**824** High Traffic Pollution Exposure Is Significantly Associated With Poorer Asthma-Related Quality Of Life In Older Asthmatics

*Dr. Jennifer A. Kannan*, Dr. David J. Bernstein, MD, FAAAAI; Ms. Cheryl Kolf, Bernstein, RN, BSN, CCRN; Dr. Patrick Ryan, PhD; Dr. Jonathan A. Bernstein, MD, FAAAAI; Dr. Manuel S. Villareal, MD, FAAAAI; Dr. Andrew M. Smith, MD, FAAAAI; Dr. Peter Lenz; Dr. Tolly Epstein, MD, MS; ¹University of Cincinnati Medical Center, Cincinnati, OH; ²Bernstein Allergy Group, Cincinnati, OH; ³Bernstein Clinical Research Center, LLC, Cincinnati, OH; ⁴Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; ⁵Division of Immunology Allergy & Rheumatology, University of Cincinnati Medical Center, Cincinnati, OH; ⁶3255 Eden Ave., HPB 350, University of Cincinnati Medical Center, Cincinnati, OH; ⁷Allergy Partners of Central Indiana, Indianapolis, IN.

**RATIONALE:** Morbidity and mortality from asthma is highest in older adults and quality of life (QOL) may be lower, although standardized measures of QOL have not been validated in this population. Predictors of asthma-related QOL in this population also have not been determined.

**METHODS:** Allergy and Pulmonary outpatients (n=164) age 65 years and older with an objective diagnosis of asthma completed the mini-Asthma Quality of Life Questionnaire (AQLQ). Demographics, medical history, and Elemental Carbon Attributable to Traffic (ECAT), a surrogate for diesel exposure, were determined. Regression was used to determine predictors of AQLQ scores.

**RESULTS:** Total AQLQ (mean ± SD= 5.4 ± 1.1), and symptom, emotional, and activity domain scores were similar to younger populations, while environmental domain scores (4.4 ± 1.7) appeared poorer. Poorer AQLQ scores were significantly associated with ED visits (adjusted [a] OR=1.3;p<0.0001) and with the Asthma Control Questionnaire (aβ=-0.7;p<0.0001). Higher ECAT exposure (aβ=-1.6;p=0.02), female gender (aβ=-0.4;p<0.006), BMI ≥ 30 kg/m²(aβ=-0.4;p<0.01), GERD (aβ=0.4;p<0.01), non-atopic status (aβ=0.5;p<0.002), and asthma onset before age 40 years (aβ=-0.5;p<0.004) were significantly associated with poorer AQLQ scores.

**CONCLUSIONS:** AQLQ scores in stable, older asthmatics were similar to those in younger populations and were predictive of other measures of asthma control, verifying that the AQLQ is an appropriate tool in older asthmatics. Traffic pollution exposure was the strongest predictor of poorer asthma-related QOL in older asthmatics.

---

**825** Effect Of Early Exposure To Traffic Related Air Pollution On The Asthma Predictive Index and Asthma at Age 7

*Dr. Priyal Amin, DO,* Prof. Linda Levin, PhD, Dr. Tolly Epstein, MD, MS; Dr. Patrick Ryan, PhD, Dr. David I. Bernstein, MD, FAAAAI; ¹University of Cincinnati, College of Medicine, Cincinnati, OH, Afghanistan; ²University of Cincinnati, Cincinnati, OH; ³Allergy Partners of Central Indiana, Indianapolis, IN; ⁴Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; ⁵Bernstein Allergy Group, Cincinnati, OH.

**RATIONALE:** The Asthma Predictive Index (API) and wheezing phenotypes identify children at risk for childhood asthma. The impact of traffic pollution on the relationship between the API and asthma is unclear. This is the first study to prospectively determine if the API and/or wheezing phenotypes at age 5 predict asthma at age 7 in a high risk birth cohort, and if exposure to traffic pollution modifies this relationship.

**METHODS:** Data from the Cincinnati Children’s Allergy and Air Pollution Study (CCAAPS) – a high risk prospective birth cohort-was used. Parent-reported or physician-diagnosed asthma was confirmed by methacholine challenge (PC_{20} ≤ 4 mg/ml or ≥ 20% FEV1 reversibility post-challenge), or prior controller treatment for asthma. API and persistent wheezing were assessed at age 3. Average daily exposure to elemental carbon attributable to traffic (ECAT) was determined at age 3. Multivariate logistic regression with adjustment for potential confounders was performed.

**RESULTS:** At age 7, 103 of 589 children had asthma. A positive API at age 3 was associated with asthma at age 7 (adjusted [a]OR=13.3; 95% CI 7.0-25.2; p<0.0001). Allergic persistent wheezing was associated with a significantly higher risk of asthma than non-allergic persistent wheezing (aOR = 10.4 vs. 5.3; 95% CI 4.1-26.0; p<0.0001). ECAT exposure was not significantly associated with asthma despite a positive API or persistent wheezing.

**CONCLUSIONS:** Both persistent wheezing and a positive API at age 3 significantly predict asthma at age 7 in a high-risk prospective birth cohort. This relationship is not modified by exposure to traffic pollution at age 3.
**827** Viral Etiology Of Early Life Wheezing Illnesses Differentially Predict Persistence Of Asthma In High-Risk Children

*Dr. Frederick Rubner, MD*1, Dr. Daniel J. Jackson, MD, Dr. Michael D. Evans, MS2, Dr. James E. Gern, MD, FAAAAI3, Dr. Robert F. Lemanske, Jr, MD, FAAAAI4, University of Wisconsin School of Medicine and Public Health, Madison, WI, 2Pediatrics, University of Wisconsin School of Medicine and Public Health, Madison, WI.

**RATIONALE:** Viral wheezing illnesses in early childhood have been shown to predict development of asthma by 6 years of age. Whether a differential effect on the risk for persistence of asthma out to age 11 years exists based on viral etiology of early childhood wheezing illnesses has not been established.

**METHODS:** 217 children were followed prospectively from birth to 11 years in the COAST (Childhood Origins of ASThma) study. The etiology of viral wheezing illnesses during early childhood was determined using nasal lavage, culture and RT-PCR. Asthma was diagnosed clinically at 11 years. Relationships between the etiology of wheezing illnesses and asthma risk were analyzed.

**RESULTS:** In univariate analyses, wheezing illnesses in the first 3 years of life with HRV (OR=6.0 95% CI 2.1, 11, p<0.0001), RSV (OR=2.9 95% CI 1.6, 5.4, p=0.008) and other viruses (OR=4.8 95% CI 2.6, 9.1, p<0.0001) were all associated with an increased risk of asthma at age 11. Using a multivariate model to adjust for histories of wheezing with more than one virus, the risk of asthma at age 11 years was significantly increased in children with HRV wheezing histories (OR=3.7 95% CI 1.7, 7.8, p=0.0008), but not in children who wheezed with RSV (OR=1.4 95% CI 0.7, 2.9, p=0.4) or other viruses (OR=2.1 95% CI 0.9, 4.7, p=0.08).

**CONCLUSIONS:** Viral etiology of wheezing illnesses in the first three years of life confers a differential risk for persistent asthma out to 11 years of age with wheezing due to HRV being the strongest overall predictor of this development.

**828** Prevalence and Severity Of Wheezing In The First Year Of Life Among Infants With Low Birth Weight

*Dr. Nathalia Barroso1, Dr. Leila Borges, MD1, Dr. Gustavo Wandalsen, MD2, Dr. Elaine Prestes3, Prof. Herberto J. Chong Neto, MD, PhD, FAAAAI4, Prof. Nelson A. Rosario, MD, PhD, FAAAAI5, Dr. Ana Carolina Dela Bianca6, Dr. Carolina Aranda7, Dr. Decio Medeiros8, Prof. Emanuel Sarinho, Prof. PhD9, Dr. Lilian Sanchez. Lacerda. Moraes, MD, MSc10, Dr. Javier Mallo11, Prof. Dirceu Sole, MD, PhD12, UNIFESP, Brazil, 2UNIFESP, Sao Paulo, Brazil, 3State University of Para, 4Federal University of Parana, Brazil, 5Federal University of Para, Curitiba, Brazil, 6Federal University of Pernambuco, 7Federal University of Sao Paulo, Sao Paulo, Brazil, 8UFPE, Universidade Federal de Pernambuco, Brazil, 9Federal University of Mato Grosso, 10University of Santiago de Chile.

**RATIONALE:** Our aim was to describe the prevalence and severity of wheezing in the first year of life among infants with low birth weight (BW).

**METHODS:** Answers from 9833 parents living in six different cities of Brazil to the International Study of Wheezing in Infants (EISIL) questionnaire were analyzed. 674 infants were born with low BW and were separated in two groups according to the weight at birth: group A (2000g to 2499g; N=499) and B (<2000g; N=175).

**RESULTS:** Compared to infants with normal BW (N=9159) those with low BW (groups A and B) had higher prevalence of recurrent wheezing (18% vs 28% and 44%, respectively; p<0.0001), hospitalization due to wheezing (8% vs 11% and 23%; p<0.01) and severe wheezing (8% vs 19% e 33%; p<0.0001). Medical diagnosis of asthma was more frequently observed only among infants in the group B (7% vs 17%; p<0.0001). Infants in the group B had significantly higher prevalence of recurrent wheezing, hospitalization due to wheezing, severe wheezing and medical diagnosis of asthma than those in group A.

**CONCLUSIONS:** Infants with low BW showed a clear higher wheezing related morbidity in the first year of life. An inverse association was noted between BW and its impact on respiratory outcomes.

**829** Interactive Exploration Of Microbial Exposure, Asthma and Allergy Using a Web-Based Tool

*Jeremy Wildfire1, Dr. Agustin Calatroni, MA, MS2, Dr. Susan V. Lynch, PhD3, Dr. Homer A. Boushey, Jr, MD, FAAAAI4, Dr. Kei Fujimura, PhD5, Dr. Marcus Rauch, PhD5, Henry Lynn1, Dr. Rhonda D. Reid, MD, PhD, FAAAAI, Chapel Hill, NC, 1University of California San Francisco, San Francisco, CA, 2University of California, San Francisco, San Francisco, CA.

**RATIONALE:** To understand the relationship between microbial exposure, asthma and allergy, analysts need new tools that facilitate intuitive exploration of complex multivariate data.

**METHODS:** We created a customizable web-based tool that allows analysts and investigators to compare microbial exposure between subgroups of interest using a series of linked visualizations. The tool is built using standard web technology, runs in any modern web browser and is designed to work with any microbial data set. To test the tool, we looked at the relationship of microbial exposure with atopy and wheeze in data from the Inner City Asthma Consortium (ICAC) Microbiota pilot study which included microbial exposure for 49,607 taxa in bedroom dust for 104 asthmatic children.

**RESULTS:** In the ICAC example, the interactive tool clearly showed an overall trend of higher microbial exposure in the first year of life in participants without evidence of atopy and wheeze at age three (full results submitted for publication). Built-in filters showed the trend to be especially strong for members of the Firmicutes and Bacteroidetes phyla, and the tool’s search functionality allowed investigators to isolate specific taxa of interest.

**CONCLUSIONS:** This new tool provides a streamlined and intuitive user interface for a 5 million record database and facilitates investigator access to the data using rigorous statistical methods. The tool will be released for free, public use in late 2013.

**830** Is There a Link Between Uncontrolled Asthma and Sensitization To Inhalant Allergens?

*Dr. Majdy Qutub, MD*1, Prof. Emad Abdulkader Koshak, MD, Dr. Mofag Tayeb2, Dr. Mohammed Alraeb2,1 King Abdul Aziz University, Jeddah, Saudi Arabia, 2King Abdul Aziz University, Rabigh, Saudi Arabia.

**RATIONALE:** For optimal asthma control, current guidelines recommend the assessment of allergy phenotype. This study investigates the relationship between asthma control and sensitization to inhalant allergens.

**METHODS:** A cross-sectional study over one year period starting from January 2011. Asthmatics were sequentially selected from the allergy clinic. Control levels were based on Global Initiative for Asthma (GINA) guideline. Sensitization assessment to inhalant allergens was measured by positive reactions on standard skin prick test (SPT). SPSS was used to analyse any statistical correlation.

**RESULTS:** 118 asthmatics with a mean age of 34±14 years were included, of which 63.6% being females. Asthma control levels were predominantly uncontrolled in 68 cases (61.8%), partially controlled in 26 cases (23.6%) and controlled in 16 cases (14.5%). SPT to common inhalant allergens was positive in 81 patients (77.9%), mainly of 54 uncontrolled (55.1%), followed by 13 of partially controlled (13.3%) and only of 9 controlled asthmatics (9.2%). The major inhalant allergens in asthmatics were House Dust Mite (*Dermatophagoides pteronyssinus* in 54.8% and *Dermatophagoides farinae* in 47.1%), cat epithelia in 33.7% and cockroach in 22.1%. Uncontrolled asthma level was significantly correlated with positive reactions on standard skin prick test (SPT). SPSS was used to analyse any statistical correlation.

**CONCLUSIONS:** This is one of the early studies that explore the potential link between asthma control and sensitization to inhalant allergens. Sensitization to indoor inhalant allergens was common in more than half of uncontrolled asthmatics. This advocates the assessment of allergic status in any asthmatic whose symptoms are not controlled.
Allergy To Cockroaches: The Need For Standardization Of Extracts For Clinical Practice

Prof. Emanuel Sarinho, Prof. PhD 1, Dr. Filipe Wanick Sarinho, MD 2, Prof. Dirceu Sole, MD, PhD 1, 2, UFPE, Universidade Federal de Pernambuco, Brazil, 1IMIP, Brazil, 2Federal University of Sao Paulo, Sao Paulo, Brazil and Dr. Isabella Londres, UFPE.

Rationale: This study aims to evaluate the agreement between skin prick test to different cockroach allergenic extracts with serum specific IgE determination in the diagnosis of cockroach allergy.

Methods: A case-control study involving 74 asthmatic and 42 non-determination in the diagnosis of cockroach allergy. prick test to different cockroach allergenic extracts with serum specific IgE were performed.

Results: The mean diameter of induced papule was considerably greater among the asthmatic patients when compared to non-asthmatic controls, regardless of the species or type of cockroach extract. The correlations between the various types of utilized extracts for the two species studied were not sufficiently strong. Hollister-Stier extract was the most sensible extract among asthmatics in this study for both B. germanica (54.1 % [N = 40]) and P. americana (59.5 % [N = 44]).

Conclusions: There are no licensed in vitro tests for individual cockroach components. The weak correlation between the different extracts clearly indicates a need for standardization of the extracts for SPT for cockroach allergy diagnosis.

Are Environmental Factors More Important Than Genetic Factors In Incident Asthma?

Dr. Efren L. Raed, MD, FAAAI. Allergy/Immunology, Penn State University College of Medicine, Hershey, PA.

Rationale: Asthma is a reversible disease marked by mucus hypersecretion, bronchial hyperreactivity, and airway obstruction. Gene and environment components are linked to this condition. We report amongst a cohort of asthmatics at a university based allergy, asthma, and immunology specialty clinic, increasing incident asthma development across age ranges and ethnic groups suggesting that environmental change may be a more important component to present day asthma than genetic components.

Methods: After informed consent and IRB approval, 287 asthmatics, recruited to the study between 2011 and 2013 were asked when their asthma symptoms began. Subjects ranged in age from 4 through 81 with an average age of 36. Ethnic ancestry was represented from all continents on the globe.

Results: 25 percent of subjects developed asthma within a 6 year period from 2007-2013; 25 percent of subjects developed asthma over a 9 year period 1998-2007; 25 percent of subjects developed asthma over a 12 year period 1986-1998; and 25 percent of subjects developed asthma over a 42 year period 1944-1986.

Conclusions: Genetic heritability changes slowly over generations. However, environmental changes can occur rapidly. Environmental triggers have been linked to asthma flares including thunderstorm induced asthma, diesel exhaust particles, and obesity. Here we report an increase in new, incident asthma across age ranges and amongst ethnic backgrounds, at an academic medical center. Further work is necessary to characterize the magnitude of the effect of environmental factors on asthma severity to give guidance on how to focus international asthma priorities and resources to advance asthma research and patient care.

Sensitization In Patients With Allergic Difficult-To-Control Asthma

Dr. Rosana C. Agondi, MD, PhD 1, Dr. Bruna Saliba 2, Dr. Carla Bisaccioni, MD 1, Dr. Marcelo Vivolo Aun, MD 1, Prof. Jorge Kalil, MD, PhD 2, Prof. Pedro Giavina-Bianchi, MD, PhD, FAAAAI 1, 2, 3Clinical Immunology and Allergy Division, University of Sao Paulo, Sao Paulo, Brazil, 4Clinical Immunology and Allergy Division University of Sao Paulo, Sao Paulo, Brazil, 5Clinical Immunology and Allergy Division University of Sao Paulo, Sao Paulo, Brazil, 1Clinical Immunology and Allergy Division, University of Sao Paulo, Sao Paulo, Brazil, 2Clinical Immunology and Allergy Division, University of Sao Paulo, Sao Paulo, MA.

Rationale: The aim of this study was to identify patients with difficult-to-control asthma (DCA) in an outpatient severe asthma tertiary hospital.

Methods: We conducted a retrospective study with 218 outpatients with severe persistent allergic asthma, in the last year. Patients were considered as DCA when they met the criteria of international consensus and compared with the group of severe asthma who did not meet these criteria. We evaluated the current age, age at onset of symptoms, spirometry, total and specific IgE and comorbidities - rhinitis, gastroesophageal reflux disease (GERD), obesity and vocal cord dysfunction (VCD).

Results: Of these patients, 78% were female, 53% were in the DCA group. The DCA group was older (56 X 48 years), and age of onset of symptoms older (19 X 16 years), higher dose of inhaled corticosteroid (184X) X 945mcg/day), lower FEV1 (62% vs.72%), higher frequency of GERD (66 X 41%). The specific IgE in DCA and severe groups found similar sensitization to mites (over 90%), and the following: molds 23% vs 24%; pets 33% vs. 24%; cockroaches 28% X 23%; pollens 10% vs. 8%. There was no difference in obesity, allergic rhinitis, VCD and total IgE.

Conclusions: In this study, patients who met the criteria for DCA were older and had later age of onset of symptoms. Lung function was worse despite more aggressive treatment in DCA patients. Besides these data, GERD was more prevalent in DCA group and sensitization in this group showed higher frequency of sensitization to pets, cockroaches, and pollens.

Sensitization To Inhaled Allergens In Elderly Patients Of An Allergy Clinic In Rio De Janeiro

Dr. Jose Luiz M. Rios, MD, PhD. Dr. Luiz C. G. Arcanjo, Fabio C. Kuschnir, Joao BM. Rios, Ana CS, Oliveira; Policlinica Geral do Rio de Janeiro, Brazil.

Rationale: For a long time, allergy was not considered to play an important role in respiratory symptoms in elderly. This concept has been reassessed recently. The aim of this study is to describe the profile of sensitization to inhaled allergens (AI) in elderly patients with respiratory allergy symptoms.

Methods: Retrospective analysis of medical records of patients older than 60 years assisted in Allergic Clinic of Policlinica Geral do Rio de Janeiro and diagnosed with asthma or rhinitis. They performed skin prick test (SPT) for aeroallergens, according to the Task Force Practice Parameters 1995, from August 2010 to August 2013.

Results: A total of 135 patients with a mean age of 68.9 years were evaluated: 98 female (72.6%). All but one patient presented rhinitis symptoms (99.3%) and 37 (27.4%) had rhinitis and asthma associated. Regarding SPT, 62.2% were positive for D. pteronyssinus, 52.6% for D. farinae, 45.2% for B. tropicalis, 15.6% for fungi mix, 12.6% for dog, 14.8% to cat, 8.1% for A. fumigatus, 32.6% for cockroach and 6.7% to grass pollen. SPT was negative in only 9.5% of the patients. There was no statistically significant difference between the frequency of sensitization to each allergen and the age or gender of the sample.

Conclusions: The frequency of sensitization to inhaled allergens was as high as in younger age groups, as like as the profile. The allergic etiology should always be investigated in elderly patients with respiratory symptoms suggestive of atopy.
835 The Evaluation Of Airway Obstruction By Lung Sound Analysis In The Patients With Asthma
Dr. Terufumi Shimoda, MD 1, Dr. Yukio Nagasaka, MD 2, Dr. Yasushi Obase, MD 3, Dr. Michiyo Imaoka, MD 1, Dr. Tomoaki Iwanaga, MD 1, Dr. Reiko T. Kishikawa, MD 1; 1Fukuoka National Hospital, Fukuoka, Japan, 2Kyoto Respiratory Center, Otowa Hospital, Kyoto, Japan, 3Kawasaki Medical School, Kurashiki, Japan.

RATIONALE: A relationship between various indices of computer-aided lung sound analysis (LSA) and respiratory function has been reported. We investigated whether LSA can be used to evaluate peripheral airway obstruction in asthmatic patients.

METHODS: A total of 49 inhaled corticosteroid naive bronchial asthma patients underwent LSA, spirometry, impulse oscillometry and airway hyperresponsiveness testing with inhaled acetylcholine. Lung sounds were recorded and analyzed using a bio-sound sensor and a sound spectrometer(BSS-01 and LSA-2008; Kenz Medico, Satama, Japan). The data were analyzed to assess correlations between the expiration-inspiration lung sound power ratio (dB) at low frequencies between 100 and 195 Hz (E/I LF) and various parameters.

RESULTS: E/I LF showed a statistically significant positive correlation with R5, R20, AX and Fres(r = −0.34, p < 0.017, r = 0.34, p = 0.018, r = 0.40, p = 0.005; r = 0.32, p = 0.024, respectively). A negative correlation was found between E/I LF and X5 (r = −0.47, p = 0.0006). E/I LF showed a negative correlation with FEV1/FVC(%) and V50,%pred and V25,%pred and V5,%pred (r = −0.41, p < 0.003; r = −0.44, p = 0.002; r = −0.49, p = 0.0004; r = −0.30, p = 0.024, respectively). E/I LF was negatively correlated with logPC20 (r = −0.30, p = 0.024).

CONCLUSIONS: E/I LF of lung sound analysis can be an indicator of central and peripheral airway obstruction in bronchial asthma patients.

836 IOS Is Useful In Younger Children Who Cannot Perform Spirometry
Dr. Shintaro Okazaki, MD, Hiroki Murai, MD, PhD, Hisako Hayashi, MD, Akiko Kawakita, MD, Motoko Yasutomi, MD, PhD, Mitsufumi Mayumi, MD, PhD, Yusie Ohshima, MD, PhD, University of Fuku, Fuku, Japan.

RATIONALE: Spirometry is a common and reliable pulmonary function test to evaluate the airway obstruction. However it is challenging for younger children to be carried out. Recently, impulse oscillation system(IOS) has been shown to evaluate the localization of airway obstruction without forced breathing. Although IOS has a potential to be applied for younger children, few data are available in asthmatic children.

METHODS: 40 asthmatic children were recruited to the study. After obtaining guardians’ informed consent, airway resistance, reactance, and flow-volume curve were measured by an IOS, Mostgraph TM(Chest Co. Japan) and a spirometer. Correlations between each parameter were analyzed using Spearman’s correlation tests. Reveresibility of airway obstruction and responsiveness to short acting beta stimulant(SABA) were evaluated by measuring before and SABA inhalation.

RESULTS: 39 patients(3-14 years old) successfully performed IOS. The younger the patient is, the variance of parameter will be larger. R5, R20, and R5-R20 have negative correlations with patients’ weight, height, body surface area, and age, whereas X5 has a positive correlation with them. The patients with large R20 values(central airway obstruction) tends to exhibit more responsiveness to SABA, whereas the patients with large R20-R5 values(peripheral airway obstruction) did not.

CONCLUSIONS: IOS can be an alternative to spirometry in younger children. Peripheral obstruction dominant asthmatic patients may be less effective in using beta stimulant.

837 The Association Of Spirometry With Asthma Control and Asthma Morbidity In Inner City Schoolchildren With Asthma
Dr. Watcharot Thongkanchitiphon, MD, PhD 1,2; 1Dr. Jonathan M. Gaffin, MD, MSc 1,3; 3Dr. Lianne S. Koppel, MD 1,3; 3Dr. William J. Sheehan, MD 1,3; 3Dr. Sachin N. Baxi, MD 1,3; 3Dr. Perdita Permaul, MD 1,3; 4Dr. Diane R. Gold, MD, MPH 1,3; 3Dr. Wanda Phipatanakul, MD, MS, FAAAAI1,3; 1Boston Children’s Hospital, Boston, MA, 2Ramathibodi Hospital, Mahidol University, Bangkok, Thailand, 3Harvard Medical School, Boston, MA, 4Division of Pediatric Allergy/Immunology, Massachusetts General Hospital, Boston, MA, 5Channing Laboratory, Brigham and Women’s Hospital, Boston, MA.

RATIONALE: Forced expiratory volume in 1 second (FEV1) percent predicted is recommended for the assessment for asthma control. Previous reports demonstrated 46% of children have normal FEV1 alone, but have low forced expiratory flow from 25% to 75% of vital capacity (FEF25-75%). It has been suggested that low FEF25-75 is more relevant to clinical impairment. In addition, bronchodilator reversibility (BDR) has been related to airway inflammation and exacerbations.

METHODS: The School Inner-City Asthma Study (SICAS) is an ongoing study evaluating the role of classroom and school allergens and mold on asthma morbidity for inner city schoolchildren with asthma. Baseline FEV1, FEF25-75 and BDR from subjects enrolled in SICAS was analyzed for morbidity outcomes.

RESULTS: Of 259 subjects, 27 (10.4%) had an isolated low FEF25-75. These subjects with a low FEF25-75 had more than double the odds of nocturnal wheezing in the past 2 weeks (OR 2.5, 95% CI 1.1–5.6) and dyspnea in the past 4 weeks (OR 2.9, 95% CI 1.0–8.0) compared with those with normal spirometry. From 175 subjects with both pre- and post-bronchodilator spirometry, 38 (22%) subjects with positive BDR (≥25% change in FEV1) had significantly greater risk for activity limitation (OR 2.9, 95% CI 1.2-6.8), nocturnal wheezing (OR 2.4, 95% CI 1.2–5.1), and school absence (OR 4.1, 95% CI 1.2–13.5) in the past 4 weeks.

CONCLUSIONS: In inner city school children with asthma, an isolated low FEF25-75, and bronchodilator reversibility were associated with increased asthma symptoms. FEF25-75 and BDR should be considered a tool for assessing asthma severity, morbidity, and control.

838 Impulse Oscillometry (IOS) Is Easier Than Spirometry For Older Asthmatic and Non-Asthmatic Subjects
Dr. Michael C. Balduzzi, MD 1, Dr. Adam Updegraff, DO 1, Dr. Kerri Rawson, PhD, MS 1, Dr.Bruce Taylor, MD 1, Dr. Monroe J. King, DO, FAAAAI 1, Dr. Richard F. Lockey, MD 1, 1University of South Florida, Tampa, FL, 2Washington University School of Medicine of Medicine, St. Louis, MO, 3Morsani College of Medicine, University of South Florida, Tampa, FL, 4University of South Florida, Largo, FL, 5Division of Allergy and Immunology, Department of Internal Medicine, University of South Florida Morsani College of Medicine and James A. Haley Veterans’ Affairs Hospital, Tampa, FL.

RATIONALE: Asthma is underdiagnosed in the elderly and some older persons find spirometry difficult. Therefore, a feasibility study comparing IOS and spirometry was performed in older asthmatics and non-asthmatics to determine patient acceptance and their ability to meet American Thoracic Society (ATS) and European Respiratory Society (ERS) standards.

METHODS: Older subjects (age ≥ 65) with physician diagnosed asthma and controls without asthma were asked to perform IOS and spirometry until they met ATS/ERS standards. They performed up to 8 trials of each unless they were unable to continue or required a rescue bronchodilator. They were asked to rate the ease of IOS and spirometry on a scale of 1-5 (easy-hard).

RESULTS: Nineteen subjects meeting ATS/ERS standards completed IOS and spirometry. Ages ranged from 65-82 (M =74.05, SD =5.27) and 58% were female. No significant differences in age or gender were found between asthma (n=13) and control (n=6) groups. IOS ratings ranged from 1 to 3 (M=1.26, SD=.56) and spirometry ratings ranged from 1 to 5 (M=2.95, SD=1.39). Using Wilcoxon Signed Ranks Test, the IOS was rated significantly easier to perform than spirometry, z =-3.37, p =.001, r = -.55.

CONCLUSIONS: IOS was easier to perform than spirometry for older subjects with and without asthma and is a valuable option when patients can’t perform spirometry.
Clinical and Spirometric Characteristics In Young Patients With Intermittent and Mild Persistent Atopic Asthma
Prof. Vera Tsybulkina 1, Dr. N. Karmova 2, Dr. Nicolai Tsybulkin 1, Prof. Lawrence M. DuBuske, MD, FAAAAI 3, Kazan State Medical University, Russia, 2George Washington University School of Medicine, DC.

RATIONALE: The majority of young (under 30 years) patients with atopic asthma (AA) have intermittent or mild persistent disease. Recognition of specific AA features in this population may allow better analysis of the disease.

METHODS: 141 male patients 16 to 28 years of age (mean 19.9±2.0 years) were assessed. 68 had intermittent (IAA) and 73 mild persistent (MPAA) atopic asthma. Patients were assessed in remission with spirometric and allergy testing.

RESULTS: Cough was present in 44.1±6.0% of IAA versus 74.0±5.1% of MPAA patients (OR=0.28; 95% CI=0.14-0.56; p<0.05); Nocturnal dyspnea symptoms in 27.9±5.4% versus 47.9±5.8% in IAA and MPAA respectively (OR=0.42; 95% CI=0.21-0.85; p<0.05). Spontaneous improvement was significantly more frequent in IAA (36.8±5.8%) than in MPAA patients (20.5±4.7%; OR=2.24; 95% CI=1.06-4.77; p<0.05). Lung volumes were similar between groups: forced vital capacity (FVC) was 4.70±0.07 in IAA (103.1±7±1.30% of predicted) and 4.89±0.09 L in MPAA (100.7±1.41% of predicted). In MPAA patients all measured airflow indices were notably lower, of which the peak flow most significantly 7.50±0.20 versus 8.34±0.19 L/sec (p<0.01) in IAA.

CONCLUSIONS: The most prevalent symptom in young male patients with mild forms of AA is a night-time dyspnea, impacting nearly half of IAA patients and three quarters of those with MPAA. Lung volumes appear to be unchanged in young subjects with mild forms of asthma, but decrease of airflow in MPAA patients is statistically significant.

Clinical Impact Of Molecular Diagnosis In Dog Allergy
Prof. Joaquín Sastre, MD, PhD, FAAAAI 1, Ms. Silvia Uriarte; Fundación Jiménez Díaz, Madrid, Spain.

RATIONALE: Allergy to dog is a frequent cause of rhinitis or asthma. The prevalence of sensitization to different dog allergens is not well known.

METHODS: We select 159 sensitized patients allergic to dog. Specific IgE measurement to dog allergens Can f 1, Can f 2, Can f 3 and Can f 5 was performed by ImmunoCAP® and/or microarray ISAC® (ThermoFisher Scientific, Sweden), a value > 0.35 kU/L or >0.3 ISU was considered as positive, respectively. Association of Specific IgE measurements was done with presence and type of rhinitis or asthma.

RESULTS: 79% of patients had specific IgE to Can f 1, 19% to Can f 2, 12% to Can f 3, and 35% to Can f 5. 44% were non-sensitized to Can f 1, 19.5% to Can f 5 and 0.6% to Can f 3. Can f 1 was associated with persistent rhinitis (p=0.01), Can f 3 with severity of rhinitis and asthma (p<0.01, p 0.01, respectively), and Can f 5 to both persistence and severity of rhinitis (p 0.02, p>0.001, respectively). Sensitization to several allergens in patients (1, 2, 3 or 4) was associated with persistent asthma or rhinitis (p 0.04, p 0.01, respectively), and with moderate severity (p 0.03). Direct contact with dogs was associated with both, persistency and severity of rhinitis (p 0.02, p 0.03, respectively).

CONCLUSIONS: Different patterns of sensitization to dog allergens in patients with dog allergy can help us to predict the severity and persistence of symptoms as well as sensitization to a higher number of dog allergens.

Asthma As An Unrecognized Risk Factor For Herpes Zoster In Adults: A Population-Based Case-Control Study
Dr. Young J. Juhn, MD, MPH 1, Dr. Hyo-Jin Kwon 1, Dr. Duk Won Bang 1, Dr. Eun Na Kim 1, Peter Wolff 2, Mr. Brian Lahr 2; 1Dept of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, MN, 2Mayo Clinic, Rochester, MN.

RATIONALE: We recently reported a significantly increased risk of herpes zoster (HZ) among children with asthma. Despite the significant disease burden and morbidity of HZ and asthma, it is unknown whether asthma is associated with risk of HZ in adults. We sought to determine whether adults with asthma are at increased risk for HZ.

METHODS: This study was designed as a population-based case-control study. All adults (aged ≥21 years) with HZ were prospectively identified among Olmsted County, Minnesota residents between 2010 and 2011. We compared the frequency of asthma between HZ cases and age- and gender-matched controls (1:2 matching) without a history of HZ. Asthma status was ascertained by predetermined criteria. Data were fit to a conditional logistic regression model to take into account matching for analysis.

RESULTS: A total of 315 HZ cases and their 630 matched controls were enrolled and of the 315 cases, 203 (64%) were females, 297 cases (94%) were Caucasians, and the mean age was 67 years (SD: 10.5). Of the 315 cases, 76 (24%) were asthmatics whereas 98 of 630 controls (16%) were asthmatics (adjusted odds ratio: 1.71, 95%CI: 1.26-2.52, p=0.007) controlling for all comorbid conditions, HZ vaccinations, and health care utilizations. Population-attributable risk percent for asthma was 10%.

CONCLUSIONS: Asthma might be an unrecognized significant risk factor for HZ in adults. Consideration for immunizing adults with asthma ages 50 years or older as a target group should be given. The impact of asthma on risk of microbial infections may go beyond airways.

The Simplified Method For Eucapnic Voluntary Hyperventilation (EVH) May Be Useful To Discriminate Between Hyperventilation and Gastroesophageal Reflux Disease (GERD) Induced Bronchospassm
Dr. Richard R. Rosenthal, MD 1,2, Mr. Harvey Howe, BS 3, Mr. Paul Knause, BS 1, 1Allergy and Clinical Immunology, Johns Hopkins University School of Medicine, Baltimore, MD, 2INOVA Fairfax Hospital, Fairfax, VA, 3Self.

RATIONALE: Eucapnic Voluntary Hyperventilation (EVH) challenge is used to establish the presence of exercise induced bronchospasm (EIB) which is consequential to the obligatory respiratory water losses attendant to the hyperventilation of exercise. It can be useful to distinguish such EIB from bronchospasm due to aspiration of gastric acid in exercise exacerbated gastroesophageal reflux disease (GERD). A patient with EIB and GERD received an EVH challenge to identify the stimulus to bronchospsam following vigorous cycling.

METHODS: Simplified EVH, previously described, was administered to a cyclist who complained of dyspnea and chest tightness following vigorous cycling and who had been treated aggressively but unsatisfactorily with conventional bronchodilators and inhaled steroids. The patient voluntarily hyperventilated dry gas to 58.6% of his estimated Maximum Voluntary Ventilation (MVV) over a 6 minute period following which pulmonary functions were conducted at 5, 10 and 15 minutes and compared to pre-challenge baseline values.

RESULTS: There was no significant change from baseline pulmonary function values following EVH challenge at 5, 10 and 15 minutes. His conventional anti-asthma therapy was discontinued and he was treated aggressively for GERD with balsofen, ranitidine, and famotidine. Consequently, the patient reported significant amelioration of his chest symptoms following vigorous cycling. 

CONCLUSIONS: Abdominal pumping action from vigorous cycling in patients with GERD may initiate and aggravate EIB due to the irritant effects of gastric acid aspiration. A negative EVH challenge may be useful to distinguish such EIB from bronchospasm due to aspiration of gastric acid in exercise exacerbated gastroesophageal reflux disease (GERD).
A Young Adult With Increased Variability Of FEF25-75 Relative To FEVI Post-Bronchial Thermoplasty

Dr. Amy M. CaJacob, MD1, Dr. Mark H. Kalenian, MD, FAAAAI2, Dr. John T. Anderson, MD1, Dr. Mark Dransfield3, Dr. Jennifer Trevor, MD1, 4, University of Alabama at Birmingham, Birmingham, AL, 2 Alabama Asthma and Allergy, PC, Dothan, AL, 3University of Alabama School of Medicine, AL.

RATIONALE: Bronchial thermoplasty (BT) is a procedure using thermal energy aimed at reducing the burden of smooth muscle in the large airways. We theorize that after BT, changes in FEF25-75 rather than FEVI may be a more sensitive marker of asthma exacerbations.

METHODS: Serial in-office spirometry was performed during well visits and during asthma exacerbations pre- and post-BT.

RESULTS: S.H. is a 30 year old female with a history of severe persistent asthma requiring frequent systemic corticosteroid bursts despite maximal medical therapy including omalizumab. She underwent three BT sessions in early 2013 resulting in increased exercise tolerance and fewer exacerbations with reduced wheezing as a symptom. Spirometry was followed frequently before and after the procedure. Pre-BT asthma exacerbations dropped FEVI and FEF 25-75 by an average of 22.6% and 41.9% respectively. Post-BT, exacerbations decreased FEVI by 11.1% and FEF 25-75 by 38.8%. Reductions in FEF 25-75 pre- vs. post-BT remained more dynamic during exacerbations relative to FEVI, but are stable over time with the percent change at 7.5% comparing pre- and post-BT values.

CONCLUSIONS: FEF 25-75 is a value that reflects small airway disease, which is a large surface area that is largely unaffected by BT. As seen in our patient, changes in FEF 25-75 may be considered when assessing exacerbations post-BT.

Interferon-γ-Release Assay Prevents Unnecessary Tuberculosis Therapy in Individuals With Positive Tuberculin Skin Test

Dr. Vered Schichter-konfino, Prof. Elias Touibi; Bnai-Zion Medical Center, Rappaport Faculty of Medicine, Technion, Haifa-Israel, Haifa, Israel.

RATIONALE: The mass influx of immigrants from tuberculosis-endemic countries into Israel was followed by a considerable increase in the incidence of tuberculosis (TB). All contacts of patients with active TB are obliged to be screened by tuberculin skin tests (TST), and if found positive treatment is considered. The aim of this study was to assess the utility of interferon-γ-release assay with a prolonged follow-up in preventing unnecessary anti-TB therapy in individuals with false positive results.

METHODS: Between 2008-2012 Quantiferon TB gold-in-tube test (QFT-G) was performed in 278 sequential individuals in who were mostly either TST positive or/and were in contact with active TB patient. Whole blood was examined by the interferon-γ-release assay. We correlated the TST diameter with the interferon assay and followed-up those patients with a negative assay.

RESULTS: QFT-G test was positive in 72 (42%) of all 171 TST positive individuals. Follow-up over 5 years was available in 128 (62%) of all QFT-G negative individuals. All remained well and did not develop active TB. There was no correlation between the diameter of TST and QFT-G positivity.

CONCLUSIONS: A negative QFT-G test may obviate the need for anti-tuberculosis therapy in more than half of those with positive TST.

Interferon-γ-Release Assay Prevents Unnecessary Tuberculosis Therapy in Individuals With Positive Tuberculin Skin Test

High Dimensional Single-Cell Mass Cytometry Demonstrates Conserved Human Toll-Like-Receptor Activation Signatures

Dr. Elena Hsieh, MD1, Dr. William O’Gorman, PhD2, Ms. Erica Savig2, Dr. Pier Federico Gherardini, PhD2, Prof. Mark Davis, PhD2, Prof. Garry Nolan, PhD2, 1Allergy and Immunology, Stanford University, Stanford, CA, 2Stanford University-Microbiology & Immunology, Stanford, CA.

RATIONALE: Aberrant Toll-like receptor (TLR) activation can result in the development of immunodeficient and autoimmune disorders. TLRs are differentially expressed between immune cell subsets, but a comprehensive analysis of how regulators across the different cell types respond in a system-wide manner has previously not been possible. We applied high dimensional single-cell mass cytometry to characterize TLR activation across immune cell subsets and individuals, with the goal of establishing a reference map against which to compare pathological processes.

METHODS: Whole blood samples (five healthy adults) were treated with diverse TLR ligands, and analyzed by mass cytometry simultaneously for surface marker expression, activation states of intracellular signaling proteins, and cytokine production.

RESULTS: TLR activation induces distinct signaling patterns in different cell subsets in a manner that suggests pre-programmed functional diversity. Most notably, TLR2 ligands activate the NF-κB, p38, and Ras/Raf/ERK pathways in classical monocytes and dendritic cells, but only the NF-κB pathway in immature NK cells and a subset of CD4 T cells. This distinct TLR signaling network structure, along with unique signatures of downstream cytokine production, was conserved between individuals (coefficient of variance of 0.08 to 0.36, and 0.09 to 0.6 respectively). These conserved TLR activation signatures suggest that genetic bias rather than environmental variation programs the response profile.

CONCLUSIONS: These tightly regulated TLR activation signatures can serve as a reference map with which to understand pathological perturbations. This experimental approach can be applied to uncover TLR activation defects in primary immunodeficiency, autoimmunity, and the study of TLR ligands as vaccine adjuvants.

Heterogeneous Nuclear Ribonucleoprotein L Regulates The Selective Expression Of Glucocorticoid Receptor Translational Isosforms In HL-60 Cells

Newton Li, MD, Ingrid Bender, Nick Lu, PhD; Division of Allergy and Immunology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL.

RATIONALE: Selective glucocorticoid receptor (GR) translational isoforms, i.e. the GR-D isoforms, mediate glucocorticoid protection of neutrophils from spontaneous apoptosis. HL-60 cells, like neutrophils, have predominantly the GR-D isoform. We determined whether the translation factor heterogenous nuclear ribonucleoprotein L (hnRNPL) plays a role in selective expression of the GR isoforms in HL-60 cells.

METHODS: Knockdown using hnRNPL shRNA in HL-60 cells was performed using retroviral transduction. Empty vector was used as controls. Western blot analyses were used to determine the level of hnRNPL and GR isoforms. The expression of GR target genes in cells treated with vehicle or dexamethasone (DEX, 100 nM, 6h) were measured using realtime RT-PCR.

RESULTS: Knockdown using hnRNPL shRNA reduced the level of hnRNPL to background level. After hnRNPL knockdown, the GR-D isoform in HL-60 cells decreased significantly and the GR-A isoform increased significantly. Reflecting the switch of the GR isoforms, GR function was altered. DEX increased the expression of IkappaB in control cells but not in cells expressing hnRNPL shRNA. In contrast, DEX increased the expression of GILZ in both control and shRNA expressing cells. In addition, TNF and retinoic acid both decreased the level of hnRNPL and switched the GR-D to the GR-A isoform.

CONCLUSIONS: The translation factor hnRNPL regulates the selective expression of the GR-D isoforms in HL-60 cells. Selective expression of GR isoforms underlies gene-specific glucocorticoid responses in HL-60 cells.
847 Dendrimeric Silica Particle Composites For IgE Determination In Patients Allergic To Amoxicillin

Dr. Maria Isabel Montañez, PhD 1,2, Dr. Yolanda Vida, PhD 3, Dr. Adriana Ariza, PhD 1, Dr. Cristobalina Mayorga, PhD 1, Dr. Maria Salas, MD, PhD 4, Dr. Miguel Blanco, MD, PhD 1, Dr. Ezequiel Pérez-Inestrosa, PhD 2, Dr. María José Torres, MD, PhD 1, 1Research Laboratory for Allergic Diseases, Hospital Regional Universitario de Málaga - FIMABIS-IBIMA, Málaga, Spain, 2Andalusian Centre for Nanomedicine and Biotechnology, BIONAND, Málaga, Spain, 3Organic Chemistry, University of Málaga, Málaga, Spain, 4Allergy Service, Carlos Haya Hospital, Málaga, Spain.

RATIONALE: Benzylpenicilloyl-dendrimer conjugates anchored to cel-lulose supports are employed in Radio-Allergy-Sorbent Test (RAST) for determining IgE specific to penicillins. Herein we report on the use of silica particles (SiO2) as new solid supports for RAST applications, since they are biocompatible, with tunable size and functionalization, and reproducible preparation processes. Thus, amoxicilloyldendrimer conjugates supported on silica particles are studied for quantifying IgE specific to Amoxicillin.

METHODS: We prepared Dendrimeric Antigens (DeAn) supported on silica particles to assemble reproducible DeAn@SiO2 composites as follows: Particles were prepared by Stöber's method, and reacted with amino-propyltriethoxysilane, succinic anhydride, and subsequently with 2nd generation PolyAmidoAmine dendrimers and amoxicillins. DeAn@SiO2 was immunologically tested, at different concentrations, by RAST using sera from 3 patients allergic to Amoxicillin and 2 controls.

RESULTS: DeAn@SiO2 resulted in monodisperse sizers of 450 nm diameter. The immunoassay using 0.4 mg of DeAn@SiO2 with the three allergic sera to amoxicillin showed around 7% of RAST. When the assay was done using 1 mg and 1.6 mg of DeAn@SiO2, the recognition increased to 14% and 18% of RAST, respectively. The percentage of RAST found on controls gave values around 0.1%.

CONCLUSIONS: DeAn@SiO2 has been successfully used for the in vitro diagnosis of allergy to Amoxicillin. A higher amount of particles in the assay increases the percentage of RAST obtained in allergic patients. The dimension of the DeAn@SiO2 is a compromise between large particles (easy handling for recovering them by centrifugation) and small particles (high functionalization and therefore better interaction with serum samples), appropriate for in vitro tests.

848 Murine Splenocytes From Peanut-Allergic Donors Transfer Peanut Allergy To Naive, IrradiatedRecipient Mice

Daphne Moutsoglou, BS, Dr. Stephen C. Dreskin, MD, PhD, FAAAAI; University of Colorado Denver, Aurora, CO.

RATIONALE: The transfer of peanut allergy through bone marrow transplantation (BMT) from peanut-allergic donors to non-ataopic recipients has been described. We hypothesize that murine BMT transfers peanut allergy from peanut-allergic donors to naive recipients.

METHODS: Naïve, female C3H/HeJ recipient mice were irradiated (8 gray) and reconstituted with bone marrow cells (BM) and splenocytes (SPL) from naïve or peanut-allergic donors. Each recipient group received equal numbers of BM and SPL in one of four combinations: naïve BM and naïve SPL, peanut-allergic BM and naïve SPL, naïve BM and peanut-allergic SPL, and peanut-allergic BM and peanut-allergic SPL. Peanut-specific IgE levels were measured by enzyme-linked immunosorbent assay. Recipients were challenged intraperitoneally with crude peanut extract and symptom scores and temperature changes were recorded 30 minutes post-challenge.

RESULTS: Mice receiving peanut-allergic BM and naïve SPL (n=9) did not have significantly elevated peanut-specific IgE, symptom scores, or decreased temperatures upon the first or second challenge compared to mice receiving naïve BM and naïve SPL (n=10). However, following the second but not the first challenge, mice receiving naïve BM with peanut-allergic SPL (n=13) had significantly elevated peanut-specific IgE (p<0.008), elevated symptom scores (p<0.0001), and decreased temperatures (p<0.0001) compared to mice receiving naïve BM and naïve SPL (n=10). Mice receiving both peanut-allergic BM and peanut-allergic SPL (n=13) also had significantly elevated peanut-specific IgE (p<0.0003), elevated symptom scores (p<0.0001), and decreased temperatures (p<0.0001) compared to mice receiving naïve BM and naïve SPL (n=10).

CONCLUSIONS: These results indicate that a cell population(s) within the SPL of peanut-allergic mice adoptively transfers peanut allergy.

849 Alternaria-Induced Releases Of IL-1 Alpha and IL-1 Beta From Airway Epithelial Cells Through Syk and PKC Signaling Pathways

Dr. Yonghan Sun 1, Hirohito Kita, MD 2, 1Gil hospital, Incheon, South Ko-re, 2Mayo Clinic Rochester, Rochester, MN.

RATIONALE: We want to examine whether Alternaria alternata is also a strong inducer of IL-1α and IL-1β from airway epithelial cells, and determine the underlying mechanism of IL-1 production and secretion.

METHODS: We stimulated normal human bronchial epithelial cells with Alternaria extract, and measured IL-1α and IL-1β by ELISA. For inhibitions, cells were preincubated before stimulation with caspase-1 inhibitor IV (YVAD-fmk), actinomycin D, bisindolylmaleimide I (BIM I: GF109203X), BAY 61-3606, and BAPTA-AM.

RESULTS: The exposure of airway epithelial cells to Alternaria induced the strong releases of IL-1α and IL-1β. Secretion of IL-1α and IL-1β depended on the preformed storage. The production or secretion of IL-1α and IL-1β were mediated through Syk and PKC signaling pathways.

CONCLUSIONS: Alternaria alternata is a strong inducer of IL-1α and IL-1β from airway epithelial cells, and the pathway may be mediated through Syk and PKC signalling.

850 Transmational Bisphenol A Exposure Accelerates Diabetes Type 1 Development In NOD Mice

Dr. Johanna Bodin 1, Dr. Anette Kochbach Bolling 1, Dr. Rune Becher 2, Prof. Frieke Kuper 2, Prof. Martinus Lovik 1, Dr. Unni C. Nygaard 1, 1Norwegian Institute of Public Health, Oslo, Norway, 2TNO Nutrition and Food Research, Zeist, Netherlands.

RATIONALE: Diabetes mellitus type 1 (T1DM) is an autoimmune disease with a genetic predisposition that is triggered by environmental factors during early life. Since bisphenol A (BPA) has been suggested to have immunomodulatory effects in mouse models, we wanted to investigate if early life exposure to BPA could accelerate T1DM development in an animal model.

METHODS: Non obese diabetic (NOD) mice were exposed to BPA (0.1, 1 and 10mg/l) in drinking water during gestation and lactation. Diabetes development in offspring was registered by weekly analysis of blood glucose levels. Further, the degree of cellular infiltration (insulitis) was determined in histological sections of pancreata, as well as phenotyping of cell populations in pancreatic islets before insulitis development.

RESULTS: The severity of insulitis in the pancreatic islets at 11 weeks of age and the diabetes prevalence at 20 weeks were significantly increased for female offspring in the highest BPA exposure group compared to the control group. Increased numbers of apoptotic cells, a reduction in tissue resident macrophages and an increase in regulatory T cells were observed in islets prior to insulitis development in transmaternally exposed offspring. The detectable apoptotic cells were identified as mostly glucagon producing alpha-cells but also tissue resident macrophages and beta-cells.

CONCLUSIONS: Transmessional BPA exposure, i.e. in utero and through milk, accelerated the spontaneous diabetes development in NOD mice. This acceleration appeared to be related to early life modulatory effects on the immune system, manifesting adverse effects later in life.
**851 Soluble Type I Interferon Receptor 2 and Soluble Type II Interferon Receptor 1 Are Independently Regulated**

Thomas B. Lavoie, PhD, Taher Fatakdawalwa, Xiao-Hong Lin, Michael Skawinski, Jonathan Ferreira, Tara Stauffer; PBL, Assay Science.

**RATIONALE:** The receptors for cytokines are frequently found soluble in the serum, although the significance of soluble receptor is unclear. Soluble Type I receptor 2 (sIFNAR2) and Type II receptor 1 (sIFNGR1) are found in healthy donors and suggested to be elevated in certain diseases such as autoimmunity and cancer. Whether the levels of these soluble receptors are coordinated has not yet been examined.

**METHODS:** Sera and plasma were commercially sourced. sIFNAR2, sIFNGR1, and IFN-Beta were determined by single analyte ELISA, IP-10 and inflammatory cytokines were determined by multiplex ELISA. Both sIFNAR2 and sIFNGR1 were examined in 40 normal donor sera. 100 normal donor, 59 Mutiple Sclerosis (MS), 67 Systemic Lupus, 16 Rheumatoid Arthritis, 11 Sjogren’s and 10 Scleroderma samples were examined for sIFNAR2. Significance was determined by 2-tail t-test using Welch’s correction.

**RESULTS:** The median sIFNAR2 levels was 2.6 ng/ml and median levels of sIFNGR1 were 3.4 ng/ml with no correlation ($r^2=0.01$) in 40 donors examined for both sIFNAR2 and sIFNGR1. MS patients on IFN therapy (n=29) had higher (p=0.0004) levels of sIFNAR2 than normal donors or those on other therapies (p=0.0001). IFN-Beta mass was measurable in 86% of patients treated with IFN and correlated with IP-10 levels ($r^2=0.747$), but not sIFNAR2 ($r^2=0.05$). Systemic Lupus patients had elevated sIFNAR2 (p=0.013). Rheumatoid arthritis, Sjogren’s, and Scleroderma patients were not significantly different from normal.

**CONCLUSIONS:** sIFNAR2 and sIFNGR1 are regulated by different mechanisms. sIFNAR2 is elevated either with IFN treatment or in certain autoimmune diseases where chronic IFN stimulation is suggested.

**852 Regulation Of Innate Immune Recognition Of Viral Infection By Epigallocatechin Gallate**

Dr. Christina L. Nance, PhD1,2, Melinda Mata, BS1, Ashley McMullen, BS1, Sean McMaster, BS1, Dr. William T. Shearer, MD, PhD. FAAAAI1, 2Baylor College of Medicine, 2Texas Children’s Hospital.

**RATIONALE:** Human dendritic cells (DC) specialize in detecting viruses and initiating innate and adaptive immune responses leading to viral elimination or control. DC are potent antigen-presenting cells (APC) that express Toll-like receptors (TLR) for recognizing viruses and viral components. We present evidence of protective effect of natural antiviral agent, green tea catechin, epigallocatechin gallate (EGCG), on innate immunity of viral infection.

**METHODS:** Langerhans and monocyte-derived DC differentiated from human CD34+ and CD14+ cells, respectively. TLR profiling determined by flow cytometric analysis and RT-PCR, cytokine profiling by Luminex platform, APC function by proliferative assay and cytotoxicity studies by MTT assay.

**RESULTS:** TLR8 receptor expression was significantly up-regulated in the presence of EGCG (0-50uM) in a dose-dependent manner (70%:50uM:EGCG:p<0.01) also TLR9 RNA expression. TLR3 and TLR6 were also upregulated by EGCG. EGCG(50uM) significantly rescued agonist-induced inhibition of TLR3 (70%:p<0.01) indicative of the protective effect of EGCG. Antigen presentation was significantly inhibited by EGCG (50uM) in the presence of HIV-1 viral protein, gp120, (45%:p<0.01). EGCG did not promote secretion of proinflammatory cytokines TNFα, IL1α, IL1β, or IL6. EGCG (25 uM) down-regulated production of cytokines linked to increased susceptibility of HIV-1 infection, IL1RA (34%) and IL8 (56%) (p<0.01, p<0.001, respectively). Chemokines protective in HIV-1, MIP-1α, MIP-1β and RANTES, were up-regulated by EGCG (25uM) (200%,330%,330% respectively:p<0.001).

**CONCLUSIONS:** Specificity of EGCG was substantiated by control catechin. EGCG was not cytotoxic to DC.

**853 Prostaglandin I2 (PGI2) Inhibits IL-33-Induced Type 2 Cytokine Responses By Mouse CD4 T Cells**

Weisong Zhou, PhD1, Jian Zhang, MS1, Kasia Golieniwska1, Dr. R. Stokes Peebles, Jr, MD, FAAAAI1; 1Division of Allergy, Pulmonary and Critical Care Medicine, Vanderbilt University School of Medicine, Nashville, TN. 2Allergy, Pulmonary, and Critical Care Medicine, Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN.

**RATIONALE:** The epithelial cell-derived cytokine IL-33 is present in lung tissue and can stimulate Th2 cytokine production by CD4 T cells. Prostaglandin I2 is a lipid molecule produced in the cyclooxygenase (COX) metabolic pathway. We have previously shown that PGI2 inhibited Th2 cytokine production by IL-4-differentiated effector Th2 cells. However, the effect of PGI2 on IL-33-induced Th2 cytokine expression by CD4 T cells is unknown.

**METHODS:** Naïve CD4 T cells of BALB/c mice were activated with anti-CD3 and anti-CD28 and treated with IL-33 plus the PGI2 analog cicaprost or vehicle.

**RESULTS:** IL-33 stimulated IL-4, IL-5 and IL-13 production by CD4 T cells and cicaprost dose-dependently inhibited IL-33-induced production of the Th2 cytokines. Furthermore, the suppressive effect of cicaprost was associated with decreased NF-kB activation in the T cells and was partially reversed by treating the cells with the p38 MAPK inhibitor SB 202190, suggesting an involvement of multiple signaling pathways in IL-33-induced Th2 cytokine production by CD4 T cells.

**CONCLUSIONS:** Since Th2 cytokines mediate allergic inflammation in the lung, our findings in this study suggest that use of PGI2 decreases IL-33-induced Th2 immunity.
854 Sequencing Of The ST2 Gene and The Identification Of Genetic Determinants Of Serum Total ST2 Levels: Strong Evidence For Replication Across European and African American Populations

Dr. Rasika A. Mathias, ScD1, Lili Huang, MPH1, Dr. Candalerial I. Vergara, MD, PhD2, Dr. Li Gao, MD, PhD2, Nicholas M. Rafael1, Joseph Potec1, Mrs. Monica Campbell1, Dr. Hironori Masuko, MD, PhD1, Justyna Fert-Bober2, James Snider1, Dr. Margaret Taub, PhD2, Dr. Ingo Ruczinski, PhD4, Dr. Terri H. Beaty, PhD1, Dr. Jennifer E. Van Eyk, PhD3, Dr. Kathleen C. Barnes, PhD, FAAAA1; 1Division of Allergy and Clinical Immunology, Department of Medicine, Johns Hopkins University, Baltimore, MD, 2Department of Medicine, Johns Hopkins University, Baltimore, MD, 3Critical Diagnostics, San Diego, CA, 4Johns Hopkins Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD.

RATIONALE: ST2 (IL1RL1), in its soluble form (sST2) neutralizes its ligand, IL-33, by acting as a decoy receptor. Serum sST2 has been used as a biomarker for disease severity and outcome for multiple inflammatory and lung diseases, including atopic asthma. We previously showed a 10-SNP haplotype as a key determinant of serum sST2 levels in targeted deep resequencing studies of ST2 in 241 samples of African ancestry (p<0.0002).

METHODS: Serum sST2 was measured by ELISA on an additional 440 African American and 196 European American samples. Four SNPs selected from the 10-SNP haplotype were genotyped using the ABI Taqman assay. Single-variant tests for the common variants were performed separately by race using the linear regression models assuming additive effects of alleles on log serum total ST2 adjusted for age, gender, asthma, batch, study and principal components to adjust for admixture.

RESULTS: All four SNPs were significantly replicated (p<0.05) in the independent African American sample. Three of the four SNPs were strongly associated with sST2 levels in the European American samples (p<10^-5). Importantly, predicted allelic effects were almost identical between the racial groups.

CONCLUSIONS: We confirmed association between sST2 levels and SNPs in a previously identified ST2 haplotype in an independent sample of 440 African Americans, and replicated this association in a European American population with identical allelic effects. Two SNPs were predicted to be in a region with minimal binding evidence for Polymerase (RNA) II (DNA Directed) Polypeptide A (POLR2A) which is a DNA-dependent RNA polymerase catalyzing transcription of DNA into RNA.

855 Salmonella Typhimurium Impedes Innate Immunity With a Mast Cell-Suppressing Tyrosine Phosphatase Sptp

Hae Woong Choi1, Rhea Brooking, PhD2, Subham Neupane1, Chun-Jin Lee, PhD3, Dr. Edward Miao, MD, PhD1, Dr. Herman F. Staats, PhD1, Dr. Soman N. Abraham, PhD1,2, 1Duke University Medical Center, Durham, NC, 2University of North Carolina at Chapel Hill, Chapel Hill, 3Duke-National University of Singapore, Singapore, Singapore.

RATIONALE: The virulence of Salmonella is linked to its invasive capacity and to suppression of adaptive immunity. These actions do not explain the rapid dissemination of Salmonella after breaching the gut.

METHODS: In vitro and in vivo infection with Salmonella Typhimurium.

RESULTS: Early in infection, S. Typhimurium suppress degranulation of local mast cells (MCs), resulting in limited neutrophil recruitment and outflow of vascular contents into sites of infection, facilitating bacterial spread. MC suppression required the tyrosine phosphatase activity of the SPI1 type III secretion effector SptP. SptP functioned by dephosphorylating the vesicle fusion protein N-ethylmaleimide-sensitive factor (NSF) and blocking phosphorylation of Syk, which are both implicated in MC degranulation. Without SptP, orally challenged S. Typhimurium failed to suppress MC degranulation and exhibited limited colonization of the mesenteric lymph nodes. Administration of SptP to sites of Escherichia coli infection markedly enhanced its virulence.

CONCLUSIONS: SptP-mediated inactivation of local MCs is a powerful mechanism utilized by S. Typhimurium to impede early innate host responses.

856 The Role Of Semaphorin 7A In Alternatively Activation Of Macrophages

Prof. Hye-Ryun Kang, MD, PhD, Dr. Hyun Seung Lee, PhD, Ms. Da Eun Park, BA, Ms. Ji Won Lee, BA, Prof. Woo-Jun Song, MD, Prof. Heung-Woo Park, MD, PhD, Prof. Sang Heon Cho, MD, PhD, Prof. Kyung-Up Min, MD, PhD; Department of Internal Medicine, Seoul National University College of Medicine, Seoul, South Korea.

RATIONALE: Th2 cytokines contribute to the alternative activation of macrophages (M2 macrophages) which is closely related with asthma pathogenesis. Semaphorin 7A (Sem7A) plays a role in regulation of immune system as well as nervous system. However, the exact role of Sem7a on alveolar macrophages (AMs) in the pathogenesis of asthma is not fully understood. We examined the expression of Sem7a in macrophage of asthmatic airway and the effect of Sem7a in the Th2 cytokine stimulated alveolar macrophages in vitro.

METHODS: The expression of Sem7a was evaluated in induced sputum inflammatory cells from asthmatic patients compared with normal controls. The effect of Sem7a on alternative activation of macrophage was evaluated by comparing expression of M2 markers in the presence and absence of Sem7A siRNA. To see the direct effect of Sem7a on macrophage, IL-4 or IL-13-stimulated alveolar macrophages were treated with recombinant Sem7a.

RESULTS: The mRNA expression of Sem7a was higher in induced sputum inflammatory cells from asthmatic patients than those from normal controls. However, sem7a expression was lower in asthmatic patients with relatively severe airway hyperresponsiveness compared with asthmatic patients with mild airway hyperresponsiveness (P<0.05). Messenger RNA expression of key markers of alternatively activated macrophage (Ym-1, CD206, Arginase-1) was enhanced in treatment with Sem7a siRNA. On the other hand, recombinant Sem7a significantly suppressed IL-4/IL-13 induced the mRNA expression of Ym-1 and CD206. FACS analysis showed that IL-4/IL-13-induced arginase-1 expression was also inhibited by recombinant Sem7a.

CONCLUSIONS: Sem7a may play some role in asthma inflammation by negatively regulating alternative activation of alveolar macrophages by IL-4 or IL-13 stimulation.
**857 Immune Perturbation In Patients With Tgfbeta Pathway Defects**

Dr. Dat Q. Tran, MD1, Mrs. Ellen Regalado2, Dr. Dianna Milewicz3;
1University of Texas Medical School at Houston, Houston, TX, 2UTHealth.

**RATIONALE:** Knowledge of TGFβ regulation of the immune system stems predominantly from animal and in vitro studies. Heterozygous mutations in TGFBR1, TGFBR2 and SMAD3 have been associated with familial thoracic aortic aneurysms and aortic dissections (TAAD). These patients offer an opportunity to study their immune development when the TGFbeta pathway is defective.

**METHODS:** Flow cytometry was used to analyze PBMC from patients with TAAD (n=9) and age-matched healthy controls (HC, n=8). Th1 and Th17 were determined with intracellular cytokine staining for IFNg and IL17A. Fopx3+ Tregs were detected with anti-Fopx3 (259D). CD19+ were analyzed for naïve (Igd+CD27-), unswitched (Igd+CD27+) and switched memory (Igd-CD27+). Plasmacytoid (CD303+DC) and myeloid (CD1c+DC) were defined within lineage-1 negative population.

**RESULTS:** %CD3-CD16+NK, CD3+CD16+NK, CD4+, CD8+ and CD4+CD45RA+ in TAAD were similar to HC. Average %CD19+ (20.5vs7.3, p=0.006) and naïve B cells (81.3vs66.6, p=0.004) were higher in TAAD. The unswitched were similar but the switched B cells were lower (8.6vs15.5, p=0.01), while the %Tregs were similar, there was a remarkable reduction (1/2-3 folds) in Fopx3 concentration based on median fluorescence intensity of Fopx3 in TAAD. There was a significant reduction of %Th1 (0.14vs0.61, p=0.01), while the Th1 were similar. %pDC (9.4vs24.1, p=0.009) and %mDC (11.4vs17.9, p=0.01) were also lower in TAAD.

**CONCLUSIONS:** These results demonstrate for the first time in humans of the involvement of TGFbeta signaling in B cells, DCs, Th17 and Treg development. Further studies and monitoring of the clinical effects of these immunological perturbations in these TAAD patients are needed to appreciate the impact of their underlying disease.

**858 Chemokine Receptors On Regulatory T Cell Surface, Surrogate Markers For Intracellular Th1 and Th2 Cytokines**

Mr. Satoru Watanabe1,2, Dr. Yoshiyuki Yamada1, Prof. Hirokazu Murakami2; 1Gunma Children’s Medical Center, Shibukawa, Gunma, Japan, 2Gunma University Faculty of Medicine School of Health Science, Maebashi, Gunma, Japan.

**RATIONALE:** To identify T-helper-1 (Th1) and T-helper-2 (Th2) cells, cyttoplasmic cytokine staining is widely used. However, this method is complicated and time-consuming. Chemokine receptors and CRTH2 have been reported to function as surrogate markers for cytoplasmic Th1 and Th2 cytokines. Regulatory T cells (Tregs) may affect such surrogate marker analysis, as they share some chemokine receptors with Th1 and Th2 cells. The aim of this study was to determine better surrogate markers for cytoplasmic Th1 and Th2 cytokine staining.

**METHODS:** With institutional review board approval, ten healthy volunteers (5 males) were included. Surface and cytoplasmic markers of CD4+ lymphocytes were analyzed by flow cytometry. Th1, Th2, and Tregs were determined using anti-IFNg-γ, IL-4/IL-13, and CD4+/CD25+/Foxp3+ cells, respectively.

**RESULTS:** The percentage of Th1 cells significantly correlated with that of CXCR3+ and CCR5+ cells (r=0.59 and 0.43, respectively). There was a significant correlation between the percentage of Th2 and CRTH2+ cells (r=0.59). No correlation was observed between the percentage of Th2 and CXCR3+, CCR4+, CCR7+, or CCR8+ cells. In Th1-related chemokine receptors, a higher frequency of CXCR3+ than of CCR5+ Tregs was observed, whereas, among Th2-related chemokine receptors, the percentage of CCR4+ and CCR7+ Tregs was similar to those of CCR8+ and CRTH2+.

**CONCLUSIONS:** Surface CCR5 and CRTH2 can substitute for cytoplasmic IFNg-γ and IL-4/IL-13 staining, respectively. In contrast, correlations between intracellular Th1 or Th2 cytokines and other surface chemokine receptors may be impaired due to their higher frequency on the surface of Tregs.
Evaluation Of Cytokine Levels In Patients With Active Pulmonary Tuberculosis Their Household Contacts-A Follow Up Study

Ms. Ramya Sivangala1, Ms. Meenakshi Ponnana1, Ms. Shruthi Thada1, Mrs. Lavanya Joshi1, Dr. Vijayalakshmi Valluri1, Dr. Sumanlatha Gaddam1, Bhagwan mahavir medical research center, Hyderabad, India, 2LEPRA India—Blue Peter Public Health & Research Centre, Hyderabad, India.

RATIONALE: Household contacts of TB patients are most likely to develop TB at a faster rate.

METHODS: In vitro T cell assays and role of cytokines (IL-2 and TGF-β) in culture supernatants stimulated with the r32kDa antigen of M. bovis BCG by ELISA (pg/ml) in each of 25 Active Pulmonary Tuberculosis (APTB) patients, their House hold Contacts (HHC) at 0, 4, 6, and 12 months and Healthy Controls (HC).

RESULTS: The mean proliferative responses were found to be significant between APTB pts at 4M, 6M and HHC at 4M compared to HC (1.225 ± 0.555, 1.061 ± 0.508, 0.99 ± 0.338, 1.518 ± 0.909 at p<0.02,0.01 & 0.03) respectively. The mean IL-2 levels were significantly low in APTB pts at 0M compared to HC (19.68 ± 12.85, 28.06 ± 23.99) at p<0.02, TGF-β levels were significantly high in APTB pts and HHC at 0M compared to HC (154.54 ± 8.55, 51.41 ± 22.84) at p<0.04, 0.02 & 0.0003.

CONCLUSIONS: Five of APTB pts turned into relapse and one of HHC were more or less similar to that in patients. Hence the present study reveals that r32kDa BCG may help to predict the susceptibility of patients towards relapse for assessing treatment outcome and also in identifying the household contacts at risk.

Semaphorin 4C Is An Intrinsic Regulator Of Cell-Cell Interaction In Th2 Stimulated Memory-B-Cells

Ms. Marianne Beland1, Dr. Marylin Desjardins, MD2,3, Ms. Di Xue4, Dr. Bruce D. Mazer, MD, FAAAAI4,5, 1Meakins-Christie Laboratories, Montreal, QC, Canada, 2Division of Allergy and Clinical Immunology, Department of Paediatrics, McGill University Health Centre, Montreal, QC, Canada, 3Mcgill University, Montreal, QC, Canada, 4Montreal Children’s Hospital, Montreal, QC, Canada, 5Meakins-Christie Laboratories, Research Institute - McGill University Health Centre, Montreal, QC, Canada.

RATIONALE: Semaphorin 4C (Sema4C) is known to play a role in axonal guidance, but we found, by expression profiling of Th2 activated human B-cells, that it is important in memory-B-lymphocyte development. The aim of this study is to understand the role of Sema4C and its ligand PlexinB2 in cell-cell interactions.

METHODS: Total B cells, CD27+ memory and CD27- B-cells were isolated from tonsils and cultured with complete media ± aCD40/IL-4/IL-21 (50ng/mL) for 5-7 days. Expression of Sema4C on stimulated B cells was measured by RT-PCR and immunofluorescence. The expression of PlexinB2 was measured on total mononuclear cells by FACS and immunofluorescence.

RESULTS: Human resting B-cells express very low levels of Sema4C. B-cells stimulated with aCD40+IL-4+IL-21 express the highest levels of Sema4C mRNA and protein. By immunofluorescence, we detect Sema4C on one pole of B-cells, in association with F-actin. This is found predominantly on CD27+ memory B-cells with little expression on CD27- B-cells. Expression of the Sema4C’s ligand PlexinB2 is detected on all B-cell populations, with the highest expression on CD19+CD27+, and CD19+CD27+CD38+ B-cells (plasmablasts). PlexinB2 expression increases upon stimulation with aCD40+IL-4+IL-21. In stimulated B-cells, PlexinB2 co-localizes to the Sema4C-F-Actin synapse.

CONCLUSIONS: When Sema4C is abundantly expressed on B cells, we see localization of the molecule to one pole of the cell, thus it may be implicated in formation of immunological synapses. The increase and localization of PlexinB2 correlates with Sema4C expression, and suggests autoregulation in memory B-cells. The Sema4C-PlexinB2 axis may play a crucial role in B cell activation and migration of memory B-cells in Th2 immune responses.
**Reduced Macrophages IL-12 Production After Stimulation By BCG/INF-Gamma Suggestive Of Impaired INF-Gamma Pathway Signalling In a Child With Disseminated Atypical Mycobacterial Infection and History Of Chemotherapy For Langerhans Cell Histiocytosis**

Dr. Eliska Furlong, MD, PhD, Dr. Richard K. S. Loh, MD, FAAAAI, Dr. Grace Wooi Kee Gong, MD, Dr. Andrew McLean-Tooke, MBChB, Princess Margaret Hospital for Children, Perth, Australia.

**RATIONALE:** Impaired INF-γ-mediated immunity is characterised by increased susceptibility to poorly virulent mycobacteria. Here, we present a case of a patient with disseminated atypical mycobacterial infection poorly responding to antimicrobial treatment and INF-γ. This in a setting of previous chemotherapy for LCH resulting in profound T-cell lymphopaenia and impaired TH1/TH17 function.

**METHODS:** Functional studies of INF-γ pathway together with sequencing of INFGR1, INFGR2, and STAT1 genes were performed.

**RESULTS:** A 21 month old boy was diagnosed with a disseminated Mycobacterium haemophilium infection after previous chemotherapy for LCH following LCH III, LCH III Salvage and HLH 2004 protocols, completed by Alentuzumab, resulting in severe T-cell lymphopaenia (<200/mm³). Despite treatment with multiple anti-microbial drugs and high dose INF-γ, the infection continued to progress. Functional in vitro studies showed impaired macrophage IL-12 production after stimulation by BCG/INF-γ and severely impaired T-cell IFN-γ and IL-17 production in response to PHA. Sequencing of INFGR1, INFGR2, and STAT1 cDNA showed no pathogenic mutations.

**CONCLUSIONS:** Progressive disseminated atypical mycobacterial infection despite multiple anti-microbial treatment and high-dose INF-γ is very suggestive of an underlying Interferon Gamma Pathway immunodeficiency. Despite no mutations found in previously described associated genes (INFGR1, INFGR2 and STAT1), we believe that a secondary immunodeficiency induced by chemotherapy alone is not a sufficient explanation to the character of the infection and that a yet not identified defect of the Interferon Gamma Pathway might be causative. This unique case also raises questions about the character of LCH, a condition which remains to be idiopathic.

**Sporadic Case Of Chronic Mucocutaneous Candidiasis (CMC) Due To A Gain-Of-Function Mutation In STAT1 In a 13 Year Old Female**

Dr. Aimee E. Baer Ellington, MD, Dr. Jennifer A. Shih, MD; Emory University, Atlanta, GA.

**RATIONALE:** Chronic Mucocutaneous Candidiasis (CMC) describes a group of immunodeficiencies with recurrent Candidal infections of integument and mucous membranes. Autosomal recessive CMC is associated with chronic candidiasis with endocrinopathies caused by an AIRE mutation. Autosomal dominant CMC has no associated endocrinopathy. Mutations involving TLR, CARD9, or DECTIN1 resulting in disruption of the Tlr17 response to Candida have been reported. Currently, there are no clear criteria for diagnosing variants of CMC or for predicting most likely manifestations.

**METHODS:** We describe a 13 year old African American female who presented with pneumonia and weight loss, and 1 year later with hemoptysis, cavitary pulmonary lesions, and progressive weight loss.

**RESULTS:** History elicited chronic Candidal infections of skin, nails, mucous membranes, and 2 prior pneumonias. No similar Candidal susceptibility was noted in the family. During the initial hospital course, concomitant autoimmune endocrinopathies were ruled out and further immune work-up was unremarkable. Esophagogastroduodenoscopy showed diffuse narrowing of her esophagus attributed to chronic candida infections, and contributing to her weight loss. A CMC variant was suspected. The patient was readmitted 1 year later with cavitary pneumonia, culture-positive for viridans group streptococci, mucosal candida, and weight loss. Further immunological investigation found a gain-of-function STAT1 heterozygous mutation resulting in impaired IL-17 immunity.

**CONCLUSIONS:** There are few case reports of sporadic CMC patients with gain-of-function STAT1 mutations presenting with recurrent pneumonia as we describe here. More investigation is needed to describe CMC phenotypes in hopes of developing diagnostic criteria for CMC variants, thus preventing excess morbidity and mortality.
867 Infections In Mannose-Binding Lectin Deficiency Patients
Dr. Mary K. Paul, MD1, Dr. Christopher Chang, MD, PhD, FAAAAI2, Dr. Magee DeFelice, MD3, Dr. Gang Ye, PhD3, Dr. Sam Soundar, PhD2. 1Thomas Jefferson University Hospital, Philadelphia, PA, 2Alfred I duPont Hospital for Children, Wilmington, DE, 3Nemours/AI duPont Hospital for Children, Philadelphia, PA, 4Nemours, Orlando, FL, 5Nemours.

RATIONALE: Mannose-binding lectin (MBL) is a component of the complement pathway and plays a protective role in innate immunity. Currently there is no consensus on the clinical relevance of MBL deficiency. Subnormal levels can often be found in healthy individuals. We conducted this study to characterize the role of MBL deficiency in recurrent infections. Our hypothesis is that severe MBL deficiency is associated with an increase in the incidence of infections, ER visits, and hospitalizations.

METHODS: We conducted a retrospective case-control study of 50 pediatric patients seen at the AIDHC/TIU Immunology clinics who had MBL levels drawn between 2010 and 2013 as part of an immune evaluation. Seventeen had severe MBL deficiency, defined as <50 ng/ml, and thirty-three had MBL levels >50 ng/ml. A Poisson regression model was used to compare frequency of different infection types, ER visits, and hospitalizations between patients with severe MBL deficiency and those without.

RESULTS: Patients with severe MBL deficiency had more ear infections per patient than those with MBL levels >50 ng/ml (p = 0.0036) and increased mean occurrences of bronchitis (p = 0.0016). However, there was no significant difference in mean occurrences of sinusitis, pneumonias, abscesses, ER visits, or hospitalizations between the two groups.

CONCLUSIONS: In this retrospective study, patients with severe MBL deficiency (<50 ng/ml) appeared to be more prone to developing bronchitis and otitis but not other types of infections. Though this finding was statistically significant, future studies are needed to establish the role of MBL deficiency in the pathogenesis of upper respiratory infections.

868 LRBA Causes Immunodeficiency and Autoimmunity By Deregulating NFkB-Mediated Multiple Immune Effectors Critical For B Cell Activation
Dr. Jia-Wang Wang, PhD1, Mrs. Michelle A. Reiser, MS1, Mrs. Kunyu Li, BS1, Ms. Eileen Rifkin1, Ms. Bangmei Wang1, Dr. Narasaih Kolliputi, PhD2, Dr. Richard F. Lockey, MD1,2. 1Division of Allergy and Immunology, Department of Internal Medicine, University of South Florida, Morsani College of Medicine, Tampa, FL, 2James A. Haley Veterans’ Affairs Hospital, Tampa, FL.

RATIONALE: The absence of lipopolysaccharide-responsive beige-like anchor (LRBA) gene causes common variable immunodeficiency (CVID), autoimmunity and chronic inflammation. It is the only CVID gene that regulates vesicle trafficking and signal transduction, required for the regulation and function of many immune molecules. It is hypothesized that LRBA deficiency causes these medical conditions by deregulating NFkB-mediated multiple immune effectors critical for B cell activation.

METHODS: LRBA was knocked down in Raji lymphoma cells by the ABS 5.2.0 DTD. She

RESULTS: Knockdown of LRBA significantly increases cell survival and downregulates CD19, CD20, transmembrane activator and calcium modulator and cyclophilin ligand Interactor (TACI), TLR4 and p42/44. It also inhibits NFkB nuclear translocation and upregulates AKT, CD21, B cell-activating factor receptor, p38, Jun N-terminal kinase, tumor necrosis factor alpha (TNFα) and IL-10. Antibodies to LRBA in vivo also decrease the proinflammatory cytokines IL-6 and TNFα.

CONCLUSIONS: Deregulation of these critical Immune effector genes and increased cell survival may contribute to CVID, autoimmunity and chronic inflammation caused by LRBA deficiency.

869 Giscelli Syndrome: A Case Treated With a Hematopoietic Stems Cells From a Cord Blood
Dr. Marisol Rico-Arroyo; Instituto Mexicano del Seguro Social.

RATIONALE: Eight months female patient whose background is second degree of consanguinity and a deceased sister at the age of two years and a half, Griscelli Syndrome type II (GSII) confirmed diagnosed. Treated with hematopoietic transplant and that dies before reaching the immunologic recovery.

METHODS: Due to the family history a study of immunodeficiency was started. Within the first months of life and according with the research the patient presented a case of ocularcutaneous hypopigmentation and a hair microscopy compatible with SGII. A protocol for hematopoietic cells transplantation is started since the patient did not have a matched donor.

RESULTS: At present the patient is the 95th day of immunologic recovery, maintained with substitution intravenous immunoglobulin without infection or other complications.

CONCLUSIONS: The SGII is an immunodeficiency within the disorder of immune diseases and the group that are characterized for ocularcutaneous hypopigmentation. It is a rare disease, with an inherited autosomal recessive pattern; the main immunologic alteration is the decrease of the cytotoxicity by the NK cells with a fatal prognosis without a treatment with hematopoietic cells transplantation. In the case presented the transplant is carried out before the hemophagocytic lymphohistiocytosis which frequently causes the death of patients with this syndrome. It is necessary the monitoring of the patient to determine the prognosis of the non-related graft.

870 Fungal Granuloma and Chronic Mucocutaneous Candidiasis Due To Autosomal Dominant Gain Of Function STAT1 Mutation
Dr. Nauman Salim, MBBS, MD1; Dr. Jennifer Leiding, MD2. 1University of South Florida, Tampa, FL, 2University of South Florida, St. Petersburg, FL.

RATIONALE: Mutations in signal transducer and activator of transcription 1 (STAT1) cause a broad spectrum of infection susceptibility: severe viral and bacterial infections, nontuberculous mycobacterial disease, and chronic mucocutaneous candidiasis (CMC). CMC is most often associated with hypermorphic mutations that lead to impaired responses to interferon gamma and diminished numbers of IL-17 producing T cells. Herein, we report a case of severe chronic fungal granuloma and mucocutaneous candidiasis due to gain of function mutation in STAT1.

METHODS: Sequencing of STAT1 was performed on PCR amplified DNA

RESULTS: A 24-year-old woman developed a large fungating mass involving the right hand over 10 months, ultimately compromising movement and function. Biopsies yielded Trichophyton tonsurans. She had persistent scaly lesions on her trunk, extremities, and dorsal surfaces of the feet that failed treatment with topical antifungals. Recurrent oral thrush, onychomycosis, and tinea corporis occurred. Immuneologic evaluation revealed normal immunoglobulin levels (IgG 2800 mg/dl, IgA 339 mg/dl, IgM 168 mg/dl) with protective vaccine titers. DHR was normal. T cell subsets (CD3 2329 cells/µl, CD4 1138 cells/µl, CD8 1106 cells/µl) were normal as were lymphocyte mitogen responses. Lymphocyte stimulation to tetanus and Candida were suboptimal. A missense mutation was found within the DNA binding domain of STAT1, c.1057G>A, p.E353K.

CONCLUSIONS: Defects in STAT1 are an increasingly recognized cause of mucocutaneous fungal susceptibility. This is the first case to our knowledge of severe fungal granuloma caused by a gain of function STAT1 mutation.
**871** Impaired T-Independent IgM Responses Due To Irak-4-, MyD88 Deficiency Or Splenectomy

**Dr. Paul J. Maglione, MD, PhD**,1, Lin Radigan1, Sam Black1, Jessica Overbe1, Dr. Emelia Bagetila2, Dr. Isabelle Meys2, Prof. Jean-Laurent Casanova, MD, PhD1,4, Dr. Capucine Picard, MD, PhD3, Dr. Charlotte Cunningham-Rundles, MD, PhD, FAAAAI1,5, Mount Sinai Medical Center, New York, NY, 2University Hospitals Leuven, Belgium, 3Hospital Necker-Enfants Malades, Paris, France, 4Rockefeller University, New York, NY.

**RATIONALE:** CD27+IgM+IgD+ B cells reside in the splenic marginal zone and mount robust T-independent antibody responses against bacteria. Human IRAK-4- or MyD88-deficiency, like splenectomy, are associated with reduction of CD27+IgM+IgD+ B cells and susceptibility to bacteria, mostly encapsulated. We investigated whether T-independent IgM against bacterial antigens was impaired in patients with IRAK-4-MyD88 deficiency or splenectomy.

**METHODS:** ELISA and carbohydrate array (functionalglycomics.org) were used for antibody analysis. Immunoglobulin production and CD27+IgM+IgD+ B cell expansion in culture after T-independent activation was measured. Antibodies from splenectomized subjects and controls were measured before and after pneumococcal carbohydrate immunization.

**RESULTS:** Patients with IRAK-4 or MyD88 deficiency have impaired production of IgM against phosphorylcholine (p = 0.0009), S. pneumoniae capsule (p = 0.002), teichoic acid from S. pneumoniae (p = 0.0032) and S. aureus (p = 0.0004), and array carbohydrates in total (p = 0.0005) and limited to S. pneumoniae or S. aureus expression (p < 0.0001) compared to controls. In vivo, we observed that PBMCs from IRAK-4-deficient patients have inhibited IgM production and replication of CD27+IgM+IgD+ B cells. Secondly, boosting of T-independent IgM by pneumococcal immunization was abated in splenectomized subjects, with anti-bacterial IgM correlating with levels of CD27+IgM+IgD+ B cells.

**CONCLUSIONS:** Reduction of CD27+IgM+IgD+ B cells by IRAK-4-MyD88 deficiency or splenectomy impairs T-independent IgM responses, including those against bacteria. IRAK-4 and MyD88 appear vital for optimal T-independent IgM responses and CD27+IgM+IgD+ B cell replication in response to bacterial antigens in humans. Appreciation of factors influencing T-independent IgM and marginal zone B cells may provide useful insight into novel therapeutic or vaccine strategies.

**872** Intestinal Perforation and Non-Tuberculous Mycobacterial Peritonitis In a Patient With Interleukin-1 Receptor Associated Kinase 4 Deficiency

**Dr. Hana B. Niewehr, MD, PhD**, Dr. Nathan Tang, MD, FAAAAI, Dr. Jennifer Leiding, MD; University of South Florida, St. Petersburg, FL.

**RATIONALE:** Interleukin-1 receptor associated kinase 4 (IRAK-4) deficiency is an autosomal recessive immunodeficiency associated with recurrent invasive bacterial infections and impaired inflammatory response due to abnormalities in Toll-like receptor signaling. Infection severity and frequency typically decrease with age. Herein we describe a 16-year-old female with IRAK-4 deficiency that developed intestinal perforations, intra-abdominal abscesses, and non-tuberculous mycobacterial (NTM) peritonitis.

**METHODS:** Bacterial cultures were performed at All Children’s Hospital, St. Petersburg, FL with molecular identification of NTM performed by National Jewish Laboratories.

**RESULTS:** This patient is a female with IRAK-4 deficiency who experienced life-threatening pneumonia, septic arthritis, pylonephritis, and sepsis from *Staphylococcus aureus* and *Streptococcus pneumoniae* and colitis from *Clostridium difficile*, *Candida albicans*, and enterovirus from 5 weeks to 7 years. She received IVIG from 7 to 10 years; subsequent infections were limited to chronic erosive sinustis due to *Pseudomonas aeruginosa*. At age 16, she experienced 2 spontaneous bowel perforations which led to recurrent intra-abdominal abscesses and peritonitis requiring numerous surgical interventions and broad-spectrum antimicrobial therapy over a 2-year period. Initial bacteria isolated included enteric flora and Pseudomonas. She developed *Mycobacterium abscessus*-induced peritonitis associated with severe protein losing enteropathy and intra-abdominal ascites.

**CONCLUSIONS:** Bowel perforations and gastrointestinal disease have been reported in few cases suggesting this is an under recognized feature of IRAK-4 deficiency. While NTM frequently causes peritoneal dialysis-associated peritonitis, *Mycobacterium abscessus* has not previously been described in IRAK-4 deficiency. This patient’s clinical course challenges the previously reported natural history of IRAK-4 deficiency of less severe invasive infections after puberty.

**873** Suspected Non-Infectious Prosthetic Valve Inflammatory Dehiscence In X-Linked Chronic Granulomatous Disease

**Dr. Monica Bhagat, MD**, Dr. Joshua A. Steinberg, MD, Dr. Frank Silvestry, MD3, Dr. Lea Surrey, MD, Dr. Andrea J. Apter, MD, MA, MSc, FAAAAI1, Dr. Patricia A. Takach, MD, FAAAAI1, Dr. Benjamin P. Soule, MD1,4, University of Pennsylvania, Philadelphia, PA, 3Medical College of Wisconsin, Milwaukee, WI, 4UPENN, Philadelphia, PA.

**RATIONALE:** Chronic granulomatous disease (CGD) is characterized by severe recurrent bacterial and fungal infections. Hyper-inflammation leading to tissue dehiscence is observed. We present a case report of a patient with CGD diagnosed with a valvular abscess requiring mechanical prosthetic valve replacement, which was complicated by suspected sterile inflammation and recurrent valvular dehiscence.

**METHODS:** Tissue culture, staining.

**RESULTS:** This patient presented with *Serratia* osteomyelitis and pneumonia by 23 months of age and was diagnosed with X-linked CGD. At age 22 he was admitted with shortness of breath and chest imaging showed lung nodules. Biopsy of nodule positive for *Philaphora richardsiae*. Developed acute congestive heart failure and echocardiogram showed an aortic perivalvular abscess. Treated with caspofungin and vancomycin. Underwent mechanical aortic valve replacement. Cardiac tissue cultures negative for infection; blood cultures negative. A new murmur was audible. Hyper-inflammation and recurrent valvular dehiscence.

**CONCLUSIONS:** We believe this is the first case report suggestive of recurrent endocarditis and peri-prosthetic valvular dehiscence in a XL-CGD patient. We suspect this outcome was due to CGD-related sterile hyper-inflammation, induced by surgical manipulation and/or the presence of prosthetic material. This case highlights the need to consider steroid therapy for such atypical sterile hyper-inflammatory pathology.
873A The Effects Of Anti-Seizure Medications On Patients With Antibody Deficiency Syndrome
Dr. Tatyana Gavrilova, MD, Dr. Harumi Jyonouchi, MD; Rutgers University of Medicine and Dentistry, Newark, NJ.

RATIONALE: Antibody deficiency is associated with both primary and secondary immunodeficiency. Secondary immunodeficiency is often caused by medications including antiepileptic drugs (AEDs). It is unknown how AEDs affect ADS patients. This study examined whether ADS subjects treated with AEDs (test group) will reveal differences as compared to control ADS subjects.

METHODS: Clinical features and laboratory findings in the test group (children N=8, adults N=5) were retrospectively reviewed in comparison with control ADS subjects (children N=18, adults N=5). In the test group, AEDs were primarily prescribed for seizure disorders (grand mal and/or partial complex seizures with variable etiology). Most of the test group subjects were prescribed multiple AEDs in the past and/or currently.

RESULTS: Children in the test group had lower levels of IgM/IgA than control ADS children (IgM 57.2 ± 32.2 vs 101.4 ± 48.6 mg/dl, IgA 37.5 ± 25.4 vs 85.0 ± 50.9 mg/dl, respectively). However, there were no differences in total and isotype switched memory B cell numbers between the test and control groups irrespective of age. In cytokine production by peripheral blood mononuclear cells (PBMCs), the test group revealed lower IL-6, IL-12, and TNF-alpha production in response to TLR7/8 agonist (p<0.05) but IL-10 production in response to T cell mitogens was higher in the test group (p<0.05).

CONCLUSIONS: Lower IgM/IgA levels in the test group children may be significantly associated with asthma presentation. The concomitant report of nasal and ocular symptoms in the last year' identified those with RC. According to the variables analyzed by the complementary WQ, and risk factors were identified by logistic regression.

874 Risk Factors Associated With The Development Of Asthma and Allergic Rhinitis Among Adolescents Living In Sao Paulo – Brazil
Dr. Fernanda Patini Furlan,1 Dr. Djanira Andrade,2 Danielli Christinni Bichuete-Silva, MD3, Dr. Tessa Rachel Tranquilini Gonçalves, MD, Dr. Inês Camelio Nunes4, Prof. Dirceu Sole, MD, PhD5, 1Division of Allergy and Clinical Immunology, Dept of Pediatrics, Escola Paulista de Medicina, Federal University of Sao Paulo, Sao Paulo, Brazil, Sao Paulo, Brazil, 4Univesidada Federal de Sao Paulo, Sao Paulo, Brazil, 5Federal University of Sao Paulo, Sao Paulo, Brazil.

RATIONALE: Active asthma (AA) and allergic rhinitis (rhinoconjunctivitis, RC) are frequent among adolescents (AD). Our objectives were to identify risk factors associated to AA and RC development among AD living in Sao Paulo, Brazil.

METHODS: A cross-sectional study in 567 AD (13-14 years old) using written questionnaires (standardized and complementary) of International Study of Asthma and Allergies in Childhood (ISAAC) was conducted in Sao Paulo, Brazil, in 2012. “Have had wheezing in the last year” identified AD with AA. The concomitant report of “nasal and ocular symptoms in the last year” identified those with RC. According to the variables analyzed nonparametric tests were applied. The groups (asthmatic and non-asthmatic) were compared with respect to exposure to several factors identified by the complementary WQ, and risk factors were identified by logistic regression.

RESULTS: The prevalence of AA and RC were 24.7% and 34.9%, respectively. Risk factors for AA manifestation were: to have RC; [OR = 1.97; 95%CI = 1.20-3.26; p = 0.008], and maternal smoking [OR = 1.87; 95%CI = 1.04-3.36; p = 0.037]. For RC, they were: to have AA [OR = 2.06; 95%CI = 1.25-3.38; p = 0.004] and to have attended daycare or nursery [OR = 1.67; 95%CI = 1.07-2.60; p = 0.024].

CONCLUSIONS: The prevalence of AA and RC are high in this studied population and to have attended day care or nursery was identified as a risk factor for both manifestations. Exposure to maternal smoking was significantly associated with asthma presentation.

875 Atopic Associations In Asthmatic Patients Readmitted Within 30 Days To The Hospital
Dr. Larisa Buyantseva, MD, MS, Dr. Melissa Rossi, Prof. Jason Liao, PhD, Dr. Timothy Craig, DO; Penn State University, Hershey, PA.

RATIONALE: Allergy is an important trigger in 50% adults and 60-90% of children with asthma. Twelve-month readmission rate for asthma in Pennsylvania was 15.1% in 2006-2010. Quality metrics are focusing on readmission in a month as an important variable. The aim of this study is to assess if history of atopy increases the likelihood of 30-day asthma readmission.

METHODS: Retrospective chart review of all adult patients with primary diagnosis of asthma who were readmitted within 30 days after the index admission was performed. Patients were identified from billing database by asthma ICD 9 code (493.9).

RESULTS: We identified 37 patients readmitted within 30 days of the index admission for asthma. Sixty-five percent were females, age 41 ± 28, 84% were Caucasians, and 24% had “severe” asthma documented in their records. Majority of patients had 1.0 ± 1.8 ICU admissions in the past. Twenty-two percent of patients were tested for allergies, but only 16% reported that they have allergies. Cats, dogs and molds were the most common allergens. Fifty-one percent were inhaled corticosteroids (ICS) and leukotriene receptor antagonists (respectively), 64% were on a combination of ICS and long-acting beta agonists, 38% on antihistamines and 8% on omalizumab. Of the above variables only asthma severity and history of ICU admissions were associated with a 30-day readmission (p<0.05).

CONCLUSIONS: History of atopy was not associated with 30-day readmission in our asthmatic population. Significant associations for readmission were found with asthma severity and a history of ICU admissions.

876 Pediatric Asthma Associated With Fungal Exposure
Dr. Cecilina Nguyen, MD,1 Dr. Christina E. Ciaccio, MD, PAAAI2, Dr. Charles Barnes, PhD,1 1Children’s Mercy Hospitals and Clinics, 2Children’s Mercy Hospital, Kansas City, MO.

RATIONALE: Asthma severity is strongly influenced by triggers and exposures. Many homes have substantial amounts of indoor fungi (mold). To determine if fungal sensitized asthmatics had a higher severity of disease than other asthmatics, we conducted the following investigation.

METHODS: A cohort of 239 asthmatic subjects enrolled in the Healthy Homes study were screened for inclusion in the dataset. Subjects had specific IgE testing for cat, dog, dust mite, cockroach, mouse, alternaria, aspergillus, cladosporium and penicillium. They also had home evaluations including presence of airborne spores, dust borne allergens or both. The subjects responded to questionnaires concerning recalled asthma symptoms and medication use. Medical records of the subjects for years 2007 to 2012 were searched for utilization including urgent care, hospitalizations and clinic visits.

RESULTS: A group of 29 asthmatic children were identified who were sensitized nearly exclusively to fungal allergens. A control group of 26 asthmatic children who were sensitized exclusively to animal and arthropod allergens was also selected. Fungal-related asthmatics were more likely to be hospitalized at least once during the study (OR = 2.10; 95% CI 0.55-8.09) and to visit the ER (OR = 1.33; CI 0.45-3.99).

CONCLUSIONS: A group of children can be identified whose asthma appears to be fungal related. This group did not have significantly more health care utilization than the non-fungal related asthmatics in this study.
877 Assessment Of Factors Associated With PPV23 Vaccine Uptake Among Young Adults With Asthma In Olmsted County, MN

Maria J. Bachman, Medical Student1, Joshua Gauger, Medical Student2, Dr. Chris Derauf, MD3, Dr. Slavica Katusic, MD4, Jen Rand-Wheeler1, YuBin Choi1, Elizabeth Krusemark1, Dr. Young J. Juhn, MD, MPH5, 1Mayo Medical School, Rochester, MN, 2Mayo Medical School, 3Dept of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, MN.

RATIONALE: Since Oct 2008, the United States’ Advisory Committee on Immunization Practices (ACIP) has recommended a single dose of 23-Valent Pneumococcal Polysaccharide vaccine (PPV-23) to asthmatics ages 19-64 years. Currently, neither PPV23 vaccine uptake rate in asthmatics nor factors associated with uptake have been assessed under the 2008 ACIP guidelines. Objective: To determine PPV-23 vaccine uptake rate among young adults with asthma and factors associated.

METHODS: The study was designed as a cross sectional study. We determined the PPV23 uptake rate during the study period (between November 1 and October 31, 2012) among asthmatics of the 1988-1989 Olmsted County Birth Cohort after the ACIP recommendations were released. Asthma status was ascertained by ICD-9 code (493). By using retrospective chart review, we obtained PPV23 vaccination history and other pertinent variables.

RESULTS: There were 371 asthmatics in the birth cohort at the time of the new PPV23 recommendation. Of the 371 subjects, 291 eligible subjects (78.4%) were enrolled. The PPV23 uptake rate was only 22.7% (66/291). A lower educational level of subjects (p=0.007), subjects’ employment status (p=0.021), the greater number of general medical examinations during the study period (p<0.001), the greater number of asthma-related visits during the study period (p<0.001), and poor asthma controls were associated with a higher PPV23 vaccine uptake rate.

CONCLUSIONS: The low PPV23 uptake rate among young adults with asthma is concerning, given the increased risk of serious pneumococcal disease among asthmatics. General medical examinations and asthma-related outpatient visits might be an important opportunity to vaccinate young adults with asthma.

878 Clinical Effectiveness In Allergic Airway Disease Of Oriton IgE Chemiphar™: A Rapid Determination System Of Allergen-Specific IgE

Dr. Tomoyuki Soma, MD1,2, Dr. Ai Masumoto3, Dr. Takehito Kobayashi, MD2, Dr. Atsushi Kamijo, MD2, Dr. Yoshitaka Uchida1,2, Prof. Kouichi Hagiwara, MD1, Prof. Minoru Kanazawa, MD1, Prof. Makoto Nagata, MD1,2, 1Department of Respiratory Disease, Saitama Medical University, Japan, 2Allergy Center, Saitama Medical University, Japan.

RATIONALE: To identify the sensitized allergen in Allergic Disease, skin prick tests (SPT) or measurement of serum allergen-specific IgE are common. Examinations like these should be required of independence on patient’s condition or medicines, or shorter time to analysis. Here, we investigated the performance of Oriton IgE CHEMIPHAR™ (CHEMIPHAR), the new detection system of serum allergen-specific IgE, which takes less time to assay.

METHODS: We determined the sensitivity, specificity and concordance rate of CHEMIPHAR system based on a Sandwich EIA for detecting serum allergen-specific IgE to common inhaled allergens in patients with allergy rhinitis (AR) or bronchial asthma (BA), using the SPT result as the ‘gold standard’. More than 0.34 IU/ml of the specific IgE by CHEMIPHAR system was defined as positive. Average diameters of minor and major axes of wheal ≤5 mm or of erythema >5 mm were considered positive in SPTs.

RESULTS: The concordance between SPT and CHEMIPHAR results was 82% over all the tests in fifty one adult patients (male/female; 27/24, AR/BA; 35/41). Using SPT, the sensitivity of CHEMIPHAR was 91% for cypress pollen and 71% for Dermatophagoides farina but was lower for cat epithelium (46%), Ambrosia artemisiafedia (56%) and 3 moulds. The specificity of the CHEMIPHAR showed less variation between allergens (81-98%) except for cypress pollen (58%).

CONCLUSIONS: Chemiphar™ system implies a favorable performance to detect sensitized inhalant allergens in allergic airway disease. This system seems to be useful and convenient because of offering information of sensitized inhalant allergens within about an hour.

879 Gender Differentially Contributes To Airway Hyperresponsiveness In Adult Asthmatics

Dr. Jeong-Hee Choi, MD1, Dr. Cheol-Hong Kim, MD2, Prof. In-Gyu Hyun, MD3, Dr. Joo-Hee Kim, MD4, Dr. Tae-Rim Shin, MD5, Dr. Sang-Myeon Park, MD7, 1Dept. of Pulmonology and Allergy, Hallym University Dongtan Sacred Heart Hospital, Hwaseong, South Korea, 2Dept. of pulmonology and Allergy, Hallym University Dongtan Sacred Heart Hospital, 3Hallym University Dongtan Sacred Heart Hospital, 4Hallym University School of Medicine, Anyang, 5Hallym University Kangnam Sacred Heart Hospital.

RATIONALE: Obesity is commonly regarded as a risk factor for asthma development, poor asthma control, and poor response to asthma therapy. However, its relationships are not always consistent. Gender difference has been reported to influence asthma severity and asthma control. We investigated the contribution of obesity to airway hyperresponsiveness and lung function before and after treatment in adult asthmatics.

METHODS: The medical records of a total of 323 adult asthmatics were analyzed retrospectively. Asthma was diagnosed based on the positive result of methacholine bronchial provocation test (PC20 ≤ 25 mg/mL) or bronchodilator test (>12% and 200 mL improvement in FEV1 after inhalation of a bronchodilator). Follow-up spirometry was performed in 120 patients after at least 3 months of asthma treatment with controller medication. Percent change between spirometry values before and after treatment was defined as [(value after treatment - value before treatment)/ value before treatment x 100]. Body mass index (BMI, weight (kg)/height2 (m2)) was categorized into underweight (<18.5), normal weight (18.5-24.9), overweight (25.0-29.9), and obese (>30) according to the WHO classification.

RESULTS: BMI did not show any significant correlation with PC20 value of methacholine provocation test and each lung function parameter before and after treatment. When we divided the study subjects according to gender and age, BMI was negatively correlated with PC20 value only in female adult asthmatics under 65 years old (r = -0.024, p = 0.036).

CONCLUSIONS: Obesity is positively correlated with the airway hyperresponsiveness in female adult asthmatics. Gender seems to differentially contribute to the relationship between BMI and airway hyperresponsiveness.
**880 Prevalence Of Sleep Disorders In Children With Asthma and Its Association With The Level Of Control Of The Disease, Smoking and Obesity**

**Dr. Lorena Rangel-Garza, MD**<sup>1</sup>, Prof. Sandra N. Gonzalez-Diaz, MD, PhD, FAAAAI<sup>1</sup>, Dr. Alejandra Macias-Weinmann, MD<sup>2</sup>, Prof. Alfredo Arias-Cruz, MD, FAAAAI<sup>1</sup>, Dr. Maria Del Carmen Zarate-Hernandez, MD<sup>3</sup>, Dr. Idalia V. Vanez-Perez, MD<sup>4</sup>, Dr. Hilda Hernandez-Sanchez, MD<sup>5</sup>, 1University Hospital Dr. Jose Eleuterio Gonzalez, UANL, Monterrey, Mexico, 2Hospital Universidad UANL, Monterrey, N.L., Mexico, 3University Hospital, Monterrey, Mexico, 4Regional Center of Allergy and Clinical Immunology. University Hospital “Dr. Jose Eleuterio Gonzalez”, Monterrey, Mexico.

**Rationale:** Patients with asthma may have sleep disturbances. Daytime sleepiness plays an important role in diagnosing the syndrome of obstructive sleep apnea (OSA). The Epworth scale is the main reference test to determine OSA. Currently, OSA is recognized as a comorbidity of asthma.

**Methods:** We survey parents of children who attended the annual asthma camp, and sleepiness was assessed using the Epworth scale, additionally in all children was performed the asthma control by an asthma control test (ACT), and gather information of passive smoking, also the body mass index was performed.

**Results:** We evaluated 50 patients, aged between 4 and 12 years (mean 8.6 years), 23 (46%) were female and 27 (54%) male. They were divided into 2 groups: Group 1 with 39 patients (78%) in which we didn’t found alterations with the Epworth scale, and group 2 with 11 patients (22%) with scores greater than 10 on the Epworth scale. We found 42% of passive smoking, and 28% of obesity and overweight. Statistical analysis was performed to compare variables between the two groups, and no association was found between passive smoking and alterations in the Epworth scale (p = 0.11), but we found association between sleep disturbance with obesity and overweight (p = 0.04) and the degree of asthma control with scores <20 on the ACT (p = 0.001).

**Conclusions:** In this study the sleep disturbances of children with asthma were directly related to the level of disease control and nutritional status of the patient, in this case obesity and overweight.

**881 Asthma and Allergic Diseases Of Preschool Children In Korea: Findings From The Pilot Study For The Korean Surveillance Survey For Childhood Asthma**

**Prof. Ji Tae Choug, MD**<sup>1</sup>, Prof. Sungchul Seo<sup>2</sup>, Dr. YongMin Cho<sup>1</sup>, Dr. Young Yoo, MD, PhD<sup>3</sup>, Dr. Wonsuck Yoon<sup>1</sup>, 1Korea Univ. Medical Center, Seoul, 2The Environmental Health Center for Asthma, Korea University, Seoul, 3The environmental health center for asthma, Department of Pediatrics, College of Medicine, Korea University, Seoul, South Korea; Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York, NY, 4Department of Life Science and Biotechnology, Seoul, South Korea.

**Rationale:** The purposes of this study were to introduce and provide preliminary data on the Korean Surveillance Survey for Childhood Asthma (KSSCA).

**Methods:** The KSSCA modified from the Behavioral Risk Factor Surveillance Survey in CDC and ISSAC was web-based questionnaire for investigating environmental risk factors related to development or exaggeration of allergic diseases. The KSSCA majorly consists of questions about the history of allergic diseases for children and their parents, as well as characteristics of their dwellings and socioeconomic status. We randomly recruited the participants with a child aged 2-6 years online, and the 2-month survey was performed in 2012. The participants responded to questionnaires of KSSCA online as well. A logistic regression analysis and odds ratios were applied for data analyses.

**Results:** A total of 1002 households participated in this survey. The percentage of households with children diagnosed with any allergic disease ever was 7.4% for asthma, 34.7% for allergic rhinitis (AR), and 35.9% for atopic dermatitis (AD), respectively. A child whose parents had at least one of any allergic disease had about 3-fold higher risk of development of allergic diseases (OR=2.86, C.I.95%: 2.20-3.72). Development of AD would decrease with living in the second or above floor of dwellings (OR=0.64, C.I.95%: 0.45-0.90). The presence of roadway, industrial complex within 1 km of their dwellings increased the risk of development of AR (OR=1.38, C.I.95%: 1.04-1.82).

**Conclusions:** Our findings indicate that the KSSCA could be a promising tool for finding environmental risk factors and social characteristics related to development of allergic diseases, with ease and less cost.
**883** Relationship Of Allergen Sensitization and LUNG Function In Adults Patients With Asthma In Allergy Clinic In Monterrey, Mexico
Dr. Hilda Hernandez Sanchez, MD, Prof. Sandra N. Gonzalez-Diaz, MD, PhD, FAAAAI, Prof. Alejandra Macias-Weinmann, MD, Prof. Alfredo Arias-Cruz, MD, FAAAAI, Dr. Idalia Vanessa Yanez-Perez, MD, Dr. Lorena Rangel-Garza, MD; University Hospital Dr. Jose Eleuterio Gonzalez, UANL, Monterrey, Mexico.

**RATIONAL**: Sensitization to aeroallergens is known as a risk factor to development of asthma. The aim is assess relationship of sensitization to aeroallergens with lung function by spirometry in asthmatic adults treated in 2010-2012 in Regional Centre of Allergy and Clinical Immunology University Hospital in Monterrey, NL.

**METHODS**: Observational, descriptive study, which consisted in a review of medical records of adult patients with asthma and sensitization to allergens tested. We obtained demographic, clinical data, results of skin tests with extracts of 36 aeroallergens and the results of pulmonary function. Were analyzed with statistical program SPSS20, and Fisher’s exact test.

**RESULTS**: From the review of medical records were selected 121 patients, gender distribution was female, in 46.3%, the mean age was 34.3 years, and age ranges were <25 years (19%), 25-44 years (49.6%), 45-64 years (28.9%), <65 years (2.5%). The most frequent are Dermatophagoides spp (60.3%), Sorghum halepense (29.8%), Prosopis spp (28.9%), Cynodon dactylon (26.4%) and Blattella germanica (17.4%). In relation to pulmonary function tests, the mean FEV1 was 83%, +18.4, with mean of reversibility of 12.95%, the age group with the greatest impaired in FEV1 was 45 to 64 years. The ch² test: relationship of FEV1 with sensitization pollen (p=0.62), fungi (p=0.75), mites (p=0.31), cat (p=0.72).

**CONCLUSIONS**: The most common are Dermatophagoides spp; the relationship of sensitization and lung function measured by spirometry in these patients was not statistically significant, which may be due previous treatment, exposure to allergen, determinants genetic, environmental conditions, infections, irritants, age, which have an important role in lung function.

**884** Targeting Patient Education: Correlating Fluctuating Pollen Counts With Patient Online Inquiries Into Asthma and Allergic Rhinitis
Dr. John M. Kern, DO1, Dr. Leonard Bielorcy, MD, FAAAAI2,3, Mr. Spencer H. Luster3,4, 1Rutgers University - NJMS, oceanport, NJ, 2Robert Wood Johnson University Hospital, New Brunswick, NJ, 3STARx Allergy and Asthma Center, Springfield, NJ, 4University of Pennsylvania, Philadelphia, PA.

**RATIONAL**: The association between patient inquiries into asthma and allergic rhinitis has been minimally investigated in regards to relative pollen/mold concentrations.

**METHODS**: Pollen/Mold counts (measured by Rotorod) were examined on a weekly averaged basis from 2011–2012 for total pollen with mold [P+M] and pollen excluding mold [P]. The [P+M] and [P] counts were compared with Google search trends in the USA using “asthma” and “allergic rhinitis” as search terms for 2005–2012. The Google trends and weekly pollen counts were examined for correlation using “least squares” method, generating an f-statistic cumulative density function to produce a p-value.

**RESULTS**: [P+M] and [P] demonstrated statistically significant relationships with searches using the keyword “asthma” with [P+M] concentration (p-value=0.006) and [P] (p-value=0.0004), and when using the keyword “allergic rhinitis” with [P+M] concentration (p-value=0.027) and [P] (p-value=0.0009). The correlation of searches for “allergic rhinitis” and “asthma” were also statistically significant to each other (p=1.34824 E-9). The search trends also revealed two semiannual peaks in asthma and allergy inquiries. The first peak occurred between March and April and the second occurred between October and November throughout the search period.

**CONCLUSIONS**: Annual pollen levels have demonstrated a statistically significant correlation with patient online searches into asthma and allergic rhinitis. Pollen concentrations more than mold concentrations impacted the searches for asthma or allergic rhinitis. There appear to be seasonal search peaks that corresponded with annual variations in pollen concentrations. Given the increased interest at these peak times, awareness campaigns may increase their future efficacy by timing initiatives to correspond with pollen spikes.

**885 Withdrawn**

**886** Elevated Exhaled Nitric Oxide Levels In Eosinophilic Esophagitis Patients With and Without Atopy
Michael Kagen, MD1, Zainab Kagen, MD2, Prof. Steve L. Kagen, MD, FAAAAI3, Joe Zondlo, MD1; 1University of Tennessee College of Medicine-Chattanooga, Chattanooga, TN, 2University of Tennessee College of Medicine-Chattanooga, TN, 3Kagen Allergy Clinic, Appleton, WI.

**RATIONAL**: Currently considered a method of determining the extent of airway inflammation alone, here we report elevated exhaled nitric oxide concentrations in patients with Eosinophilic Esophagitis, including a child with no asthma or atopy.

**METHODS**: Following a detailed medical history and physical examination, five patients with asthma-like symptoms and dysphagia underwent allergen skin testing, spirometry and exhaled nitric oxide measurements (FeNO).

**RESULTS**: All five patients had high initial FeNO concentrations (81 ppb to 176 ppb). Three adult males and one adult female had positive immediate allergen skin test reactions to a inhalant and food allergens and hyper-eosinophilia in esophageal biopsies; a 14-year-old girl with esophageal stricture and elevated esophageal eosinophils had no skin test reactions to food or inhalant allergens, normal spirometry and a flat inspiratory flow-volume loop. FeNO measurements are a cost-effective and quantitative means of determining the degree of eosinophilic inflammation within the airways. Indeed, FeNO measurements have become the standard of care in the evaluation and management of patients with asthma, for the concentration of nitric oxide in exhaled breath reflects the degree of eosinophil infiltration within the chest. Allergy and asthma specialists often evaluate pediatric and adult patients with symptoms of wheezing, chest tightness and nocturnal coughing episodes. Today’s standard of care requires the performance of spirometry, allergen skin testing and FeNO studies in such patients. As these five patients demonstrate, elevated FeNO levels may indicate the presence of excessive eosinophils within the esophagus as well as the airways.
Older Mice Intranasally Sensitized with Aspergillus Fumigatus Develop Stronger Eosinophilic Esophageal Inflammation Compared to Their Younger Counterparts

Dr. Antonella Clauferoni, MD, PhD1, Simona Barni, MD2, Cara Smith, BS3, Valsamma Abraham, PhD4, Peng Guan, BS5, Dr. Francesca Saretta, MD5, Katie Ruyman, BS1, Hamid Bassiri, MD, PhD5, Dr. Kim E. Nichols, MD6, Dr. Jonathan M. Spergel, MD, PhD, FAAAAI1,2,3,4,5,6

1Children’s Hospital of Philadelphia, 2University of Florence Italy, Italy, 3Children’s Hospital of Philadelphia, 4University of Pennsylvania, 5Ospedale Di Palmanova, ASS 5 Bassa Friulana, Pagnacco, Italy. 6Children’s Hospital of Philadelphia, Philadelphia, PA. 7The Children’s Hospital of Philadelphia, Philadelphia, PA.

RATIONALE: Eosinophilic esophagitis (EoE) is characterized by esophageal eosinophilia (EsoEo) and Th2 inflammation. Manifestations of active inflammation occur in children, whereas those of chronic inflammation are common in adults. We used an EoE mouse model to define how age may influence inflammation in EoE.

METHODS: Three groups (n = 10) of different age BALB/c mice YM = 6-8 weeks, MM = 12-14 weeks, and OM = 20-22 weeks were intranasally sensitized with 100 µg of Aspergillus fumigatus or control saline 3 times a week. After 4 weeks esophageal tissue was immunostained for EsoEo using anti-major basic protein. Lymphocytes from gut and liver were analyzed by flow-cytometry for invariant natural killer T cell (iNKTs) and T regulatory cells (Treg). Institutional IACUC approved the study. ANOVA was used for statistical analysis. P < 0.05 was considered statistically significant.

RESULTS: Sensitized OM compared to YM and MM had: 1) higher EsoEo (mean ± SD = 5.9 ± 3.1; 2.1 ± 5.5; 1.5 ± 5.15) (p = 0.0103); lower percentages (%) and absolute numbers (#) of iNKTs in the gut (0.4 ± 0.2 ; 1.6 ± 1.5; 3.4 ± 1.0) (p = 0.003) and in the liver (2.3 ± 1.1; 43.1 ± 26.3; 29.4 ± 19.7) (p = 0.001); higher % and # of Treg in the gut (3.6 ± 5.4; 0.06 ± 0.1; 1.9 ± 1.6) (p = 0.0002) and lower in the liver (0.8 ± 1.1; 16 ± 15.9; 43.3 ± 3.6) (p = 0.004) and data not shown.

CONCLUSIONS: OM compared to their younger counterparts, showed more severe EsoEo associated with different levels iNKTs and Treg. Older mice may have different immune regulatory responses that favor a more severe eosinophilic differentiation. Differences in immunological responses to allergens may explain the different clinical picture observed in adult and children.

Crito-1 Is Elevated In Pediatric Subjects With Eosinophilic Esophagitis

Lisa Beppu, BS1, Arjun Andrew Anilkumar, BS2, Richard Kurten, PhD3, Ranjan Dohl, MD4, David Broide, MB ChB2, Seema Sharma Acvess, MD, PhD, FAAAAI5, 1University of California San Diego, Department of Pediatrics, Division of Allergy and Immunology, 2University of California San Diego, Department of Medicine, Division of Allergy and Immunology, 3University of Arkansas for Medical Sciences, Little Rock, AR, 4University of California San Diego, Rady Children’s Hospital, Department of Pediatrics, Division of Gastroenterology, 5Pediatrics, University of California San Diego, La Jolla, CA.

RATIONALE: Eosinophilic esophagitis (EoE) is a chronic antigen mediated allergic response leading to tissue remodeling that includes basal zone hyperplasia and fibrosis in both pediatric and adult patients. Crito-1, a member of the CFC-EGF family, is known to induce epithelial to mesenchymal transition (EMT) and epithelial cell proliferation. The role of Crito-1 in EoE has yet to be characterized.

METHODS: Immunohistochemistry and qPCR were utilized to quantitate Crito-1 and its receptor, Glypcican-1, in biopsies and cultured primary esophageal epithelial cells from pediatric EoE and non-diseased control subjects.

RESULTS: Immunohistochemistry and quantitative image analysis using a Crito-1 specific antibody on paraffin-embedded specimens from active EoE subjects (n = 43) and non-diseased controls (n = 6) demonstrated elevated Cripto-1 in the epithelium of EoE patients compared to normal (p = 0.0005). Elevated Crito-1 in the epithelium correlated with epithelial basal zone hyperplasia (r = 0.80, p = 0.0001). In addition, immunohistochemistry and quantitative PCR confirmed the presence of the Crito-1 receptor, Glypcican-1, in both paraffin-embedded specimens and cultured primary esophageal epithelial cells from EoE patients.

CONCLUSIONS: Pediatric EoE subjects have elevated epithelial Crito-1 compared to control which may allude to a mechanistic pathway in which the signaling molecule binds to its receptor, Glypcican-1, and has downstream effects contributing to tissue remodeling.
890 Comprehensive Analysis Of Offending Milk Protein Components In Non-IgE-Mediated Gastrointestinal Food Allergies By Antigen-Specific Lymphocyte Proliferation Test

Dr. Tetsuo Shoda, MD, Dr. Ichiro Nomura, MD, PhD, Dr. Hideaki Morita, MD, PhD, Dr. Akio Matsuda, PhD, Dr. Hirohisa Saito, MD, PhD, Dr. Kenji Matsumoto, MD, PhD; Department of Allergy and Immunology, National Research Institute for Child Health and Development, Tokyo, Japan.

RATIONALE: We recently reported that infant patients with non-IgE-mediated gastrointestinal food allergies (GI allergy) can be classified into 4 distinct clusters according to the presence or absence of vomiting and bloody stool (JACI 2011). Milk is the offending food in almost all infants with GI allergy; however, the precise offending milk protein components remain unclear. The present study aimed at identifying offending milk protein components using the antigen-specific lymphocyte stimulation test (ALST).

METHODS: Infants with gastrointestinal symptoms who fulfilled at least 3 of Sicherer’s (J Pediatr 1998) criteria for GI allergy were identified from a nationwide online registration system and enrolled in the study. PBMCs from 302 patients (Cluster 1: 71; Cluster 2: 61; Cluster 3: 52; Cluster 4: 118) were cultured with various individual LPS-depleted milk protein components (α-lactalbumin, β-lactoglobulin, αs-, β- and κ-caseins) for 5 days, and cell proliferation was measured by 3H-thymidine-uptake.

RESULTS: Positive proliferative responses were seen in 74.6%, 73.8%, 46.2% and 54.2% of the patients in Clusters 1, 2, 3, and 4, respectively. The positive response rates for single milk protein components ranged from 26.7% to 75.5%. The most frequent offending milk component for Clusters 1 and 2 (food protein-induced enterocolitis syndrome) was β-casein, but β-lactoglobulin for Clusters 3 and 4 (enteropathy and proctocolitis). PBMCs from patients in Cluster 1 tended to proliferate in response to more antigens compared with the other clusters.

CONCLUSIONS: Different sensitization pathways and/or mechanisms may be involved in the onset of the various types of GI allergy.

891 Milk Elimination Diet For Treatment Of Eosinophilic Esophagitis

Elizabeth Erwin, MD1, Patrice Kruszewski2, Dr. John Russo, MD1, Thomas A. E. Platts-Mills, MD, PhD, FAAAAI1, 1Nationwide Children’s Hospital, Columbus, OH, 2Nationwide Children’s Hospital, 3Division of Asthma, Allergy & Immunology, University of Virginia Health System, Charlottesville, VA.

RATIONALE: Current dietary treatment for eosinophilic esophagitis (EoE) is effective but highly restrictive. Milk is the food that is most frequently identified as a problem. We recently reported that infant patients with non-IgE-mediated gastrointestinal food allergies (GI allergy) can be classified into 4 distinct clusters according to the presence or absence of vomiting and bloody stool (JACI 2011). Milk is the offending food in almost all infants with GI allergy; however, the precise offending milk protein components remain unclear. The present study aimed at identifying offending milk protein components using the antigen-specific lymphocyte stimulation test (ALST).

METHODS: Infants with gastrointestinal symptoms who fulfilled at least 3 of Sicherer’s (J Pediatr 1998) criteria for GI allergy were identified from a nationwide online registration system and enrolled in the study. PBMCs from 302 patients (Cluster 1: 71; Cluster 2: 61; Cluster 3: 52; Cluster 4: 118) were cultured with various individual LPS-depleted milk protein components (α-lactalbumin, β-lactoglobulin, αs-, β- and κ-caseins) for 5 days, and cell proliferation was measured by 3H-thymidine-uptake.

RESULTS: Positive proliferative responses were seen in 74.6%, 73.8%, 46.2% and 54.2% of the patients in Clusters 1, 2, 3, and 4, respectively. The positive response rates for single milk protein components ranged from 26.7% to 75.5%. The most frequent offending milk component for Clusters 1 and 2 (food protein-induced enterocolitis syndrome) was β-casein, but β-lactoglobulin for Clusters 3 and 4 (enteropathy and proctocolitis). PBMCs from patients in Cluster 1 tended to proliferate in response to more antigens compared with the other clusters.

CONCLUSIONS: Different sensitization pathways and/or mechanisms may be involved in the onset of the various types of GI allergy.

892 Pediatric Eosinophilic Esophagitis: A 10-Year Experience At A Canadian Tertiary Care Centre

Dr. Jason A. Ohayon, MD1, Perri R. Tutelman2, Dr. Jefferson Terry, MD, PhD3, Dr. Mary E. Sherlock, MB BCh, BAO, PhD2, 1Department of Pediatrics, McMaster Children’s Hospital, McMaster University, Hamilton, ON, Canada, 2Department of Pediatric Gastroenterology and Nutrition, McMaster Children’s Hospital, McMaster University, Hamilton, ON, Canada, 3Department of Pathology and Molecular Medicine, McMaster Children’s Hospital, McMaster University, Hamilton, ON, Canada.

RATIONALE: Eosinophilic Esophagitis (EoE) is characterized by esophageal dysfunction with characteristic eosinophilic infiltration. This study describes the clinical symptoms, endoscopic/histologic findings, allergic characteristics and treatment outcomes in a pediatric population over a 10-year period at a Canadian tertiary care centre.

METHODS: Children (< 18 years) who underwent an esophagogastroduodenoscopy (EGD) were identified and their records reviewed. Descriptive statistics were used to summarize the cohort characteristics.

RESULTS: A total of 94 cases were identified (75.5% male). The median age was 13.2 (IQR=15.6-8.0) years. 58 (62%) of the cases presented with dysphagia. 79 (84%) patients had abnormal macroscopic EGD findings. The median peak eosinophil count on histology was 70 (IQR=109-47) eosinophils/mm2. 68 patients underwent allergy testing; 49 (72%) and 10 (18%) were found to have positive food and environmental allergic results, respectively. Approximately half of the patients treated with corticosteroids reported symptomatic improvement while over three-quarters of patients reported an improvement on allergy avoidance dietary therapy. At a median follow-up of 31.1 (IQR=81.8-13.4) months, 16 (17%) patients had no change in symptoms from diagnosis, 53 (56%) patients continued to experience symptoms but at a decreased severity, and 17 (18%) experienced a complete resolution of symptoms. Eight (9%) of patients were lost to follow up.

CONCLUSIONS: Combined allergen avoidance and medical treatment resulted in an improvement in the majority of EoE patients (74%); complete symptomatic resolution remains elusive requiring further investigation into other treatment options.
Clinical Characteristics Of Eosinophilic Esophagitis - a Case Series Of 30 Patients
Dr. Susana D. Piedade1, Dr. Diana Silva1,2, Dr. Bruno Simões1,3, Dr. Angela Gaspar1, Dr. Sandra Morgado1, Dr. Filipa Santos2, Dr. Mário Morais-Almeida1; 1Immuonallergology Department, Hospital CUF Descobertas, Lisbon, Portugal, 2Immuonallergology Department, Hospital São João, Oporto, Portugal, 3Pediatrics Department, Hospital CUF Descobertas, Lisbon, Portugal.

RATIONALE: Eosinophilic esophagitis (EoE), an increasingly recognized disease worldwide, in both pediatric and adult patients, represents a clinical challenge. The aim of our study was to describe the clinical and endoscopic features of a series of patients diagnosed with EoE.

METHODS: In August 2013, a retrospective analysis was performed of the clinical files of patients with EoE criteria followed at our Hospital. A consecutive sample of 30 patients was obtained. All patients underwent a clinical, endoscopic and food sensitization evaluation protocol.

RESULTS: Patients were followed during a median period of [10.5;2.3] year, had median age of 15[9;32] years and 57% were male. The median age of EoE presentation was at 15[7;33] years. The most commonly reported symptoms were food impaction (67%), dysphagia (53%), abdominal pain (40%), vomits (37%) and heartburn (37%); the first 2 were significantly more frequent in adults and adolescents. Children’s (≥12 years) main complaint was vomits (60%) and failure to thrive occurred in 2 cases. Most had personal history of allergic disease (87%) and aeroallergens sensitization (71%). In endoscopic evaluation 3 patients had esophageal stenosis. Histologically 60% had ≥20 eosinophils/hpf and 23% had micro-abcesses. Food sensitization was found in 63% of the patients, mainly to cow’s milk (40%), cereals (37%), egg (26%), nuts (26%) and peanut (20%).

CONCLUSIONS: EoE clinical presentation differs accordingly to age group. Allergic disease and food sensitization are very common in these patients, demanding a multi-disciplinary diagnostic and therapeutic approach to improve prognosis.

Characteristics Of Eosinophilic Esophagitis Among Children Living In Rural, Southern United States
Ms. Erin O’Brien1,2, Dr. Troy Gibbons, MD1,2, Dr. Amy M. Scurluck, MD1, Dr. Jennifer Olivier, MD1,2, Mallikarjuna Rettiganti, PhD1,2, Maria Melguizo Castro1,2, Ms. Peggy L. Chandler, APN1,2, Audrey Fendley, RD1,2, Dr. Helen Casteel, MD1,2, Dr. Maryelle VonLanthen, MD1,2, Dr. Stephen Fiedorek, MD1,2, Dr. Tamara T. Perry, MD1,2, Stacie M. Jones, MD1,4, Dr. Robbie D. Pesek1,2; 1University of Arkansas for Medical Sciences, Little Rock, AR, 2Arkansas Children’s Hospital, Little Rock, AR, 3University of Arkansas for Medical Sciences and Arkansas Children’s Hospital, Little Rock, AR, 4Arkansas Children’s Hospital Research Institute, Little Rock, AR.

RATIONALE: Eosinophilic esophagitis (EoE) is a growing problem among pediatric patients with varying clinical disease patterns among populations studied. Our purpose was to characterize clinical parameters of disease among children living in a rural, southern US region.

METHODS: Retrospective chart review was performed on patients (ages 2 to 18 years) from Allergy and/or Gastroenterology Clinics at Arkansas Children’s Hospital from 2006 to 2012 with ICD9 codes for EoE and tissue eosinophilia >15 eosinophils/hpf on endoscopy. Data collected included demographics, symptoms, diet history, and allergen profiles (foods and aeroallergens) via skin (PST) and specific IgE (sIgE) testing.

RESULTS: 140 children were identified with mean(SD) age at diagnosis of 7.2(4.49) years; 78% male; 86% Caucasian, 100% insured, 77% in rural Arkansas. Comorbidities included asthma (40%), eczema (32%), food allergy (38%), allergic rhinitis (45%). Of those, 21 (17.2%) had PPI-responsive disease; 99 (82.5%) had persistent tissue eosinophilia with 72 (73%) having ≥1 follow-up endoscopy. Common presenting symptoms were heartburn/regurgitation (64%), pain (61%), nausea/vomiting (59%), dysphagia (44%). Milk was the most commonly reported food to cause symptoms (24%). Allergen testing was performed to foods (40% PST: 60% sIgE) and to aeroallergens (30% PST; 20% sIgE). Common sensitizing allergens (PST/sIgE) included foods: milk (17.8/61%), egg (26.1/43.9%), soy (20.5/51.7%), wheat (4.7/54.4%), peanut (35.4/57.4%); and aeroallergens: molds (35.4/42.1%) and pollens with grasses (63/58.8%) >trees (48.3/55.8%) >weeds (34.5/57.9%).

CONCLUSIONS: Children with EoE in the southern US have high food and aeroallergen sensitization rates. Better understanding of disease prevalence and the role of seasonal patterns of disease is warranted to improve disease management.
**896** Eosinophilic Esophagitis In The Puerto Rican Pediatric Population  
Dr. Carmen M. Pimentel, MD, Dr. Angel M. Rivera, MD, Dr. Iona K. Malinow, MD, Dr. Cristina J. Ramos, MD, Dr. Anardi Agosto-Mujica, MD, Dr. Rita Diaz, MD, Dr. Sylvette Nazario, MD; University of Puerto Rico School of Medicine, San Juan, PR.

**RATIONALE:** Eosinophilic esophagitis (EoE) has been rarely recognized in Hispanics. Our goal is to describe the clinical characteristics, skin prick test (SPT) and food atopy patch test (APT) results in a Puerto Rican pediatric population with EoE.

**METHODS:** A retrospective analysis of all pediatric patients with EoE seen at the Allergy/Immunology Clinics of the University of Puerto Rico School of Medicine between July 2012 and June 2013.

**RESULTS:** Thirty six patients (age 0.8-18 years) with biopsied-confirmed EoE were identified. Seventy one percent were males. Most were atopic (91.4%). Allergic rhinitis was the most frequent diagnosis (83.3%) and dust mite was the most common sensitivity (83.3%). EoE symptoms included abdominal pain, emesis, dysphagia, and nausea (56.3%, 56.3%, 46.8%, and 43.7% respectively). Food SPT was positive in 88.9% of cases. Egg, milk, oat, and corn (44.4%, 29.6%, 25.9%, and 25.9% respectively) were the most prevalent positives. APTs were positive in 88.9%. Wheat, beef, and chicken (41.7%, 36.1%, and 36.1% respectively) were the most prevalent positives. There was an association between SPT oat (RR = 0.43) with eosinophil counts in esophageal biopsy, unlike APT wheat (RR = -0.28), chicken (RR = -0.19) and beef (RR = -0.10).

**CONCLUSIONS:** This is the first study to describe results of both food SPT and APT in a Hispanic EoE pediatric population. APT results differed from other published cohorts. Dietary, gut microbial flora and host immune factors may explain these differences. Prospective studies are needed to evaluate efficiency of combining these testing methods in directing successful dietary elimination.

**897** Challenges With Measurement Of IgE Antibodies To Minor Components In Food Allergy; Eosinophilic Esophagitis, Peanut Allergy, and Delayed Anaphylaxis To Mammalian Meat  
Anubha Tripathi, MD1, Lisa J. Workman, BA1, Scott Commings, MD, PhD2, Barrett Barnes, MD2, Prof. Robert G. Hamilton, PhD, D. Abmii, FAAAAI1, Thomas A. E. Platts-Mills, MD, PhD, FAAAAI1, Elizabeth Erwin, MD12, 1Division of Allergy, Asthma & Immunology, University of Virginia Health System, Charlottesville, VA, 2Division of Pediatric Gastroenterology, University of Virginia Health System, Charlottesville, VA, 3Johns Hopkins University School of Medicine, Baltimore, MD, 4Nationwide Children’s Hospital, Columbus, OH.

**RATIONALE:** No one diagnostic modality currently identifies the foods responsible for development of Eosinophilic Esophagitis (EoE): skin testing (prick, patch) is sometimes positive and serum IgE titers are often low-level positive.

**METHODS:** IgE to food and inhalant allergens was measured in sera of adults and children with biopsy-diagnosed EoE by: ImmunoCAP (CAP), and for component specificity, by ISAC (112-component biopsy chip assay), serial (1/2 to 1:8) dilution CAP assays, and component CAP assays (milk, wheat). Results were compared to those for subjects with anaphylaxis after ingestion of peanut, milk, and mammalian meat.

**RESULTS:** ISAC component analysis of EoE sera for aerallergens correlated well with analysis by CAP, however, for foods, was largely negative. For dilution assays, no change (undiluted value vs. calculated titer) was noted for: aerallergens (mite, cat) in EoE sera or peanut and milk in anaphylaxis sera; in contrast, calculated titers up to six times the undiluted value were noted for foods in EoE sera (milk, wheat, peanut) and in mammalian meat allergy sera (beef, pork). CAP assays for 5 milk components revealed positivity to minor components in greater than 50% of EoE sera.

**CONCLUSIONS:** ISAC results suggest that the components of foods currently recognized as important allergens may not be relevant in EoE. Differences in dilution assay results among EoE and anaphylaxis sera, in addition to predominance of positive titers for minor milk components in EoE sera, elucidate that assaying undiluted serum can significantly underestimate IgE levels and that comprehensive component analysis may be the key to understanding food sensitivity in EoE.

**898** Serum IgE To Allergen Components In Patients With Eosinophilic Esophagitis  
Maria Slack, MD1, Princess U. Ogbugo, MD, FAAAAI2, Anubha Tripathi, MD3, Lisa J. Workman, BA3, Thomas A. E. Platts-Mills, MD, PhD, FAAAAI3, Elizabeth Erwin, MD4, 1Nationwide Children’s Hospital, Columbus, OH, 2Wexner Medical Center at the Ohio State University, Columbus, OH, 3Division of Allergy, Asthma & Immunology, University of Virginia Health System, Charlottesville, VA, 4Nationwide Children’s Hospital.

**RATIONALE:** Milk, wheat, egg, soy, and peanut are common problem foods for adults and children with eosinophilic esophagitis (EoE). Current recommended diets for treatment are challenging to maintain long term. We examined specific IgE to allergen components among patients with EoE.

**METHODS:** In a cohort of adults (n = 24) and children (n = 30) with EoE, we measured levels of specific IgE to common foods (ImmunoCAP). IgE antibodies to milk and peanut component proteins were also measured.

**RESULTS:** In the whole cohort, milk and/or peanut sensitization was identified in 44.4% and 33.3% respectively. In 82% of patients who had sensitization to milk, we found detectable specific IgE to at least one component. No single component was dominant; 58.8% had specific IgE to Bos d 4, 52.9% to Bos d 5, 41.2% to Bos d 8, and 23.5% to Bos d 9. The geometric mean titer of specific IgE to milk was higher in patients with EoE to two or more components (p = 0.01). Specific IgE to at least one component for peanut allergen was detected in 71.4% of patients. In contrast with milk, specific IgE to Ara h 8 or Ara h 9 was most frequently identified in patients with EoE (42.9% for each component). Specific IgE to Ara h 1 and Ara h 2 was found in only 14.3%.

**CONCLUSIONS:** Sensitization to distinct milk components may differentially influence inflammation and symptoms. The negative results for Ara h 1, 2, and 6 in most EoE patients suggest that some individuals with EoE may not need to avoid peanut.

**899** Eosinophilic Gastroenteritis Due To Egg Allergy Presenting As Acute Pancreatitis  
Dr. Kevin Tse, MD, UCSD, Dr. Sandra C. Christiansen, MD, FAAAAI; Southern CA Permanente Med Grp, San Diego, CA.

**RATIONALE:** Eosinophilic gastroenteritis (EGE) is a disease characterized by eosinophil infiltration of the gastrointestinal tract. Most patients present with nonspecific symptoms of gastrointestinal pain, bloating, nausea, vomiting, diarrhea, malabsorption and ascites. Here we present a case of acute pancreatitis in a 25 year-old female within 1 hour after ingestion of an egg-containing product.

**METHODS:** Serologic testing by Immunocap performed to commonly allergic foods. Endoscopy performed during admission for acute pancreatitis.

**RESULTS:** During one of these attacks, her lipase was elevated to 2400 U/L. Endoscopic biopsies revealed increased eosinophils in the duodenum without villous blunting or acute inflammation. Charcot Leyden crystals were also noted on a stool sample. In vitro allergy testing demonstrated a level III sensitization to egg, all other tested foods were negative. Removal of egg from this patient’s diet has lead to complete resolution of her symptoms.

**CONCLUSIONS:** One previous case report discussed a patient with milk allergy resulting in EGE with acute pancreatitis. A possible mechanism by which food-hypersensitivity related EGE may cause acute pancreatitis is due to obstruction of the pancreatic duct from local duodenal inflammation. When unexplainable gastrointestinal symptoms are observed in patients with positive food allergy testing, EGE triggered by food allergies should be included in the diagnosis.
**900**

**Patient Ratings Of Various Eosinophilic Esophagitis Treatment Options**

**Dr. Samantha K. Lin**, MD, **Dr. Neelu Kalra**, MD, **Dr. Gisoo Ghaffari**, MD, FAAAAI, Penn State Hershey Medical Center, Hershey, PA.

**RATIONALE:** Eosinophilic esophagitis (EoE) can be treated with various combinations of a proton pump inhibitor (PPI), topical steroid (TS), and elimination diet (D). This study assessed which treatments patients were using and sought to determine patient/caregiver ratings of EoE symptoms, response to treatment, and tolerability of therapy.

**METHODS:** After IRB approval, patients with biopsy proven EoE followed in our allergy clinic were selected for a questionnaire based phone survey and chart review. Severity of symptoms before and after treatment and overall response to treatment were rated on a scale from 0-5, with 0 being lowest.

**RESULTS:** Survey data were obtained for 79 out of 138 patients (ages 9-76 yrs, mean 36 yrs ± 20.1). Dysphagia (76%), food impaction (63%), and regurgitation (46%) were the most common moderate/severe pre-treatment symptoms, with these decreasing to 11%, 14%, and 8% post-treatment, respectively. Overall, moderate/severe symptoms decreased by 82% with treatment. The most commonly reported treatment regimens were PPI+TS (27%), PPI alone (22%), and PPI+TS+D (15%). Topical steroid containing treatment groups as a whole had significantly higher treatment response ratings than the non-topical steroid containing treatment groups (average ratings 4.205 vs 3.465, p=0.003). Only 0.07% of patients on TS reported side effects (oral thrush or dryness), 0.05% of patients on a PPI reported side effects (GI symptoms, rash), while 28% rated their EoE diet impossible or near impossible to follow.

**CONCLUSIONS:** Overall, responses to EoE treatment were good. Use of a topical steroid was associated with significantly higher treatment response ratings and very few side effects.

---

**902**

**Evaluation Of Antigenic Triggers and Etiologies In Eosinophilic Esophagitis: A Single Center Experience**

**Dr. Tanvi Patel**, **Dr. Sarah Glover**, **University of Florida, Gainesville, FL.**

**RATIONALE:** Eosinophilic esophagitis (EoE) is a chronic antigen mediated disorder. The current literature suggests that EoE is largely induced by food antigens. Herein we report a single center experience identifying other factors that may be significant contributors to the disease.

**METHODS:** Retrospective chart review was conducted on 69 patients that presented over the last two years. All patients were confirmed to have greater than 15 eosinophils per high power field, and had been treated with proton pump inhibitors and topical steroids. Information regarding sex, age, past medical history, and laboratory data was collected. Institutional review board approval was obtained for the collection of this information.

**RESULTS:** Approximately 58 percent had environmental allergies while only 28 percent had food allergies. Nine percent had selective IGG deficiency, and an estimated 15 percent had auto-inflammatory or underlying autoimmune disease. Three individuals were identifed with latent enteroviral infection, two of which had low or no interferon.

**CONCLUSIONS:** Intriguingly, we found that there were more environmental allergies than food allergies present among our patients. The antigen mediated etiology of EoE may vary by region such that environmental allergies are more prevalent triggers in the southeast portion of the country. Furthermore, there is significant overlap of EoE with auto inflammatory and subtle immunodeficiency. Our observations showed a significant number of patients had selective IgG deficiency and one patient had selective IgM deficiency. As such, further immune work up should be considered in patients with EoE refractory to standard therapy with acid suppression and the six food elimination diet.

---

**903**

**Eosinophilic Esophagitis and Selective IgA Deficiency. A New Combined Disorder**

**Dr. Eric Gonzalez Hernandez**, **Dr. Vylma Velazquez**, MD, **Dr. Carlos Camacho**, MD, **Dr. Sheilla Capre**, **Hospital Episcopal San Lucas, Ponce, PR.**

**RATIONALE:** Eosinophilic esophagitis (EoE) is an emerging disease characterized by inflammation of the esophagus caused by predominance of eosinophils. Selective deficiency of IgA is the most common immune deficiency. It is defined as decreased or absent levels of serum IgA (<0.05-0.07 g/L) in a patient with normal serum levels of IgG and IgM. Reviewing the literature we have not found any articles that describe any patient with both conditions.

**METHODS:** Endoscopic study showed 100% eosinophils in biopsy of esophageal tissue. Serum IgA levels below 15g/L, IgG and IgM within normal limits. Increase IgE levels, skin-testing positive for dust mite.

**RESULTS:** 14 years old male evaluated by Pediatric Gastroenterology service due to abdominal pain, vomiting and gastroesophageal reflux of 3 years evolution that got worst during the last 6 months, when he presented dysphagia. His past medical history includes; multiple formula changes, recurrent infections, otitis, sinusitis, and bronchiolitis, atopic dermatitis and urticaria. Adenoidectomy and tonsillectomy at 4 years old. Gastroduodenoscopy study done in 2005 showed the presence of 100% eosinophils in esophageal biopsy. At this moment patient was refer to the allergy service for evaluation. Patient present allergic rhinitis, sinusitis and an area of cellulitis over right cheek. Serum IgG and IgM were within normal limits, IgA was<15 g/L, IgE was increased with positive skin testing for dust mites. Rest of close family was tested for serum IgA, all within normal limits.

**CONCLUSIONS:** We believe this is the first reported case of a selective IgA deficiency with eosinophilic esophagitis in a child.
AB262 Abstracts

904 Cephalosporin Cross-Reactivity In Skin Test
Dr. Jong-Myung Lee, MD1, Dr. Min-Hye Kim1,2, 1Regional Pharmacovigilance Center, Kyungpook National University Hospital, Daegu, South Korea, 2Department of Internal Medicine, Kyungpook National University School of Medicine, Daegu, South Korea.

RATIONALE: Cephalosporin hypersensitivity is increasing because of its frequent use. It is frequent in the real world to avoid all cephalosporins even if a patient has a hypersensitivity reaction to only one cephalosporin. The aim of this study was to evaluate cephalosporin cross-reactivity using the skin test.

METHODS: Patients who experienced beta-lactam antibiotics hypersensitivity and positive skin test were recruited retrospectively. Prick and intradermal test were performed with culprit drug and other beta-lactam antibiotics; penicillin G (10,000 IU/mL), ampicillin (20 mg/mL), cefazolin (1st generation, 2 mg/mL), cefotiam (2nd generation, 2 mg/mL), ceftriaxone (3rd generation, 2 mg/mL).

RESULTS: A total of 7 adult patients were enrolled. Among them, 2 patients (2/7, 28.6%) showed selectively positive reactions to cefotiam. Five patients (5/7, 71.4%) showed cross-reactivities between: 1) cefaclor and ampicillin, 2) cefaclor, ampicillin, and cefotiam, 3) cephalosporins and cefotiam, 4) cefazolin and cefotiam, 5) cefotiam and ampicillin. Cross-reactivity with ampicillin was observed in 3/7 (42.9%), and cross-reactivity among cephalosporins was shown in 3/7 (42.9%).

CONCLUSIONS: Cross-reactivity rate and ampicillin and cephalosporin was higher than expected, although all cross-reactivities were limited to the 1st generation and 2nd generation cephalosporins. Surprisingly, cefotiam that is known to have a different side chain showed cross-reactivities with other beta-lactam antibiotics. The further studies are needed to investigate the molecular mechanisms of cross-reactivities between beta-lactam antibiotics.

905 Rituxan Hypersensitivity and Management
Dr. Johnson T. Wong, MD, FAAAI1, Dr. Aleena Banerji, MD1, Dr. Timothy P. Lax, MD2, Dr. Aidan Long, MD, FAAAI1, Dr. Michael T. Wilson, MD, PhD3, Dr. Caroline Sokol, MD, PhD3, 1Division of Rheumatology, Allergy, and Immunology, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, 2Division of Rheumatology, Allergy, and Immunology, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, 3Massachusetts General Hospital.

RATIONALE: Rituxan hypersensitivity can be severe and limiting. Understanding its pattern and desensitization may permit administration in difficult cases.

METHODS: All patients referred for the management of Rituxan hypersensitivity at Massachusetts General Hospital over the past 5 years were reviewed. Clinical data, skin test result and desensitization outcomes were reviewed.

RESULTS: 25 patients were referred over the 5 year period. 23 were patients with lymphoma of various types, 1 with MS, and 1 with AIA/ITP. Of the 25 patients have a reaction during their first course of treatment c/w cytokine release syndrome, with the range up to course #10. 14 subjects failed additional attempts at slower infusions and additional pretreatment prior to the consultation. The data suggest that additional mechanisms may develop in these patients. The 25 patients underwent 168 continuous IV desensitizations based on 3 related protocols, with all but one completed successfully. Overall 22% of the desensitizations were complicated by a reaction. The average hypersensitivity reaction grade was 3.0 (2-4) prior to desensitization and 1.3 with desensitization. Skin test(s) were performed in 18 of the patients with 5 patients positive upon initial testing and 2 more converted from skin test negative to positive. Skin test outcome was not prognostic of likelihood of complications during desensitizations.

CONCLUSIONS: Severe hypersensitivity reactions may complicate Rituxan treatment of patients with lymphoma that can persist despite slowing the infusions and additional pretreatment. Nearly all patients can be successfully desensitized with a reduction in the severity score. Skin test does not appear to be of prognostic significance.
907 Clinical Presentation and Outcomes Of Children Undergoing Evaluation For Drug Allergy
Dara Mairiang, MD, Dr. Wiparat Manuyakorn, MD, Wasu Kamchaisatian, MD, Soamurat Vilayuk, MD, Suwat Benjompitik, MD; Division of Pediatric Allergy/Immunology/Rheumatology, Department of Pediatrics, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.

RATIONALE: Drug allergy is a major problem encountered among general practitioners and allergists. Patients are frequently overdiagnosed as drug allergy without proper confirmatory tests. The aim of this study was to assess the prevalence, clinical presentation and outcomes of children that underwent evaluation for drug allergy.

METHODS: Medical records of children suspected drug allergy who underwent evaluation for drug allergy from 2007 to 2013 were reviewed.

RESULTS: Sixty children were evaluated for drug allergy. The most common suspected drug was antibiotics (72.3%), followed by acetaminophen (7.7%) and NSAIDs (3%). In the group of antibiotics, B-lactam antibiotic was the most common. The onset of symptom was highly variable (median 4.5 hours; 0.08-168) in which non-immediate onset was the majority. Skin and mucocutaneous reactions were the most common presentation (85.9%) particularly urticaria (50.7%) and maculopapular rash (28.2%). Only 26.6 percent of children were confirmed allergic to offending drugs (20% by skin test and 6.6% by DPT). Twenty three percent of them had positive DPT despite negative skin test. DPT reactions did not correlate with presenting symptoms of drug allergy. There were no differences in age, onset nor primary symptom of drug allergy between confirmed allergic and non-allergic group. History of atopy, autoimmune disease and malignancy were not associated with DPT outcomes.

Conclusions: Drug allergy is commonly reported but only a minority of children have true allergy. There were no precise clinical predictors for drug allergy. Thus, DPT remains the gold standard for diagnosis.

908 Analysis Of Drug Hypersensitivity Reactions In A Large Series Of Children
Dr. Maria Angeles Zambonino1, Dr. Candelaria Muñoz2, Dr. Jose Luis Corzo, MD2, Dr. Gloria Requena2, Dr. Adriana Ariza, PhD3, Dr. Cristobalina Mayorga, PhD4, Dr. Antonio Urda2, Dr. Miguel Blanca, MD, PhD1, Dr. María J. Torres, MD, PhD4, Allergy Service, Carlos Haya Hospital, Málaga, Spain, 2Pediatric Service, Carlos Haya Hospital, Málaga, Spain, 3Research Laboratory for Allergic Diseases, Hospital Regional Universitario de Malaga - FIMABIS-IBIMA, Malaga, Spain.

RATIONALE: Allergic reactions to drugs in children are less frequent and less studied than in adults. The aim of the study was to analyse the clinical data, sensitization profile and diagnostic methods used in children with clinical history of hypersensitivity reactions to drugs.

METHODS: We evaluated children aged 1-14 years with a diagnosis suggestive of hypersensitivity reactions to drugs from 2006 to 2012. The allergological work-up depended on the drug involved and included skin testing, in vitro testing and drug provocation test (DPT).

RESULTS: Out of 866 children evaluated, 128 (14.8%) were confirmed as allergic whereas 738 (85.2%) had good tolerance to the culprit drug and were considered non-allergic. Allergic children were significantly older (8 vs. 4 years), higher number of males (67.2% vs. 49.5%) and more atopic (22.7 versus 10.8%) than those non-allergic. In non-allergic, reactions appeared more often with fever (84.1% versus 68%) and after the first contact with the culprit drug (5.7% versus 0.8%). Non-immediate hypersensitivity to BL (42.19%) followed by cross-intolerance reactions to NSAIDs (34.38%) were the most common confirmed diagnosis, whereas other drugs represented only 21.5% of diagnosis. Regarding the diagnostic methods, 2 (1.6%) were diagnosed by in vitro tests, 5 (3.9%) by skin testing and 121 (94.5%) by DPT.

CONCLUSIONS: Nearly 15% of the children evaluated were confirmed as allergic, being non-immediate hypersensitivity to BL followed by cross-intolerance to NSAIDs the most frequent diagnosis. DPT was necessary in 95% of cases to confirm the diagnosis.

909 Assessing IgE-Mediated Reactions In Children Presenting To An Allergy Clinic With A Suspected Antibiotic Allergy
Mr. Christopher Miller, BSc1, Dr. Marie-Noel Primeau, MD2, Dr. Christine Lejtenyi, MD3, Dr. Elaine J. Medoff4, Ms. Nofar Kimchi5, Dr. Moshe Ben-Shoshan, MD, MSc6, 3Division of Clinical Epidemiology, Department of Medicine, McGill University Health Centre, Montreal, QC, Canada, 4McGill University Health Center, Montreal, QC, Canada, 5Montreal Children’s Hospital, Montreal, QC, Canada, 6Technion American Medical Students Program, Israel, 3Division of Paediatric Allergy and Clinical Immunology, Department of Paediatrics, McGill University Health Center, Montreal, QC, Canada, 7Montreal Children’s Hospital, Montreal, Montreal, Canada.

RATIONALE: To characterize immediate and delayed-type skin eruptions associated with β-lactam and other antibiotics and to assess the presence of IgE-mediated reactions (through the use of provocative challenges) among children referred to an allergy clinic due to potential antibiotic allergy.

METHODS: Our research team approached children referred to the Montreal Children’s Hospital allergy clinic with suspected antibiotic allergy. After parents consented, the treating allergist filled a standardized questionnaire on the clinical characteristics, suspected antibiotic exposure and management of the reaction and all children were offered an oral antibiotic challenge. Descriptive statistics were used to characterize the reactions.

RESULTS: Among 142 patients assessed for antibiotic allergy between March 2012 and August 2013, 43.2% were males. The median age was 1.9 years (IQR 1.1, 3.7) at the time of reaction and 3.8 years (2.1, 6.2) at the time of assessment. The majority [53.0% (95%CI, 43.9%, 61.0%)] reported reactions after 1-3 days of treatment and in 62.6% (53.9%, 70.5%) symptoms persisted for 1-3 days. Amoxicillin was the major culprit (74.8%) and the common symptom was hives (75.9%). Almost half (46.1%) were seen in a healthcare facility and 58.1% were treated there with antihistamines. Among 141 consenting to an oral challenge, 2 (1.41% (95%CI, 0.2%, 5.6%)) were positive (hives within 1 hour after exposure), consistent with the diagnosis of an IgE-mediated reaction. All those reacting to the challenge had previous reactions occurring within 2 hours of exposure.

CONCLUSIONS: Our data emphasizes the importance of assessment for suspected antibiotic allergy, especially given frequent need for antibiotic therapy in children.
190 Hypersensitivity Drug Reactions (HDR) In Latin America. Similarities and Differences Between Children and Adults

Dr. Ricardo Cardona-Villa, MD,1 Dr. Edgardo J. Jares, MD,2 Dr. Maximiliano Gómez3, Dr. Luis Felipe C. Esinza, MD,4 Dr. Mario Sánchez-Borges, MD, FAAAIA5, Dr. Alfredo Arias Cruz,2 Dr. Carlos Serrano,2 Dr. Mabel Noemi Cuello, MD,6 Ivan Cherrez,2 Dr. Andrea Zanacchi10, Prof. Alicia De Falco11, Dr. Silvana Monsell12, Dr. Adolfo Salvaterra12, Dr. Susana Barayazarri16, Dr. Susana Diez-Zuloaga1, Dr. Blanca Maria Morfin-Maciel, MD13, Dr. Paola Toche Pinaud14, Dr. Sandra GonzálezDíaz14, Dr. Juan F. Schuhl, MD, FAAAIA15,16,1 Universidad de Antioquia, Medellin, Colombia, 2.C.M.P. SA, Buenos Aires, Argentina, 3Hospital San Bernardo, Santa Cruz, Argentina, 4Universidade Federal de São Paulo, São Paulo, Brazil, 5Clínica El Avila, 6a transversal Altamira, piso 8, consultorio 803, Caracas, Caracas, Venezuela, 7Hospital Universitario, Monterrey, Mexico, 8Fundación Valle del Lili, Cali, Colombia, 9Consultorios San Juan, San Juan, Argentina, 10Respiralab - Hospital Kennedy, Guayaquil, Ecuador, 11Nouvel Hospital San Roque, Córdoba, Argentina, 12Universidad Nacional de La Plata, La Plata, Argentina, 13Fundación San Luis, Argentina, 14Hospital Mocel, Mexico City, Mexico, 15Clinica Las Condes, Santiago, Chile, 16British Hospital, Montevideo, Uruguay.

RATIONALE: HDR are frequent motives for consultation in Allergology services. Possible etiologic factors and clinical presentation differences between Latin American children and adults have not been described yet.

METHODS: An observational cross sectional study using a modified ENDA questionnaire was implemented in 19 allergology units in 11 Latin-American countries, reporting patients presenting HDR in the last year before consultation. Causal relationship was categorized according to WHO-UMC Causality Categories: certain, probable, possible, unlikely and conditional.

RESULTS: 727 patients, 144 (19.8%) of them under 18 years old, presented 732 reactions. Female gender was 71.7% in adults, and 50% in children. Atopic history was present in 44.9 and 63.8% and a history of previous drug reaction in 31.9 and 36.9% of adults and children, respectively. Fourteen percent of adult, and 10.7% of children had presented previous reactions with the same drug. The clinical picture of the reaction in adults and children was angioedema in 47.9 and 48.6%, urticaria in 44.5 and 41.8%, maculopapular and macular exanthema in 20.3 and 22.6%, erythema multiforme and SJS in 3.6 and 2.7% respectively. Certain and probable causal relationships were attributed in adults and children to NSAIDs in 55.7 and 60.3%, beta lactams in 11.2 and 19.8%, non beta lactam antibiotics in 8.4 and 2.5%, anticonvulsants in 3.2 and 1.7%, chemotherapy 0.8 and 2.5% of patients, respectively.

CONCLUSIONS: Female sex was predominant in adults but not in children. NSAIDs and antibiotics were the drugs implicated in more than 75% of patients. Beta lactam antibiotics were more frequently involved in children.

911 Copy Number Variations In ALOX5 and PTGER1 Genes Are Associated With Susceptibility To AERD and MNSAID-UA

M. María Del Carmen Plaza Serón, Bsc1, Dr. Pedro Ayuso Parejo, PhD1, Dr. Natalia Blanca-López, MD, PhD2, Dr. Inmaculada Doña, MD, PhD3, Dr. José A. Cornejo-Garcia, PhD4, Dr. María José Torres, MD, PhD5, Dr. Javier Fernández4, Dr. Jose Julio Laguna, MD, PhD5, Dr. Verónica Godínez6, Ms. Miriam Osorio6, Mrs. Luisa Galindo, RN7, Dr. Gabriela Canto, MD, PhD8, Dr. Miguel Blanco, MD, PhD9, Allergy Service, Infanta Leonor Hospital, Madrid, Spain, 2Allergy Service, Carlos Haya Hospital, Málaga, Spain, 3Research Laboratory, Carlos Haya Hospital, Málaga, Spain, 4UMH Alicante G.University Hospital - Allergy Sect., Alicante, Spain, 5Hospital La Cruz Roja Hospital, Madrid, Spain, 6Research Laboratory, Carlos Haya Hospital-FIMABIS, Málaga, Spain.

RATIONALE: Aspirin-exacerbated respiratory disease (AERD) and Multiple NSAID–triggered urticaria and/or angioedema and anaphylaxis in patients without pre-existing chronic urticaria (MNSAID-UA) are considered the most frequent entities. The underlying mechanism proposed is based on the pharmacological properties of the NSAIDs. These reactions occur as a result of mast cell activation and subsequent degranulation and generation of lipid-derived mediators. These cells can be activated by IgE-dependent and IgE-independent mechanisms that share common signaling pathways. In this work, we aimed to analyze the association between single nucleotide polymorphisms (SNPs) in key genes involved in mast cell activation and MNSAID-UA.

METHODS: A total of 450 patients with MNSAID-UA and 500 individuals who tolerated NSAIDs were included. Nine SNPs in 5 genes (rs290986 in STK, rs714104 in LATT, rs2228246 and rs533381 in PLCLG1, rs2307198, rs12749354 and rs12746200 in PLA2G4A; and rs35211496 and rs1805034 in TNFRSF11A genes) were genotyped using TaqMan® probes.

RESULTS: MNSAID-UA patients were subdivided according to the type of response and significant differences were found between MNSAID-UA patients who only developed urticaria and the following SNPs: rs2228246, OR = 0.30 (95% CI = 0.11-0.82; P =0.031) rs35211496, OR = 2.67 (95% CI = 1.15-6.21; P =0.009) rs35211496 and rs1805034 in TNFRSF11A genes were not found in genotype frequencies of these SNPs between MNSAID-UA and tolerant.

CONCLUSIONS: We found an association between non synonymous polymorphisms rs2228246 PLCLG1 and rs35211496 TNFRSF11A and the non encoding SNP rs12746200, which could be involved in PLA2G4A regulation and urticaria induced by multiple NSAIDs.
913 Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)-Induced Acute Urticaria: A Genome-Wide Association Study In The Spanish Population

Dr. Jose a. Cornejo-Garcia, PhD1, Dr. Mike Lee2, Dr. Natalia Blanca-Lopez, MD, PhD3, Dr. Lieh-Bang Liu4, Dr. Chien-Hsian Chen4, Dr. Immaculada Doria, MD, PhD3, Veronique Godineau4, Dr. Jose Julio Laguna5, Dr. F. Javier Fernandez, MD, PhD6, Dr. Pedro Ayuso Parejo, PhD7, M.r. Maria del Carmen Plaza-Serón, Bsc8, Dr. Gabriela Canto, MD, PhD9, Dr. Miguel Blanca, MD, PhD10. 1Research Laboratory, Carlos Haya Hospital, Malaga, Spain, 2Laboratory for International Alliance on Genomic Research, RIKEN Center for Integrative Medical Sciences, Yokohama Kanagawa, Japan, 3Allergy Service, Infanta Leonor Hospital, Madrid, Spain, 4Division of Rheumatology, Allergy and Immunology, Chang Gung Memorial Hospital at Lin-kou, Kwei-san, Tao-yuan, Taiwan, 5Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan, 6Allergy Service, Carlos Haya Hospital, Malaga, Spain, 7Hospital De La Cruz Roja, Madrid, Spain, 8UMH Alicante G.University Hospital - Allergy Sect., Alicante, Spain.

RATIONALE: The most important group of medications responsible for hypersensitivity drug reactions (HDRs) is NSAIDs, with acute urticaria/angioedema (AUA) induced by cross-intolerance the most frequent clinical entity. Most of the genetic studies carried out have focused in the study of single nucleotide polymorphisms in genes related with prostaglandins and leukotrienes synthesis. In order to identify new genetic variants potentially involved in NSAIDs-induced AUA we conducted a GWAS in a Spanish population.

METHODS: Patients and controls were recruited in clinical centers integrated in the Spanish Network for Allergic Diseases. All patients experienced more than 2 episodes with at least 2 different unrelated NSAIDs, and those with airways or chronic urticaria were excluded. Whole-genome scan was conducted using Axiom Genome-Wide CEU Array chip on 308 NSAIDs-induced AUA patients and 144 NSAIDs tolerant age, sex-matched controls.

RESULTS: Although no SNPs reached genomewide p-value after Bonferroni correction, our results revealed 32 SNPs with suggestive significant associations (10^{-5}<p<10^{-5}) with NSAIDs-induced AUA. The lowest p values corresponded to polymorphisms located on chromosome 17; rs7225428 in GOSR2 (p=1.11x10^{-6}), rs197111 (p=7.68x10^{-5}), and rs1071682 in EFTUD2 (p=1.77x10^{-5}).

CONCLUSIONS: The identification of new variants potentially associated with NSAIDs-induced AUA opens up new clues for understanding the mechanisms underlying this disease, the most important clinical entity induced by HDRs.

914 Tolerance To COX-2 Inhibitors In Children With Multiple Hypersensitivity To Non-Steroidal Anti-Inflammatory Drugs

Dr. Jose Luis Corzo Higuera, MD3, Dr. Maria Angeles Zambruno2, Dr. Candelaria Muñoz2, Dr. Cristobalina Mayorga, PhD2, Dr. Gloria Requena3, Dr. Antonio Urda1, Dr. Miguel Blanca, MD, PhD2, Dr. Maria J. Torres, MD, PhD4, 1Pediatric Service, Carlos Haya Hospital, Malaga, Spain, 2Allergy Service, Carlos Haya Hospital, Malaga, Spain, 3Research Laboratory for Allergic Diseases, Hospital Regional Universitario de Malaga - FIMABIS-BIMA, Malaga, Spain, 4Allergy Service, Carlos Haya Hospital, Malaga, Spain.

RATIONALE: Multiple hypersensitivity to non-steroidal anti-inflammatory drugs (NSAIDs) can affect children, with the mechanism proposed being inhibition of the cyclooxygenase enzyme-1 (COX-1). In these patients non-chemically related NSAIDs, even COX-2 inhibitors, can induce the reaction, hampering treatment of fever and inflammatory processes. We have retrospectively analyzed tolerance to etoricoxib, a selective COX-2 inhibitor, and to meloxicam, a preferential COX-2 inhibitor, in children diagnosed of multiple hypersensitivity to NSAIDs, confirmed by drug provocation tests (DPT).

METHODS: We analyzed the clinical records of all children (aged 1-14 years) diagnosed with multiple hypersensitivity reactions to NSAIDs in the Pediatric Allergy Unit during the period January 2006 to January 2013.

In all cases tolerance to paracetamol, etoricoxib and meloxicam was also assessed.

RESULTS: The study included 41 children with a diagnosis confirmed by a DPT with acetyl salicylic acid and the culprit NSAID. DPT with paracetamol and etoricoxib was negative in all children. However 2 (4.9%) children developed a reaction after the administration of meloxicam, one developed lip angioedema two hours after its administration and the other lip and eye angioedema one hour after.

CONCLUSIONS: These data indicate that both etoricoxib and meloxicam are good alternatives for treatment in older children with multiple hypersensitivities to NSAIDs. More studies with larger populations need to be conducted.

915 Aspirin Allergy In A High Risk VA Population And Potential Benefit From Aspirin Desensitization

Bhavisha Patel, MD2, Joseph Karls2, Sandra Tompkins2, Dawn Nyland2, Jo Ann Clough2, Jane Ludwig2, Sameer K. Mathur, MD, PhD, FAAAI1,2, 1University of Wisconsin School of Medicine and Public Health, Madison, WI, 2William S. Middleton Veterans Hospital, Madison, WI.

RATIONALE: There is strong evidence for the use of aspirin as part of anti-platelet therapy in patients with cardiovascular disease. However, there is a population of patients who are unable to take aspirin due to a listed allergy to aspirin. In order to improve the utilization of aspirin, we sought to better understand the prevalence and nature of aspirin allergies.

METHODS: In an IRB-approved protocol (HS-2012-0685), the medical records of all veterans admitted to the William S. Middleton Veterans Hospital from 1999 to 2004 were accessed. We used discharge codes to identify the group admitted with cardiovascular diagnoses and cross-referenced pharmacy allergy records to identify the subset with aspirin allergy listed.

RESULTS: There were 20,476 patient discharge records analyzed. Of those, 1609 (7.86%) were discharged with a cardiovascular diagnosis including cerebrovascular event, transient ischemic attack, coronary bypass, percutaneous cardiovascular procedure, acute myocardial infarction, cardiac arrest, angina, or chest pain. Of these 1609 patients, 28 patients (1.74%) had an aspirin allergy. We estimate an overall prevalence of aspirin allergy in the VA population of 1.76%.

CONCLUSIONS: The prevalence of aspirin allergy in the VA patients with cardiovascular disease is 1.74%. This group of patients is currently not gaining the benefits of secondary prevention from aspirin utilization and represents a target group of candidates for aspirin desensitization.
916 Novel Protocol For Successful Aspirin Desensitization In a Patient With Laryngeal Angioedema To Aspirin
Dr. Nikki Garg, MD, Dr. Pratik Patel, MD, Dr. Sindhuara Bandi, MD; Rush University Medical Center, Chicago, IL.

Rationale: Most established aspirin desensitization protocols have been studied in patients with aspirin exacerbated respiratory disease (AERD). Induction of drug tolerance protocols for other types of reactions to aspirin are less well studied. It is unclear whether these protocols are true desensitizations or graded challenges. Many patients with IgE mediated reactions to aspirin experience symptoms even after the protocols are completed.

Methods: A 71 year old patient presented with angina and a history of aspirin-induced angioedema which occurred 40 years ago. He again developed physician observed laryngeal angioedema at an outside hospital after ingesting 162 mg of aspirin during a standardized desensitization. His symptoms resolved after receiving steroids and diphenhydramine. Upon transfer to our hospital, cardiology requested that he take aspirin 325 mg daily before placement of a cardiac stent to avoid surgical intervention. He was pretreated with montelukast 10 mg and diphenhydramine 50 mg daily during the protocol. On day 1 he received 15 mg, 30 mg, and 60 mg of aspirin 3 hours apart. On day 2 he received 60 mg, 81 mg, and 120 mg of aspirin 3 hours apart. On day 3 he received 120 mg, 240 mg, and 325 mg of aspirin 3 hours apart.

Results: He tolerated the protocol without issue and continues to tolerate 325 mg aspirin daily one month after stent placement.

Conclusions: Aspirin desensitization for symptoms other than AERD is poorly understood. This novel protocol could be considered in patients with reactions other than AERD including more classical allergy symptoms like laryngeal angioedema.

917 Allergy To Beta-Lactams In Patients Consulting Allergy Center Of The Antioquia University, Colombia
Dr. Elizabeth Lopez1, Dr. Kaddy Juliana Beltran2, Dr. Jorge Sanchez1, Dr. Ricardo Cardona-Villa, MD3; 1Universidad de Antioquia, Medellin, Colombia, 2Universidad de Antioquia, Medellin, Colombia.

Rationale: To determine the immunological component of patients who are tested with suspected of adverse reaction to beta-lactams in clinical allergology center of Antioquia University in the period between January 2008 and October 2013.

Methods: Patient histories were obtained of electronic medical records, and they were offered investigation for penicillin allergy with specific IgE, skin prick tests, intradermal tests (IDT), patch test and drug challenge tests. Patients with case histories of reactions to other beta-lactams were also subsequently challenged with the culprit drug.

Results: 350 allergy tests were made, 33 (15.6%) specific IgE by immunoCAP, 78 (36.9%) IDT, 13 (6.1%) patch test and 92 drug challenge tests. We studied 125 patients, 71 (56.8%) were females. 73 patients had an immediate reaction, and 52 a non-immediate reaction. The severity of the reported reactions was low in most cases: cutaneous rash and/or angioedema 95 (73.6%), anaphylaxis 10 (7.7%), lower respiratory symptoms 2 (1.5%), non-specific symptoms 8 (6.2%). The drug most frequently involved was amoxicillin in 62 patients (49.6%), crystalline penicillin G 17 (13.6%), benzathine penicillin 15 (12%), cephalaxin 13 (10.4%). Analysis of clinical histories showed that patients with a well-defined history of allergy and a history of anaphylaxis were more likely to have a positive test compared to patients with vague histories.

Conclusions: The data suggest that case history is often insufficient to discriminate between immediate reactors and non-immediate reactors. A minority of patients presenting with a history of beta-lactam allergy have evidence of immune-mediated hypersensitivity in this study.

918 Effect Of Penicillin Allergy On Outpatient Antibiotic Prescriptions At VA Hospital
Mark Biagtan, MD1,2, Bryan Babler, BS Pharm RPh2, Sujani Kakumanu, MD1,2, Sameer K. Mathur, MD, PhD, FAAAAI1,2; 1University of Wisconsin School of Medicine and Public Health, Madison, WI, 2William S. Middleton Veterans Hospital, Madison, WI.

Rationale: There is often overreporting of penicillin allergy. We sought to characterize the classes of antibiotics prescribed for penicillin-allergic patients in the outpatient setting compared to the general population, and their associated costs. We hypothesized that patients designated as penicillin-allergic are more likely to receive more expensive broad-spectrum antibiotics compared to non-penicillin-allergic patients.

Methods: In an IRB-approved protocol (HS-2012-0685), the William S. Middleton VA Hospital medical records database was accessed to identify patients with a penicillin allergy reported in 2008 and their subsequent outpatient antibiotic prescription history from 2009 through 2012 compared to the non-penicillin-allergic population. The percentage of patients receiving each class of antibiotics was compared. VA antibiotic prices were used for estimates of cost differences.

Results: 102 penicillin-allergic patients were identified with 352 outpatient antibiotic orders. Compared to the non-penicillin-allergic population (12,563 patients with 61,146 outpatient antibiotic orders), a significantly greater proportion of penicillin-allergic patients were prescribed clindamycin, macrolides, 3rd/4th generation cephalosporins, and vancomycin, and a significantly smaller proportion were prescribed penicillin class antibiotics. Penicillin-allergic patients had a 60% greater average estimated antibiotic cost.

Conclusions: Penicillin-allergic patients are prescribed a different pattern of antibiotics, which are also more expensive, compared to non-penicillin-allergic patients. Thus, evaluation in the Allergy clinic of the penicillin allergy may facilitate the use of more appropriate and cost-effective penicillin-related antibiotics.

919 Value Of Clavulanic Acid In Basophil Activation Test For Evaluating Immediate Reactions To The Combination Amoxicillin-Clavulanic Acid
Dr. Cristobalina Mayorga, PhD1, Dr. Adriana Ariza, PhD2, Dr. Inmaculada Dota, MD, PhD3, Dr. Maria Angeles Zambonino3, Dr. Maria Isabel Montañez, PhD1, Dr. Maria Salas, MD, PhD3, Ms. Maria Dolores Ruiz3, Ms. Lidia Melendez, Lab. Tech.1, Mrs. Maria D. Cañamero1, Dr. Miguel Blanco, MD, PhD1, Dr. Maria J. Torres, MD, PhD3; 1Research Laboratory for Allergic Diseases, Hospital Regional Universitario de Malaga - IBIMA, Málaga, Spain, 2Research Laboratory for Allergic Diseases, Hospital Regional Universitario de Malaga - FIMA-BIS-IBIMA, Malaga, Spain, 3Allergy Service, Carlos Haya Hospital, Málaga, Spain.

Rationale: Amoxicillin (AX) is frequently administered combined to other beta-lactam, the clavulanic acid (CLV). Although initially thought to have a low immunogenic capacity, immediate allergic reactions to CLV have been reported in a 30% of patients allergic to AX-CLV. Basophil activation test (BAT) has shown promising results demonstrating specific recognition of CLV determinants. The aim of this study was to assess the value of BAT in the evaluation of immediate allergic reactions to clavulanic acid.

Methods: Patients with a strong clinical history of having suffered an immediate reaction after AX-CLV administration were evaluated. The allergological study followed the European Academy guidelines, included skin test with penicillin G, AX, and CLV determinants and drug provocation test when indicated. BAT were carried out using AX and CLV at different concentrations (2.5, 1.25, 0.25 and 0.05 mg/ml).

Results: Among 75 patients included, 64 were finally diagnosed as allergic, 26 to AX and 38 to CLV. The sensitivity of BAT was 60% and the specificity 81.8%. The inclusion of AX determinant produced a BAT sensitivity of 54.1% whereas CLV determinant produced a BAT sensitivity of 78.6% with a specificity of 91% and 82% respectively. In patients diagnostic as allergic to AX the BAT sensitivity was 50% whereas in patients allergic to CLV, BAT sensitivity was 65.8%.

Conclusions: The inclusion of clavulanic acid in the basophil activation test increase its diagnostic capacity in patients with immediate allergic reaction to the combination amoxicillin-clavulanic acid.
920 Persistence Of Penicillin Allergy Label Despite Documented Tolerance
Matthew Feldman, MD, Dr. David A. Khan, MD, FAAAAI; University Texas SW Medical Center, Dallas, TX.

RATIONALE: Up to 90% of those who report an allergy to penicillin are able to tolerate penicillin without a reaction after full evaluation and testing. Anecdotally, some patients continue to report a penicillin allergy despite tolerating other penicillin antibiotics. We sought to evaluate the prevalence of persistently reported penicillin allergy despite evidence of penicillin administration and tolerance in the Electronic Medical Record (EMR).

METHODS: We utilized a multi-step search algorithm to query Parkland Memorial Hospital’s EMR from March 2012 through March 2013. We identified all outpatients who had a penicillin reported as an allergy in their EMR. We then identified those patients who were subsequently prescribed a penicillin antibiotic despite their allergy. Patient charts were then reviewed by the study team to verify the algorithm and to look for any documented allergic reactions. Patients who were evaluated for penicillin allergy by our Allergy Division were excluded.

RESULTS: From March 2012 through March 2013, 1,624,429 outpatient encounters occurred consisting of 285,248 unique patients. Of those 285,248 patients, 18,488 (6.5%) reported a penicillin allergy. Forty-two of the 18,488 penicillin allergic patients (0.23%) were administered a penicillin antibiotic despite the documented allergy. No subsequent reactions were recorded. All 42 patients continued to have penicillin listed as an active allergy in the EMR.

CONCLUSIONS: In a one year sample, a small but measurable patient population persistently reports a penicillin allergy despite prior tolerance to a penicillin. Obtaining a brief but thorough drug allergy history with EMR review, if available, may reduce improper labeling of penicillin allergy.

921 Allergy To Betalactams In Brazil: Placebo Effect Or Misdiagnosis?
Dr. Manoela Crespo-Magalhães1, Dr. Marcelo Vivolo Aun, MD3, Dr. Roberta Almeida-Castro2, Dr. Marisa Rosimeire Ribeiro, MD3, Dr. Laila Sabino Sabino Garro, MD, PhD1, Prof. Jorge Kalil, MD, PhD1, Prof. Antonio Abilio Motta, MD, PhD3, Prof. Pedro Giavina-Bianchi, MD, PhD, FAAAAI1; 1Clinical Immunology and Allergy Division, University of Sao Paulo, Sao Paulo, Brazil, 2Clinical Immunology and Allergy Division, University of Sao Paulo, Sao Paulo, Brazil, 3Clinical Immunology and Allergy Division, University of Sao Paulo, Sao Paulo, Brazil.

RATIONALE: Betalactam antibiotics (BLs) are primarily responsible for hypersensitivity drug reactions (HDR) in developed countries, although in Brazil they are less frequent than non-steroidal anti-inflammatory drugs reactions. Much of these BLs reactions are not reproduced in drug provocation tests (DPT), suggesting another agent was involved or the presence of co-factors such as concomitant viral infection. We evaluated results of DPT in patients who sought assistance for HDR with BLs.

METHODS: Retrospective observational study through analysis of medical records of patients treated between 2005 to 2012 with a history of HDR to BLs. We analyzed data using the ENDA questionnaire about epidemiological profile, medications involved, type of reaction and results of DPTs.

RESULTS: We evaluated 84 patients (91.7% female). Aminopenicillins were cited by 52 patients (61.9%) and 23.8% reported reactions to cephalosporins. No patient reported reaction to carbapenems or monobactams and 14.3% reported previous reactions to both aminopenicillins and cephalosporins. The skin was affected in 94% of the sample (75% urticaria and/or angioedema) and 59.5% of patients had an immediate reaction. Only 3 patients had a positive DPT (3.6%), two of which reacted to placebo (pruritus and wheals).

CONCLUSIONS: Incidence of allergy to BLs is low in Brazil. Many of the patients with a history of RHD to BLs are afraid of a re-exposure, even under medical supervision in a hospital setting, and often react to other drugs by the placebo effect. The DPT is essential to avoid unnecessary exclusion of this class of drugs and should always be controlled with placebo to prevent misinterpretation.

922 Prevalence Of Reported Penicillin Allergy In a Tertiary Allergy Immunology Clinic In The United States
Dr. Sara M. May, MD, Andrew Nickels, MD, Dr. Michael Park, MD, FAAAAI; Mayo Clinic, Rochester, MN.

RATIONALE: It has been reported that benzylpenicilloyl is no longer the most relevant hapten of the penicillin drugs and therefore amoxicillin and other penicillin derivatives should be used for skin testing. European studies documented that adverse reactions were reported to amoxicillin in 64.8% cases and reactions to penicillin and benzylpenicillin 3.8% and 2.8% respectively. This chart review was conducted to determine if this similar trend occurred in a tertiary clinic in the United States.

METHODS: Retrospective chart review of all patients seen in a tertiary care Allergy/Immunology clinic evaluated with a reported penicillin allergy from January 2011 through current time. Patient records were incomplete and these data were excluded.

RESULTS: During this time, 3494 patients were identified and 7 patients were excluded. Demographics: 2269 (65.1%) female, 1217 (34.9%) male. Mean age was 53.4 years (SD +/- 18.6 years). Of these patients, 2,672 (76.7%) reported a penicillin allergy, 620 (17.8%) reported an allergy to amoxicillin, 147 (4.2%) reported an allergy to other β-lactam based antibiotics. Eighty five patients reported an allergy to both penicillin and amoxicillin. Skin testing was positive in 38 (1.1%) patients; 26 to benzylpenicilloyl and/or minor determinants, 12 to amoxicillin and 1 to both.

CONCLUSIONS: We demonstrate that adverse drug reactions to penicillin are still reported more frequently than to other penicillin derivatives in the United States. Therefore, skin testing with benzylpenicilloyl and minor determinants are still essential in the evaluation of penicillin allergy.
Successful Oxacillin Desensitization With Interrupted Dosing Versus Continuous Infusion

Dr. Melinda Braskett, MD¹, Dr. Monika Saeedian, MD²; ¹UCLA Med Center - Mattel Children’s Hospital, Los Angeles, CA, ²University of California, Los Angeles.

RATIONALE: We present a case with a failed desensitization to oxacillin using a continuous infusion that was successful with q4h dosing and illustrates the importance of testing for penicillin minor determinants.

METHODS: Initial oxacillin desensitization was performed with target dose of 12g/day continuous infusion. Solutions at 0.24, 2.4 and 24 mg/ml were made and the rate was doubled q15 minutes until target dose was achieved. Second desensitization was performed with target dose of 2g q4h. Solutions at 0.08, 0.8, and 8 mg/ml were made and the rate was doubled q15 minutes until target dose was achieved.

RESULTS: 35 yo female with history of asthma and urticaria with penicillin presented with MSSA osteomyelitis failing cephalosporins. Penicillin skin test demonstrated positivity to minor determinants. Initial oxacillin desensitization was performed, with target goal of 12g/day. Two hours after completion she had diffuse urticaaria. She required diphenhydramine around the clock to tolerate the oxacillin infusion. We speculated these findings were artifact of slow infusion rate, therefore a repeat desensitization was performed with target goal of 2g q4h. Patient experienced wheezing and pruritus during the last step. She responded to methylprednisone and albuterol and successfully completed the protocol. No post-desensitization complications followed and she tolerated subsequent doses.

CONCLUSIONS: Although once daily continuous infusion for antibiotic dosing has multiple advantages including increased time at MIC and decreased requirement for nursing, it may not be or be attainable for some drug allergy patients, possibly due to a concentration dependent mechanism. Additionally, this case illustrates the importance of testing for minor determinants.

IgE To Penicillins With Different Specificities Can Be Identified By a Multiepitope Macromolecule. Bihaptenic Penicillin Structures and IgE Specificities

Dr. Adriana Ariza, PhD¹, Dr. Cristobalina Mayorga, PhD², Dr. Maria José Jose Torres, MD, PhD³, Dr. Maria Isabel Montaínez, PhD³, Dr. Ezequiel Pérez-Inestrosa, PhD⁴, Dr. Antonio Jesús Ruiz-Sánchez, PhD⁴, Dr. Rosa María Rodríguez-Guéant, MD, PhD⁴, Dr. Tahía Fernández, PhD⁴, Dr. Jean Louis Guéant⁵, Dr. Miguel Blanca, MD, PhD⁶; ¹Research Laboratory for Allergic Diseases, Hospital Regional Universitario de Malaga - FIMABIS-IBIMA, Malaga, Spain, ²Research Laboratory for Allergic Diseases, Hospital Regional Universitario de Malaga - IBIMA, Malaga, Spain, ³Allergy Service, Carlos Haya Hospital, Málaga, Spain, ⁴Andalusian Centre for Nanomedicine and Biotechnology, BIONAND, Malaga, Spain, ⁵Allergy Service, Carlos Haya Hospital, Málaga, Spain, ⁶Andalusian Centre for Nanomedicine and Biotechnology-BIONAND, and Department of Organic Chemistry, Faculty of Sciences, University of Malaga, Málaga, Spain, ⁷Laboratory of Cellular and Molecular Pathology in Nutrition, Faculty of Medicine, University of Nancy, Nancy, France, ⁸Research Laboratory - FIMABIS Foundation, Málaga, Spain.

RATIONALE: Though IgE can recognize the penicilloy determinant or the side chain structure of penicillins in immediate hypersensitivity reactions, the specificity of the IgE cannot be discriminated from the clinical history and skin testing. The aim of this study was to develop a radioimmunoassay system to detect IgE antibodies of different specificities.

METHODS: Poly-L-lysine (PLL) was bound to cellulose discs and conjugated with increasing concentrations of benzylpenicillin (BP), amoxicillin (AX), or both drugs in order to make BPO-PLL, AXO-PLL and BPO-AXO-PLL solid phases, respectively. These were used in direct RAST and RAST inhibition studies to verify the structures recognized by serum IgE antibodies from penicillin-allergic patients.

RESULTS: IgE antibodies from penicillin-allergic patients that recognized the nuclear part and the side chain structure of penicillins were detected using BPO-AXO-PLL solid phases. Single (one hapten) or combined (two hapten) solid phases produced similar results of RAST inhibition studies. Individual sera that recognized the common nuclear determinant and the side chain specific determinant showed the same values of RAST positivity than sera from patients, which recognized only one determinant.

CONCLUSIONS: The use of a solid phase with a carrier molecule conjugated with two determinants (AX and BP) is helpful to recognize IgE antibodies against either of these determinants, achieving the same positivity as using a solid phase with a single hapten. These combined solid phases are useful for screening sera with different specificities.

Cephalosporin Prescribing Habits In Penicillin Allergic Patients

Dr. Shannon D. Tiedeken, MD¹, Dr. Christopher Chang, MD, PhD, FAAAAI², Dr. Gang Ye, PhD³; ¹Nemours, A.I. duPont Hospital for Children, Conshohocken, PA, ²Alfred I duPont Hospital for Children, Wilmington, DE, ³Nemours, Orlando, FL.

RATIONALE: Cross reactivity between penicillins and cephalosporins has been estimated to be up to 20%. However, more recent studies on 3rd and 4th generation cephalosporins have shown limited cross reactivity with penicillin. Because of the risk of anaphylaxis from cephalosporin use in penicillin allergic patients, it has been recommended that penicillin allergic patients avoid cephalosporins as well, until they have successfully passed a drug challenge. But is common practice concordant with these guidelines?

METHODS: Pediatricians and pediatric residents completed an anonymous online survey. The survey included questions related to physicians’ cephalosporin prescribing habits based on the type and severity of reaction, clinical experience, level of training, and alternate antibiotic of choice.

RESULTS: 75 physicians completed the survey, including 38 pediatricians and 37 resident physicians. 96% of physicians would consider prescribing cephalosporins in penicillin allergic patients without further testing. Macrolides (72%) were the alternative drug of choice. 96% and 77% of physicians prescribe cephalosporins despite a reported history of gastrointestinal upset or rash after penicillin exposure, respectively. Pediatricians appeared to be less likely to prescribe cephalosporins in well-documented penicillin allergic patients than resident pediatricians, but the data was only marginal significant (OR = 2.97, p = 0.05). Similarly, PGY-3 resident pediatricians were less likely to prescribe than their PGY-1 counterparts.

CONCLUSIONS: More experienced physicians were likely to avoid prescribing cephalosporins to penicillin allergic patients with a well-documented allergy. Several factors may influence this trend including clinical experience, litigious exposure, and continuing medical education. Further investigation can help understand these trends and further assist in appropriate antibiotic prescription.
926 Radiocontrast Media Reactions: Rectifying Misconceptions About Shellfish Allergy and Iodine “Allergy” In An Academic Institution
Dr. Amber N. Pepper, MD1, Dr. Emma Westermann-Clark, MD, MA1, Dr. Necessi Talejea, MD2, Dr. Richard F. Lockey, MD, MD1, 1Department of Internal Medicine, University of South Florida Morsani College of Medicine, Tampa, FL, 2Division of Allergy and Immunology, Department of Internal Medicine, University of South Florida Morsani College of Medicine and James A. Haley Veterans’ Affairs Hospital, Tampa, FL.
RATIONALE: Healthcare professionals (HP) perpetuate misconceptions regarding radiocontrast media (RCM) reactions and their relationship to shellfish allergy and iodine “allergy.” The impact of an educational intervention was tested to dispel these myths.
METHODS: A survey was administered before and after separate grand rounds lectures about anaphylaxis to internal medicine, emergency medicine, pediatrics, and radiology audiences at the University of South Florida Morsani College of Medicine. Pre- and post-test responses were analyzed to assess the impact of the intervention on beliefs about RCM reactions and their perceived relationship to shellfish allergy and iodine “allergy.” Training level and specialty were assessed. Institutional review board approval and informed consent were obtained.
RESULTS: One hundred and thirty-five (135) HP attended the grand rounds; 105 completed both pre- and post-tests, 7 only the pre-test, and 23 arrived too late to complete the pre-test or declined to participate. The mean pre- and post-test correct response scores were 39% and 90%, respectively (p<0.005). Pre-test correct response scores for shellfish and iodine questions were 44% and 27%, respectively, indicating higher baseline knowledge about shellfish allergy than iodine “allergy” (p<0.005). The intervention had a greater impact on respondents’ knowledge about iodine “allergy” than shellfish allergy, most likely due to the difference in baseline knowledge (p<0.005). Pre-test correct response scores for emergency medicine (54%) and internal medicine (31%) differed significantly (p=0.033). There was no statistically significant correlation with training levels.
CONCLUSIONS: An educational intervention helps rectify misconceptions among HP about RCM reactions and their perceived relationship to shellfish allergy and iodine “allergy.”

927 Clinical Predictors Of The Outcome Of Medication Challenges
Dr. Farah Khan, DO1,2, Dr. Christopher Chang, MD, PhD, FAAAAI2, Dr. Gang Ye, PhD3, 1Thomas Jefferson University Hospital, Philadelphia, PA, 2Alfred I duPont Hospital for Children, Wilmington, DE, 3Novours, Orlando, FL.
RATIONALE: A medication challenge is performed to confirm or rule out an IgE-mediated allergy to a medication. It is done in selected patients when the suspicion based on clinical history is low. Despite this, anaphylaxis is the most significant risk of a medication challenge. We conducted this study to identify clinical predictors of the outcome of medication challenge to help determine which patients are at risk of failing.
METHODS: We reviewed medical records of patients who underwent a medication challenge at Al duPont Hospital for Children. 2-18 year olds who had challenges to penicillins, cephalosporins, azithromycin, local anesthetics, and other medications were included. A multiple logistic regression model was used to evaluate the following factors as independent predictors of successful medication challenge: medication, age when reaction occurred, age at challenge, gender, time between medication ingestion and reaction, type of reaction, coexisting medication allergy, and atopy.
RESULTS: 48 challenges were evaluated, including 25 penicillin (19 passed), 5 cephalosporin (4 passed), 6 azithromycin (5 passed), 3 topical anesthetics (0 passed) and 7 miscellaneous medications (7 passed). Overall, 37/48 passed the challenge. A positive association was found between a failed challenge and time between ingestion and reaction. Immediate reactions (onset <1 day after medication exposure) had a 50%-chance of failing (p= 0.005). In addition, patients with multiple medication allergies had a 35% chance of failing (p=0.04).
CONCLUSIONS: This study suggests that early onset of reaction after medication exposure and history of multiple medication allergies may be reliable predictors of medication challenge outcomes.

928 Clinical Experience With Oxaliplatin (O) Desensitization (OD): A Case Series
Dr. Adam Updegraff, DO1, Dr. Devang R. Doshi, MD, FAAAAI2, 1University of South Florida, Tampa, FL, 2William Beaumont Hospital, Royal Oak, MI.
RATIONALE: Oxaliplatin is a platinum based cancer drug, and hypersensitivity reactions to O limit the ability to receive chemotherapy.
METHODS: This is a retrospective analysis from May 2008 to October 2012 of patients who underwent OD after experiencing a hypersensitivity or severe adverse reaction to O. Each OD consisted of four infusions. Patients received intravenous (IV) diphenhydramine, 50mg; fomotidine, 20mg; dexamethasone, 50mg; and oral acetylsalicylic, 625mg an hour prior to the OD. The total O dose was based on body surface area. Subsequently, 1/1000th of the total O was added to 100mL of 0.9% normal saline (NS) and infused over one hour; 1/100th of remaining O in 100mL NS was infused over the second hour; 1/10th of the remaining O in 100mL NS was infused over the third and fourth hours; the remaining O in 500mL was infused over the fifth and sixth hours. An additional dose of dexamethasone, 50mg IV was given prior to the final infusion.
RESULTS: 29 patients underwent one or more OD (total, 85). One did not complete the OD due to flushing, tachycardia, and wheezing. The remaining 84/85 (99%) were successful. 60/85 (71%) reported no side effects. 24/85 (28%) experienced rash, flushing, palmar erythema or shortness of breath, all but one of which resolved following diphenhydramine, 50mg IV. One patient received epinephrine, 0.3mg IM, due to throat tightness and dyspnea with resolution of symptoms.
CONCLUSIONS: OD, using a standard protocol, provides a safe and effective method for patients with hypersensitivity or severe adverse reactions to O to receive chemotherapy.

929 Clinical Value Of a Negative Skin Test To Contrast Radio Media (CR) In Further Exposures
Dr. Luiz C. G. Arcanjo, Dr. Tania M. T. Gonzalez, Flavia C. Loyola, Matheus Ribeiro, Alfredo Alves Neto, Tatiana L. Carvalho, Dr. Jose Luiz M. Rios, MD, PhD; Policlinica Geral do Rio de Janeiro, Brazil.
RATIONALE: Adverse reactions after administration of radiocontrast (RC) are common and can be caused by toxicity of their components or mediated by the immune system. Recent studies highlight the involvement of immune system reactions after RC using. Skin testing (ST) has shown a good clinical value in hypersensitivity reactions, helping the diagnosis of IgE-mediated mechanisms, and lymphocytes mediated reactions (delayed reactions). The objective is to demonstrate the negative predictive value of ST in performing safety procedures with administration of RC.
METHODS: Retrospective observational study of records of patients who underwent allergy testing for RC, in PGRJ, from January 2010 to August 2013. A recent telephone contact with these patients checked if they underwent further procedures with RC and if any complication occurred.
RESULTS: Forty two skin tests for RC were performed. 36 women (81%): ten with non-ionic contrast (9 iobitrol, 1 ioversol), 26 with ionic contrast (meglumina) and 5 fluoresceina. Only one test was positive (2.3%). Twenty two patients with negative ST were phone contacted: 14 (34.4 %) underwent new RC procedures and showed no adverse reactions. 8 (19.5%) have not been exposed to the RC after the test. Only 1 (2.43 %) patient, with negative test, presented a minor reaction 12 hours after RC administration (rash). Twenty patients could not be contacted. The negative predictive value (NPV) of the test was 92.8%.
CONCLUSIONS: ST reaction to the RC has a NPV of 92.8 % and even the reaction presented was not severe. More tests are necessary to corroborate these results.
Perioperative Reactions: Are They So Infrequent?

Dr. Claude M. Urbain, MD1, Dr. Alberto Lafuente, MD2, Dr. Gracia Javaloyes, MD, PhD3, Dr. Paula Cabrera-Freitag, MD, PhD1, Dr. Juan De La Borbolla Moran, MD1, Dr. M. Jose Goikoetxea, PhD, MD1, Dr. Rafael Moncada, MD2, Dr. Maria L. Sanz, MD, PhD1, Dr. Marta M. Ferrer, MD, PhD, FAAAAI4, Dr. Gabriel Gastaminza, MD, PhD1, 1Department of Allergy, Clinica Universidad de Navarra, Spain, 2Department of Anesthesia, Clinica Universidad de Navarra, Spain, 3Department of Allergy, Clinica Universidad de Navarra, Spain, Pamplona, Spain, 4Department of Allergy, Clinica Universidad de Navarra, Pamplona, Spain.

RATIONALE: The incidence of perioperative hypersensitivity reactions reported in the literature is highly variable, ranging from 1/1361 to 1/20000 procedures in different countries in Europe and Oceania. The aim of this study was to determine the incidence of allergic reactions during general anesthesia in Clinica Universidad de Navarra and to establish the frequency of the allergic reactions occurring for each of the drugs used.

METHODS: Patients suffering a reaction suggestive of hypersensitivity over a 30-month period (Feb-2008 to Aug-2010), that occurred during a procedure with general anesthesia and intubation or regional anesthesia with sedation were included. Prick and intradermal skin tests were performed. The study was approved by local Ethics Committee.

RESULTS: A total of 16946 surgical procedures were performed (53% males, mean age 51.6 years). Forty-four periesthetic reactions were recorded (ratio 1/385). Fifty-seven percent occurred during the induction of anesthesia (48% grade 1, 20% grade 2, 32% grade 3). Thirty-four percent had a rash as the sole manifestation, detecting an IgE-mediated mechanism in one-third of these. Five procedures (11%) were suspended given the severity of the reactions. Fifty percent were IgE-mediated reactions and in 7% a non-IgE agent was found (cold and NSAID-intolerance). Frequencies of reactions for different drugs were: protamine (1/468), cisatracurium (1/1388), amoxicillin-clavulanate (1/1968), atracurium (1/2039), diprynone (1/1519).

CONCLUSIONS: Periesthetic reactions were more frequent than previously reported. It is important to perform an allergological study to all patients suffering suspicious hypersensitive periesthetic reaction, including those with mild symptoms, since a substantial number are IgE-mediated reactions.

Causes Of Perioperative Allergic Reactions – Our Experience In The Last Two Years

Dr. Lourdes Arochena, MD, Mrs. Deborah Hughes, RN, Dr. Bryan N. Fernandes, MD, Dr. Marina Tsoumani, MD, Dr. Susana F. Marinho, MD, PhD; University Hospital of South Manchester NHS Foundation Trust, Manchester, United Kingdom.

RATIONALE: Allergic reactions during general anaesthesia (GA) are frequent and usually due to one of several drugs. The study of these patients is essential to prevent future reactions, but not all patients are referred to the Allergy Clinic to clarify the reaction.

METHODS: Retrospective report of all patients referred to our Centre through a specific pathway, from September 2011 to August 2013. Skin prick, intradermal and drug provocation tests undertaken as appropriate.

RESULTS: 18 patients investigated; mean age 58.05 ± 9.60 years. Surgeries varied (6 orthopedic, 2 laparotomies, 2 cardiac, 2 laparoscopies, 1 cystoscopy, 1 septoplasty, 1 fat graft, 1 angiogram, 1 thoracotomy, 1 ERCP). Most patients received NMBAs, propofol, fentanyl and midazolam; chlorhexidine was used in 13 patients, povidone iodine in 6; and latex in 14. Additionally, some received antibiotics (9), local anaesthetics (4), etomidate (3), contrast media (2), ondansetron (1) and diclofenac (1). Reactions comprised anaphylaxis (7), urticaria (5), hypotension (2), facial angioedema (3) and dyspnoea (1). Mast cell tryptase was raised in 4 patients (mean 40.4 μg/l, normal in 1, not measured in 13. Specific IgE to drugs were negative in all but 1 patient, positive to suxamethonium (1.2kua/l). Allergy was confirmed in 9 patients, dermatoglyphism impeded study in 2, pharmacological cause was observed in 1 and cause was not identified in 6. Causes were NMBas in 5 patients and midazolam in 3, chlorhexidine (2), povidone iodine (1), and ondansetron (1).

CONCLUSIONS: GA allergy investigation allowed identification of a cause in most patients, enabling them to have further anaesthesia with safe alternatives.
933 A New In Vitro Flow Cytometry Method For Detection Of Delayed Drug Sensitization To Local Anesthetics. The Lymphocyte Activation Test (LAT)
Dr. Massimo Caruso, PhD, FIT, AAAAI 1, Dr. Rosalia Emma, Dr. Raffaella Lizzio, Prof. Riccardo Polosa, MD, PhD, FAAAAI; University of Catania, Catania, Italy.
RATIONALE: For the proper assessment of delayed anaphylactic reaction to drugs (DAR) there is a lack of reliable laboratory methods, besides the lymphocyte transformation test (LTT), but it requires 6-7 days of cells incubation and the use of radioactive isotopes, with obvious limitations in its diffusion. It would be useful to have a reliable in vitro test to screen patients quickly.
METHODS: Twenty-six patients addressed by dentists for DAR to local anesthetics (LAs) Lidocaine, Mepivacaine and Articaine were studied by LAT, with 3 control samples: 5 healthy donors (HD), 5 atopic subjects (AS) and 5 subjects with immediate reaction (IRS) to LAs. WBCs were incubated at 37°C for 12-16 hours with LAs and a calcium/brefeldin A enriched buffer, fixed-permeabilized and labeled by fluorescent mAbs to CD4/CD69 and intracellular IL-4 to flow-cytometric analysis. Stimulation index (SI) between stimulated and non-stimulated CD69-IL4 TH-positive cells was calculated. SI≥2 was considered as positive.
RESULTS: HD, AS and IRS showed no-positivity to LAT while the 26 subjects referring DAR to LAs, 9 showed positivity by LAT (34,61%), of which 4 on 10 subjects to Lidocaine (40%), 2 on 9 subjects to Mepivacaine (22.22%) and 3 on 7 subjects to Articaine (42.85%).
CONCLUSIONS: LAT vs LTT result extremely fast, simple, repeatable and operators-safe. The data evidenced that LAT have high specificity and good sensitivity. A comparison with the LTT should be done, even the gaps in specificity of LTT. Our preliminary results are very promising and LAT could represent an useful support for the prevention of perioperative adverse reactions.

934 Utility Of ICD-9-CM Codes For Identification Of Allergic Drug Reactions
Dr. Rebecca Saff, MD, PhD 1, Dr. Carlos Camargo, Jr. MD, DrPh 1, Dr. Susan A. Rudders, MD 2, Dr. Sunday Clark, MPH, ScD 1, Dr. Aidan Long, MD, FAAAAI 1, Dr. Aleena Banerji, MD 1; Division of Rheumatology, Allergy, and Immunology, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, 2Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, 3Department of Pediatrics, Rhode Island Hospital, Alpert School of Medicine at Brown University, Providence, RI, 4Department of Emergency Medicine, Weill Cornell Medical College, New York, NY.
RATIONALE: Data on the epidemiology of drug allergy is limited due to the difficulty in identifying these patients for study. Identifying cases of drug allergy by ICD-9-CM codes is a potentially valuable approach but has the limitation of yielding incomplete or inaccurate information as it relies on the coding of each individual physician evaluating the patient. Our objective was to better understand the utility of ICD-9-CM codes for identification of allergic drug reactions.
METHODS: We reviewed medical records of all patients treated in the emergency department of three Boston medical centers between January 1, 2001, to December 31, 2006, who were assigned ICD-9-CM codes for anaphylaxis, urticaria, angioedema, and allergy.
RESULTS: Among 5994 charts, we identified 861 (14%) allergic drug reactions. For each major ICD-9-CM code, the percentage with allergic drug reaction was: allergic urticaria (708.0), 17%; urticaria unspecified (708.9), 9%; anaphylaxis (995.0), 26%; angioneurotic edema (995.1), 18%; unspecified adverse effect due to unspecified drug (995.2), 35%; and allergy unspecified (995.3), 16%. In adults, 28% of drug reactions were attributed to antibiotics, 13% to ACE inhibitors, and 7% to NSAIDs including aspirin. In children, drug reactions were predominantly attributed to antibiotics (48%).
CONCLUSIONS: ICD-9-CM allergy codes can be used to identify allergic drug reactions but a broad set of codes must be included. Further study of these codes in the inpatient and outpatient setting is necessary to better understand the utility of ICD-9-CM codes for improving epidemiology research on drug allergy.

935 Vancomycin Use and Vancomycin Resistant Enterococcus Are Increased In Patients With Reported Penicillin Allergy
Dr. Vinitha Reddy, MD 1, Dr. Faoud T. Ishmael, MD, PhD, FAAAAI 2; 1Penn State Hershey Medical Center, Hershey, PA, 2The Pennsylvania State University College of Medicine, Hershey, PA.
RATIONALE: Penicillin (PCN) allergy has a reported high prevalence and occurs in approximately 10% of the population. Patients with reported PCN allergy are often treated with alternative antibiotics, which may lead to resistant infections such as Vancomycin Resistant Enterococcus (VRE). We hypothesized that patients with reported PCN allergy are more likely to receive vancomycin, and that vancomycin-related complications are more common.
METHODS: After IRB approval, a list was compiled of both hospitalized patients who received vancomycin as well as patients with VRE infection. Retrospective review of electronic records was performed from hospitalized patients of all ages in 2011 to obtain antibiotic allergy information.
RESULTS: Over a 12 month period there were a total of 6,720 patients who were reported as PCN allergic and 89,352 patients who were non PCN allergic. Of the reported PCN allergic patients, 17% patients compared to 3.9% non PCN allergic patients received vancomycin (RR 4.25, CI 3.99-4.53, p<0.0001). Of 138 patients with VRE, 78% received vancomycin. Of these VRE patients, 28% were reported as PCN allergic and 72% were non allergic. All of the reported PCN allergic VRE patients received vancomycin compared to only 85% non-PCN allergic VRE patients.
CONCLUSIONS: PCN allergy is associated with increased risk of vancomycin use and VRE infection. Future studies are needed to determine whether inpatient penicillin allergy testing can improve antibiotic utilization.

936 Detection Of Caustive Drugs Using Measurement Of Interferon-αwith Quantiferon-TB Gold Test In Severe Drug Allergy: Preliminary Study
Dr. Young-Hee Nam, MD 1, Dr. Kyong-Hee Kim, MD 2, Dr. Dong Sub Jeon, MD 1, Dr. Hye-Won Lee, MD 3, Hee-Joo Nam 4, Mr. Soo-Keol Lee, MD 5; 1Department of Internal Medicine, College of Medicine, Dong-A University, Busan, South Korea, 2Department of Laboratory Medicine, College of Medicine, Dong-A University, South Korea, 3Department of Internal Medicine, College of Medicine, Dong-A University, South Korea, 4Department of Pharmacy, Dong-A University Hospital, South Korea, 5Dong-A University College of Medicine, Pusan, South Korea.
RATIONALE: Delayed-type drug hypersensitivity reactions (DHT) is very heterogeneous and T-cell mediated. Detection of drug-specific T cells in patients with DHT is important to diagnose drug allergy. This study was performed to evaluate the diagnostic role of drug-induced release of interferon (IFN)-γ using Quantiferon-TB Gold (QFT) in severe drug allergy.
METHODS: Eleven patients with DHS in Dong-A university hospital were recruited. We collected heparinized whole blood of subjects and incubated with drugs at 37°C, then harvest the plasma. IFN-γ in blood was measured by using QFT test.
RESULTS: The clinical manifestations of the study subjects were DRESS (n=8), SJS syndrome (n=2), and TEN (n=1). The causative drugs based on the clinical history and medical records were antibiotics (n=5), anticonvulsants (n=3), antituberculosis drug (n=3), and NSAIDs (n=1). A total of 67 were tested with different concentration and incubation time of drugs. Five patients showed positive responses (12 of 67 tests, 17.9%), which had a tendency to be more sensitive to higher concentration and longer incubation time of drugs.
CONCLUSIONS: Drug-specific IFN-γ was detected by using QFT in severe drug allergy. Further studies are needed to evaluate the role of this method for diagnosis of DHS in more patients and with various drugs.
Successful Rapid Desensitization Glatiramer Acetate In a Patient With Multiple Sclerosis

Dr. Ekaterini I. Syrigou, PhD 1, Dr. Photis Psarros 2; 1Department of Allergy, “Sotiria” General Hospital, Athens, Greece, 2Department of Allergy, Athens Naval Hospital, Greece and Prof. Konstantinos Syrigos, Athens School of Medicine, Greece.

RATIONALE: Glatiramer acetate (GA) is an injectable immunomodulatory drug currently used for reducing the frequency of relapses in patients with multiple sclerosis (MS). Although long-term studies have suggested that GA is a generally safe, effective and well tolerated drug, discontinuation of treatment may be required in up to 10% of cases due to severe systemic postinjection reactions. Notably, there are only sparse data on desensitization protocols for patients with hypersensitivity to GA.

METHODS: A 51-year-old female with multiple sclerosis treated with GA was referred to our department for evaluation of chronic urticaria. Allergy workup, including percutaneous and intradermal skin testing, confirmed the diagnosis of hypersensitivity to GA and the patient underwent a rapid (3-hour) desensitization procedure. Desensitization was performed by subcutaneous administration of increasing dosages of GA, at a starting dose of 20µg followed by gradual dose escalation up to 20mg.

RESULTS: The desensitization procedure was well tolerated with no adverse events. The patient was able to resume GA treatment with no recurrence of any hypersensitivity reaction during a follow up period of 3 months.

CONCLUSIONS: This case illustrates that rapid subcutaneous desensitization may allow continuation of GA treatment in patients with a history of systemic postinjection reactions. However, the safety and effectiveness of this protocol should be further validated in future studies.

Hypersensitivity Reaction To Denosumab In Patient With Osteoporosis: Desensitization Methodology

Dr. Antonio Foncubierta, MD, PhD, MPH 1, 2, Dr. Diego Gutierrez, MD, PhD 1, Dr. Fermín Medina, MD 3, Dr. Salvador Fernandez, MD, PhD 3, Dr. Maria Jose Fernandez 4, Dr. Juan Luis Anguita, MD 5, 4Servicio Andaluz de Salud: UGC Joaquin Pece, 5Universidad de Cadiz, 3Hospital Universitario Puerta del Mar, 4Hospital Universitario Carlos Haya, 5Complejo Hospitalario de Jaen.

RATIONALE: Denosumab is a human monoclonal antibody with a high affinity and specificity for RANKL (Receptor activator of nuclear factor Kappa B), preventing it from activating its receptor, RANK, on the surface of osteoclasts and their precursors. We report the case of a 65-year-old woman with a history of generalised osteoporosis, intense bone pain and risk of fracture, referred to Allergy Department after failed treatments for osteoporosis with bisphosphonate therapy, who experienced an adverse reaction to Denosumab one week after the first dose of the drug, resulting in generalised urticaria, bilateral eyelid angioedema and a pruriginous lesion at the injection site.

METHODS: We performed skin prick tests for neumoallergens and latex, and further prick tests with undiluted and 1:10 and 1:100 dilutions of Denosumab, which were repeated on 10 control subjects who had had no prior contact with the drug; patch test responses to Denosumab were performed if assessed by an adequate anamnesis.

RESULTS: The skin prick tests for neumoallergens and latex were negative in the patient with an allergy to Denosumab and in the control group of healthy subjects. Total IgE was below 100 kU/l and specific IgE tests were negative. The patch test responses were negative. An 8-step desensitization protocol was implemented.

CONCLUSIONS: This case illustrates that rapid subcutaneous desensitization may allow continuation of GA treatment in patients with a history of systemic postinjection reactions. However, the safety and effectiveness of this protocol should be further validated in future studies.

Patient With Severe Primary IGF-I Deficit and Mecasermin Allergy: Desensitization Methodology

Dr. Diego Gutierrez, MD, PhD 1, Dr. Antonio Foncubierta, MD, PhD, MPH 2, Alfonso M. Lechuga, MD, PhD 1, Dr. Maria Jose Fernandez 4, Juan Luis Anguita, MD, PhD 5, Jose Luis Lechuga, MD, PhD 3, Hospital Universitario Puerta del Mar, 5Servicio Andalus de Salud: UGC Joaquín Pece, 4Universidad de Cadiz, 3Complejo Hospitalario de Jaen.

RATIONALE: Allergic reactions have been reported in approximately 8% of patients receiving mecasermin. However, only twice have such reactions been published in patients with severe primary IGF-I deficit. We report a patient with severe primary IGF-I deficit and a history of respiratory and food allergies who developed raised itchy wheals on legs, arms and thorax on the tenth day of treatment.

METHODS: Full allergy testing was carried out, including skin prick test with 10 mg/ml mecasermin, intradermal injections with 1:10 and 1:100 dilutions of the drug, total and specific IgE measurements. We performed a desensitization regimen on eight steps with increasing concentrations of mecasermin at 15 minutes intervals, up to the 10 mg/ml concentration of the commercial preparation. The protocol was implemented at 0.12 mg/kg which is the maximum required by the patient for growth optimization. Premedication with deflazacort, deschloroperefrin and montelukast was employed one hour prior to implementation of the protocol.

RESULTS: The skin prick test were positive to house dust mite. Total IgE was upper 100 kU/l and specific IgE tests were positive to house dust mite and egg white. The prick test with 10 mg/ml mecasermin and intradermal injections with 1:10 and 1:100 dilutions of the drug were negative. The 8-step desensitization protocol, was completed in two hours. The patient has now been under therapy for 4 weeks, with a notorious growth response, and no further allergic reactions of any kind.

CONCLUSIONS: We present the first successful desensitization protocol to mecasermin, in a patient with severe IGF-I deficiency.
Quinolones Allergy In An Allergy Unit. Our Experience In 3 Years

Dr. Tamara Fernandez-Teruel1, Gabriela Zambrano, MD2, Celia Pinto1, Beatriz Ameiro, MD3, Dr. Roberto Pelta1, Manuel De Barrio1; 1Department of Allergy, Gregorio Marañón University Hospital, Madrid, Spain, 2Department of Allergy, Gregorio Marañón University Hospital, Madrid, Spain, Spain.

Rationale: Quinolones form a family of synthetic antibiotics. The aim of this study was to determine the incidence, type of reaction, responsible drug, diagnosis and cross-reactivity to this drugs.

Methods: A retrospective and descriptive study was performed in our Allergy Service from January 2010 to December 2012. Clinical records, data of skin tests and controlled challenge tests (CCT) were analyzed from all patients with suspected hypersensitivity reactions to Quinolones.

Results: We studied 115 adults patients with a suspected drug allergy reactions to quinolones, confirming in 45(39.1%). Immediate 24(53%) and non-immediate 21(47%) reactions. Exantheme occurred in 18(40.3%), Urticaria/Angioedema 15(33.3%), Anaphylaxis 7(15.5%), FDE 3(6.6%), and cutaneous itch 2(4.4%). Ciprofloxacin was responsible of the reaction in 42.2%, followed by Levofloxacin 33.3% and Moxifloxacin 24.5%. Intradermal tests were positive in 2(4.4%) (Levofloxacin), 29 negative. Patch test (PT) were positive in 5(11.1%) with the implicated drug (2 for Ciprofloxacin, 3 for Moxifloxacin) and negative in 9. CCT were positive in 7 (15.5%) (4 Ciprofloxacin, 2 Levofloxacin and 1 Moxifloxacin); were negative in 32. Due to patients age, comorbidity, negative tests and severity of reactions the diagnosis was based on anamnesis in 69 %. We studied cross-reactivity in 27 patients, of which 5(18.5%) have it (2 PT positives and 3 CCT positives).

Conclusions: Exanema are the most frequent reactions, and Ciprofloxacin the main quinolones involved. The diagnosis was supported by clinical history, positives skin tests and CCT. It’s important to study cross-reactivity between quinolones in order to give therapeutics options to patients.

A Successful Desensitization Protocol For Filgrastim

Brett Hronek, MD1, Anthony Kulczycki, Jr, MD, FAAAAI2; 1Washington University School of Medicine, St Louis, MO, 2Washington University School of Medicine, St. Louis, MO.

Rationale: Filgrastim (Neupogen) is a granulocyte colony-stimulating analog that stimulates the proliferation and differentiation of granulocytes used clinically to prevent or treat neutropenia in patients undergoing chemotherapy. This is the first report of a successful desensitization to filgrastim of a patient with filgrastim hypersensitivity.

Methods: This desensitization protocol was a modification of a protocol published for molgramostim.

Results: A 71 year-old man with multiple myeloma and treatment associated myelodysplastic disorder was admitted to hospital for a bone marrow transplant on a study protocol that required filgrastim treatment 21 days after the start of induction chemotherapy. Ten years earlier he first received filgrastim and developed chest tightness that resolved without treatment. Eight months ago he received his second course of filgrastim and developed chest tightness, palpitations, dyspnea, and wheezing 2-3 minutes after administration. He was treated with methylprednisolone and diphenhydramine intravenously with symptom resolution within one hour. The patient had already started induction chemotherapy including high-dose dexamethasone and anti-emetics, and therefore skin testing could not be performed. A 15-step desensitization protocol was performed successfully using sequential doses (µg) subcutaneously: 0.0012, 0.0024, 0.03, 0.06, 0.12, 0.3, 0.6, 1.2, 3, 6, 12, 30, 60, 120, and 255, to a final cumulative dose of 488 mcg over approximately 5 hours. He successfully received 480 mcg in one dose the following day.

Conclusions: We believe this is the first reported desensitization protocol to filgrastim. This protocol may be used in patients with hypersensitivity to filgrastim.

Are Proton Pump Inhibitors(PPI) Naive? A Case Of Drug Reaction With Eosinophilia and Systemic Symptom (DRESS) Secondary To Lansoprazole

Dr. Aidiya Uppalapati, MD1, Dr. Sindhura Gogineni, MD1, Dr. Sravantika Koneru, MBBS2, Dr. Ghassan Kamel, MD3; 1St. Louis University, St. Louis, MO, 2Mamata Medical College, 3Saint Louis University, Saint Louis.

Rationale: DRESS is a severe adverse drug induced reaction. Mortality rate is up to 10%. PPI’S are widely used. DRESS syndrome associated with PPI has been reported only in 1 case so far. We report a case of DRESS due to lansoprazole.

Methods: Case report.

Results: A 40 years old Caucasian female patient with past medical history of liver cirrhosis stage 3 secondary to alcohol was recently started on lansoprazole. A month later she was admitted with complaints of pruritis, generalized erythematous rash over the back and front of the chest, maculopapular rash over the extremities and palmar erythema. Patient was also noted to have acute kidney injury (AKI)-2.6 mg/dl, hyperbilirubinemia-22 mg/dl, acute respiratory failure requiring supplemental oxygen at admission. WBC count was noted to be elevated-17, 000 cells/mm3 with 31% bandemia. A highest absolute eosinophil count of 4300/mm3 was noted during the hospitalization. She was started on steroids, empiric antibiotics. Liver biopsy showed fatty infiltration. Skin biopsy showed perivascular inflammatory infiltrate with elevated eosinophils. Autoimmune antibodies and hepatitis work up were negative. Human herpes virus (HHV)-6 immunoglobulin G titer was elevated at 22.33(Positive >0,99). With worsening respiratory status and hypotension patient was intubated and started on vasopressors. Initial Cultures were negative but after about 2 weeks of hospital stay patient’s bronchoalveolar lavage grew aspergillus. Inspite of starting on antifungals patient died from multiorgan failure. Autopsy was also suggestive of DRESS as cause of death.

Conclusions: PPI’s may be naïve. They can cause significant hypersensitivity reactions including DRESS.

Increased Of PCT and CRP In Dress Syndrome By Two Drugs Structurally Unrelated Molecular In The Same Patient

Dr. Rafael A. Perez Arango; Ramón and Cajal University Hospital, Spain.

Rationale: DRESS syndrome is a life threatening adverse drug reaction most commonly associated with aromatic antiepileptic agents. We present a young man with two episodes of DRESS caused by two drugs structurally unrelated molecular with elevation of PCT and CRP at least on one occasion.

Methods: Clinical evaluation and blood tests including serial measurements of PCT and PCR performed to confirm the diagnosis.

Results: 35 year old man black who in 2002 given prophylactic phenytoin for seizures by cerebral tuberculoma. Three weeks after fever up to 39°C, generalized pruritis, headache, nausea and vomiting. He presented important bilateral palpebral angioedema and rash on lower limbs. Analytical: Creatinine: 1.11 (previous 0.96), eosinophils: 4.500 GPT: 210 GOT: 74 GGT: 113. Offending drug is stopped and corticosteroids started presenting clinical and laboratory improvement within days. In May 2013, during controlled oral challenge test for suspected hypersensitivity to beta-lactams, received 500 mg of amoxicillin and after 3-4 hours presented generalized hives, malaise, asthma, T: 39.1°C and hypotension maintained. Analytical: PCT: 61 PCR: 89 Eosinophils: 930. Renal and hepatic function were normal. Infectious disease was excluded. In both cases, in a few days has intense skin desquamation and improvement of analytical parameters.

Conclusions: we believe this is the first reported case of dress syndrome caused by two drugs with different chemical structure and effects debuting as infectious disease that causes elevation of inflammatory markers of severity in at least once.
Non-Immediate Skin Reactions Due To Antibiotics
Gabriela Zambrano, MD1, Dr. Tamara Fernandez2, Beatriz Ameiro, MD2, Celia Pinto, MD2, Alberto Alvarez-Perea, MD2, Manuel De Barrio, MD2, 1Department of Allergy, Gregorio Marañón University Hospital, Madrid, Spain, Spain, 2Hospital general universitario gregorio marañón, Madrid, Spain.

RATIONALE: Antibiotics have been described as a frequent cause of non-immediate skin reactions (NIR). Our goal was to determine: incidence, type of reaction, culprit drug and diagnosis of NIR to antibiotics in our service.

METHODS: A descriptive, retrospective study was performed at a third level hospital in Madrid. Electronic records from patients that consulted about possible drug hypersensitivity reactions to antibiotics from January 2010 to December 2012 were reviewed. Data of skin tests and controlled challenge tests (CCT), if performed, were analyzed.

RESULTS: During the study period, 784 patients were attended with suspected antibiotics hypersensitivity, of which 531 presented immediate reactions and 253 NIR. NIR was established in 72 patients (29%). Clinical presentations were maculopapular exanthema (54%), delayed urticaria (21%), fixed drug eruption (8%), erythema multiforme (4%), DRESS (2%), acute generalized exanthematous pustulosis (2%), others (4%). Culprit drugs were beta-lactams (41%), quinolones (27%), macrolides (14%), sulfonamides (13%), others (5%). Diagnosis was based on skin tests in 19 patients, among which 14 were intradermal (57% beta-lactams, 22% quinolones, 14% cotrimoxazole, 7% macrolides) and 5 patch test (80% quinolones, 20% betalactams). CCT turned out positive in 23 patients (48% beta-lactams, 22% macrolides, 17% quinolones, 4.3% cotrimoxazole, others 8.6%). Diagnosis was based on anamnesis in 41%, in patients with comorbidities or severe reactions with negative tests and highly suggestive anamnesis.

CONCLUSIONS: Most of NIR to antibiotics were maculopapular exanthema and urticaria. Beta-lactams was the main group involved, followed by quinolones. Although skin tests are useful, anamnesis and -in some cases- CCT are necessary to achieve a diagnosis.
948 Vitamin K Anaphylaxis Confirmed With Skin Test
Dr. Min-Hye Kim1,2, Dr. Jong-Myung Lee, MD1, 1Regional Pharmacovigilance Center, Kyungpook National University Hospital, Daegu, South Korea, 2Department of Internal Medicine, Kyungpook National University School of Medicine, Daegu, South Korea.

RATIONALE: Vitamin K (phytonadione) is one of the hemostatic agents that reverse warfarin activity. Vitamin K anaphylaxis is extremely rare and there is no case report that confirmed Vitamin K anaphylaxis with skin test. Here we report a case of vitamin K anaphylaxis confirmed with skin test.

METHODS: Skin prick test was performed with suspected causal drugs; vitamin K (1:1, 1:10 diluted solution) and tranexamic acid (1:1, 1:10 diluted solution).

RESULTS: 20-year-old male patient was administrated intravenously with vitamin K and tranexamic acid without any adverse reaction on the day of hemorrhoidectomy. Several minutes after the 2nd injection of the drugs on the next day, he felt whole body itching sensation and started to get urticaria, lip and laryngeal angioedema, dyspnea, and subsequently loss of consciousness and hypotension (SPr 50 mmHg). Skin test showed positive reactions to native vitamin K and 1:10 diluted vitamin K, and negative reactions to tranexamic acid with same concentrations. A provocation test with intravenous tranexamic acid was negative.

CONCLUSIONS: 20-year-old male patient was administrated intravenously with vitamin K and tranexamic acid without any adverse reaction on the day of hemorrhoidectomy. Several minutes after the 2nd injection of the drugs on the next day, he felt whole body itching sensation and started to get urticaria, lip and laryngeal angioedema, dyspnea, and subsequently loss of consciousness and hypotension (SPr 50 mmHg). Skin test showed positive reactions to native vitamin K and 1:10 diluted vitamin K, and negative reactions to tranexamic acid with same concentrations. A provocation test with intravenous tranexamic acid was negative.

949 Successful Rapid Induction Of Temporary Drug Tolerance To Colistimethate Sodium
Dr. Colleen S. Adkins, MD1, Dr. James Ryan Bonner, MD, FAAAA2; 1University of Alabama, Birmingham, AL, 2Alabama Allergy & Asthma Center, Birmingham, AL.

RATIONALE: In the cystic fibrosis (CF) population, use of colistin is increasingly common due to emergence of multi-drug resistant (MDR) gram negative infections; largely with Pseudomonas aeruginosa. Although immediate-type hypersensitivity to this medication is rare, in the CF population it may be more prevalent. We found only one case of a patient who was desensitized to intravenous (IV) colistin using a conservative protocol. Here we present a patient who completed a more rapid protocol for induction of temporary drug tolerance to colistimethate.

METHODS: Skin prick at 75mg/mL and intradermal testing at 0.25mg/ml was performed. To desensitize, we started with a 1:15,000 dilution of the drugs on the next day, he felt whole body itching sensation and started to get urticaria, lip and laryngeal angioedema, dyspnea, and subsequently loss of consciousness and hypotension (SPr 50 mmHg). Skin test showed positive reactions to native vitamin K and 1:10 diluted vitamin K, and negative reactions to tranexamic acid with same concentrations. A provocation test with intravenous tranexamic acid was negative.

RESULTS: 20-year-old male patient was administrated intravenously with vitamin K and tranexamic acid without any adverse reaction on the day of hemorrhoidectomy. Several minutes after the 2nd injection of the drugs on the next day, he felt whole body itching sensation and started to get urticaria, lip and laryngeal angioedema, dyspnea, and subsequently loss of consciousness and hypotension (SPr 50 mmHg). Skin test showed positive reactions to native vitamin K and 1:10 diluted vitamin K, and negative reactions to tranexamic acid with same concentrations. A provocation test with intravenous tranexamic acid was negative.

CONCLUSIONS: Skin prick test was performed with suspected causal drugs; vitamin K (1:1, 1:10 diluted solution) and tranexamic acid (1:1, 1:10 diluted solution).

950 Anaphylactic Reaction During a Folfox Scheme Administration Secondary To Calcium Folinate: A Case Report
Dr. Maria Alicia Urena Tavera, MD1, Dr. Miriam Zamora Verduga1, Mrs. Denisse Angel Pereira2, Dr. Ricardo Madrigal-Burgalea, MD3, Dr. Pilar Berges, MD, PhD3, Dr. Emilio Alvarez-Cuesta1, 1Ramón y Cajal University Hospital, Spain, 2Ramón y Cajal University Hospital, Madrid, Spain.

RATIONALE: Calcium folinate has multiple medical uses, it can be used in synergistic combination with the chemotherapy agent 5-fluorouracil in treating colon cancer. There’s no many cases of calcium folinate hypersensitivity reactions reported in the literature, either with or without positive skin tests.

METHODS: 66 years old women with colon adenocarcinoma, who was on her second chemotherapy scheme with oxaliplatin, 5-fluorouracil and calcium folinate. During her sixth administration of oxaliplatin and calcium folinate, she presented genitals, otic and scalp itching, followed by sneeze and malaise, reasons why the infusion was stopped, treating the symptoms and restarting the infusion tolerating it without reactions. The seventh administration was indicated and the patient presented the same set of symptoms, proceeding with the same protocol, but when the infusion was restarted, 30 minutes later she presented nausea and diaphoresis, stopping the infusion definitely. The patient was referred to our Allergy Division Desensitization Program and underwent risk assessment, skin testing and controlled challenge.

RESULTS: Prick and intradermal test with oxaliplatin (0.5 mg/ml and 5 mg/ml) and calcium folinate (10 mg/ml), immediate reading: Negative. Total IgE and basal tryptase: Normal - Calcium folinate controlled challenge: Positive. - Oxaliplatin controlled challenge: Negative.

CONCLUSIONS: We report an anaphylactic reaction secondary to calcium folinate. Allergy reaction secondary to calcium folinate is infrequent and concomitant administration with oxaliplatin may acts as a confusion factor. Skin testing was negative for calcium folinate in this patient. However, cases of positive skin test have been reported, therefore we recommend to perform skin testing previous to controlled challenge.
Dual Hypersensitivity To Oxaliplatin Revealed Following Rapid Drug Desensitization: A History Of Anaphylaxis and New-Onset Hemolytic Anemia

Dr. Jared Silver, MD, PhD1, Dr. Timothy Kyin, MD1, Dr. Mariana C. Castells, MD, PhD, FAAAAI2, Brigham and Women’s Hospital, Boston, MA, 1Division of Rheumatology, Allergy and Immunology, Department of Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA.

Rationale: Oxaliplatin is a third generation platinum chemotherapy for colorectal cancer within FOLFOX regimens. After multiple exposures, hypersensitivity reactions are reported and some are IgE-mediated, including anaphylaxis. Co-existing type II hypersensitivity may also develop.

Methods: A 56yo male with metastatic colon cancer treated with FOLFOX manifested disease progression and with first re-exposure to oxaliplatin developed palmar erythema and with second re-exposure developed anaphylaxis (flushing, chest pressure, and dyspnea). Oxaliplatin skin testing was positive. The patient completed six oxaliplatin desensitizations using the BWH 3-bag 12-step protocol. Breakthrough reactions included fevers, chills, palmar erythema, back pain, and SOB. During the seventh desensitization, he presented with fever, rigors, palpitations, dizziness, and EKG changes. Desensitization was discontinued.

Results: EKGs demonstrated ST/T-wave abnormalities without troponin leak. Labs demonstrated 1.8 gm/dL decrease in hemoglobin (9.8 to 8.0 gm/dL, normal range 13.5-18), normal tryptase (5.6 ng/ml), troponin leak. Labs demonstrated 1.8 gm/dL decrease in hemoglobin (9.8 to 8.0 gm/dL, normal range 13.5-18), normal tryptase (5.6 ng/ml) (reference range <1.5), elevated total bilirubin (from 1.0 mg/dL to 3.1 (normal range 0-1)), elevated LDH (865 U/L (normal range 135-225)), reduced haptoglobin (<8mg/dL (normal range 30-200)), and positive direct Coombs testing. Platelets decreased by 117 K/μL to 142 (normal range 150-450). He was diagnosed with oxaliplatin-induced autoimmune hemolytic anemia. Oxaliplatin was discontinued.

Conclusions: To our knowledge, this is the first reported case of a patient with type I hypersensitivity to oxaliplatin manifesting a type II hypersensitivity during chemotherapy desensitization. All desensitization providers should remain vigilant not only for direct drug toxicity and breakthrough type I hypersensitivity, but also for alternative forms of hypersensitivity which contraindicate agent-specific desensitization.

Urgent Patient Lenalidomide Desensitization For Delayed Hypersensitivity Reactions In 5 Patients With Multiple Myeloma

Dr. Min Jung Lee, MD1, Dr. Paige G. Wickner, MD2, Dr. Robert Schlossman, MD3, Dr. Paul Richardson, MD4, Dr. Jacob Laubach, MD5, Dr. Mariana C. Castells, MD, PhD, FAAAAI2, Brigham & Women’s Hospital, Boston, MA, 1Brigham & Women’s Hospital, Chestnut Hill, MA, 2Dana Farber Cancer Institute, Boston, MA, 3Division of Rheumatology, Allergy and Immunology, Department of Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA.

Rationale: Lenalidomide is an immunomodulatory agent used in the treatment of multiple myeloma, myelodysplastic syndrome, and mantle cell lymphoma. Rash has been reported in nearly 30% of treated patients and severe rashes require discontinuation of the drug. There are no reports of outpatient desensitizations for delayed cutaneous reactions to lenalidomide.

Methods: Five patients presenting with delayed skin-limited hypersensitivity reactions to lenalidomide consistent with generalized maculopapular rashes, urticaria, and/or angioedema greater than 3-7 days after starting treatment were evaluated for desensitization. The protocol involved doubling doses with varying day intervals. The first dose was administered in the allergy clinic. The exclusion criteria for desensitization were ≥ 2 of the following: 1) Unexplained fever 2) Mucosal or conjunctival involvement 3) Blistering rash 4) Persistent elevation of: absolute eosinophil count, liver enzymes, or other evidence of drug-induced end organ damage. Once the patient reached the maintenance dose, lenalidomide was continued daily for prescribed course.

Results: None of the patients had sustained elevations of the laboratory values mentioned above during desensitization and did not have systemic signs or symptoms. All patients were able to reach maintenance doses. We followed the patients during their treatment period and there were no adverse side effects with the reintroduction of lenalidomide.

Conclusions: The use of lenalidomide in refractory or relapsed multiple myeloma can be complicated by cutaneous hypersensitivity reaction. These delayed hypersensitivity reactions are amenable to outpatient desensitization as previously seen in desensitizations to oral allopurinol and sulfonamides.
954 Anaphylactic Reaction To Bacitracin Zinc Topical Antibiotic Ointment: A Case Report

Dr. Jake D. Lenington, MD1, Dr. David R. Scott, MD2, Dr. Anthony Montanaro, MD, FAAAI1, 1Oregon Health and Science University, Portland, OR, 2Allergy and Asthma Center of Western Colorado, 3Oregon Health Science University, Portland, OR.

RATIONALE: IgE mediated hypersensitivity reactions to topical antibiotics although uncommon have been reported in the literature. We describe a case of a 70-year old male with a history of recurrent unexplained anaphylaxis.

METHODS: A 70 yo man presented to allergy clinic with a history of three episodes of acute flushing, throat swelling, and symptoms of hypotension. His most severe episode occurred at a dermatology clinic shortly after skin cancer excision. Other episodes occurred in the patient’s home and were temporarily related to application of various topical antibiotic treatments.

RESULTS: Prior testing at an outside allergy clinic included negative skin testing to lidocaine, chlorhexidine, and latex, normal levels of C4, serum tryptase, 24-hour urinary N-Methylhistamine, 11-beta PGF2 alpha, urinary metanephrines and 5HIAA. Skin prick testing with histamine control was negative for polymixin B, neomycin sulfate, and mupirocin ointment. Bacitracin skin prick performed in duplicate in a 50% saline dilution 1:10 was positive with wheal and flare measuring 6 / 15 mm, 5.5 / 15 mm vs. histamine 6 / 12 mm.

CONCLUSIONS: The patient’s history and skin testing suggest an IgE mediated hypersensitivity reaction to bacitracin zinc ointment. Skin testing furthermore allowed for a safe alternative agent. This case supports prior reports and provides awareness for topical bacitracin zinc induced hypersensitivity reactions.

955 Withdrawn

956 Ocular Surface Disease Index (OSDI) and Pollen Counts (PC)

Mr. Spencer H. Luster1, Dr. Leonard Bielory, MD, FAAAI2; 1STARx Allergy and Asthma Center, Springfield, NJ; University of Pennsylvania, Philadelphia, PA, 2Rutgers University, New Brunswick, NJ; Robert Wood Johnson University Hospital, New Brunswick, NJ.

RATIONALE: Ocular allergies (OA) and dry eye disease clinically overlap. The OSDI, a validated questionnaire with 12 questions (3 domains) (symptoms (5 questions), visual function (4 questions), environmental triggers (3 questions)), for measuring dry eye was evaluated for correlations to PC.

METHODS: OSDI (n=47) were completed between April 2013 and June 2013, inclusive. OSDI scores were calculated for the 3 domains and the total score using the validated method for calculating overall OSDI score (sum of responses * 25/questions answered). Pollen counts (grains/m²) included total, total trees, total grass, and total weeds. OSDI domain scores were tested for PC correlation with same day, 1, 2 and 3 Days Before, and with the previous 7-Day Average. Patients were either on OA medication (OAMed(+)) (n=18) or not(-) (n=29).

RESULTS: OAMed(-) had significant positive correlations for Domain 1 vs 2 Days Before, Total Pollen (p = 0.027) and Domain 1 vs 3 Days Before, Total Pollen (p = .024). OAMed(+) had significant positive correlations for Domain 2 vs 3 Days Before, Total Pollen (p = .021) and Domain 2 vs 7 Day Average, Total Pollen (p = .047). Tree pollen was significant for the same 4 points as Total Pollen with a p-value within p = .02 of the Total Pollen p-value.

CONCLUSIONS: The OSDI in total and its third domain were not correlated to PC. OAMed(+) responses regarding “tasks” significantly correlated to PC. OAMed(-) responses regarding “visual function” significantly correlated to PC. In both cases, results were noted with PC measured at least 2-3 days prior to the OSDI being completed.

957 Efficacy and Safety Of a New Olopatadine Hydrochloride, 0.77% Ophthalmic Formulation In Patients With Allergic Conjunctivitis Using The Conjunctival Allergen Challenge (CAC) Model (NCT01479374)

Gail Torkildsen1, Thomas Macejko2, Abhijit Narvekar3, Mark Bergmann4, 1Andover Eye Associates, Andover, MA, 2Apex Eye, Fairfield, OH, 3Alcon Laboratories, Inc., Fort Worth, TX, 4Apex Eye, Cincinnati, OH.

RATIONALE: To assess the safety and efficacy of olopatadine 0.77% in patients with allergic conjunctivitis.

METHODS: This Phase 3, multicenter, double-blind, parallel-group study randomized patients (N=202; ≥18 years; ≥1 year history of allergic conjunctivitis) to olopatadine 0.77% (n=66), olopatadine 0.2% (n=68), or vehicle (n=68). Endpoints included ocular itching (OI; at 3, 5 and 7 minutes post-CAC), conjunctival redness (CR) and total redness (TR; both at 7, 15 and 20 minutes post-CAC) at onset of action and 16- and 24-hours duration of action for olopatadine 0.77% versus vehicle or olopatadine 0.2%.

RESULTS: Olopatadine 0.77% was superior (p<0.0001) to vehicle for OI at all 3 post-CAC time-points at onset, 16- and 24-hours duration of action. Least square (LS) means were: −1.52, −1.51, −1.48 (onset); −1.50, −1.47, −1.38 (16 hours); −1.58, −1.48, −1.38 (24 hours). LS means for CR were significantly lower for olopatadine 0.77% versus vehicle at all 3 post-CAC time-points at onset (p<0.0001) and 16-hours (pg<0.0015). At 24-hours, olopatadine 0.77% was superior to olopatadine 0.2% at all 3 post-CAC time-points for OI (pg<0.0149), CR (pg<0.0402) and TR (pg<0.0383). All other sign and symptom comparisons versus vehicle supported the 24-hours duration of efficacy of olopatadine 0.77% (all p<0.05). No clinically relevant differences in safety parameters or adverse events were observed between treatment groups.

CONCLUSIONS: Olopatadine 0.77% was superior to vehicle and olopatadine 0.2% for the treatment of allergic conjunctivitis. Olopatadine 0.77% has a safety profile comparable to olopatadine 0.2%. Olopatadine 0.77%’s superior efficacy versus olopatadine 0.2% for 24 hours after treatment support potential once-daily administration.
AC subjects have multiple symptoms beyond itch that differentiate them from normals: scratchiness, grittiness, burning, and soreness.

CONCLUSIONS: Ocular symptoms are proportionately more important in the more symptomatic subjects with cat allergic rhinoconjunctivitis and this should be considered when making treatment decisions.

METHODS: Pooled analysis of two double-masked, randomized, multicenter, active and placebo controlled studies using the Conjunctival Allergen Challenge (CAC™) model of allergic conjunctivitis. Subjects were randomized 1:1:1 to alcaftadine 0.25%, olopatadine 0.2%, or placebo (artificial tear). The primary efficacy measure was subject-evaluated mean ocular itching 16 hours post dose. Itch was measured at 3, 5, and 7 minutes post allergen challenge.

RESULTS: A total of 284 subjects were enrolled in the 2 studies. At 16 hours post dose, subjects treated with alcaftadine demonstrated a significantly lower overall mean itch score at the 3, 5 and 7 minute timepoints than those treated with olopatadine (alcaftadine: 0.68 versus olopatadine: 0.92, p = 0.0390). Both alcaftadine and olopatadine treated subjects achieved significantly lower mean ocular itching scores versus placebo (mean itch: 2.10, p < 0.0001), and both treatments were safe and well tolerated.

CONCLUSIONS: Once daily alcaftadine 0.25% ophthalmic solution demonstrated greater efficacy in preventing overall ocular itching compared to olopatadine 0.2% in a CAC™ model at 16 hours post dose. Alcaftadine and olopatadine both provided highly effective relief versus placebo and were safe and well tolerated.
**Cetirizine Significantly Relieves Ocular Allergy Symptoms In Subjects With Seasonal Allergic Rhinitis**

*Dr. Mitesh Patel, PharmD1, Dr. Eduardo Urdaneta, MD1, Ms. Kathleen B. Franklin, BSN, RN,2, Ms. Xiaoyan Tian, MS2, Dr. Mei-Miao Wu, Dr. PH3, Ms. Qiong Du, MS1, McNeil Consumer Healthcare, Fort Washington, PA, 3Franklin Consultants, LLC., Phoenixville, PA, Johnson & Johnson Consumer Products, China, Shanghai, China, 1J & J Consumer Products, US, Morris Plains, NJ.*

**RATIONALE:** Evaluate the efficacy of cetirizine for ocular allergy symptom relief in subjects with seasonal allergic rhinitis (SAR).

**METHODS:** Seven randomized placebo-controlled SR studies of cetirizine 5, 10, or 20 mg daily were evaluated post hoc. Total ocular symptom score (TOSS) was evaluated in each study. TOSS was sum of the severity scores for itchy eyes and watery eyes in all studies; one study also included red eyes. Individual symptom scores were rated on a 4-point scale (0 = none to 3 = severe). Subjects with baseline itchy eye scores ≥1 were included in the analysis. Changes from baseline in TOSS over a 2-week treatment period, by day in the first week, and weekly were assessed.

**RESULTS:** Over a 2-week treatment period, mean changes from baseline in TOSS for the cetirizine groups (N = 1255) ranged from -2.11 to -2.65 for 5mg, -1.26 to -2.63 for 10mg, and -2.97 for 20mg; representing improvement relative to baseline of 50% to 67.4% for 5mg, 35.1% to 62.2% for 10mg, and 61.2% for 20mg. Compared with placebo (N = 878), TOSS improvements were statistically superior in 4 studies and for TNSS in 5 studies. In these studies, treatment effect size ranged from 0.52 to 0.65 for 5mg, 0.40 to 0.58 for 10mg, and 0.78 for 20mg. First week by-day analysis showed significant improvements in TOSS for cetirizine subjects compared with placebo in the majority of studies. Weekly TOSS in weeks 1 and 2 for the cetirizine groups were significantly reduced compared with placebo in 5 studies.

**CONCLUSIONS:** Cetirizine 10mg once daily effectively relieves ocular allergy symptoms in subjects with SAR.

---

**Cetirizine Effectively Relieves Both Ocular Allergy Symptoms and Nasal Allergy Symptoms In Subjects With Seasonal Allergic Rhinitis**

*Dr. Eduardo Urdaneta, MD1, Ms. Xiaoyan Tian, MS2, Dr. Mei-Miao Wu, Dr. PH3, Ms. Qiong Du, MS2, Ms. Kathleen B. Franklin, BSN, RN,2, Dr. Mitesh Patel, PharmD3, McNeil Consumer Healthcare, Fort Washington, PA, 2Johnson & Johnson Consumer Products, China, Shanghai, China, 1J & J Consumer Products, US, Morris Plains, NJ, 3Franklin Consultants, LLC., Phoenixville, PA.*

**RATIONALE:** Evaluate efficacy of cetirizine 10mg daily for ocular and nasal allergy symptom relief in subjects with seasonal allergic rhinitis. Evaluate efficacy of cetirizine 5mg daily were evaluated post hoc. Total ocular symptom score (TOSS) was evaluated in each study. TOSS was sum of the severity scores for itchy eyes and watery eyes in all studies; one study also included red eyes. Individual symptom scores were rated on a 4-point scale (0 = none to 3 = severe). Subjects with baseline itchy eye scores ≥1 were included in the analysis. Changes from baseline in TOSS over a 2-week treatment period, by day in the first week, and weekly were assessed.

**METHODS:** Over a 2-week treatment period, mean changes from baseline in TOSS for the cetirizine groups (N = 1255) ranged from -2.11 to -2.65 for 5mg, -1.26 to -2.63 for 10mg, and -2.97 for 20mg; representing improvement relative to baseline of 50% to 67.4% for 5mg, 35.1% to 62.2% for 10mg, and 61.2% for 20mg. Compared with placebo (N = 878), TOSS improvements were statistically superior in 4 studies and for TNSS in 5 studies. In these studies, treatment effect size ranged from 0.52 to 0.65 for 5mg, 0.40 to 0.58 for 10mg, and 0.78 for 20mg. First week by-day analysis showed significant improvements in TOSS for cetirizine subjects compared with placebo in the majority of studies. Weekly TOSS in weeks 1 and 2 for the cetirizine groups were significantly reduced compared with placebo in 5 studies.

**CONCLUSIONS:** Cetirizine 10mg once daily effectively relieves ocular allergy symptoms in subjects with SAR.
Nanoparticle Engineering For The Immunomodulation Of Dendritic Cells

Dr. Xavier le Guevel, PhD 1, Dr. Tahia Fernández, PhD 2, Dr. Adriana Ariza, PhD 3, Dr. Maria Isabel Montañez, PhD 4, Dr. Maria J. Torres, MD, PhD 5, Dr. Cristobalina Mayorga, PhD 6, Dr. Miguel Blanca, MD, PhD 7, Bio-nund, Campanillas, Spain. 1Research Laboratory - FIMABIS Foundation, Málaga, Spain. 2Research Laboratory for Allergic Diseases, Hospital Regional Universitario de Málaga - FIMABIS-IBIMA, Málaga, Spain. 3Research Laboratory for Allergic Diseases, Hospital Regional Universitario de Málaga - IBIMA, Málaga, Spain. 4Allergy Service, Carlos Haya Hospital, Málaga, Spain. 5Research Laboratory, Carlos Haya Hospital-FIMABIS, Málaga, Spain.

RATIONALE: Nanotechnology and particularly nanoparticles (NPs) have gained a tremendous interest over the last 10 years in the field of immunotherapy. One of the most successful strategies of using NPs for specific immunotherapy is based on targeting dendritic cells (DCs), which play a central role on the activation of the immune system. Engineered nanoparticles can specifically be designed to either target or avoid interactions with the immune system leading to an immune stimulation or and immunosuppression responses. However, the understanding through systematic studies on the exact effect of size, shape or surface charge of NPs to the interaction and the immune response of DCs remains unclear. We aim to assess the impact of gold NPs with different physico-chemical parameters to the immunological response of DCs.

RESULTS: Thus, immature DCs were incubated with a series of gold NPs of the non-specific binding for the pegylated NPs in DCs with an increased proliferation. Investigation of the NPs biodistribution suggests a decrease in the cytoplasm by an endocytotic process. The capacity to induce maturation and T-cell proliferation were investigated. Biodistribution of NPs in cells was determined by fluorescence microscopy.

CONCLUSIONS: These results are encouraging to develop smart carriers for target inflammatory and inflammation-associated disorders.

Specific Immunotherapy Modified T-Cells Responses In a Spanish Population Of Der p Allergic Patients

Dr. Tahia Fernández, PhD 1, Dr. Cristobalina Mayorga, PhD 2, Dr. Enrique Gomez 2, Mrs. Rosa Garcia 1, Mrs. Maria Isabel Sanchez 2, Dr. Ana Aranda, PhD 3, Ms. Miriam Osorio 2, Dr. Miguel Blanca, MD, PhD 4, Dr. Maria José Torres, MD, PhD 5, 1Research Laboratory - FIMABIS Foundation, Málaga, Spain. 2Research Laboratory, Carlos Haya Hospital-FIMABIS, Málaga, Spain. 3Research Laboratory of allergic diseases - Carlos Haya Hospital. FIMABIS Foundation. Spain. 4Allergy Service -Carlos Haya Hospital. Spain. 5Allergy Service, Carlos Haya Hospital, Málaga, Spain.

RATIONALE: Specific immunotherapy (sIT) is nowadays the aetiolog-ical treatment for allergic disorders, it induces changes in lymphocyte Th-subsets from Th2 to Th1-Treg profile, however, the underlying mechanism is still not fully understood. We aim to study the changes in T-cell subsets during Dermatophagoides pteronyssinus (Der p) sIT.

METHODS: Ten patients with Der p allergy receiving SCIT for 1 year were included. Six allergic subjects that refused the treatment were included as controls. Peripheral blood mononuclear cells (PBMCs) were obtained at different time-points during sIT (basal T0; 3 months T1; 6m T2; 12m T3). PBMCs were cultured under non-stimulated or with Der p1 at 10 mg/ml conditions, during 6 days. T-cells subsets (Th1, Th2, Th9, Th17 ,Treg) were analysed by flow-cytometry. Results were expressed as (%-Der p1 stimulated cells/%-Non-stimulated cells). Samples results from each time were compared with basal.

RESULTS: sIT-Der p1 induced changes in T-cells subsets at different time-points. Th1 cells significantly increased at T2 (p=0.035). Th2 significantly decreased at T2 (p=0.011) and T3 (p=0.005). Th9 cells increased from T1 (p=0.026 at T1, T2 and p=0.035 at T3). Th17cells significantly decreased at T3 (p=0.035). Treg cells showed increased tendency during sIT. No differences for any of the subpopulation analysed were observed in controls.

CONCLUSIONS: sIT-Der p1 induced immunological changes at early stages. Patients disclosed changes in frequencies of different T-subsets, with a reduction of effector T-cells (Th2/Th17) and increases of Th1, Th9 and Treg. These data demonstrated that patients experienced an immune deviation from Th2 to Th1/Treg, detectable after 3 months of sIT.

Efficacy Of 300IR 5-Grass Pollen Sublingual Tablets In Grass Pollen-Associated Allergic Rhinoconjunctivitis: Pooled Analysis By Level Of Pollen Exposure

Prof. Alain Didier, MD, PhD 1, Prof. Ulrich Wahn, Prof Dr Med 2, Mr. Yann Amistan, Msc 3, Dr. Robert K. Zeldin, MD 4; Larrey Hospital, CHU, Toulouse, France, 2Charite, Berlin, Germany, 3Stallergenes S.A., Antony, France.

RATIONALE: The efficacy of the 300IR 5-grass pollen sublingual tablet administered according to a pre- and co-seasonal regimen has been demonstrated. Here, we present the results of a pooled efficacy analysis by level of pollen exposure.

METHODS: Adults and adolescents/children were enrolled in one of four double-blind, natural field studies and randomized to receive placebo or 300IR 5-grass pollen sublingual tablet daily beginning 4 months prior to and continuing through the grass pollen season. The severity of each of six rhinoconjunctivitis symptoms (0-3 scale) and the use of rescue medication were recorded daily. Derived scores were the rhinoconjunctivitis total symptom score (RTSS, scale 0-18) and the rescue medication score (RMS, scale 0-3). Efficacy was evaluated using the daily Combined Score [daily CS = (RTSS/6 + RMS)/2]. Centers were divided into 3 tertiles, each containing approximately one third of patients based on the area under the curve of the daily pollen counts at each center. A post-hoc analysis was performed using a repeated measures linear mixed model by category of pollen exposure.

RESULTS: Of the 1,381 participants in the Full Analysis Set, 665 received 300IR and 716 received placebo. Significant differences in daily CS between the two groups were observed in each category (p<0.005). The relative LS mean differences vs. placebo were -31.5% in the low-pollen exposure group, -22.5% in the medium-pollen exposure group and -27.9% in the high-pollen exposure group.

CONCLUSIONS: Treatment with 300IR 5-grass pollen extract sublingual tablet was effective in patients with allergic rhinoconjunctivitis, regardless of the level of grass pollen exposure.
The Print Survey II: Perceptions Regarding Injection Number and Technique

Dr. Michael S. Tankersley, MD, FAAAAI1, Dr. Sandy Yip, MD2, Dr. Christopher A. Coop, MD3, Wilford Hall Ambulatory Surgical Center, Joint Base San Antonio, San Antonio, TX, 2Wilford Hall Ambulatory Surgical Center, Lackland AFB, TX.

RATIONALE: The dry needle technique is a non-evidenced based intervention previously reported to be used by 13% of allergists as an effort to prevent or limit the size of local reactions to immunotherapy. The technique is performed by using a separate (i.e. dry) needle to inject the allergen extract into the patient’s arm rather than using the needle from which the extract was drawn up into the syringe.

METHODS: De-identified surveys were given to all immunotherapy patients to complete voluntarily.

RESULTS: There were 344 of 363 (94.8%) immunotherapy patients (age, 4-80 years) who completed surveys. For local reactions smaller than the size of their palm, 56.0% (75/134) felt that the dry needle technique moderately or mostly decreased or completely resolved their risk of local reactions. For large local reactions larger than the size of their palm, 62.2% (79/127) noted the dry needle technique moderately or mostly decreased or completely resolved their risk of large local reactions. For systemic reactions, 68.2% (75/110) felt that the dry needle technique moderately or mostly decreased or completely resolved their risk of systemic reactions. Finally, 59.1% (75/127) stated that the dry needle technique moderately or mostly decreased or completely resolved their pain from immunotherapy injections.

CONCLUSIONS: The majority of patients perceived that the dry needle technique decreased or completely resolved their local reactions, large local reactions, systemic reactions and pain from immunotherapy injections. The dry needle technique should be further investigated.

Allergy Immunotherapy: Characteristics and Risk Factors For Recurrent Systemic Reactions

Kerline Ductan, MD1, Ewa Schafe, MD, FAAAAI2, Rachel E. Story, MD3, Deeba Masood, MD4, Paul Detjen, MD5, Ying Zhou, PhD5, 1Department of Internal Medicine, University of Chicago-NorthShore, Evanston, IL, 2Allergy and Immunology, NorthShore University HealthSystem (NUHS), IL, 3Kenilworth Medical Allergy & Immunology, Kenilworth, IL, 4Center for Clinical and Research Informatics (CCRI), NUHS Research Institute, Evanston, IL.

RATIONALE: It is well established that patients with moderate to severe and/or uncontrolled asthma receiving allergen-immunotherapy (AI) have a significant risk to experience systemic reactions. We reviewed AI patients at NUHS to evaluate for characteristics and risk factors in those patients who have had repeated systemic-reactions (SR).

METHODS: Data from AI patient charts from January 2008 and January 2013 were reviewed retrospectively. Patients were age between 4 to 80 years old. Information regarding patients with repeated SR included but was not limited to: demographics, asthma, allergen extract concentration/content, protocol, previous SR, prior large local reactions > = 25mm, onset of SR, clinical manifestation of SR, and treatments received.

RESULTS: Of the 306 patient charts reviewed, 251 had no SR, 44 had one SR, and 11 had > = 2 SR. No statistical difference (p = 0.05) was found for patients with 0 or 1 versus > = 2 SR when compare with age, asthma, antigen-type and other data reviewed. Comparing patients who had > = 2 SR, 72.73% received Beta-2-agonist Inhale/Nebulizer treatments compared to only 40.91% of those who had only 1 SR, which is marginally significant with a p = 0.0587. Also 100% of patients with > = 2 SR received prednisone treatment during the first SR, but only 75% of those with 1 SR, with a p = 0.0637. Patients with asthma are more likely to develop repeated SR than those without asthma (OR:2.66 (0.42,12.17)), with the increase of age, the odds are increased (OR:1.03 (0.99,1.08)).

CONCLUSIONS: Although not demonstrating statistical significance, there was shown an increase odds ratio for repeated SR in patients with asthma.

Allergen Specific Immunotherapy In Monosensitized and Polysensitized Allergic Rhinitis Patients

Dr. L. Maslova1, Dr. Leonid P. Titov, MD, PhD2, Prof. Lawrence M. Dubuske, MD, FAAAAI3, 1Republican Scientific and Practical Center for Epidemiology and Microbiology,Minsk, Belarus, 2Republican Scientific and Practical Center for Epidemiology and Microbiology,Minsk, Belarus, 3George Washington University School of Medicine, DC.

RATIONALE: In the past, immunotherapy has been administered subcutaneously with mono-sensitized allergic rhinitis patients felt to have the best responses in Europe. The development of immunotherapy using sublingual drops has provided a safer and more convenient alternative and allowed re-examination of immunotherapy in polysensitized patients.

METHODS: 60 patients with pollen, dust mite and mold allergy underwent specific immunotherapy with allergen extracts (Sevapharma a.s., Prague, Czechrepublic) administered sublingually for two years. In Group 1 were monosensitized patients (n=30) treated with individual tree, grass, or weed pollen allergen extracts. In Group 2 were polysensitized patients (n=30): 15 who were treated with pollens and dust mites allergen extracts; 15 who were treated with pollens and mold allergen extracts. The diagnosis of allergy was made by clinical history, positive skin tests to allergen extracts with specific IgE >/= class 3. Sublingual immunotherapy (SLIT) involved a build-up or induction phase and maintenance phase with the maximum dose 10000 ISK, PNU – 10 drops given 3 times/ week.

RESULTS: SLIT was effective in reducing subjective clinical symptoms and drug consumption, with a highly significant reduction of more than 60% in symptom/medication scores including the polysensitized patients. Comparable efficacy was seen in those patients treated with multiple allergens who were polysensitized. Adverse effects were limited to a small number of mild local reactions.

CONCLUSIONS: These results confirm the efficacy and safety of pollen, dust mites and molds SLIT for both monosensitized and polysensitized adults with allergic rhinitis, suggesting that SLIT may change the European paradigm of preferential responses in monosensitized allergic rhinitis patients.

The Effect Of The Ragweed Sublingual Immunotherapy Tablet MK-3641 On Rescue Medication Use

Dr. Sandra M. Gawchik, DO, FAAAAI1, Dr. Peter S. Creticos, MD, FAAAAI2, Kevin R. Murphy, MD3, Dr. Gary D. Berman, MD, FAAAAI4, Dr. David I. Bernstein, MD, FAAAAI5, Dr. Jennifer Maloney, MD6, Dr. Amarjot Kaur, PhD7, Dr. Hendrik Nolte, MD, PhD8, 1Asthma and Allergy Associates, Chester, PA, 2Johns Hopkins Division of Allergy & Clinical Immunology, 3Boys Town National Research Hospital, Boys Town, NE, 4Allergy and Asthma Specialists, Minneapolis, MN, 5Bernstein Allergy Group, Cincinnati, OH, 6Merck, Whitehouse Station, NJ.

RATIONALE: Allergic rhinitis with/without conjunctivitis (AR/C) sufferers often rely on pharmacotherapy to relieve symptoms. Although the main goal of immunotherapy is long-term disease modification, reducing or eliminating the need for pharmacotherapy is desirable. METHODS: Data were pooled from two multinational randomized placebo-controlled trials that evaluated efficacy and safety of short ragweed sublingual immunotherapy tablet (SLIT-T), MK-3641 (Merck/ALK; Ambrosia artemisiifolia). Subjects with ragweed-pollen–induced AR/C were randomized to once-daily MK-3641 (including 6 or 12 Amb 1-A doses) or placebo. During pollen season all subjects could use AR/C rescue medication including oral/ocular antihistamines and intranasal/oral corticosteroids. We examined rescue medication use among groups.

RESULTS: In pooled results from the two studies, 109 of 340 (32%) subjects receiving placebo used no rescue medication over the season, versus 144 of 324 (44%) subjects receiving 6 Amb a 1-U and 159 of 318 (50%) subjects receiving 12 Amb a 1-U. These differences represented 37% and 56% improvements over placebo. Among 6 and 12 Amb a 1-U subjects, 19% and 27% fewer versus placebo used oral antihistamine; 25% and 35% fewer used ocular antihistamine; and 26% and 41% fewer used intranasal corticosteroids (oral corticosteroid was used by <5 subjects in any group).

CONCLUSIONS: The SLIT-T treatment MK-3641 reduced rescue medication use among subjects with ragweed-pollen–induced AR/C.
973

Exposures That Alter The Early Life Microbiome and The Risk Of Asthma

Amy S. Feldman, MD1, Pingsheng Wu, PhD, MS1,2, Kristina James, MD3, Tebebe Gebretsadik, MPH1,2, Gabriel Escobar, MD3,4, Kezia N. Carroll, MD5, Sherian Xu Li, MS1, Eileen Walsh, RN, MPH2, Ed Mitchel, MS3,4, Dr. Tina V. Hartert, MD, MPH2, Division of Allergy, Pulmonary, and Critical Care Medicine, Department of Medicine, and Center for Asthma and Environmental Sciences Research, Vanderbilt University School of Medicine, Nashville, TN, 2Department of Biostatistics, Vanderbilt University School of Medicine, Nashville, TN, 3Peninsula Allergy & Asthma Center, Soldotna, AK, 4Kaiser Permanente Medical Care Program, Oakland, CA, 5Kaiser Permanente Northern California, Perinatal Research Unit, Division of Research, 6Department of Pediatrics, Vanderbilt University School of Medicine, Nashville, TN, Vanderbilt University School of Medicine, Nashville, TN.

RATIONALE: The microbiome is speculated to play a role in the development of asthma. We hypothesize that the collective contribution of exposures or events known to alter the infant microbiome increase the risk of asthma.

METHODS: PRIMA is a retrospective birth cohort of infants and pregnant women enrolled in Kaiser Permanente Northern California (KPNC) and Tennessee Medicaid (TennCare) programs who were followed until age 6 years for childhood asthma. We determined whether maternal, perinatal, and infant exposures known to alter the microbiome were associated with increased asthma risk using multivariable logistic regression.

RESULTS: Among 269,800 infants (82,203 from KPNC and 187,597 from TennCare), 34,259 (12.7%) developed asthma by age 6. The association of early life exposures and later development of childhood asthma risk was determined adjusting for covariates. These include birth exposures: C-section (adjusted odds ratio [aOR] for asthma, 1.14; 95% Confidence Interval [CI], 1.10-1.17), and maternal antibiotics (aOR, 1.29; 95% CI, 1.23-1.35); infant exposures: having no siblings (aOR, 1.23; 95% CI, 1.20-1.28), and each additional infant antibiotic course (aOR, 1.14; 95% CI, 1.13-1.15). We further created a composite exposure and classified infants based on the number of exposures. With every additional exposure, there was a 24% increase in odds of childhood asthma adjusting for covariates (aOR, 1.24; 95% CI, 1.22-1.26).

CONCLUSIONS: Measured exposures that are known to alter the microbiome (e.g. C-section, antibiotics) were associated with an increased risk of asthma. Increasing number of perinatal and infant exposures conferred a higher risk of asthma in a dose dependent manner.

974

Ethnic Differences Of Reported Asthma Symptoms In Urban School-Based Screening Surveys

Dr. Margee Louisias, MD1, Dr. Joanne Sordillo, ScD2,3, Mrs. Chuxia Fu, MS4,5, Dr. Wanda Phipatanakul, MD, MS, FAAAI6,7, Brigham and Women’s Hospital, Boston, MA, 2Channing Division of Network Medicine, Brigham & Women’s Hospital, Harvard Medical School, Boston, MA, 3Harvard Medical School, Boston, MA, 4Harvard School of Public Health, Boston, MA, 5Channing Laboratory, Brigham and Women’s Hospital, Boston, MA, 6Boston Children’s Hospital, Boston, MA, 7Vanderbilt University School of Medicine, Nashville, TN.

RATIONALE: School-based screening surveys may identify uncontrolled asthma and asthma symptoms in children.

METHODS: School Inner-City Asthma Study is a NIH/NAIAD prospec- tive cohort evaluating school and classroom-specific environmental risk factors and asthma morbidity of urban children. We computed descriptive statistics and analyzed asthma symptoms by race from the school-wide screening surveys used to identify asthmatics for the cohort.

RESULTS: 7032 children were screened. Median age was 8 years [IQR 6-10]. Racial breakdown was: 44% Hispanic, 30% Black, 13% White, 6% Mixed, 6% Asian, and 1% Native American. 22% of students reported a history of asthma and by race, 42% were Hispanic, 35% were Black, 10% were White, 6% were Mixed, 6% were Asians, and 1% were Native American.[p <0.0001]. Most asthmatic respondents reported significant morbidity. 68% reported missed school days or medical care in the past year due to asthma, which most Hispanics reported [p<0.05]. 77% had exercise-induced symptoms, which disproportionally affected Native Americans (87%) vs. the other groups (65-80%), [p=0.02]. 78% had nighttime symptoms and 17% weren’t on asthma medication, but these issues weren’t significantly different by race. 45% of all respondents reported asthma symptoms without a prior asthma diagnosis, which included a significant proportion from each race. However, the percentage of subjects experiencing symptoms without an asthma diagnosis was lowest in whites at 37% (vs. 48% of Hispanics, 44% of Blacks, 48% of Mixed, 46% of Asians, and 48% of Native Americans) [p<0.0001].

CONCLUSIONS: School-based asthma screening surveys are a useful tool to identify students, of particular racial groups, who warrant further surveillance.

975

Year One Daycare Attendance Predicts Asthma At Age Seven: The Cincinnati Childhood Allergy and Air Pollution Study (CCAAPS)

Dr. Gang Cheng, MD, PhD1, Linda Levin, PhD2, Dr. Andrew M. Smith, MD, FAAAI3, Dr. Tolly Epstein, MD, MS4, Patrick Ryan, PhD5, Grace K. LeMasters, PhD2, Dr. David I. Bernstein, MD, FAAAI1, 1Division of Immunology Allergy & Rheumatology, University of Cincinnati Medical Center, CINCINNATI, OH, 2University of Cincinnati, Cincinnati, OH, 3325 Eden Ave., HPB 350, University of Cincinnati Medical Center, Cincinnati, OH, 4Allergy Partners of Central Indiana, Indianapolis, IN, 5Cincinnati Children’s Hospital, Cincinnati, OH.

RATIONALE: Studies vary with respect to the reported effects of daycare attendance on asthma. We evaluated the independent and combined effects of daycare and respiratory infections on the development of asthma at age 7 in a prospective birth cohort.

METHODS: At age 7 the study sample included 591 children out of 881 enrolled at birth in the Cincinnati Childhood Allergy and Air Pollution Study. Daycare hours and number of respiratory infections were reported in follow-up questionnaires through age four. At age 7 years, asthma diagnosed for 96 children (16%), based on asthma symptoms combined with FEV1 reversibility and methacholine testing. Logistic regression was used to investigate the associations between asthma and daycare attendance and respiratory infections at ages 1 to 4.

RESULTS: In the univariate analyses, daycare attendance at 12 months was associated with an increased risk of asthma (Odds ratio[OR]=1.8, 95% Confidence Interval[CI]=1.1-3.0). Both upper and lower respiratory infections at 12 months also increased the risk of asthma (OR=2.4 [1.4-4.1]; OR=2.3 [1.5-3.7], respectively). In the final multivariate logistic model, daycare attendance and number of lower respiratory infections at 12 months increased the risk of asthma (OR=1.2 [1.1-1.5]; OR=1.5 [1.2-1.8], respectively). However, threshold of greater than 35 hours per week of daycare attendance actually reduced the risk of asthma (OR=0.7 [0.6-0.9]).

CONCLUSIONS: Depending on duration of attendance, daycare in early childhood can either increase or reduce risk of asthma at age 7.
976 Determining Risk Levels Of The Composite Asthma Severity Index (CASI) Rebecca A. Zabel, Dr. Peter J. Gergen, MD, MPH, Dr. Christine A. Sor, PharmD, Jeremy Wildifire, Jr, Mr. Agustin Calatroni, MA, MS, Dr. Herman Mitchell, PhD, ’Rho, Inc., Chapel Hill, NC. 1AAIBDAITNIH, Bethesda, MD, 2University of Wisconsin, Madison, WI.

**RATIONALE:** The Composite Asthma Severity Index (CASI) was developed to capture the inherent intensity of the disease in asthmatic children and adolescents. It quantifies severity by combining information about impairment, risk, and the amount of medication required to maintain control. Understanding what values of the index translate to, in terms of severity, will enable the CASI score to be useful in a clinical setting.

**METHODS:** Using screening data from 700 children in the Asthma Phenotypes in the Inner City (APIC) study, we measured the CASI score (ranging from 0 to 20), as well as numeric and categorical physician assessments of asthma severity (numeric: 0 to 100; categorical: high, medium, low).

**RESULTS:** In APIC, the mean and standard deviation for CASI were 4.4 and 2.96. Since APIC enrolled both severe and non-severe asthmatics, this population had lower CASI scores than previous ICAC studies enrolling moderate to severe asthmatics only (mean = 6.2, SD 2.98 in the Asthma Control Evaluation). CASI and the numeric physician assessment of severity were significantly correlated (correlation 0.63, 95% CI [0.58-0.67]). Participants categorized as low severity had a median CASI of 2 (interquartile range [1-3]), while medium and high severity groups had medians of 5 (IQR [3-6]) and 7 (IQR [5-10]), respectively.

**CONCLUSIONS:** CASI is the only quantitative measure of asthma severity that incorporates impairment, risk and controller medication in a single measure. Establishing risk levels for CASI gives physicians important context for interpreting the CASI in clinical settings.

977 BMI and Asthma Severity In An Elementary and Middle School Inner City Population Dr. Christina G. Kwong, MD, RMS, Ms. Christina Mahl, RN, Ms. Lisa D. Henry, PNP-BC, Dr. Deborah Loman, PhD, CPNP, Dr. Robert C. Strunk, IV, MD, FAAAAI, Ms. Lisa A. Meadows, PNP-BC, Dr. Alyssa G. Ellis, MD, 1Washington University School of Medicine, Saint Louis, MO, 2St. Louis Children’s Hospital, Saint Louis, MO, 3St. Louis University School of Nursing, Saint Louis, MO.

**RATIONALE:** Previous studies have shown an association between overweight/obese status and asthma incidence in the pediatric population. However, the relationship between BMI and asthma severity is unclear due to limited data and conflicting results. We hypothesized that increasing BMI would be associated with increased asthma severity.

**METHODS:** The Healthy Kids Express Asthma Program at St. Louis Children’s Hospital recruited 189 patients from an inner-city population who attended one of four elementary or middle schools for a cross-sectional study. Asthma severity was determined per NHLBI criteria. BMI percentile was calculated using the CDC BMI-for-age growth chart. A multivariate analysis was used. ANCOVA analysis controlled for age and gender.

**RESULTS:** At the time of exam, children were age 5-15 years with a mean age of 9.8 years. 51.9% were male and 48.1% female. No association was found between BMI percentile and increased asthma severity (ANCOVA overall factor 0.909, p = 0.438). However, there is a trend towards increased severity for obese versus normal weight patients (Intermittent Asthma N=81: Mean BMI Percentile 72.2, Mild Persistent N=66: 75, Moderate Persistent N=35: 74.6, Severe Persistent N=7: 90.6).

**CONCLUSIONS:** Increased BMI percentile is not associated with increased asthma severity in a cross-sectional study of elementary and middle school aged children from a predominantly inner-city population.

978 Novel NK Cytotoxicity Assay Enables Drug Discovery For Hemophagocytic Lymphohistiocytosis Dr. Jinzhu Li, MD, PhD, Ms. Sarah E. Figueira, Ms. Julie Ferrel, Dr. Kimberly A. Risma, MD, PhD, FAAAAI, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH.

**RATIONALE:** Drugs correcting cytotoxic deficiency are currently unavailable but highly desirable for treating hemophagocytic lymphohistiocytosis (HLH), a condition characterized by various degree of fundamental defect in lymphocyte cytotoxicity. Discovery efforts have been thwarted by a lack of high throughput screening (HTS) assay. We hypothesized that a novel granzyme B specific biosensor would allow HTS of NK cell cytotoxicity and facilitate drug development.

**METHODS:** Biosensor was created by linking the termini of firefly luciferase with a granzyme B cleavage site, which rendered the luciferase inactive until cleaved by granzyme B. NK cytotoxic biosensor assay was performed in 96-well plate by mixing the effector cell NK92 with the biosensor expressing- target K562, whereby the biosensor detects the delivery of granzyme B into the live targets in real time.

**RESULTS:** Luciferase activity rose within 10 minutes of NK92:K562 contact, plateaued at 75 minutes and gradually declined. The biosensor detected induction of luciferase at effector:target ratio as low as 0.1:1 and target number lower than 600/well. The biosensor was suppressed by granzyme B inhibitor C20, and shRNA knockdown of granzyme B. Activated NK cells from PBMC also triggered the biosensor and the luminescent signal correlated with 11Cr release assay. HTS of NK92 cells with the biosensor assay in 384-well plate identified signal enhancing hits from 1591 small molecule compounds.

**CONCLUSIONS:** Granzyme B specific luciferase biosensor assay is a sensitive and specific real time cytotoxic assay that is suitable for HTS of NK cytotoxicity. The assay allows further discovery and development of drugs for treatment of HLH.

979 Exploitation Of The Host Ubiquitin System By Respiratory Syncytial Virus Nonstructural Protein 2 Jillian N. Whelan, Kim C. Tran, Ruan R. Cox, Jr, Damian B. van Rossum, Randen L. Patterson, Michael Teng; 1Division of Allergy and Immunology, Department of Internal Medicine, and the Joy McCann Culverhouse Airway Diseases Research Center, University of South Florida Morsani College of Medicine, Tampa, FL; 2The Pennsylvania State University, University Park, PA.

**RATIONALE:** Respiratory syncytial virus (RSV) is the cause of lower respiratory tract infection in young children worldwide. RSV nonstructural protein 2 (NS2) is one of the first and most abundantly expressed proteins following an infection. NS2 is a multifunctional protein important for viral replication and disease pathogenesis and is essential for RSV-induced proapoptotic degradation of host STAT2. We investigated the mechanism by which NS2 interacts with the host ubiquitin system during infection.

**METHODS:** 293T cells were transfected with various plasmid DNA. Co-immunoprecipitations were performed for protein-protein interactions and western blotting for protein expression. NS2 mutations were designed using computational analysis (ada-BLAST search) and generated via site-directed mutagenesis. ImageQuant TL v2005 software was used for densitometry analysis.

**RESULTS:** Co-transfection of 293T cells with expression plasmids encoding NS2 and ubiquitin resulted in an increase in ubiquitinated host proteins as compared to ubiquitin expressed alone. Co-transfection of NS2 with the ubiquitin mutant inhibiting poly-ubiquitin chain formation maintained equal levels of host protein ubiquitination. NS2 co-immuno-precipitated with specific ubiquitin ligase complex proteins. Mutation of residues important in NS2’s ubiquitination function identified several residues that affected NS2-induced ubiquitination of host proteins.

**CONCLUSIONS:** Results indicate that NS2 induces mono-ubiquitination of an array of host proteins possibly via interaction with host ubiquitin ligase complex proteins. NS2-induced ubiquitination likely targets host anti-viral processes and can be limited through mutation of key NS2 residues.
**980 Epigenetic Regulation Of Dendritic Cell Migration**

**Dr. Timothy P. Moran, MD, PhD**, Dr. Hideki Nakano, PhD, Dr. Hrisavgi Kondilis-Mangum, PhD, Dr. Paul Wade, PhD, Dr. Donald Cook, PhD, Duke University Medical Center, Durham, NC; National Institute of Environmental Health Sciences, NIH, Research Triangle Park, NC.

**RATIONALE**: The chemokine receptor CCR7 is critically important for the trafficking of lung dendritic cells (DCs) to lymph nodes (LN), where they orchestrate the development of allergic responses to inhaled allergens. Our objective was to investigate the molecular mechanisms that regulate lineage-specific CCR7 expression in DCs.

**METHODS**: Ccr7 expression and function was evaluated in conventional DCs (cDCs) and monocyte-derived DCs (moDCs) generated from bone marrow (BM) of wild type or Ccr7(+/−) reporter mice. Chromatin immunoprecipitation assays were performed to assess epigenetic modifications of the Ccr7 locus in BM-derived DCs, primary lung DC subsets and progenitor populations.

**RESULTS**: BM-derived cDCs expressed Ccr7 following activation with lipopolysaccharide and migrated efficiently to CCR7 ligands both in vitro and in vivo. By contrast, BM-derived moDCs did not express Ccr7 or respond to CCR7 ligands. The Ccr7 promoter in BM-derived moDCs was enriched for the transcriptionally repressive histone modifications H3K27 tri-methylation, consistent with epigenetic regulation of gene expression. In the lung, similar repressive histone modifications at the Ccr7 locus were detected in CD11b(hi)Ly-6C(hi) moDCs, but not in migratory CD103+ cDCs. Furthermore, progenitors for lung cDCs and moDCs had disparate levels of H3K27 tri-methylation at the Ccr7 promoter, indicating that epigenetic regulation of Ccr7 occurs early during DC lineage commitment.

**CONCLUSIONS**: Lineage-specific epigenetic mechanisms regulate CCR7-dependent DC migration, and thus help dictate the functional role of DC subsets. Manipulating epigenetic pathways could provide a novel strategy for the improvement of DC-based immunotherapies and the treatment of allergic diseases.

**981 LRBA Subcellular Localization: Evidence Of The LRBA’s Role In Vesicle Trafficking From The Golgi To Cell Membrane And Endocytosis**

**Mrs. Michelle A. Reiser, MS**, Dr. Jia-Wang Wang, PhD, Mrs. Kunyu Li, BS, Dr. Richard F. Lockey, MD, Division of Allergy and Immunology, Department of Internal Medicine, University of South Florida, Morsani College of Medicine, Tampa, FL; Division of Allergy and Immunology, Department of Internal Medicine, University of South Florida Morsani College of Medicine and James A. Haley Veterans’ Affairs Hospital, Tampa, FL.

**RATIONALE**: Mutation or deletion of lipopolysaccharide responsive beige-like anchor (LRBA) gene causes common variable immunodeficiency, autoimmunity and chronic inflammation. However, the underlying molecular mechanism by which this occurs is unknown. LRBA is similar in structure to the lysosomal trafficking regulator gene. Therefore, it is hypothesized that LRBA may function as a regulator of vesicle trafficking. Its subcellular localization may help to decipher its function.

**METHODS**: Immunofluorescent staining of cultured H293 cells was conducted using a polyclonal antibody to LRBA and monoclonal antibodies against various organelle-specific proteins. Confocal images were obtained with an Olympus FV1000 MPE multiphoton laser scanning microscope and the accompanied software (FV10-ASW and JACop)) were used for colocalization analysis. Time lapse video was obtained of live RAW264.7 cells stably transfected with LRBA-GFP using a Leica TCS SP2 laser scanning confocal microscope.

**RESULTS**: LRBA is co-localized with three Golgi proteins (GM-130, P-230, and GS-28), early endosome antigen 1 (an early endosome marker), the RIIb and RIIc subunits of protein kinase A (PKA), and the microtubule protein, tubulin. A video of a live cell stimulated with LPS shows LRBA-positive vesicles budding from the Golgi and moving into the cell membrane.

**CONCLUSIONS**: LRBA is extensively associated with the endomembrane/vesicle trafficking system, which includes the Golgi complex, endosomes, lysosomes, plasma membrane and microtubules. LRBA also is associated with PKA. These results suggest that LRBA may play a role in membrane/vesicle trafficking and signal transduction required for the regulation and function of many immune molecules.

**982 Differential Role Of Dendritic Cell Subsets In Shaping T-Cell Responses To Respiratory Viruses**

**Dr. Meera Rani Gupta, MD**, Dr. Deepthi Kolli, PhD, Dr. Antonella Casola, MD, Dr. Roberto P. Garofalo, MD; University of Texas Medical Branch, Galveston, TX.

**RATIONALE**: Respiratory syncytial virus (RSV) and Human Metapneumovirus (hMPV) are significant respiratory pathogens. The cellular response after infection likely determines the short- and long-term sequela of disease. Myeloid Dendritic cells (mDCs) play a pivotal role in shaping adaptive immune responses in the respiratory tract; however, few studies have examined how interactions of RSV or hMPV with individual mDC subsets affects skewing of anti-viral responses.

**METHODS**: BDCA-1+ and BDCA-3+ mDCs were isolated from peripheral blood of healthy adults using FACS sorting, infected with RSV or hMPV (MOI=5) for 24 hours, and co-cultured with allogenic CD4+ T-cells. After 7 days, the percentage of CD4+T-cells expressing IFN-γ (Th1), IL-4 (Th2), IL-17a (Th17), CD25 and FOXP3 (Tregs) was examined using flow cytometry. Statistically significant differences in subset distribution between uninfected and infected co-cultures were determined using student’s paired t-test.

**RESULTS**: RSV-infected BDCA-1+ mDCs induced expansion of Th1 cells (p=0.03), hMPV-infected BDCA-1+ mDCs tended towards expansion of Th1 (p=0.08) and Th17 populations (p=0.09). RSV-infected BDCA-3+ mDCs induced expansion of Th2 cells (p=0.01) and Tregs (p=0.04), whereas hMPV-infected BDCA-3+ mDCs induced expansion of Th17 cells (p=0.003).

**CONCLUSIONS**: These results demonstrate a subset-specific role for BDCA-1+ and BDCA-3+mDCs in regulating T-cell responses during RSV infection, as well as a virus-specific effect of RSV on skewing anti-viral immune responses. Identifying the characteristics of adaptive immune responses during infection helps understand the implications for long-term disease. Defining the role mDC subsets play in shaping adaptive immune responses is critical for developing vaccine and treatment strategies against these respiratory pathogens.
Effect Of Prenatal Exposure To Indoor PM2.5 and Environmental Tobacco Smoke Affecting Lower Respiratory Tract Infection Was Modified By ROS Genes: Cocoa Study

Dr. Song I. Yang, MD 1, Dr. Eun Lee, MD 1, Dr. Young Ho Jung, MD 1, Kil-Yong Choi 2, Mi-Jin Kang, MS 2, Ho-Sung Yu 2, Cheol Min Lee 2, Prof. Youn Ho Shin, MD, PhD 1, Prof. Kangmo Ahn, MD, PhD 1, Prof. Kyung Won Kim, MD, PhD 1, Prof. Soo-Jong Hong, MD, PhD 1, Cocoa study Group 2, 3Childhood Asthma Atopy Center, Department of Pediatrics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea, 2Asan Institute for Life Sciences, University of Ulsan College of Medicine, Seoul, South Korea, 3Institute of Environmental and Industrial Medicine, Hanyang University, Seoul, South Korea, 4Department of Pediatrics, Cha University Hospital, Cha University College of Medicine, Seoul, South Korea, 5Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, 6Department of Pediatrics, Yonsei University College of Medicine, Seoul, South Korea, 7COCOA study group.

RATIONALE: Prenatal air pollution exposure associates with impaired fetal growth, decreased lung function, respiratory morbidity and mortality. We aimed to investigate the influence of prenatal indoor fine particulate matter (PM2.5) and environmental tobacco smoke (ETS) exposure and genetic polymorphisms on the susceptibility to respiratory tract infection (RTI) in infancy.

METHODS: Demographic, environmental factors and diagnosis of RTI in the first year of life were evaluated in 231 infants from a birth cohort of the general population in Korea between 2007 and 2011. Indoor PM2.5 was measured during the third trimester and mothers were asked about ETS exposure during pregnancy. Nuclear factor (erythroid-derived 2)-like 2 (NRF2, rs6726395), glutathione S-transferase pi 1 (GSTP1, rs1695) and glutathione S-transferase mu 1 (GSTM1, copy number variation) genotyping was performed.

RESULTS: Prenatal indoor PM2.5 or ETS exposure increased the risk of bronchiolitis and lower RTI (LRTI), but not upper RTI (URTI), in infancy. They also synergistically increased susceptibility to bronchiolitis and LRTI (aOR 5.20; 95% CI 1.10-24.61, aOR 5.18; 95% CI 1.40-19.24, respectively), but not URTI. This synergistic effect was increased by Nrf2 (aOR 10.23; 95% CI 1.02-102.57, aOR 14.01; 95% CI 1.42-138.02, respectively) and GSTM1 null genotypes (aOR 9.45; 95% CI 1.03-86.78, aOR 7.07; 95% CI 1.02-31.95, respectively).

CONCLUSIONS: Indoor PM2.5 and ETS exposure during the prenatal period synergistically increased susceptibility to bronchiolitis and LRTI, but not URTI. This effect was modified by polymorphisms in reactive oxygen species-related genes.

IgE Anti-Respiratory Syncytial Virus Antibodies In Older Asthmatic Children

Mira Mandal 1, Dr. Rauno O. Joks, MD, FAAAAI 2, Dr. Kevin Norowitz, MD 1, Dr. Diana Weaver, MD 1, Dr. Helen G. Durkin, PhD 1, Dr. Martin H. Bluth, MD, PhD 2, Dr. Stephan Kohlhoff, MD 2, Dr. Tamar A. Smith-Norowitz, PhD 1, SUNY Downstate Medical Center, Brooklyn, NY, 3SUNY Downstate Medical Center, Center for Allergy and Asthma Research, Brooklyn, NY, 4SUNY Downstate Medical Ctr, Brooklyn, NY, 5Center for Allergy and Asthma Research, State University of New York Downstate Medical Center, Brooklyn, NY, 6Wayne State University Medicine, Detroit, MI, 7Center for Allergy and Asthma Research at SUNY Downstate, Brooklyn, NY.

RATIONALE: Respiratory syncytial virus (RSV) causes severe lower respiratory tract disease in infant and young children, and is a serious public health concern, as is the increase in pediatric asthma in the United States. However, it remains unknown if IgE and RSV antibodies (Abs) play a role in development of asthma.

METHODS: Total serum IgE, and IgE and IgG anti-RSV Ab responses were studied in older asthmatic compared with non asthmatic children (M/F, mean age: 14) (N= 30, N=43, respectively) (UniCAP total IgE Fluoroenzymeimmunoassay (IU/mL), enzyme-linked immunosorbent assay (U/mL; OD value).

RESULTS: Total serum IgE levels were increased 3-fold in asthmatic compared with non asthmatic children (323 + 217, 107 + 116, P= 0.0003). Further, IgE anti-RSV Ab levels were 1.5-fold higher in asthmatic compared with nonasthmatic children (P = 0.01). IgG anti-RSV Ab levels were slightly increased in the asthmatic children (112 + 32, 81+ 59, P=0.003). Interestingly, values of IgE anti-RSV Abs positively correlated with IgG anti-RSV Abs.

CONCLUSIONS: The presence of IgE anti-RSV abs in older children further lends support to an important role of RSV infection in asthma.

Asthma Symptoms and Rhinovirus In A Longitudinal Children’s Cohort

Dr. Euan R. Tovey, PhD 1, 2, Dr. S. Stelzer-Braid, PhD 3, 4, Dr. B. G. Toelle, PhD 5, Ms. C. M. Willenborg, BSc 5, Dr. H. K. Reddel, PhD, MBBS 5, 6, Ms. F. L. Garden, MPH 1, 2, Prof. A. Jaffe, PhD, MD 4, 5, Ms. R. Strachan 5, Dr. B. G. Oliver, PhD 1, 2, Dr. Y. C. Belessis, MBBS 1, 2, Prof. G. B. Marks, PhD, MD 1, 2, Prof. W. D. Rawlinson, PhD, MD 1, 3, 4, 5, Woolcock Institute of Medical Research, Sydney, Australia, 6University of Sydney, Australia, 3Virology Division, SEALS Microbiology, Prince of Wales Hospital, Sydney, Australia, 4University of NSW, Australia, 5Sydney Children’s Hospital, Randwick Australia.

RATIONALE: Emergency presentations for asthma are strongly associated with rhinovirus (HRV) infections in children. However, community viral infections are common and often mild or asymptomatic, and the role of viruses in changing daily symptoms is less clear. We hypothesized such infections would be associated with increased symptoms.

METHODS: 67 children, aged 5-12, with moderately severe asthma, self-collected nasal-wash and exhaled breath samples and recorded their recent asthma and cold symptoms and current lung function, twice per week for 10 weeks. The presence of 8 viruses, including rhinovirus (HRV), was analysed by PCR. A mixed model, to account for repeated measures, was used to determine the current and delayed impact of viruses on symptoms and lung function.

RESULTS: 25.5% of nasal samples and 11.5% of breath samples were positive for HRV; only 1.8% were positive for other viruses. The presence of HRV in nasal wash, but not in breath, was associated with the presence of symptoms; adjusted odds ratios: cough 2.53, (95%CI 1.62-3.94), wheeze 3.05, (95%CI 1.89 to 4.93), self-reported febrile 2.07, (95%CI 1.17 to 3.64) and coryzal symptoms 1.95, (95%CI 1.14 to 3.32) over the previous 3-4 days. These associations remained 3-4 days later, but generally not 7 days later. There was no association between any virus positivity and changes in electronically recorded PEFR and FEV1.

CONCLUSIONS: In a longitudinal study of children with moderate asthma, the presence of rhinovirus in nasal wash, but not in exhaled breath, was associated with worsening of several indices of respiratory symptoms for up to a week.
Maternal Transfer Of Der p 1 and Blo t 5 Allergens and Their Respective Specific Antibodies Through Placenta and Colostrum

Dr. Patricia Macchiaverni1, Christina Arslanian2, Dr. Valerie Verhasselt3, Prof. Antonio Condino-Neto, MD, PhD4, 1Department of Immunology, Institute of Biomedical Sciences, University of Sao Paulo, SP, Brazil, 2Institute of Biomedical Sciences, Department of Immunology, University of Sao Paulo, Sao Paulo, Brazil.

RATIONALE: Dermatophagoides pteronyssinus (Der p) and Blomia tropicalis (Blo t) are respiratory allergens that represent a major cause of allergic asthma. Placental transfer and breastfeeding are potential routes of allergen exposure in very early life. To date, no study has demonstrated the presence of those respiratory allergens in paired samples of human cord blood and breast milk samples.

METHODS: We assessed whether Der p 1 and Blo t 5 allergens and were transferred through placenta and colostrums in the presence of specific antibodies. The maternal transfer was analyzed in a cohort of 91 paired samples of colostrum and umbilical cord blood.

RESULTS: We detect Der p 1 and Blo t 5 in 29% and 9.6% of cord blood samples (median 62.2 pg/mL and 892.4 pg/mL, respectively). In colostrum 58.6% of samples were positive for Der p 1 and 41.3% for Blo t 5 (range 0-869.9 pg/mL and 0-1281 pg/mL, respectively). Der p and Blo t-specific IgG1, IgG2, IgG3 and IgG4 were present in cord blood of almost all neonates in a wide range of values, but strongly correlated to maternal levels. More than 90% of cord blood samples were positive for specific IgM, for both allergens. In colostrums, specific IgA and IgG levels were also variable among samples.

CONCLUSIONS: We demonstrated that respiratory allergen can be transferred through placenta and colostrums and that the first actively stimulates the neonate immune system intra uterus. Those observations bring new hypothesis in understanding causal pathway of allergic airway sensitization and raise questions for future strategies for prevention of allergic disease.

Rhinovirus Infection Is Associated With Changes In The Airway Microbiome

Dr. Kirsten Klopfer, MD1, Dr. Valeriy Poroyko, PhD2, Mrs. Rose Vrtis, BS3, Mrs. Tressa Pappas, BS4, Dr. Theresa Kang, PhD5, Dr. Wai-Ming Lee, PhD6, Mr. Michael D. Evans, MS7, Dr. Ronald E. Gangnon, PhD8, Dr. Yury Bochkov, PhD9, Dr. Robert F. Lemanske, Jr, MD, FAAAAI10, Dr. James E. Gern, MD, FAAAAI11, 1Riley Hospital for Children at Indiana University Health, Indianapolis, IN, 2University of Chicago, Chicago, IL, 3University of Wisconsin School of Medicine and Public Health, Madison, WI.

RATIONALE: Rhinovirus (RV) infection can cause a spectrum of illness from asymptomatic infection to moderate asthma exacerbations. Based on recent findings that the upper airway microbiome is altered in children with asthma, we examined the upper airway microbiome of children with asthma before and during RV infection to determine if changes occur and if they correlate with asthma exacerbation severity.

METHODS: 30 children with asthma, ages 4-12 years, provided five consecutive weekly nasal samples during September and scored cold and asthma symptoms daily. We selected 15 subjects with asymptomatic RV-infection and 15 subjects with moderate asthma exacerbation associated with RV-infection. Bacterial DNA was extracted from samples at baseline and during RV infection. 16S-rRNA gene sequences targeting the v4 region were analyzed utilizing Mothur and Primer v6 software.

RESULTS: 2,499 taxa were identified with 61 bacterial genera at 1% abundance level. 73% of annotated sequences consisted of Streptococcus (19%), Dolosigranulum (18%), Corinebacterium (14%), Staphylococcus (13%), and Moraxella (8%). RV infection was associated with increased abundance of Dolosigranulum, Corinebacterium, and Moraxella, while RV-negative samples were associated with increased abundance of Streptococcus, Staphylococcus, Gemella and Neisseria (p=0.016). During RV infection, no difference was observed in microbiota composition between subjects with asymptomatic RV infection and those with RV-associated moderate asthma exacerbations (p=0.33).

CONCLUSIONS: RV infection causes changes in the upper airway microbiome; however, there were no significant differences in microbial community metrics related to asthma exacerbations. Further investigation is needed to determine if the baseline microbiome is different in children who experience moderate asthma exacerbations during RV infection.

Natural History Of Esophageal Remodeling In Pediatric Eosinophilic Esophagitis Treated For Four Years

Dr. Jessica Rajan, MD1,2, Dr. Robert Newbury, MD3,4, Arjun Andrew Anilkumar, BS5,6, Ranjan Dohil, MD7, Dr. David H. Broide, MB, ChB, FAAAAI1, Seema Sharma Acesve, MD, PhD, FAAAAI2, 1Scripps Clinic Medical Group, San Diego, CA, 2Division of Allergy/Immunology, 3Department of Pediatrics, 4Division of Pathology, 5Department of Medicine, 6Department of Pediatrics, Division of Gastroenterology, 7Division of Gastroenterology, UCSD, Rady Children’s Hospital, San Diego, 8Department of Medicine, San Diego, CA, 9Pediatrics, University of California San Diego, La Jolla, CA.

RATIONALE: Eosinophilic esophagitis (EoE) diagnosis and management requires repeated tissue procurement and provides a model system to study long-term eosinophil associated tissue remodeling.

METHODS: We assessed 84 esophageal biopsies from 13 pediatric EoE subjects followed for an average of 45 months during routine clinical care. Tissue remodeling was quantitated using image analysis and standardized scoring tools.

RESULTS: Baseline average epithelial eosinophil counts were 98±13 per hpf, average time to recurrence of eosinophilia was 17.5 months and was associated with medication non-adherence or addition of an antigenic food. Control and recurrence of epithelial eosinophilia was associated with basal zone hyperplasia (r=0.61, p<0.0001) and dilated intracellular space (r=0.63, p<0.0001) severity. Forty-six biopsies had ≥3 instances with evaluable lamina propria (LP). Initial responders to therapy had prolonged control (20.5 months) of fibrosis which was associated with decreased fibrosis scores (2.5 to 0.5, maximum=3), epithelial eosinophils (64±2 to 32±21 per hpf.), LP eosinophils (16.5±10.5 to 2.6±1.2 per hpf), and TGFβ1-positive cells (1856±206 to 1426±190 per mm²). Initial/prolonged non-responders to therapy had persistent fibrosis (score=3), increases in LP eosinophils (11±5 t 23±5 per hpf, p<0.05 compared with responders) and TGFβ1-positive cells (1117±190 to 1899±311 per mm²) over time (25.5 months). Non-responders had elevated TGFβ1-positive cells compared with non-EoE patients (p<0.03).

CONCLUSIONS: Initial response to therapy may be associated with an ability to control remodeling while initial therapeutic non-response may predict persistent and/or progressive esophageal remodeling.
Diagnostic Inaccuracy Of Biopsy Evaluations In Eosinophilic Esophagitis Underscores The Value Of a Secondary Review Process

Emily Stucke, BA1; Dr. Katherine E. Clarridge, MD, MSc1,2; Dr. Margaret Collins, MD3; Dr. Lisa J. Martin, PhD1; Carol J. Henderson, PhD, RD, LD4; Dr. Marc E. Rothenberg, MD, PhD, FAAAAI1; 1Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; 2University of Cincinnati.

RATIONALE: Eosinophilic esophagitis (EoE) is a chronic relapsing disease characterized by the accumulation of eosinophils in esophageal epithelium. The recommended threshold for diagnosis is a peak value of 15 intraepithelial eosinophils per high power field (hpf). Interobserver variability in quantifying eosinophils could therefore affect diagnosis. We queried the diagnostic accuracy of eosinophil counts determined by the clinical pathology service at our institution by reexamining existing slides.

METHODS: One observer completed a second review of 477 esophageal biopsies to quantify intraepithelial eosinophils. The peak eosinophil count on second review was compared to the peak eosinophil count specified in the final surgical pathology report. Wilcoxon matched-pairs signed rank test and coefficient of variation were used to compare the counts. Sensitivity and specificity were calculated using the second review as the gold standard.

RESULTS: Of the 477 biopsies included in the study, 106 (22%) had a pathology report count between 1-14 eosinophils/hpf and 23 of these (22%) had a second review count of ≥15/hpf. Using a coefficient of variation threshold of 0.1 to signify consistency, 225 (47%) of the pathology reports did not correspond to second review counts. We found that a single slide review detects EoE with a specificity of 99%, but a sensitivity of only 80%.

CONCLUSIONS: Second review of esophageal biopsies to quantitate eosinophils yields higher values which potentially impact clinical decisions in ~5% of esophageal biopsies. We propose that eosinophil counts between 1-14 eosinophils/hpf require additional investigation and are likely to yield a diagnosis of EoE in ~22% of biopsies.

Development Of Eosinophilic Esophagitis To Food After Development Of IgE Tolerance To The Same Food

Dr. Solrun Melkorka Maggadottir, MD1; Dr. David Hill, MD, PhD2; Dr. Terri F. Brown-Whitehorn, MD3; Dr. Jonathan M. Spergel, MD, PhD, FAAAAI1; 1Children’s Hospital of Philadelphia, Philadelphia, PA; 2Children’s Hospital of Philadelphia, 3The Children’s Hospital of Philadelphia, Philadelphia, PA.

RATIONALE: Eosinophilic esophagitis (EoE) is characterized by chronic, isolated esophageal infiltration with eosinophils triggered by foods. Atopic disease and IgE-mediated food allergy are common in EoE. The pathogenesis of EoE is elusive with recent data suggesting a mechanism of disease independent from IgE. We evaluated the frequency of IgE-mediated food allergy in subjects with EoE, and compared culprit food allergens in subjects with IgE-mediated food allergy who went on to develop EoE.

METHODS: A retrospective analysis of 1025 children with EoE seen at the Children’s Hospital of Philadelphia in 2000-2012. A causative food was identified in 425 subjects. Skin prick tests (SPTs) were conducted and clinical IgE-mediated reactions identified. A food was considered to cause EoE if elimination led to resolution of esophageal eosinophilia or reintroduction led to reoccurrence of EoE.

RESULTS: The most common foods causing EoE in 425 subjects were milk, egg, wheat and soy. We describe a subgroup of 17 subjects that developed EoE to a food after outgrowing IgE-mediated allergy to that food. The EoE causative foods were not different in this subgroup, and atopic disease was present in most subjects (94%). Two subjects had normal esophageal biopsies in the setting of IgE-mediated allergy, outgrew their IgE-mediated allergy, and subsequently developed EoE to same food upon re-introducing the food into their diet.

CONCLUSIONS: Along with recent studies, our findings suggest that the pathophysiology in EoE is distinct from that of IgE-mediated allergy. However, prior IgE-mediated food allergy may predispose subjects to developing EoE to the same food.

Mast Cells, Eosinophils and Eosinophilic Esophagitis

Dr. Jay Jin, MD, PhD; Dr. Jeffrey Alexander, MD; Hirohito Kita, MD; Ms. Diane Squillace, MS; Dr. Joseph A. Murray, MD; Dr. Amanda Anora, MD; Dr. Yvonne Romero, MD; Dr. Thomas Smyrk, MD; Dr. Catherine R. Weiler, MD, PhD, FAAAAI; Mayo Clinic, Rochester, MN.

RATIONALE: Eosinophilic esophagitis (EoE) is an increasingly recognized disease entity in adults. Studies show a role for eosinophils and mast cells in its pathogenesis.

METHODS: Upper and mid-esophageal biopsy slides from adult patients (n=36) with dysphagia were stained for eosinophil counts (H&E), and immunostained for eosinophil-derived neurotoxin (EDN) and eosinophil major basic protein (MBP). Gene expression was studied by microarray analysis. All patients were consented before the procedure. All research protocols were approved by the Mayo Clinic IRB.

RESULTS: EoE patients (n=12; median age 36; 10 male, 2 female) had higher EDN and MBP tissue protein levels as quantified by immunofluorescence. The measured levels of intracellular and extracellular EDN and MBP correlated with eosinophil counts in the EoE patients (median eosinophil count 48±36 cells/high power field (HPF)) compared to controls (n=14; median age 47.2; median eosinophil count 2.8±4 cells/HPF). Genetic microarray analysis showed eotaxin-3 expression was 8-fold higher, eotaxin-2 was 1.3-fold higher, and Charcot-Leyden crystal protein was 2.4-fold higher than controls. For mast cell markers, cathepsin-G precursor expression was 6.2-fold higher, high affinity IgE receptor alpha chain was 2.1-fold higher, carboxypeptidase A3 was 4.5-fold higher, and both cathepsin C and tryptase were 3-fold higher than controls. All fold-changes reached statistical significance (p<0.002). Of note two control patients showed the control phenotype but matched the EoE genotype.

CONCLUSIONS: The significant increase in eotaxin-3 gene expression in EoE patients is in agreement with previously reported expression levels in children. The increase in mast cell markers supports a role for mast cell involvement in EoE.
CD3 and CD68 Cells Produce IL-9 in Pediatric Eosinophilic Esophagitis
Arjun Andrew Anilkumar, BS1, Lisa Beppu, BS2, Richard Kurten, PhD2, Dr. Robert Newbury, MD3, Ranjan Dohil, MD1, David Broide, MB ChB2, Seema Sharma Acheves, MD, PhD, FAAAI1,2, Department of Medicine; Division of Allergy/Immunology; 3Department of Pediatric University of California San Diego; Division of Allergy and Immunology, University of Arkansas for Medical Sciences, Little Rock, AR; Department of Physiology and Biophysics, Department of Pediatrics; Division of Pathology, Department of Pediatrics, Division of Gastroenterology; Division of Gastroenterology, UCSD, Rady Children’s Hospital, San Diego, University of California San Diego, Department of Medicine, Division of Allergy and Immunology, Pediatrics, University of California San Diego, San Diego, La Jolla, CA.

RATIONALE: Eosinophilic esophagitis (EoE) is a chronic allergic disease of increasing prevalence. IL-9 is elevated in EoE submucosa and may play a role in its pathogenesis.

METHODS: We used esophageal biopsies and quantitative immunohistochemistry/immunofluorescence from pediatric EoE (n=11) and control subjects (n=6) to evaluate IL-9+, CD3+, and CD68+ cells. Double immunofluorescence demonstrated the cellular subsets that produced IL-9. The effect of IL-13 on IL-9 receptor expression in cultured esophageal epithelial cells was analyzed using qPCR.

RESULTS: EoE subjects had significantly more IL-9+ cells (947.5 +/- 60.6 per mm2), CD3+ (1183 +/- 202 per mm2), and CD8+ (951.3 +/- 280.8 per mm2) cells than non-diseased controls (IL-9 = 51.1 +/- 11.7, p<0.0001; CD3+ = 168.0 +/- 24.2, p<0.0001; and CD8+ = 126.5 +/- 25.7, p<0.05). Double immunofluorescence showed that both CD3+ and CD8+ cells produced IL-9. 41.8% of CD3+ and 26.7% of CD8+ cells co-expressed IL-9. Further, IL-13 treatment of cultured esophageal epithelial cells increased IL-9 receptor mRNA expression.

CONCLUSIONS: CD3+ and CD8+ cells are sources of IL-9 in EoE and treatment of esophageal epithelial cells with IL-13 increases the expression of the IL-9 receptor. As such, a mechanistic pathway whereby T cell derived IL-9 acts on the esophageal epithelium in the presence of IL-13 to drive esophageal epithelial abnormalities in IL-9.

### 993 Longitudinal Effect Of Food Allergy Education On Epinephrine Availability In Public Schools
Dipika Patel, MD1, Gwendolyn Johnson, BSN, RN, MD2, Danielle Guffey, MS1, Charles Minard, PhD1, Carla Davis, MD1, Baylor College of Medicine, Houston, TX, 2Houston Independent School District, Houston, TX.

RATIONALE: The effect of school nursing food allergy education is unknown. We hypothesized that a didactic educational session for nurses would increase the identification of food allergic children, decrease allergic reactions, and increase the availability of epinephrine injectors.

METHODS: A survey pre and post a didactic session was administered in 2011 to school nurses addressing caustive foods, allergic reactions, and appropriate treatment. A survey one year later was completed by school nurses and outcomes measured. Statistical analysis was performed with the Wilcoxon signed rank test and McNemar’s test. The correlation between the number of food allergic students and number of epinephrine injectors was estimated using Spearman’s rank correlation.

RESULTS: A total of 197 school nurses responded to the survey in at least one year (2010,2012,2013). Sixty-two nurses responded to the survey before and after education with 39 responding all 3 years. The percent of schools with allergic reactions decreased (15% in 2010,0% in 2012, p=0.0143) and the decrease was sustained in 2013 (5%, p=0.1537). Epinephrine injectors increased (median=1/school in 2010,2 in 2012, p<0.001). The correlation between the number of students with food allergies and epinephrine injectors increased from 2010(r2=0.43) to 2012(r2=0.82).

CONCLUSIONS: Education significantly impacted school preparedness for food allergic reactions, evidenced by increased correlation between the number of food allergic students and number of epinephrine injectors. Food allergic reactions significantly decreased after education. This data showed a longitudinal effect, supporting implementation of standardized nursing education programs in public schools.

### 994 Population Response To Change In Infant Feeding Guidelines For Allergy Prevention
Dr. Dean Tej, MD1,2, Prof. Katrina Jane Allen, MD, PhD, FAAAI1,2, Ms. Rachel Peters, MPH2, Dr. Jennifer Koplin, PhD2, Prof. Mini L. K. Tang, MD, PhD, FAAAI3, Prof. Lyle Gurrin, PhD2, Prof. Anne-Louise Ponsonby, PhD2, Dr. Adrian Lowe, PhD2, Prof. Melissa Wake, MD, PhD2, Prof. Shyamali Dharmage, MD, PhD2,4, Royal Children’s Hospital, Victoria, Australia, Murdoch Children’s Research Institute, Victoria, Australia, The University of Melbourne, Melbourne, Australia, 4University of Melbourne, Victoria, Australia.

RATIONALE: It is unclear if population infant feeding practices have changed since Australian allergy guidelines were revised to no longer delay introduction of dietary allergenic solids.

METHODS: In a population-based, cross-sectional study (HealthNuts) of 5,276 infants recruited between 2007-2011, parents reported on infant feeding in the first year of life. Multinomial logistic regression was used to investigate the associations between recruitment year and feeding practices.

RESULTS: Participants recruited after national allergy guidelines were updated in 2008 were more likely to introduce solids at age 4 months (adjusted multinomial odds ratio (aMOR) 1.21; 95%CI [1.02-1.45], p=0.032) and less likely to introduce solids at age 6 months (aMOR 0.80; 95%CI [0.69-0.92], p=0.002, egg after 6 months (aMOR 0.82; 95%CI [0.71-0.94], p=0.004), and peanut after 12 months (aMOR 0.70; 95%CI [0.49-0.98], p=0.037). While parents recruited after changed guidelines were less likely to utilize an infant formula (aMOR 0.84; 95%CI [0.72-0.98], p=0.023), there was an increase used of partially hydrolyzed formulas (aMOR 1.37; 95%CI [1.12-1.70], p=0.003) amongst formula-fed infants. These changes were modified by socio-demographic factors, with families with a higher socioeconomic status and those without a family history of allergies being less likely to delay allergenic solids; families with a history of food allergy were more likely to choose a partially hydrolyzed formula.

CONCLUSIONS: Updated national allergy guidelines have been associated with reduced delay in introduction of solids, egg and peanut, and an increase in partially hydrolyzed formula use among formula-fed infants. Higher socioeconomic status and absence of family history of allergies were associated with improved uptake of feeding guidelines.
996 Differences In Food Allergy Quality Of Life Between Caregivers In A Clinic-Based and a Caregiver-Reported Food Allergic Population

Dr. Matthew J. Greenhawt, MD, MBA, MSc; Department of Internal Medicine, The University of Michigan Medical School, Division of Allergy and Clinical Immunology, Ann Arbor, MI.

RATIONALE: Food allergy is associated with diminished caregiver quality of life (QoL), but little is known about differences in QoL between caregivers self-reporting a child with food allergy (CSRFA) and caregivers with children followed at a food allergy referral center clinic (FARC).

METHODS: An internet survey containing the 17-question, validated FAQL-PB index and screening questions regarding the child’s most severe food reaction was administered to caregivers of milk, egg, peanut, or tree nut allergic children. CSRFA were recruited via the email/social media networks of The Kids with Food Allergies Foundation, and FARC caregivers from the University of Michigan Allergy and Immunology Clinics (who were given the option of a written survey).

RESULTS: There were 2003 CSRFA and 305 FARC respondents. FAQL-PB Cronbach’s-α for the population was 0.94 and the mean total QoL score was 2.67. Mean peanut QoL score was significantly higher (worse QoL) than tree nut (p<0.001) or milk (p=0.001), and egg score significantly higher than tree nut (p<0.001) or milk (p=0.001). Compared to CSRFA, FARC caregivers had significantly lower mean total QoL score (1.8 vs. 3.2, p<0.0001). Furthermore, FARC caregivers had significantly lower QoL scores for all allergens (mean difference range 0.89-1.32; peanut p<0.001, tree nut p<0.001, milk p=0.006, egg p=0.001) and all 17 individual FAQL-PB domains (mean difference range 0.51-1.65; all p<0.0001) than CSRFA.

CONCLUSIONS: CSRFA with milk, egg, peanut or tree nut allergic children may have significantly worse QoL compared to FARC caregivers. Large clinically and statistically significant differences were noted in the total, allergen-specific, and domain-specific QoL scores.

997 Food Allergy Management In An Urban Pediatric Population

Dr. Jennifer M. Camacho, MD, Dr. Stephanie Albin, MD, Dr. Doerthe A. Andreue, MD, Dr. Julie Wang, MD, FAACAI; The Icahn School of Medicine at Mount Sinai, New York, NY.

RATIONALE: Limited data exists on food allergy management in the urban pediatric population.

METHODS: Dietary adherence, adherence to allergy clinic appointments, and carrying of epinephrine auto-injectors (EAI) was assessed among patients with known food allergies via a questionnaire and review of the electronic medical record.

RESULTS: The response rate was 76% (42 of 55). The median age of the patients was 5 years, 62% were male. 45% were black and 44% were Hispanic. 90.5% had multiple food allergies. Patients had a median of 2 food allergic reactions in the past year. 24% have required epinephrine to treat allergic reactions in the past and, 60% have had emergency department visits and/or hospitalizations for food allergic reactions.

While the majority adhered to the recommended food avoidance diet, 20% did not. Of these, 38% followed a more restrictive diet and 63% avoided fewer foods than was advised. 45% attended all scheduled allergy clinic appointments in the past two years with a significant difference in age between those who did and did not attend (4.2 years vs 6.7 years, p=0.04). 33% had an EAI at the visit. Reasons for not having an EAI included the expiration of the device, forgetting to bring it, and believing it unnecessary to have. No differences were found between those who did and did not have an EAI with them at the visit.

CONCLUSIONS: While the majority was adherent to dietary recommendations, there is a high degree of noncompliance with clinic appointments and EAI carriage in this urban food allergic pediatric population.
**Treatment With Synthetic Peptide Immuno-Regulatory Epitopes Derived From Grass Allergens Leads To a Substantial Reduction In Grass Allergy Symptoms In The Environmental Exposure Unit**

Dr. Anne K. Ellis, MD, Msc FAAAAI,1,2, Dr. Charles W. Frankish, MD3, Ms. Kristen Armstrong, MSc4, Dr. Mark Larche, PhD5, Ms. Lisa Steacy, BSc6, Dr. Rod Hafner, PhD6, 1Allergy Research Unit, Kingston General Hospital, Kingston, ON, Canada, 2Departments of Medicine and Biomedical & Molecular Science, Queen’s University, Kingston, ON, Canada, 3Kanata Allergy Services, Kanata, ON, Canada, 4Adiga Life Sciences Inc., Hamilton, ON, Canada, 5McMaster University/St. Joseph’s Healthcare, Hamilton, ON, Canada, 6Circassia, Oxford, United Kingdom.

**RATIONALE:** Previously, we identified a series of Synthetic Peptide Immuno-Regulatory Epitopes (SPIRE) derived from grass allergens and showed these were safe and well-tolerated. Here we evaluated whether treatment with Grass-SPIRE resulted in reduction in grass allergy symptoms.

**METHODS:** Subjects attended the Environmental Exposure Unit (EEU) at baseline, approximately 4 months before the grass season and at Post Treatment Challenges (PTC) after the peak of the grass season, approximately 25 weeks after starting Grass-SPIRE dosing. EEU challenge consisted of 4 consecutive days of 3-hour rye grass exposure. The target mean hourly range of pollen count was 3500±500 grains/m3. Total Rhinoconjunctivitis Symptom Score (TRSS) was recorded every 30 minutes on a scale of 0-24. 280 subjects were randomised to one of three Grass-SPIRE dosing regimens, or placebo.

**RESULTS:** 8x6nmol Grass-SPIRE showed a mean change in the TRSS scores at PTC of -5.4 versus -3.8 on placebo (p<0.05) in the protocol specified primary endpoint (all timepoints Days 2, 3, 4 participants with scores at PTC of -5.4 versus -3.8 on placebo (p<0.05). The protocol specified secondary endpoint in subjects with mean Baseline TRSS>8 confirmed the result (Grass-SPIRE -5.1, placebo -3.8; p<0.05). The protocol specified secondary endpoint in subjects with mean Baseline TRSS>12 showed a larger treatment effect (Grass-SPIRE -5.3, placebo -3.4; p<0.05).

**CONCLUSIONS:** Treatment with 8x6nmol Grass-SPIRE over 14-weeks showed a substantial reduction in grass allergy symptoms in an EEU model of grass allergy. The treatment effect was greater in the more symptomatic subjects. Results from testing Grass-SPIRE are similar to those obtained with other SPIREs including cat and house dust mite.

---

**Epicutaneous Immunotherapy Induces Epigenetic Changes In Sensitized Mice**

Lucie Mondoulet, PhD1, Dr. Vincent Dioszeghy, PhD3, Mrs. Mélanie Ligouis2, Mrs. Véronique Dhelet3, Mrs. Emilie Putaux1, Mrs. Camille Plaquet1, Prof. Christophe Dupont, MD, PhD2, Pierre Henri Benhamou, MD2, 1DBV Technologies, Bagneux, France, 2Hospital Necker Enfants Malades, Paris, France.

**RATIONALE:** Epicutaneous immunotherapy has been shown to rebalance Th2 allergic immune response. The aim of this study was to investigate in sensitized mice if epigenetic modifications may be involved in the mechanism of action of EPIT in comparison to sublingual immunotherapy (SLIT).

**METHODS:** Sixty BALB/c mice were orally sensitized to milk and then treated by epicutaneous immunotherapy (EPIT) or by sublingual immunotherapy (SLIT) or not desensitized (Sham). Mice were killed immediately or 8 weeks after the end of treatment. In another set of experiment, mice were sensitized to peanuts and divided into the same groups for treatment (EPIT, SLIT, Sham). Ten naive mice were also included in the study. DNA methylation was analysed in spleen samples taken for all mice at each sacrifice.

**RESULTS:** EPIT in milk- or peanut-sensitized mice significantly increased methylation in the CpG islands of GATA-3 versus Sham (respectively 64.5% vs 23.6%, p<0.05; 86.1% vs 37%, p<0.05). This result was correlated to a significant decrease of GATA-3 mRNA expression (0.5 vs 1.7 in Sham, p<0.01). This epigenetic modification was maintained 2 months after the end of immunotherapy (68.5% vs 18.6% in Sham, p<0.05). Lower GATA-3 methylation was obtained after SLIT (44.9% mice) linked to a high GATA-3 mRNA expression.

**CONCLUSIONS:** EPIT seems to act as a strong immunomodulator, modifying the DNA transcription factor by epigenetic modifications.
1002 Stable Conjugates Between A Novel Toll-Like Receptor 7 Ligand and Protein Allergens As Modulators Of TH2 Responses In Vitro and In Vivo

Dr. Lucia Fili1, Dr. Alessandra Vultaggio1, Dr. Elisa Cardilicchia1, Dr. Cinzia Manuelli1, Dr. Andrea Casini2, Dr. Francesca Nencini1, Dr. Laura Maggi1, Dr. Sara Pratesi1, Dr. Giulia Petroni1, Dr. Francesca Boscaro1, Prof. Ernesto Giovanni Occhiatto2, Prof. Sergio Romagnani1, Prof. Enrico Maggi1, Prof. Paola Parronchi1, 1University of Florence, DENOTHE Center, Florence, Italy, 2University of Florence, Dept. of Chemistry “U. Shift”, Florence, Italy, 3University of Florence, Mass Spectrometry Center (CISM), Florence, Italy.

RATIONALE: The allergen-specific immunotherapy represents a relevant approach to treat respiratory allergy. A strategy for novel vaccine formulations is to stably link adjuvants with the allergen. The in vitro and in vivo effects of natural Dermatophagoides pteronyssinus 2 and Ovalbumin chemically conjugated to a 8-OH modified adenine (nDer p2-Conj and OVA-Conj) in allergic inflammation were investigated.

METHODS: In human setting Toll-like receptor activation on transfected HEK293 cells, stimulation of innate cells, assessment of the functional phenotype of specific T-cell lines and clones by means of flow cytometry, real-time PCR, expression of Th-related transcription factors, variation of allergenicity by BASOTEST. In murine models pre-priming and therapeutic protocols with assessment of TH2-mediated airway inflammation by means of cytology, histology, real-time PCR, and humoral responses by ELISAs.

RESULTS: nDer p2-Conj induced human innate cells to produce IFN-α and IL-12 via TLR7 triggering. As a consequence, the conjugate reverted T1/2-prone allergen T cell lines into IFN-γ-producing cells (T1/2γ/0 phenotype). nDer p2- and OVA-Conj-primed mice exhibited reduced airway hyperreactivity, eosinophil infiltration and airway IL-13 expression, increased IFN-γ and IL-10 levels in allergen-stimulated T cells, up-regulation of allergen-specific IgG2a and reduction of IgE levels. Into therapeutic protocol, OVA-conj redirected established allergen-specific T1/2 cells responses into protective phenotypes. No evidence of increased autoantibodies, autoimmunity manifestations or B cell expansion was found.

CONCLUSIONS: The co-delivery of a protein with allergenic properties as a stable conjugate induce modulatory cytokines from innate cells and re-directs in vitro and in vivo pathogenic T1/2 responses without eliciting harmful effects.

1003 TSLP Induces Corticosteroid Resistance In Natural Helper Cells Via STAT5 Pathway

Hiroki Kabata1, Kazuyo Moro1, Koichi Fukuagawa1, Yusuke Suzuki1, Katsunori Masaki1, Tomoko Betsuyaku1, Shigeo Koyasu1,2, Prof. Koichiro Asano, MD1, 1Keio University School of Medicine, Tokyo, Japan, 2RIKEN Center for Integrative Medical Sciences, Kanagawa, Japan.

RATIONALE: We previously reported that IL-33-induced eosinophilic inflammation and type-2 cytokine production in the airways is dependent on natural helper (NH) cells in vivo, and it becomes resistant to corticosteroids in the presence of TSLP. In the present study, we investigated the corticosteroid sensitivity of IL-33-stimulated NH cells in vitro.

METHODS: NH cells were isolated from the lungs or fat-associated lymphoid cluster (FALC) in the mesentery of C57BL/6 mice by means of flow cytometry. These cells were cultured in the presence of IL-33 with or without dexamethasone (10⁻⁹-10⁻⁵M) and various cytokines including TSLP. After 4 days, cell number and type-2 cytokine concentration in the supernatant were measured. Survival and apoptosis were evaluated by PI and BrdU/7-AAD staining. We also examined the expression of glucocorticoid receptor (GR) and STAT5 with Western blotting, and that of Bcl-xL with flow cytometry.

RESULTS: Dexamethasone efficiently suppressed proliferation, induced apoptosis, and inhibited type-2 cytokine production in NH cells stimulated with IL-33 alone. In contrast, NH cells co-stimulated with IL-33 + IL-2, IL-7, or TSLP were protected from dexamethasone-induced apoptosis. TSLP exhibited no effects on GR translocation, but significantly increased the expression of anti-apoptotic protein, Bcl-xL. As previously reported, IL-2, IL-7, and TSLP shared the activity to phosphorylate STAT5, and the treatment with a STAT5 inhibitor reversed the TSLP-induced corticosteroid-resistance in NH cells.

CONCLUSIONS: TSLP induces corticosteroid resistance in NH cells via STAT5 pathway. STAT5 inhibitors could be a new therapeutic option for corticosteroid-resistant severe asthma.

1004 Impairment Of IL-27’s Differential Effect On CD4+T Cells In Asthma

Dr. Zhihong Chen1, Shanze Wang2, Xiaopeng Q2, Prof. Chunxue Bai1, Prof. Hua Huang2, 1Zhongshan Hospital, Fudan University, Shanghai, China, 2National Jewish Health, Denver, CO.

RATIONALE: Th2 cells play critical roles in the pathogenesis of allergic asthma. Established Th2 cells have been shown to resist reprogramming toward Th1 cells. We sought to understand the mechanisms by which asthmatic CD4+ T cells develop resistance to IL-27-mediated inhibition of Th2 differentiation.

METHODS: We isolated and cultured CD4+ T cells from healthy individuals and allergic asthmatic patients and tested whether IL-27 can inhibit IL-24 production by the cultured CD4+ T cells using ELISA. STAT1 phosphorylation was analyzed by Western blot and flow cytometry. Suppressor of cytokine signaling (SOCS) mRNA expressions were measured by qPCR. The siRNA method was used to knockdown SOCS3 mRNA expression.

RESULTS: We demonstrated that CD4+ T cells from asthmatic patients resisted human IL-27-mediated suppression of IL-4 production. We observed that repeated exposures to Th2-inducing conditions rendered healthy human CD4+ T cells resistant to IL-27-mediated inhibition. Using an in vitro murine culture system, we further demonstrated that repeated or higher doses of IL-4, but not IL-2, stimulation upregulated SOCS3 mRNA expression and impaired IL-27-induced STAT1 phosphorylation. Py-STAT1 expression was impaired in Th2 memory cells circulating in peripheral blood isolated in asthmatics, but not in normal subjects. Knockdown of SOCS3 expression restored IL-27-mediated inhibition.

CONCLUSIONS: Our findings demonstrate that differentiated Th2 cells can resist IL-27-induced reprogramming toward Th1 cells by downregulating STAT1 phosphorylation and upregulation of SOCS3 and may explain why asthmatic CD4+ T cells are resistant to IL-27-mediated differential inhibition.
1005 Profile Of Food Allergen-Specific T Cells In Allergic and Clinically Tolerant Individuals

David Chiang, MS1, Alexander V. Grishin, PhD1, Madhan Maslalamani, PhD1, Miriam Merad, MD, PhD2, A. Karolina Paliouka, MD, PhD1,2, Hideki Ueno, MD, PhD3, A. Wesley Burks, MD, MAAA4,5, Stacie M. Jones, MD1, Andrew H. Liu, MD6, Scott H. Sicherer, MD, MAA1, Robert A. Wood, MD, MAA1,6, Wendy Davidson, PhD7, Hugh A. Sampson, MD, MAA1,8, M. Cecilia Berin, PhD1,2; 1Icahn School of Medicine at Mount Sinai, New York, NY, 2Cockrell Research Institute for Immunology Research, Dallas, TX, 3University of North Carolina, Chapel Hill, NC, 4University of Arkansas for Medical Sciences and Arkansas Children’s Hospital, Little Rock, AR, 5National Jewish Health, Denver, CO, 6Johns Hopkins University Medical Center, Baltimore, MD, 7National Institutes of Health, Bethesda, MD, 8Pediatrics, Icahn School of Medicine at Mount Sinai, New York, NY.

Rationale: The interplay between antigen-specific T-effector and regulatory cells in food allergy and tolerance is poorly understood in humans.

Methods: Using blood from children allergic to peanut and/or egg versus clinically tolerant controls (including healthy, outgrown food allergy, or allergic to other foods), we designed 13-color flow cytometry panels to profile peanut or egg-specific T cell responses 6-18h after stimulation. Antigen-specific cells were identified as live/CD3+/CD4+ T cells, and profiled for regulatory markers (CD25+/CD127+/Foxp3+), cytokines (IL-4/IL-13/IL-10/IFN-g), and homing markers (CCR6/CCR4/CCR5/CCR9).

Results: Allergic subjects had detectable peanut-responsive CD40L+ T cells above background (median 206 per million CD4+ vs. 37 at 6h and 408 vs 56 at 18h, n=20 and 13, p<0.0001 and p=0.0002). In healthy controls, there were few detectable peanut-responsive cells above background at 6hrs (84 vs. 66, n=3). Similar responses were observed in egg-stimulated samples from children allergic (n=13) or clinically tolerant (n=6) to egg. Egg and peanut-specific T cells in allergic subjects co-expressed IL-4 and IL-13, but little or no IFNg or IL-10. In control subjects Tg2 cytokine expression was absent with minimal IFNg or IL-10.

Antigen-specific “Tregs”, defined as CD40L+/CD25+ T cells, were significantly increased beginning 18h after allergen stimulation, were present in both allergic and tolerant individuals, and were enriched for skin-homing (CCR4+) and mucosal-homing (CCR6+) receptor expression.

Conclusions: Antigen-specific “Tregs” with tissue homing phenotypes are detectable in both allergic and tolerant subjects, while antigen-specific Th2-effector cells are unique to allergic individuals. These results suggest that food allergy is not due to a quantitative deficiency in allergen-specific Tregs; regulatory function remains to be addressed.

1006 Follicular Helper T Cells Mediate IgE Antibody Production and Allergic Immune Responses in Mice

Takao Kobayashi, PhD1, Koji Iijima, PhD1, Hirohito Kita, MD2; 1Mayo Clinic, Rochester, MN, 2Mayo Clinic Rochester, Rochester, MN.

Rationale: Follicular helper T (Tfh) cells develop when animals are infected with helminths. However, little is known about the roles for Tfh cells in allergic airway diseases.

Methods: Mice were exposed intranasally to endotoxin-free ovalbumin (OVA) with or without IL-33 or IL-1β. Adaptive immune responses to OVA were analyzed by using IL-4 reporter mice, gene-deficient animals, and adoptive transfer approaches.

Results: Airway exposure of naive mice to OVA plus IL-33 induced OVA-specific IgE and IgG1; when challenged with OVA, these mice developed robust Th2 cytokine response and airway eosinophilia. Exposure of naive mice to OVA plus IL-1β induced comparable levels of anti-OVA IgE/IgG1 and IL-4, but minimal IL-5, IL-13 and eosinophilia. Isolation of IL-4-positive CD4+ T cells and microarray analysis showed that IL-33 induces antigen-specific Th2 cells and Tfh cells and that IL-1β induces mainly Tfh cells. Mice deficient in ICOS (Icos–/–), which is critical for development of Tfh cells, developed Th2 cells and anti-IgE/IgG1 antibodies normally when exposed to OVA plus IL-33. In contrast, when exposed to OVA plus IL-1β, Icos–/– mice showed decreased numbers of Th cells and reduced levels of anti-OVA IgE/IgG1. Finally, CD4-deficient animals recovered production of anti-OVA IgE/IgG1 antibodies when they were reconstituted with Tfh cells.

Conclusions: IL-1β-family cytokines regulate development of antigen-specific Th2 cells and Tfh cells in the airway. Th cells mediate IgE antibody production and modest airway inflammation, while Th2 cells mediate both antibody production and inflammation. The roles for Th cells in human allergic diseases need to be investigated.

1007 Analysis Of Circulating Rhinovirus-Specific CD4+ T Cells Using Novel MHC Class Ii Tetramers Reveals Marked Expansion Of Effector Memory Cells In Infected Subjects

Lyndsey Munching1, Rachana Agrawal, PhD2, Julia Wisniewski, MD3, Paul Wright1, William W. Kwock, PhD2, Ronald Turner, MD4, Judith A. Woodfolk, MDChB, PhD, MAA1,2, University of Virginia Health System, Charlottesville, VA, 3Benaroya Research Institute at Virginia Mason, Seattle, WA.

Rationale: Little is known about T cell mechanisms of human rhinovirus (HRV) infection, despite the link to asthma. Our objective was to provide proof-of-concept for elucidating properties of circulating virus-specific CD4+ T cells in HRV-infected individuals using novel MHC II/peptide tetramers.

Methods: HRV-39 seronegative, non-allergic subjects who were HLA-DR*0401-positive were infected intranasally with HRV-39. PBMCs isolated 28 days before inoculation, at day 0, and days 5 and 21 post-infection, were stained with PE-labeled HLA-DR*0401 tetramers containing HRV-39 epitopes. Cells were enriched using an anti-PE column, then stained for surface markers and analyzed by flow cytometry.

Results: A discrete population of tetramer-positive CD4+ T cells was detected at each time point using tetramers containing two novel epitopes of HRV-39 capsid proteins. Before infection, circulating HRV-specific T cells constituted 0.2-1.2% of CD4+ T cells following enrichment, corresponding to a precursor frequency of 4/10,000 to 6/1,000 CD4+ T cells. Five days post-infection, numbers increased to 1.2-10% of enriched cells (precursor frequency = 3/10,000 to 6/1,000 CD4+ T cells). Additionally, virus-specific T cells with a central memory phenotype (CCR7+/CD45RO+) decreased, whereas effector memory (CCR7-CD45RO+) and lung-homing (CCR5+) cells increased. At day 21, HRV-specific T cell numbers contracted, or else were further expanded among a subset of subjects.

Conclusions: In subjects infected with HRV-39, circulating virus-specific CD4+ T cells expand and convert to an effector memory phenotype. Our findings demonstrate the feasibility of using tetramers containing epitopes of viral capsid proteins to accurately enumerate and phenotype HRV-specific CD4+ T cells in infected subjects.