vs 0.69±1; p <0.001) and a 68% reduction in hospitalizations (0.65±0.88 vs 0.21±0.51; p <0.001). 72% of calls for respiratory complaints were resolved without hospital visit.

**CONCLUSIONS:** The CHAMP multidisciplinary team is connected with medical providers but extends beyond clinic walls to bring services into the community, making medical and social services more accessible and reducing hospital utilization.
**266 The childhood asthma-associated metabolite 12,13 DiHOME, suppresses regulatory T cells**

Sophia R. Levan1, Kei E. Fujimura, Ph.D.1, Din Lin1, Nicholas W. Lukacs2, Dennis R. Owby3, Christine C. Johnson4, and Susan V. Lynch. Ph.D.1
University of California San Francisco, San Francisco, CA, 2University of Michigan Medical School, Ann Arbor, MI, 3Medical Center of Augusta, Saint Marys, GA, 4University of Michigan, Livonia, MI.

**RATIONALE:** 12,13 DiHOME is enriched in neonates with a perturbed gut microbiota, who are at significantly higher relative-risk of developing predominantly multi-sensitized atopy at age two and parental reported doctor-diagnosed asthma at age four. This oxylipin can suppress regulatory T cell (Treg) populations *ex vivo* and is structurally similar to known ligands of peroxisome proliferator-activated receptor gamma (PPARγ). Loss of PPARγ impairs immune tolerance and prevents Treg maturation in mice. Therefore, we hypothesize that 12,13 DiHOME contributes to allergic sensitization in humans via inhibition of PPARγ signaling on human dendritic cells (DCs) resulting in suppression of Treg populations.

**METHODS:** Human DCT cell co-culture assays and a murine model of allergic airway sensitization were used to evaluate the effects of 12,13 DiHOME treatment. Flow cytometry, a cytometric bead array, and qPCR were used to quantify Treg frequency and function. Linear mixed-effects model was used for data analysis.

**RESULTS:** Treatment of human DCs with 130 μM 12,13 DiHOME did not reduce cell viability but significantly decreased IL-10 secretion (p = 0.0009) and Treg frequency (p = 0.0004). This was consistent with the decrease observed using an established PPARγ inhibitor, GW9662. C57B6 mice, treated (via peritoneal injection) with 30 mg/kg 12,13 DiHOME and subjected to allergic airway sensitization using cockroach antigen, exhibited a significant decrease in lung Tregs (p = 0.019). Current efforts are examining PPARγ-regulated gene expression.

**CONCLUSIONS:** These data indicate that 12,13 DiHOME suppresses Treg populations in a manner consistent with inhibition of PPARγ signaling, indicating a potential mechanism for loss of immune tolerance in early life.

---

**267 Shared Genetic Etiology and Ancestry Variations between Asthma and Major Complex Diseases**

Tesfaye B. Mersha, PhD1,2, Christine Cassidy3, Elisabet Johansson, Ph.D.1, and Gurjit (Neeru) K. Khurana, PhD1, and Gurjit (Neeru) K. Khurana Hershey, MD, PhD1,4; 1University of Cincinnati, Cincinnati, OH, 2Cincinnati Children’s Hospital Medical Center, Cincinnati, OH, 3University of Cincinnati, Cincinnati, OH, 4Cincinnati Children’s Hospital Medical Center, Cincinnati, OH.

**RATIONALE:** Although epidemiological and clinical evidence supports the observation that subjects with asthma often have other complex diseases such as autoimmune, infectious, and metabolic disorders, little is known about genetic architecture for such comorbidities. The objectives of this study were twofold: a) determine the shared genetic risk factors and biological pathways between asthma and other complex diseases in the context of GWAS data; b) analyze racial ancestry variations among GWAS risk variants.

**METHODS:** We explore over 20,000 unique GWAS SNPs associated with 1,480 diseases or traits and extract risk variants among asthma and other disease ontologies (ie, asthma, metabolic, autoimmunity, cardiovascular, inflammation, infection, mental and cancer). We calculated Jaccard similarity index to determine relatedness, and pathway analysis to identify functional enrichments at the gene/pathway levels.

**RESULTS:** We found more shared genetic loci than expected by chance alone (significant hypergeometric p-value for asthma-autoimmune (<2x10^−29), asthma-inflammation (<1.9x10^−22), asthma-cancer (<4x10^−14), asthma-metallic (<3x10^−14), asthma-mental (<6x10^−14), asthma-infection (<5x10^{-7}) and asthma-cardiovascular (<1.1x10^{-7}). The Jaccard index for asthma-disease etiology pairs ranged 7%-20%. Significantly over-represented pathways include the Th Helper cell differentiation (fold enrichment = 13.7, p-value = 2.1 × 10^{-14}). Ancestry variations in allele frequency was found for multiple diseases particularly for autoimmune, infection, and metabolic-related risk variants.

**CONCLUSIONS:** Our results show that the degree of interconnection between asthma and specific complex disease genetic loci couldn’t be explained by random chance alone, suggesting shared molecular mechanisms. An in-depth understanding of shared loci/pathways could provide valuable insights into the causal pleiotropic therapeutic targets that may contribute to comorbidity among complex diseases.

---

**268 Surfactant Protein-D (SP-D): a Potential Therapeutic Target for Seasonal Allergic Rhinitis**

Iesha Singh1, Asif Qaseem2, Ansar Pathan2, Rebecca Parkin1, Uday Kishore2, Stephen R. Durham, MA, MD, FRCP1, and Mohamed H. Shamiji, PhD1.

**RATIONALE:** Murine studies have shown that pulmonary surfactant protein-D (SP-D), an innate immune molecule, can modulate type I mediated allergic inflammation. We hypothesized that SP-D inhibit grass pollen induced basophil activation and histamine release. Furthermore, SP-D inhibits CD23-mediated facilitated allergen presentation (FAP) by B cell to CD27+CD4+CRTH2+ (Th2) cells and Th2 cytokine responses in subjects with seasonal allergic rhinitis.

**METHODS:** A recombinant fragment of human SP-D was expressed in Escherichia coli BL21 (DE3). The binding of SP-D to *Phleum pratense* extract was examined by FAR Western blot and ELISA. Whole blood and PBMCs were collected from grass pollen allergic (n = 29). The effect of SP-D on basophil activation and histamine release was assessed using intracellularly labeled-Diamine Oxidase (DAO) and surface markers (CD63 and CD203c) by flow cytometry. The immunomodulatory effect of SP-D on Th2 cells responses was also investigated.

**RESULTS:** SP-D was shown to bind *Phleum pratense* in a dose-dependent and calcium-dependent manner (p = 0.001). The proportion of allergen stimulated CD63+ and CD203c^bright CRTH2+ basophils were decreased (p = 0.009; p = 0.04) when the cells were exposed to SP-D. Similarly, a reduction in DAO CD63+ (p = 0.001) and DAO CD203c^bright (p = 0.01) CRTH2+ basophils was also observed. Co-operative binding of allergen-IgE complexes to B cells was reduced by 51% (p = 0.002). SP-D suppressed allergen-driven CD27+CD4+CRTH2+ T cell proliferation (FAP) (p = 0.01) and IL-4, IL-5 (all p < 0.01). Moreover, CD40/IL-4 and IL-21 mediated IgE production by B cells was inhibited by SP-D (77.12%; p = 0.02).

**CONCLUSIONS:** For the first time, we have shown that SP-D inhibit grass pollen-induced basophil responses at single cell level, T and B cell responses. These findings indicate a potential therapeutic values of SP-D in allergic inflammation.
**Hox5 paralogous genes modulate Th2 cell function during chronic allergic inflammation via regulation of Gata3**

Catherine Ptaschinski, Steven M. Hrycay, Leilani Marty Santos, Matthew A. Schaller, Deneen M. Wellick, and Nicholas W. Lukacs; University of Michigan, Ann Arbor, MI.

**RATIONALE:** The HOX5 proteins (HOXA5, HOXB5 and HOXC5) are important in lung development, however our preliminary results indicate that these genes continue to function beyond the embryonic stage. We therefore asked whether they contribute to the development of allergic airway disease in adult mice.

**METHODS:** Hox5 mutant mice and WT littermate controls were treated with cockroach allergen (CRA) and lung inflammation was measured by flow cytometry and histology. Mediastinal lymph node (MLN) cells with cockroach allergen (CRA) and lung inflammation was measured by following CRA exposure, including increased numbers of CD4+ T cells.

**RESULTS:** Hox5 mutant mice have increased lung inflammation following CRA exposure, including increased numbers of CD4+ T cells. Cells from the MLN of these mice produce significantly more Th2 cytokines when restimulated. These mice also produced more mucus in the lungs compared to WT mice. These results were replicated using bone marrow chimeras, in which mice that received Hox5 mutant bone marrow demonstrated exacerbated Th2 pathology compared to mice that received WT bone marrow, indicating a primary role for the hematopoietic system. When naïve T cells were skewed to Th2 cells, Hox5 mutant cells produced more Th2 cytokines and expressed more Gata3 than WT cells. Expression of HOX5 protein in Jurkat cells resulted in binding to the Gata3 gene at known STAT6 sites, indicating cooperation between these transcription factors in Gata3 gene regulation.

**CONCLUSIONS:** These results indicate a novel role for HOX5 proteins as regulators of Th2 cell differentiation during allergic disease.

**Whole Genome Sequencing Identifies Four Novel Variants in the Epidermal Differentiation Complex That Increase Risk and Severity for Atopic Dermatitis**

Rasika A. Mathias1, Sameer Chavan2, Meher Boorgula3, William O. C. Cookson, MD, DPhil4, Saffron Willis-Owen5, Nicholas M. Rafaels6, Jon M. Hanifin, MD, FAAAAI7, Amy Pallier8, Lynda C. Schneider, MD, FAAAAI9, Richard Gallo, MD, PhD10, Emma Guttmann-Yassky, MD, PhD11, Peck Y. Ong, MD, FAAAAI12, Ingo Ruczinski13, Terri Beaty14, Li Gao1, Lisa A. Beck, MD, FAAAAI15, Miriam Moffat16, Donald Y. M. Leung, MD, PhD, FAAAAI17,18 and Kathleen C. Barnes, PhD, FAAAAI17,18. Johns Hopkins, BALTIMORE, 2University of Colorado, Denver, 3University of Colorado, DENVER, 4Imperial College London, London, United Kingdom, 5Imperial College, LONDON, United Kingdom, 6Department of Medicine, University of Colorado, Denver, 7Oregon Health and Science University, Portland, OR, 8Northwestern University, CHICAGO, 9Harvard Medical School, Boston, MA, 10Division of Dermatology, University of California, San Diego, San Diego, CA, 11Mount Sinai Health System - Dermatology, New York, NY, 12Children’s Hospital Los AngelesUSC, Los Angeles, CA, 13Johns Hopkins University, BALTIMORE, 14Department of Dermatology, University of Rochester Medical Center, Rochester, NY, 15Imperial College, LONDON, 16K226, National Jewish Health, Denver, CO, 17University of Colorado Denver, Aurora, CO.

**RATIONALE:** Whole genome sequencing was performed in an independent European sample of 693 AD cases and 693 controls.

**RESULTS:** We identified 12 SNPs with a p <0.001 comparing AD to non-atopic controls including the well documented stop gain mutation in FLG (rs61816761, p = 0.0003). Four of these SNPs were replicated in an independent European population (p<0.00001) including the stop gain mutation in FLG, two intergenic SNPs and one noncoding RNA (FLG-AS1). Odds ratios for all SNPs were >3 in the AD subjects from the ADRN study increased with carrier status (i.e. AD subjects with all four risk alleles were more severe compared to those with 0-3 risk alleles, p<0.05).

**CONCLUSIONS:** We have identified for the first time that non FLG variants in the EDC could result in added burden for risk and increased severity of AD.
272 **House Dust Bacterial Microbiome in Smoking and Pet Owning Homes**

**Ryan D. Akin**¹, Daniel P. Heruth, Ph.D.¹, Shui Qing Ye, MD, Ph.D.¹, Jay M. Portnoy, MD, FAAAAI², Christine E. Giaccio, MD², Min Xiong, PhD³, and Charles S. Barnes, PhD, FAAAAI⁴, ¹Children’s Mercy Hospital, Kansas City, MO, ²University of Chicago Medicine and Biological Sciences, Chicago, IL.

**RATIONALE:** The home bacterial community of allergic and asthmatic individuals has been a growing area of interest in the field of respiratory disease.

**METHODS:** Dust DNA samples (n=21) were taken from homes in the Healthy Homes Project. DNA was isolated using the MoBio-PowerLyzer-PowerSoil DNA isolation kit and bacterial 16s rDNA was amplified with universal primers for V3 and V4 hypervariable regions. Multiplexed 16S ampliconTruSeq™ sequencing was performed on an Illumina HiSeq1500. Paired end reads were demultiplexed and analyzed using QIIME. The bacterial microbiome of non-smoking homes (n=13) was compared to smoking homes (n=8). Similarly, the microbiome of homes without pets (n=11) was compared to homes with pets (n=10).

**RESULTS:** 21 dust samples received a total of 104,760 counts across 1,042 operational taxonomic units. Common bacterial phyla included Proteobacteria, Bacteroidetes, Firmicutes, and Actinobacteria. Higher levels of Proteobacteria and Bacteroidetes were observed in the smoking group and the pet group. The smoking group also had higher levels of Firmicutes. More of the family Moraxellaceae was observed in smoking homes (n=13) was compared to smoking homes (n=8). Similarly, the microbiome of homes without pets (n=11) was compared to homes with pets (n=10).

**CONCLUSIONS:** These results suggest that smokers’ and pet owners’ microbial biome is not as abundant and less diverse.

273 **Nasal Mucosal Irritation By Microbial Volatile Organic Compounds (MVOCs): A Pilot Study**

**Dennis Shusterman, MD, MPH¹, Ping Wang, PhD, MEng², and Kazukiyo Kumagai, PhD, MPH, MEng², ¹University of California, San Francisco, Richmond, CA, ²California Department of Public Health, Richmond, CA.

**RATIONALE:** Nasal symptoms can be associated with indoor mold overgrowth, even absent documented allergic sensitization. An alternative pathogenic mechanism - mucous membrane irritation by microbial volatile organic compounds (MVOCs) - has been proposed. We conducted a pilot human study of nasal irritation by two MVOCs: 1-octen-3-ol and 3-octanol, hypothesizing that the former would show greater irritant potency based upon the compounds’ relative irritant potencies in rodents.

**METHODS:** Serial dilutions of the two test compounds were prepared in odorless mineral oil vehicle, with headspace vapor concentrations documented by gas chromatography. Eight-step dilution series, with descending step concentration ratios of ~0.75, were prepared. A nasal lateralization protocol was utilized, effectively eliminating odor cueing. Ten subjects (7 females), aged 23-69, were tested on four separate days, with each test compound presented twice in alternating / counterbalanced order. Individual lateralization thresholds, taken as dilution step (reflecting % saturation vapor pressure), were averaged across subjects.

**RESULTS:** Eight subjects were reliably able to lateralize stimuli for one or both test compounds. Among the 16 trials completed by these 8 subjects for each compound, 1-octen-3-ol was successfully lateralized in 15/16, and 3-octanol in 11/16. The mean dilution step at threshold was 3.13 for 1-octen-3-ol, and 2.58 for 3-octanol (step 0 = neat).

**CONCLUSIONS:** When presented as brief (~ 4 sec.) stimuli, high concentrations of identified MVOCs can act as nasal mucous membrane irritants. Both detectability and dilution step, although not differing significantly, exhibited trends consistent with animal experimental data. Studies involving more protracted exposures with larger sample sizes may yield more realistic irritant threshold estimates.

274 **Comparative Analysis of Sanger and Illumina MiSeq Sequencing for Determining Indoor Fungal Diversity**

**Angela R. Lemons, MS¹, Charles S. Barnes, PhD², and Brett J. Green, PhD, FAAAAI³, ¹Health Effects Laboratory Division, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Morgantown, WV, ²Children’s Mercy Hospital, Kansas City, MO.

**RATIONALE:** Diversity studies utilizing sequencing technologies have elucidated a wider array of fungal species, particularly those belonging to the phylum Basidiomycota, typically overlooked using traditional methods of assessment. With the emergence of next-generation sequencing technologies, we aimed to compare the fungal diversity captured using Sanger and Illumina MiSeq sequencing approaches to determine the reproducibility of the datasets.

**METHODS:** Genomic DNA originating from a previous study (n=4) were submitted for Sanger and Illumina MiSeq sequencing of the internal transcribed spacer (ITS) rRNA regions. Sanger sequencing utilized the primer pair ITS1F-ITS4R while Illumina combined the paired reads of primer sets ITS1F-ITS2R and ITS3F-ITS4R. The fungal diversity acquired from each sequencing method were compared.

**RESULTS:** Sequencing the ITS1-2 regions showed differences in fungal species distribution captured using Sanger and Illumina MiSeq. Sanger sequencing elucidated fungi placed in the phyla Ascomycota (54%) and Basidiomycota (46%). In contrast, Illumina sequencing of the ITS1-2 regions (ITS1F-ITS4R) revealed 129,859 fungal sequences from which 98% were placed in the Ascomycota. Examination of the sequences showed a lack of assembly of the paired reads that resulted in the removal of Basidiomycete sequences from the analysis. Limiting Illumina sequencing to the ITS1 region (ITS1F-ITS2R) showed a distribution similar to that observed with Sanger sequencing, with 243,589 sequences placed in the Ascomycota (67%) and Basidiomycota (33%).

**CONCLUSIONS:** This study demonstrates the importance of evaluating limitations of new sequencing technologies before implementation in an environmental or epidemiological survey. The results of this study additionally suggest that the ITS1 region provides the most reproducibility between sequencing platforms.
275 An Association Between Indoor Fungal Spore Count, Ethnicity and Socioeconomic Status in Children with Asthma

Hani Hadi, MD;1,2 Kevin Kennedy, MPH CIEC;2, Charles S. Barnes, PhD;3 and Marcia A. Chan, PhD;4 1Division of Allergy & Immunology, Children’s Mercy Hospitals and Clinics, Kansas City, MO, 2Children’s Mercy Hospital, Kansas City, MO.

RATIONALE: Higher Alternaria spore counts are associated with increased asthma exacerbations. We hypothesize that associations between asthma symptoms and other fungal spores exists and that these associations may be related to socioeconomic status and ethnicity.

METHODS: We measured indoor spore counts in the homes of 178 patients with intermittent and persistent asthma enrolled in the Kansas City Safe and Healthy Homes Program. Spore counts for Alternaria, Aspergillus/Penicillium and Cladosporium were obtained using the Buck BioAire B250 spore trap. Inclusion criteria included family income <80% Kansas City median family income (KC-MFI). Data was analyzed using Prism (GraphPad, San Diego).

RESULTS: Overall, there were significantly higher Aspergillus/Penicillium spore counts than either Alternaria or Cladosporium in these homes (p = 0.0006). However, Cladosporium spore counts were significantly higher in homes of Hispanic children compared to African-Americans, Caucasians and Other ethnicities in which family income was >50% but <80% KC-MFI (p = 0.0010). Furthermore, in homes of children of Other ethnicities comparison of spore counts revealed significantly higher Cladosporium spore counts in which family income was <50% KC-MFI (p = 0.039).

CONCLUSIONS: Overall, levels of Aspergillus/Penicillium compared to Alternaria or Cladosporium spores were higher in homes of low-income Kansas City children with asthma. However, higher levels of Cladosporium spores were detected in homes of Hispanic children and in homes of children of Other ethnicities in the lowest income group. These results suggest that race/ethnicity and socioeconomic status may influence the species of mold that is most prevalent in these homes.

276 The Effect Of SLC9A3 On Esophageal Epithelial In Eosinophilic Esophagitis (EOE)

Chang Zeng1, David Wu, PhD1, Simone Vanioti, PhD1, Taekoo Noah, PhD1, Eitaro Aihara, PhD2, Artem Barski, PhD1, Andrej Kartashov1, Mark Rochman, PhD1, Joseph Sherrill, PhD1, Marc E. Rothenberg, MD, PhD, FAAAAI1, and Simon P. Hogan, PhD1; 1Children’s Hospital Medical Center, Cincinnati, OH, 2University of Cincinnati, Cincinnati, OH, 3Children’s Hospital Medical Center, Cincinnati, OH.

RATIONALE: RNAseq analyses identified SLC9A3 (Na+/H+ exchanger family Member 3) as one of the most upregulated genes in esophageal biopsy specimens (ESBS) from patients with EoE. One of the major histopathological features of EoE is dilated intercellular spaces (DIS), and DIS formation is thought to be related to altered intracellular pH and epithelial Na+ transport. The contribution of SLC9A3 to DIS formation and histopathologic changes in EoE is largely unknown. Herein, we define the effect of increased SLC9A3 expression on esophageal epithelial function.

METHODS: We examined ESBSs from patients with active EoE or healthy controls (NL) to define the relationship between the expression level of SLC9A3, inflammation and histopathological changes in EoE. Interleukin-13 (IL-13)–induced EPC2–air-liquid interface (ALI) in vitro culture system and SLC9A3 pharmacological inhibitors were employed to define the influence of SLC9A3 on esophageal epithelial dysfunction.

RESULTS: SLC9A3 expression was induced 33-fold in EoE patients compared to NL. The expression level of SLC9A3 positively correlated with the level of inflammation [cos(hp) (r^2 = 0.47, p < 0.05)] and DIS formation (r^2 = 0.51, p < 0.005). Employment of IL-13-induced EPC2–ALI model and SLC9A3-specific inhibitor (S3226) revealed that SLC9A3 was associated with esophageal dysfunction including decreased resistance (RT) (p < 0.05), decreased extracellular pH ([pH]} (p < 0.05), increased acid secretion (p < 0.05) and proliferation rate (p < 0.0001) and DIS formation.

CONCLUSIONS: SLC9A3 is overexpressed in EoE patients and in IL-13-induced EPC2–ALI model system and SLC9A3 function contributes to esophageal epithelial dysregulation and DIS formation.

277 Lipid Abnormalities Associated with Skin Lesions in Atopic Dermatitis

Evgeny Berdyshnev, PhD, Elena Goleva, PhD, Irina Bronova, PhD, Cydney Rios, BS, Nathan Dyjack, BS, Agata Wesolowska-Anderersen, MD, Clifton F. Hall, MS, Brittany N. Richers, BS, Patricia A. Taylor, NP, Caroline Bronchick, RN, Max, A. Seibold, PhD, and Donald Y. M. Leung, MD, PhD, FAAAAI; National Jewish Health, Denver, CO.

RATIONALE: Sphingolipids (ceramides and sphingomyelins) play an important role in establishing the water retaining properties of skin. The basis of lipid abnormalities in atopic dermatitis (AD) is poorly understood.

METHODS: Lipid profiles from skin tape strips of 15 healthy controls, 20 AD and 5 psoriasis patients were analyzed by targeted liquid chromatography tandem mass spectrometry and lipid pathway transcrptome by RNAseq.

RESULTS: The relative proportion of sphingolipids with long-chain fatty acids (C22–C32) was decreased in lesional AD skin (Mean±SD 73.9±4.1%, 80.4±5.5% of total ceramides for AD lesional skin and normal skin, respectively, p<0.05) while short-chain fatty acid sphingolipids (C14–C20) were increased in AD. A similar pattern was observed in skin free fatty acids. Parallel significant changes in the expression of enzymes involved in sphingolipid metabolism were found in AD lesional skin by RNAseq (fatty acid elongases ELOVL1, ELOVL4 (increased), ELOVL3, ELOVL6 (decreased); enzymes and regulators of de novo sphingolipid biosynthesis SPTLC2 (increased), ORMDL3 (decreased); regulators of ceramide levels ceramidase ASAH1 (decreased) and sphingomyelinase SMPD1 (increased). In contrast, psoriatic skin demonstrated a relative increase of long-chain (86.1±3.8% of total ceramides, p<0.05 compared to normal skin) and decreased short-chain ceramides.

CONCLUSIONS: This study identifies novel lipid changes in AD skin that may account for increased transepidermal water loss in AD skin. We hypothesize that sphingolipid biosynthesis and the elongation of fatty acids are metabolic processes affected by the atopic immune response. In contrast to AD, increased levels of long-chain ceramides in psoriasis skin reflect different underlying pathways.
**278 Serum IgE Specific for Alpha-Gal Sugar Moiety Can Bind Glycolipid**

Onyinye Iweala, MD, PhD\(^1\), Patrick J. Brennan, MD, PhD\(^2\), and Scott P. Commins, MD, PhD\(^3\). University of North Carolina, Chapel Hill, NC, 2Brigham and Women’s Hospital / Harvard Medical School, Boston, MA.

**RATIONALE:** Alpha-gal meat allergy, characterized by anaphylaxis to mammalian meat, is a growing concern in non-primate mammalian tissues. Meat fat content appears to impact reaction severity in alpha-gal-allergic patients. Because antigenic lipids are presented in complex with CD1 antigen-presenting molecules, we hypothesized that delayed anaphylaxis in alpha-gal allergy may be explained by alpha-gal-specific IgE binding to glycolipids complexed with CD1, since CD1-based presentation of glycolipids requires additional time for assembly and loading. Because CD1d presents the canonical invariant NK T cell glycolipid agonist alpha-galactosylceramide, a molecule structurally similar to alpha-gal, we measured IgE-binding to this isofrom.

**METHODS:** Sera from alpha-gal allergic subjects containing alpha-gal-specific IgE (n=5) were incubated with biotinylated human CD1d monomers loaded or loaded with either alpha-gal-containing glycosphingolipid isogloboside 3 (iGb3) or galactose-alpha-1,4-containing globotriaosyl ceramide (Gb3) coupled with streptavidin attached to the solid phase of a sandwich immunosassay.

**RESULTS:** CD1d monomers loaded with alpha-gal containing iGb3 bound IgE (2.6 ± 0.7 IU/mL) whereas unlaoded CD1d did not. Less IgE binding (0.49 ± 0.2 IU/mL) was present in GB3 loaded monomers. In contrast, serum from a subject without alpha-gal IgE was negative for iGb3 and GB3 binding.

**CONCLUSIONS:** Alpha-gal-specific IgE from mammalian meat-allergic subjects binds glycolipid complexed with human CD1d and does so with increased specificity to glycolipids containing the alpha-1,3 linkage. Thus, antigen presentation of dietary lipid through CD1 molecules may represent a mechanism of delayed food allergy.

---

**279 Genetic variants in HLA are a significant risk factor for peanut allergy independent of asthma**

Yuka Asai, MD, MSc, FRCP\(^1\), Aida Al-Eslami, PhD\(^2\), Loubna Akhbar, PhD\(^3\), Moshe Ben-Shoshan, MD, MSc\(^4\), Andrew Sandford, PhD\(^2\), Rick Chin, MSc\(^4\), Stephen T. Cheuk, BSc, MSc, MD, FRCP\(^1\), Jennie Hui, PhD\(^5\), William (Bill) Musk, FRACP\(^6\), Michael Hunter\(^7\), Alan James, FRACP\(^5\), Ann E. Clarke, MD, MSc, FRCPC\(^4\), and Stephen T. Cheuk, BSc, MSc, MD, FRCP\(^1\), 1Queen’s University, Kingston, ON, Canada, 2University of British Columbia, Vancouver, BC, Canada, 3McGill University, Montreal, QC, Canada, 4University of California, Calgary, AB, Canada, 5Arid Mountain Allergy and Asthma Clinic, Calgary, AB, Canada, 6University of Western Australia, Perth, Australia.

**RATIONALE:** We previously identified HLA and FLG in candidate gene studies in a large Canadian group of individuals with PA. A genome-wide association study (GWAS) on peanut allergy (PA) also found HLA to be associated with PA. To further investigate genetic factors associated with PA we conducted a PA GWAS.

**METHODS:** Cases (N=987, Canadian peanut allergy registry) and hypercontrols (N=987, Bassleton Cohort) were genotyped (Illumina Omni 2.5M + exome). Main effect analysis and stratified analyses to examine the effect of other food allergies (OFA) and asthma were conducted. Meta-analysis was conducted incorporating data from previous PA GWAS. Further exploration of the effect of asthma included previously genotyped asthma data (Study on Asthma, Genes and the Environment, Canadian Asthma Primary Prevention Study) and a known asthma SNP in HLA (rs3129890).

**RESULTS:** SNPs in HLA, ANGPT4, ARHGAP24, CTNNA3, SKAP1, and a region of long non-coding RNA were identified; only SNPs in HLA-DOB1 reached genome-wide significance (p < 3.61x10^-8). Meta-analysis with the discovery GWAS increased the significance of the top SNP (rs313497b, p = 2.15x10^-10) to 10^-18. Odds ratios increased in cases with PA only versus those who also have OFA. There was no difference between those with and without asthma. The top PA SNP was not significant in the asthma studies (p = 0.14) and appears to have the opposite direction of effect in asthma.

**CONCLUSIONS:** HLA-DOB1 is associated with PA; this appears to be independent of asthma. New loci were identified that share common characteristics of response to external stimuli and link to the actin cytoskeleton.
281 Cost Considerations in Allergy and Immunology Practice Parameters

Akalilah J. Jefferson, MD, MSc; National Institutes of Health, Bethesda, MD.

RATIONALE: Many physician specialty societies are addressing cost in their clinical guidelines as health care costs rise. Our aim is to describe how cost is addressed within allergy and immunology guidelines during the height of health care reform in the U.S.

METHODS: We searched PubMed, the National Guideline Clearinghouse, the AAAAI website, the ACAAI website, and the Joint Task Force website for practice parameters published over a 5 year period (2010-2015).

Two measures were used to determine how cost has been addressed: (1) what percentage of practice parameters explicitly consider cost in the development of clinical guidelines, measured through review of methodological statements, and (2) what percentage of practice parameters consider cost in specific recommendation justifications.

RESULTS: An inventory of 22 practice parameters were identified. Of the 22 guidelines, none explicitly integrated cost into their methodology. Eighteen (82%) had no information on cost considerations, and 4 (18%) mentioned language that they explicitly excluded cost from consideration in methodological statements. Of the 22 guidelines, 14 (64%) had at least 1 recommendation that included language indicating that cost was considered during its development. Eight (36%) did not include any language indicating cost was used to justify any recommendations.

CONCLUSIONS: While none of the practice parameters explicitly considered cost in guideline methodology, almost two thirds considered cost to justify specific recommendations. This suggests that cost is important to the specialty, but a standard way of approaching cost has not been well developed and adopted. We propose adoption of explicit cost consideration through use of the GRADE system.

282 An Economic Evaluation of Epinephrine Autoinjectors for Peanut Allergy

Katherine Bean, and Marcus S. Shaker, MD, MS, FAAAAI; 1Geisel School of Medicine, Hanover, NH; 2Dartmouth-Hitchcock Medical Center, Lebanon, NH.

RATIONALE: Three commercial epinephrine autoinjectors with different costs are available in the United States: Epipen (EPN), Adrenaclick, and Epinephrine injection, USP autoinjector (EIA).

METHODS: Decision analysis software (TreeAge Pro, Williamstown MA) was used to evaluate costs of living with food allergy. A comparative prescription drug pricing service (www.goodrx.com; accessed 8/27/16) was used to incorporate costs of EPN or EIA into Markov microsimulations for children with peanut allergy over a twenty-year time horizon. Annual event probabilities were modeled and costs also included provider visits, ambulance transports, emergency care, hospitalizations, grocery costs, and job-related opportunity costs.

RESULTS: The lowest EPN and EIA double pack costs were $166.00 and $144.62, respectively. Assuming annual prescriptions for two double packs (home and school), the mean costs of living with peanut allergy totaled $144.62, respectively. Of the 22 guidelines, none explicitly integrated cost into their methodology. Eighteen (82%) had no information on cost considerations, and 4 (18%) mentioned language that they explicitly excluded cost from consideration in methodological statements.

Two measures were used to determine how cost has been addressed: (1) what percentage of practice parameters explicitly consider cost in the development of clinical guidelines, measured through review of methodological statements, and (2) what percentage of practice parameters consider cost in specific recommendation justifications.

RESULTS: An inventory of 22 practice parameters were identified. Of the 22 guidelines, none explicitly integrated cost into their methodology. Eighteen (82%) had no information on cost considerations, and 4 (18%) mentioned language that they explicitly excluded cost from consideration in methodological statements.

Of the 22 guidelines, 14 (64%) had at least 1 recommendation that included language indicating that cost was considered during its development. Eight (36%) did not include any language indicating cost was used to justify any recommendations.

CONCLUSIONS: While none of the practice parameters explicitly considered cost in guideline methodology, almost two thirds considered cost to justify specific recommendations. This suggests that cost is important to the specialty, but a standard way of approaching cost has not been well developed and adopted. We propose adoption of explicit cost consideration through use of the GRADE system.

283 Where Do Children with Asthma Die? A National Perspective from 2003 to 2014

Anna J. Chen Arroyo, MD, MPH1; and Christine Pal Chee, PhD2; and N. Ewen Wang, MD3, 1Brigham and Women’s Hospital, Boston, MA; 2Stanford University, Stanford, CA; Veterans Affairs Palo Alto, Health Economics Resource Center, Menlo Park, CA; 3Stanford University Medical School, Stanford, CA.

RATIONALE: Deaths from asthma, especially among children, are sentinel events that can be avoided with timely interventions. Studying the location of asthma deaths provides important insight that can help target efforts to prevent future deaths.

METHODS: We used the National Center for Health Statistics Mortality Multiple Cause-of-Death public use data from 2003 to 2014 to identify out-of-hospital (home or dead on arrival), outpatient (Emergency Department or clinic), and inpatient deaths by age, sex, race and ethnicity among children (<19 years) with asthma as the underlying cause of death, using the Marasculo procedure to compare differences. Rates were calculated using bridged-race population estimates.

RESULTS: There were a total of 2571 pediatric asthma deaths. The average annual mortality rate was six times higher in black as compared to Hispanic and white children (9.29, 1.54, and 1.28 deaths per 1,000,000 persons, respectively). Asthma deaths occurred more frequently in the outpatient setting (51%) compared to the out-of-hospital (14%) and inpatient setting (30%). In the outpatient and out-of-hospital setting, a higher proportion of deaths occurred in black children (59%, 50%) compared to white (24%, 35%) or Hispanic children (12%, 10%, p-value <0.05). Similarly in the inpatient setting, a higher proportion of deaths occurred in black children (50%) compared to white (30%) or Hispanic children (14%, p-value <0.05). Over time, the proportion of outpatient and out-of-hospital deaths have decreased as inpatient deaths have increased.

CONCLUSIONS: Variation in the location of pediatric asthma deaths by race/ethnicity may imply differential access to care. Understanding these differences may guide future interventions more effectively.

284 Improving the Use of Spirometry in the Diagnosis and Management of Asthma with an EMR Alert

Dawn Lei, MD1, and Kristin Sokol, MD, MS, MPH2; 1Beth Israel Deaconess Medical Center, Boston, MA; 2Dept of Medicine, Division of Allergy and Immunology, Beth Israel Deaconess Medical Center, Brookline, MA.

RATIONALE: The 2007 National Heart, Lung, and Blood Institute Guidelines for the Diagnosis and Management of Asthma and AAAAI's Choosing Wisely campaign recommend that asthma should not be diagnosed or managed without spirometry. In an effort to facilitate the implementation of these guidelines, a quality improvement project to design and implement an electronic medical record (EMR) reminder system was undertaken.

METHODS: A retrospective pre-intervention cross-sectional analysis of spirometry use in asthma was completed using the EMR system at a tertiary care institution. The primary outcome was to determine the percentage of asthma patients with spirometry testing. The secondary outcome was to evaluate the rate of acute asthma exacerbations in patients with and without spirometry testing. After review of this data and current guidelines, an EMR reminder system was generated and implemented with a plan for post-intervention data review.

RESULTS: Pre-intervention analysis revealed poor guideline adherence with only 26.2% of all asthma patients having spirometry performed. In patients with current asthma, defined as a physician’s diagnosis of asthma and an albuterol prescription in the past year, 22.8% of those patients with recent spirometry had an acute exacerbation, compared to 46.6% in patients without recent spirometry and 25.1% in patients with no record of spirometry.

CONCLUSIONS: We recommend the initiation of an EMR reminder system to improve guideline compliance and expect that post-intervention data analysis will reveal an appropriate increase in use of spirometry. This will ideally result in a reduction of acute asthma exacerbations and could reduce costs associated with acute asthma care.
Matthew A. Rank, MD, FAAAAI1, Molly M. Jeffery, PhD2, Che G. Ngutor, PhD2, and Nilay D. Shah, PhD2,1 Mayo Clinic, Scottsdale, AZ, 2Mayo Clinic, Rochester, MN.
RATIONALE: Utilization trends for omalizumab have not been previously described, despite availability of omalizumab since its 2003 FDA approval for asthma.
METHODS: Using a large US insurance database, OptumLabsTM Data Warehouse, that includes privately insured and Medicare Advantage patients we identified omalizumab users in 2003-2015. Individuals with diagnostic codes for chronic idiopathic urticaria after 7/1/2013 were excluded from the cohort. New use of omalizumab was calculated for the entire cohort. Persistence of use, defined as the duration of use from initiation to discontinuation, was calculated in users who had pharmaceutical coverage for at least 6 months after stopping omalizumab to limit censoring based on insurance coverage.
RESULTS: We identified 8,545 omalizumab users from 2003-2015 who met our inclusion criteria (64% female, 72% white, 11% Black, 9% Hispanic, 3% Asian, and 5% unknown race/ethnicity). The rate of individuals starting omalizumab for asthma had an initial peak in 2005 at 9.56 new users per 100,000 insured people and declined until 2012 to 5.22 new users per 100,000 insured people. New omalizumab users have increased since 2012, peaking in 2015 with 12.13 new users per 100,000 insured people. The majority of individuals who started omalizumab used it for <1 year (59%); another 14% used for 1-2 years, 7% for 2-3 years, 3% for 3-4 years, 2% for 4-5 years, and 15% for >5 years.
CONCLUSIONS: Since 2012, the rate of new omalizumab users for asthma increased more than two-fold. Fewer than half of those who start omalizumab continue for longer than 1 year.

286 Dupilumab Improves Sense of Smell and Reduces Anosmia Among Patients with Nasal Polyposis and Chronic Sinusitis: Results from a Phase 2a Trial
Robert M. Nacelcro, MD, FAAAAI1, Daniel L. Hamilos, MD, FAAAAI2, Berrylin J. Ferguson, MD3, Claus Bachert, MD, PhD4, Peter W. Hellings, MD, PhD5, Joaquim Mullol, MD, PhD, FAAAAI6, Philippe Gevaert, MD7, Donghui Zhang8, Asif Khan8, Chunpeng Fan8, Vijay N. Joshi9, Náhíl Amin10, Gianluca Pirizzo11, Neil MH Graham11, Herbert W. Staudinger, MD8, Annette Grabher12, and Leda Mannen12,13
1University of Chicago, Chicago, IL, 2Massachusetts General Hospital, Boston, MA, 3University of Pittsburgh Medical Center, Pittsburgh, PA, 4Ghent University Hospital, Ghent, Belgium, 5University Hospitals Leuven, Leuven, Belgium, 6Hospital Clinic-IDIBAPS, Barcelona, Catalonia, Spain, 7Ghent University Hospital, Gent, Belgium, 8Sanofi R&D, Bridgewater, NJ, 9Sanofi R&D, Chilly Mazarin, France, 10Regeneron Pharmaceuticals, Inc., Tarrytown, NY, 11Regeneron Pharmaceuticals, Tarrytown, NY, 12Sanofi R&D, Berlin, Germany.
RATIONALE: Loss of smell is a major consequence for chronic sinusitis patients with nasal polyps and is a severity marker with significant impact on quality of life. In a phase 2a study in nasal polyposis (NP) patients, dupilumab significantly improved endoscopic, radiographic and clinical endpoints. The effect of dupilumab on smell function is evaluated here.
METHODS: Sixty adult NP patients refractory to intranasal corticosteroids were assigned (1:1) to 16 weeks of weekly subcutaneous 300mg dupilumab (including one 600mg loading dose) or placebo on top of daily mometasone furoate nasal spray (MFNS). Smell function was assessed by University of Pennsylvania Smell Identification Test (UPSIT; range 0–40), daily patient assessment of smell loss severity (range 0–3), and Sino-Nasal Outcome Test (SNOT-22) item 12: “decreased sense of smell/taste (range 0–5).”
RESULTS: At week 16, significant (p<0.0001) improvements in dupilumab versus placebo were observed in UPSIT (LS mean [LSM] difference of 14.78 [95% CI: 10.90, 18.65]) and daily AM patient assessment of smell loss severity (LSM difference of -1.28 [95% CI: -1.73, -0.84]). Patients’ proportions in the anosmia UPSIT category decreased from 83.3% (n=25) to 10.7% (n=3) with dupilumab vs. from 73.3% (n=22) to 65.2% (n=15) with placebo. Similarly, dupilumab significantly improved SNOT-22 item related to smell/taste (LSM difference from placebo: -2.06; p<0.001). Injection site reactions, headache, and nasopharyngitis were the most frequently reported adverse events with dupilumab.
CONCLUSIONS: In NP patients on daily MFNS background therapy, dupilumab significantly improved the sense of smell and reduced anosmia over a 16 week treatment period.

287 Activation of Basophils and Eosinophils By EtOH in Alcohol Sensitive Patients with CRS and Asthma
Spencer C. Payne, MD1, Robert D. Peters, MD1, Julie A. Negri, BA1, John W. Steinke, PhD, FAAAAI2, and Larry Borish, MD, FAAAAI3, 1University of Virginia, Charlottesville, VA, 2Asthma and Allergic Diseases Center, Charlottesville, VA, 3University of Virginia Health System, Charlottesville, VA.
RATIONALE: Reactions to alcoholic beverages are commonly reported in patients with CRS and asthma, especially those with concomitant aspirin-exacerbated respiratory disease. This effect appears to be greatest with red wine, but is noted with other beverages. We therefore explored the ability of ethanol and polyphenolic compounds commonly found in alcoholic beverages to directly activate eosinophils and basophils.
METHODS: Eosinophils and basophils were obtained from subjects with asthma/CRS with and without alcohol sensitivity. Eosinophils were purified by density centrifugation and negative selection magnetic affinity purification. Basophils were studied using fresh whole blood isolates and basophils identified via flow cytometry as the CD123+ granulocyte population. Both cell lines were exposed to components of red wine including ethanol, red wine extract and two representative polyphenolic compounds, resveratrol and catechin. Evidence of granulocyte activation was then measured via flow cytometry and ELISA for basophils and eosinophils respectively.
RESULTS: Basophil activation (upregulation of CD203c) was consistently seen with exposure to red wine extract but not with resveratrol. Further, in patients reporting alcohol sensitivity, high concentrations of alcohol (0.1%) induced basophil activation. This was not seen in basophils from patients without alcohol sensitivity. Additionally, subjects reporting sensitivity to alcoholic beverages reacted to catechin but not resveratrol. Studied eosinophil populations did not react to any of the experimental substances.
CONCLUSIONS: Reactivity to alcoholic beverages in subjects with CRS and asthma may reflect in part the ability of ethanol acting in synergy with the polyphenolic compound catechin to activate basophils. Sensitivity to alcoholic beverages does not appear to involve eosinophils or resveratrol.
**288 Age-Related Differences in B-Cell Inflammatory Responses in Nasal Polyps**

Ara Jo, PhD1, Jianjun Chen, MD1, Richard F. Lockey, MD, FAAAAI1, Lydia A. Sah, BS2, Roderick G. Carter, BS2, David B. Conley, MD2, Robert C. Kern, MD3, Bruce K. Tan, MD, MS4, Anju T. Peters, MD, FAAAAI5, Leslie C. Grammer, MD, FAAAAI2, Robert P. Schleimer, PhD, FAAAAI2, and Seong Ho Cho, MD, FAAAAI1; 1Division of Allergy-Immunology, Department of Internal Medicine, Morsani College of Medicine, University of South Florida, Tampa, FL; 2Division of Allergy-Immunology, Department of Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL.

**RATIONALE:** Age-related differences in the inflammatory changes of nasal polyps (NP) were previously reported. Such differences in B-cell-related inflammatory changes are not well known even though B cell activation markers are increased in NP.

**METHODS:** Sinonasal tissues and nasal lavage fluids (NLF) from young (18-49), mature (50-64), and older adults (≥65) with NP, and from healthy controls from the same age groups were collected. A murine model of NP using ovalbumin and staphylococcal enterotoxin B treatment in 3 age groups of mice was generated: young (2 months), middle-aged (12 months) and old-aged (20 months). Levels of B cell activating factor (BAFF) and anti-dsDNA antibody were measured by ELISA and expression of a plasma cell marker, CD138, examined using immunohistochemistry.

**RESULTS:** In NP subjects, there was a trend for increased BAFF protein levels in NLF (18-49) and mature adults (50-64) with NP compared to healthy controls. Levels of anti-dsDNA antibody were significantly increased in older subjects with NP compared to healthy controls (7.9 vs 68.8 IU/ml, p = 0.003). Furthermore, mature adults (50-64) with NP showed greater CD138 expression than other two groups. In the murine model of NP, BAFF protein levels were significantly increased in NLF compared to controls in the middle-aged (12 months) NP group (29.4 vs 299.2 pg/ml, p = 0.007). Enhanced B cell activation in NP showed a similar age-related pattern between human subjects and the murine model of NP.

**CONCLUSIONS:** This study of human NP and a murine model of NP demonstrates age-related differences in B-cell inflammatory responses in NP.

**289 Basophil Activation in Aspirin Exacerbated Respiratory Disease**

Whitney W. Stevens, MD, PhD1, Kathryn E. Hulse, PhD1, Julie A. Poposki, MS1, Lydia A. Sah, BS2, James Norton, MS1, Roderick G. Carter, BS2, Atsushi Kato, PhD3, Leslie C. Grammer, MD, FAAAAI4, Kathleen E. Harris, BS1, Anju T. Peters, MD, FAAAAI4, Caroline P. E. Price, BS2, David B. Conley, MD2, Robert C. Kern, MD2, Stephanie S. Smith, MD2, Bruce K. Tan, MD, MS5, Kevin C. Welsh, MD2, and Robert P. Schleimer, PhD, FAAAAI1; 1Department of Medicine, Division of Allergy-Immunology, Northwestern University Feinberg School of Medicine, Chicago, IL; 2Department of Otolaryngology, Northwestern University Feinberg School of Medicine, Chicago, IL.

**RATIONALE:** Aspirin Exacerbated Respiratory Disease (AERD) is characterized by the triad of chronic rhinosinusitis with nasal polyps (CRSwNP), asthma, and intolerance of cyclo-oxygenase-1 (COX-1) enzyme inhibitors. While the underlying pathogenesis is not fully understood, AERD nasal polyps (NP) have been characterized as having an enhanced type-2 inflammatory phenotype. The role that basophils may play in AERD remains unclear and was the focus of the current investigation.

**METHODS:** NP and peripheral blood was obtained during routine endoscopic sinus surgery from consented AERD patients. CRSwNP patients who were tolerant of COX-1 inhibitors served as controls. Single cell suspensions were prepared from NP or blood and stained for markers of basophil lineage (CD45, FcεRI, CD127, CD203c, 2D7) and activation (CD63) for analysis by flow cytometry.

**RESULTS:** The mean number of basophils (CD45+ CD203c+ FcεRI+ CD127+) detected in AERD NP was elevated ~3-fold compared to CRSwNP (p = 0.03). While the number of peripheral blood basophils did not differ between the two conditions (p = 0.88), the number of basophils strongly correlated with the number of CD45+ Siglec 8+ eosinophils detected within the same NP specimens (r = 0.61, p = 0.006). There was a trend toward more basophils having CD63+ co-expression in AERD than CRSwNP NP (p = 0.08). In contrast, basophils from AERD NP tended, on average, to have a lower expression of the granule content marker 2D7 than matched peripheral blood or control CRSwNP NP, suggesting greater degranulation in AERD.

**CONCLUSIONS:** There is enhanced basophil recruitment and activation in AERD compared to CRSwNP nasal polyps which could contribute to the differences in disease pathogenesis and severity.

**290 Group 2 Innate Lymphoid Cells Are Increased in Nasal Polyps in Patients with Eosinophilic Chronic Rhinosinusitis**

Ichiro Tojima1, Hideaki Kozuki2, Shino Shimizu2, Takao Ogawa1, Masahiko Arikata1, Hiroki Kita, MD3, and Takeshi Shinzumu2; 1Shiga University of Medical Science, Otsu, Japan; 2Shiga University of Medical Science, Otsu, Japan; 3Mayo Clinic, Rochester, MN.

**RATIONALE:** Group 2 innate lymphoid cells (ILC2s) represent a critical innate cellular source of type 2 cytokines and may play important roles in various diseases. We examined the role of ILC2s in the pathogenesis of two subgroups of chronic rhinosinusitis with nasal polyps (CRSwNP); eosinophilic and non-eosinophilic CRS (ECRS and non-ECRS).

**METHODS:** We analyzed the prevalence of ILC2s in sinonasal mucosa and in peripheral blood from patients with ECRS and non-ECRS. Patients with CRS without nasal polyps (CRSsNP) and those without CRS were used as controls. ILC2s were analyzed by FACS and were identified as lineage- CD45+ CD127+ CRTH2+ cells. Isolated nasal epithelial cells were stimulated with Alternaria and the amounts of IL-33 in the supernatants were analyzed using ELISA.

**RESULTS:** The prevalence of ILC2s in nasal tissues was significantly higher in patients with ECRS compared to those with non-ECRS or CRSsNP. ILC2 prevalence correlated positively with the number of eosinophils in tissues. The prevalence of ILC2s in blood was not different between patients with ECRS and those with non-ECRS, while the percentage of blood eosinophils was significantly higher in patients with ECRS. The prevalence of blood ILC2s was higher in patients with allergic rhinitis (AR) and elevated serum IgE levels. Alternaria-induced IL-33 secretion was significantly increased in nasal epithelial cells derived from patients with ECRS as compared to those from patients with non-ECRS or CRSsNP.

**CONCLUSIONS:** ILC2s may be involved in the pathogenesis of CRSwNP, in particular in patients with tissue eosinophilia (i.e. ECRS).
AB92 Abstracts

291 Investigation of Peanut-Specific T Effector (Teff) and T Regulatory (Treg) Cells in the Blood of Allergic and Non-Allergic Individuals

Katherine Weissler1, Marjohn Rasooly 1, Mary L. Farrington, MD2, David M. Robinson, MD2, Fatima S. Khan, MD, PhD3, 1Laboratory of Allergic Diseases, NIAID, NIH, Bethesda, MD, 2Clinical Center, NIAID, NIH, Bethesda, MD.

RATIONALE: Peanut allergy is potentially life-threatening and generally has a poor prognosis. Recent data suggests the skin may be an important route of initial sensitization to peanut, and that early oral exposure to peanut is protective. In mice, Tregs are central to the development of tolerance to food, although definitive data in humans is lacking. We sought to quantify and phenotype peanut-specific Teffs and Tregs in individuals with and without peanut allergy.

METHODS: Whole blood was obtained from peanut allergic and non-sensitized/non-allergic individuals and stimulated with crude peanut extract or media alone. Peanut-specific Teffs and Tregs were identified based on upregulation of CD154 (CD40L) or CD137 (4-1BB), respectively. Flow cytometry was used to evaluate expression of cytokines and homing receptors.

RESULTS: Differential upregulation of CD154 and CD137 efficiently distinguished peanut-specific Tregs (>90% Foxp3+) and Teffs (<10% Foxp3+). Peanut-reactive Tregs did not produce cytokines and were found at a similar or greater frequency in the blood of peanut allergic individuals compared to non-allergic controls. Peanut-specific Teffs from allergic individuals produced predominantly IL-13 to peanut while non-allergic subjects expressed mostly IFN-γ. No significant difference in expression of skin (CLA) homing receptors on peanut-specific T cells was identified, although greater numbers of peanut-specific Teffs expressed gut (α4β7) homing receptors in allergic versus non-allergic individuals.

CONCLUSIONS: Established peanut allergy is not associated with a deficiency in or altered homing of peanut-specific Tregs in the blood. Peanut-specific Teff cells are Th2- rather than Th1-skewed in peanut allergic subjects, and may be more likely to traffic to the gut.

292 CD4+ T cell Responses in Cow’s Milk allergy

Diego Archila, PhD1, Mary L. Farrington, MD2, David M. Robinson, MD2, Fatima S. Khan, MD, FAAAAI3, and William W. Kwok, PhD1, 1Benaroya Research Institute at Virginia Mason, Seattle, WA, 2Virginia Mason Medical Center, Seattle, WA, 3Altru, Grand Forks, ND.

RATIONALE: Cow’s Milk Allergy (CMA) is the most common food allergy in children with β-lactoglobulin and casein proteins as the major milk allergens. Casein consists of several isoforms: αs1-casein, αs2-casein, β-casein and κ-casein. Little is known about specific T-cell responses toward these allergens in adults and children with CMA and non-allergic subjects.

METHODS: A total of 23 milk allergic subjects, including 10 adults and 13 children, and 18 milk non-allergic subjects were recruited. T cell responses toward β-lactoglobulin, αs1-casein, αs2-casein, β-casein and κ-casein were evaluated by CD154+ up-regulation assays and tetramer assays.

RESULTS: T cell responses were significantly higher in allergic subjects compared to non-allergic subjects. No significant difference in frequencies between adults and children with CMA were observed. With tetramers, β-lactoglobulin, αs1-casein, αs2-casein, β-casein and κ-casein-epitope specific memory T cells were detected in 30%, 80%, 40%, 65% and 45% of 20 allergic subjects. Majority of allergen-specific cells were CCR4+. Variable expressions of CCR6, CD27 and CRTH2 were observed in these cells. With CD154+ up-regulation assay, cytokine profiles of Bos d-specific cells were examined. Amongst the cytokines producers, majority of cells produced IL-4 and IL-13. A subgroup of children with CMA had cells that coproduced IL-4 and IL-17.

CONCLUSIONS: αs1-casein was the major allergen in eliciting T cell responses. In adults with CMA, a committed Th2 response was observed. On the other hand, in children with CMA, Tcf7L2/Tc17 responses were more prevalent, suggesting that these T-cell populations are not fully committed into the Th2 phenotype and could play a role in CMA outgrowth.

293 Identification and Characterization of T Cell Epitopes in Mouse Allergy

Luise Westerberg1, Sinu Paul2, Bjoern Peters3, Alessandro Sette, PhD4, and Veronique Schulten, PhD2, 1La Jolla Institute for Allergy and Immunology, La Jolla, 2La Jolla Institute for Allergy and Immunology, La Jolla, CA, 3La Jolla Institute for Allergy and Immunology, San Diego, CA, 4La Jolla Institute for Allergy & Immunology, La Jolla, CA.

RATIONALE: Mice (Mus musculus) are ubiquitous, existing in every climate all over the world, both indoors and out. Mouse allergy has become a prevalent disease affecting mostly laboratory workers and inner-city households. Although several allergenic proteins has been identified in mouse epithelium and urine, little is known about their immunogenicity.

METHODS: Using a combination of proteomics and bioinformatics, we sought to map T cell epitopes using PBMC from mouse allergic patients. Peptides derived from the major allergen Mus m 1, its variants, other proteins derived from mouse urine and epithelial extract as well as homologs to other mammalian allergens were screened for T cell reactivity in PBMCs from mouse allergic patients by ELISPOT.

RESULTS: Screening of ~1200 peptides lead to the identification of 59 different T cell epitopes from 18 different proteins that elicited cytokine production in PBMC from 2 or more allergic donors. Ninety-two percent of the total response targeted murine urinary proteins.

CONCLUSIONS: To the best of our knowledge, this is the first study to identify T cell epitopes from mouse proteins. The set of peptides characterized herein will serve as a tool to study mouse-specific T cells in different contexts. Mouse allergy in has been described as a correlate of asthma disease. Studying antigen-specific T cell responses in allergic, asthmatic and healthy but exposed individuals may give us great insight into what immunological events are associated with onset of disease. Furthermore, clearly defined T cell epitopes holds great value for the development of an immunotherapeutic approach.
Rhinovirus Infection Induces Dual Amplification of Virus- and Allergen-Specific T Cells with Discrete Phenotypes in Allergic Asthmatics

Lyndsey M. Muehlberg, MS1, Peter W. Heymann, MD1, Paul W. Wright1, Cara E. Wogsland2, Jonathan M. Irish, PhD2, William W. Kwok, PhD3, and Judith A. Woodfolk, MBChB, PhD, FAAAAI1, Pamela A. Frischmeyer-Guerrerio, MD, FAAAAI1, 395

RATIONALE: Rhinovirus (RV) induces acute episodes of asthma in allergic individuals. The T-cell mechanisms underlying the interplay between RV and allergy are unclear. Here, for the first time, we simultaneously monitor RV- and allergen-specific CD4+ T cells in asthmatics following experimental RV challenge using peptide/MHCII tetramers.

METHODS: HLA-diverse allergic asthmatics (n=9) and healthy control subjects (n=10) were inoculated intranasally with RV-A16. PBMC were collected before inoculation, and at days 4, 7, and 21 post-inoculation. Antigen-specific T cells were identified by dual staining with RV and allergen MHCII tetramers selected based on IgE profile. Molecular signatures were analyzed by multi-color flow cytometry and mass cytometry.

RESULTS: Both RV- and allergen-specific memory T cells were readily detectable prior to RV infection in asthmatics, whereas allergen-specific T cells were rare in controls. RV-specific Th1 cells (CXCR3+CCR4−) and allergen-specific Th2 cells (CXCR3−CCR4+) expanded following infection in asthmatics. RV-specific cells became activated and increased expression of the respiratory-homing marker CCR5 regardless of disease status; however, RV-specific responses were augmented in asthmatics. Analysis of lineage-specifying transcription factors in T cells by mass cytometry revealed a major population of memory CD4+ T cells that co-expressed T-bet and CCR5. These cells were rapidly sequestered from the periphery following inoculation, consistent with homing to the respiratory tract.

CONCLUSIONS: Parallel monitoring of circulating RV- and allergen-specific T cells during experimental infection reveals an enhanced RV-specific Th1 response in allergic asthmatics, concomitant with a minor allergen-specific Th2 response. Our findings are consistent with dysregulated Th1 immunity to rhinovirus in allergic asthma.

TGF-β pathway activation primes naïve lymphocytes to support atopic phenotypes in humans

Jonathan Lyons, MD1, Yihiu Liu, PhD1, Chi A. Ma, PhD1, Xiaomin Yu1, Michael O’Connell1, Jason Hughes2, Joshua McElwee2, Kelly D. Stone, MD, PhD, FAAAAI3, Pamela A. Frischmeyer-Guerrerio, MD, PhD4, Steven M. Holland, MD5, Alexandra F. Freeman, MD6, and Joshua D. Milner, MD1, 1NIH/NIAID/LAD/GPAS, Bethesda, 2Merck Research Laboratories, Boston, 3NIH/NIAID/LAD, Bethesda, MD, 4NIH/NIAID/LAD/FARU, Bethesda, MD, 5NIH/NIAID/LCID/IS, Bethesda, MD, 6NIH/NIAID/LCID, Bethesda, MD.

RATIONALE: Non-immunologic connective tissue phenotypes are common among atopic syndromes and have been associated with increased cell-intrinsic TGF-β activity suggesting a contributing role in atopy. Among individuals with STAT3 or recently recognized ERBB2IP mutations displayed elevated IL4Rx expression ex vivo. IL4Rx cells exhibited greater STAT6 phosphorylation in response to IL-4, and expression of the STAT6-target CD23 was elevated on patient B cells. In naïve CD4 cells, elevated IL4Rx expression enhanced GATA3 induction, and selective SMAD3 inhibition reduced IL4Rx expression and limited GATA3 induction, in vitro.

CONCLUSIONS: TGF-β can promote IL-4/IL4Rx/GATA3 axis activation in human T cells in vitro, and enhanced lymphocyte-intrinsic TGF-β activity is associated with elevated Th2 cytokine-expressing memory cells and serum IgE in humans. SMAD3 inhibition limits this effect, suggesting a novel pathway for treatment of atopic disorders associated with STAT3 or TGF-β pathway disruptions. Furthermore, IL4Rx blockade may be more effective in patients with reduced STAT3 or enhanced TGF-β signaling.