**655** Relationship Between Exhaled Breath Temperature and Ear Temperature in Otherwise Healthy Persons during Febrile Infectious Illness

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**Rationale:** Exhaled breath temperature (EBT) is proposed as a non-invasive marker of inflammation in obstructive airway diseases. EBT and core body temperature (CBT) are not identical in normal persons. This study assesses associations between EBT and CBT during febrile illnesses.

**Methods:** Six generally healthy subjects, including 5 men, aged 42–64 years, had daily EBT assessed for 5 months and 2 years. All used hand-held devices specifically engineered for personal use, the X-halo®. They measured ear temperature (ET) to assess CBT. The EBT devices had data uploaded automatically on an Internet site. The subjects were instructed to record ET at 8-hour intervals if the measurement exceeded 37°C. Frequency of EBT measurements were increased during febrile illnesses.

**Results:** Six episodes of fever were documented during the study: 2 cases of rhinovirus infections in which EBT rose by 1.2–1.9°C above baseline, preceding by 24–72 hours a moderate increase of ET (up to 38°C); 2 cases of influenza in which EBT rose by >2.0°C about 6 hours before ET (up to 40°C); and 2 cases of bacterial infections, urinary and GI, in which EBT rose by = 1.0°C simultaneously with ET (up to 39°C).

**Conclusions:** EBT rises during incipient viral infections earlier than CBT as seen by ET, providing a window of opportunity for early treatment. EBT assessment allows early detection of illness in patients at risk of exacerbation of underlying obstructive airway diseases.

**656** Pulmonary Embolism in a Patient with Factor V Leiden Mutation, Presenting with Symptoms of Asthma Exacerbation

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**Rationale:** The differential diagnosis of asthma is extensive. Pulmonary embolism may present with similar symptoms to asthma. We present a case of pulmonary embolism in a patient with moderate persistent asthma and Factor V Leiden mutation who presented with symptoms of an asthma exacerbation.

**Methods:** Our patient was referred for evaluation and treatment of moderate persistent asthma.

**Results:** A 52 year old woman with a Factor V Leiden mutation presented with a history of moderate persistent asthma. Symptoms included cough, wheezing, and shortness of breath. She had been previously treated with montelukast with no significant benefit. She could not tolerate medications with long-acting beta agonists due to anxiety side effects. She was placed on fluicasone propionate 220 mcg two puffs twice daily with benefit. However, after two months, she developed worsening shortness of breath symptoms with wheezing. On exam, she had normal heart rate (80), respiratory rate (12), and blood pressure (110/70). Lung exam was clear to auscultation without any wheezes, rhonchi, or rales. Fluticasone dose was increased with some benefit in two days, however, mild symptoms still occurred. She then developed chest discomfort, which was exacerbated by arm movement. She was referred to emergency department for further evaluation, and CT pulmonary angiography revealed a pulmonary embolism. She was successfully treated with anticoagulant therapy.

**Conclusions:** This case demonstrates the importance of considering pulmonary embolism in the differential diagnosis of an asthma exacerbation, especially in a patient with a hypercoagulable state, such as Factor V Leiden.

**657** The Asthma Control Test (ACT): Does It Reliably Assess Asthma Control in African American Adolescents with Persistent Asthma?

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**Rationale:** Measurement properties of the Asthma Control Test (ACT) are lacking in adolescent asthmatics, particularly among African Americans who may under-report asthma symptoms and experience more asthma-related morbidity and mortality.

**Methods:** We propose that the accepted ACT scores used to determine asthma control would have poor agreement with physician assessment of control in African American adolescents. We conducted an ongoing prospective study of African American children ages 12-18 with persistent asthma. After completing the ACT and spirometry, the physician (blinded to ACT score) performed a standardized assessment of asthma control. Agreement of an ACT score > 19 with physician assessment of control was used to measure sensitivity, specificity, and Cohen κ.

**Results:** Data for 22 subjects who completed at least one visit were included in the analysis. Using a cut point of > 19 for asthma control, the ACT and physician’s assessment were somewhat in agreement (κ = 0.374, p = .08). In addition, a cut point of > 19 had a sensitivity of 77.8% and specificity of 61.5% in this population.

**Conclusions:** Our results show only a fair level of agreement between ACT score and physician assessment of asthma control in African American adolescents with persistent asthma. While not statistically significant, our data suggest that our effect size could be significant, but a larger sample size is needed in order to reach significance. The cut off score of 19 was less specific for determining asthma control in African American teens compared to previous studies of ACT accuracy in Caucasian adults.

**658** Characterization of Urge to Cough in Patients with the Common Cold: Results from a US Internet Survey

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**Rationale:** Cough is typically thought to be a reflex, requiring primaryafferent input to the brainstem, leading to reflex changes in respiration. Urge to cough represents an additional dimension, involving complex sensory and cognitive processes in higher brain centers. Individual experiences, perspectives, and management options for urge to cough were investigated.

**Methods:** An Internet survey exploring cough attributes in respondents who had contracted the common cold within the last 3 months was fielded in April 2015. Those with chronic cough were excluded. Demographics, urge to cough attributes and impact, and management choices were elicited.

**Results:** Of 19,530 screened, 2,708 met inclusion/exclusion criteria; 58% female; 85% white; 19% smoked tobacco; 8% used e-cigarettes. Urge to cough was experienced by 97.8% of respondents and was uncontrollable in 64%. Uncontrollability of urge to cough (62%), throat clearing (40.4%), and sore throat (35.6%) were the most bothersome aspects. Common triggers included talking, cold air, or changing position. Attempts to prevent/treat urge to cough occurred in 74.3%; over-the-counter (OTC) drugs/syrups or lozenges were at least somewhat effective in 83% and 78%, respectively. Prescriptions were used by 12.9%, and 89% felt they were “somewhat” or “very” effective. Healthcare provider (HCP) advice was elicited by 16% and received by 86%. Advice included prescription medications (66.5%), OTC medications (45.7%), herbal remedies (15.1%), and home remedies (12.6%); 96% followed HCP advice.

**Conclusions:** Urge to cough frequently accompanies the common cold. This Internet survey provided characterization of urge to cough attributes. Enhanced understanding of cough perception may lead to insights relevant to novel therapy.
Sterility Practices in Bronchodilator Administration in Allergy Office Settings

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Rationale: Due to the need for asthma diagnosis and surveillance, the bronchodilator reversibility test is commonly used. Yet, there are no complete, standardized guidelines for bronchodilator administration. Various methods are used to clean the Metered Dose Inhalers (MDIs), but some physicians may not even take sterility into account. We seek to determine what methods allergists use to administer bronchodilators and allergists’ opinion of bronchodilator sterility of their practice.

Methods: A questionnaire was approved and distributed by the American Academy of Allergy, Asthma, and Immunology (AAAAI) to all member allergists in North America. Responses were tabulated after a three-week period.

Results: Of the 487 allergists who responded, 83.98% use MDIs for bronchodilator reversibility testing, with 59.34% using MDIs with a spacer and 24.64% using MDIs without a spacer. Several allergists, or 58.52%, use a nebulizer to administer the bronchodilator. With regards to sterility with MDI use, of 449 respondents, 9.13% wipe inhalers with a cleansing agent, 18.71% use a new inhaler between patients, and 38.75% use a new disposable attachment for a reused inhaler, respectively. Only 69.25% of allergists felt that their bronchodilator administration was sterile. Notably, 14.05% of allergists felt their bronchodilator administration was unsterile, and 16.70% of members were unsure of sterility. Notably.

Conclusions: A significant number of allergists do not use sterile techniques when administering bronchodilators. This disregard for sterility can cause negative consequences for patients, such as the spread of infection. From this survey, it is evident that there is need for guidelines for sterile bronchodilator administration in allergy practices.

Serum Tryptase and Sputum Cellular Profile in Relation to Asthma Severity

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Rationale: Tryptase is released by mast cells (MC) along with histamine and serves as a marker of MC activation, which in turn contributes to asthma development, severity and tissue remodeling as well. The objective of this study is to investigate the potential role of MC activation and sputum cellular profile (CP) in asthma severity.

Methods: Based on spirometric FEV1%, subjects aged 20–40 years old were grouped into mild/moderate asthma group (mild/moderate group) (n=15), severe asthma group (severe group) (n=15) and healthy control group (control) (n=15). All groups have been subjected to clinical examination, plain chest x-ray, CBC, total serum IgE (tIgE), serum b-tryptase assay and induced sputum CP.

Results: A significant reduction in FEV1% was demonstrated in mild/moderate and severe groups compared with control (mean ± SD: 74.8 ± 3.1, 65.3 ± 8.4, 72.8 ± 2.3 respectively, p<0.0001). b-tryptase and tIgE, revealed a significant increase in mild/moderate and severe groups compared with control (b-tryptase: mean ± SD: 4.8 ± 1.1 & 13.3 ± 10.6, p<0.001 & 0.0001 respectively, tIgE: mean ± SD: 324.2 ± 137 & 2433.4 ± 880.5 respectively, p<0.0001 for both asthma groups). Significant sputum monocyte was only evident in mild/moderate asthmatics compared with control (mean ± SD: 87.3 ± 78.2 & 30.3 ± 14.4, p=0.01), indicating increased sputum monocyte/macrophage lineage in this group. While, severe group as compared to control, expressed a significant rise in sputum neutrophil CP (mean ± SD: 248.5 ± 97.5 & 173.3 ± 82.2 respectively, p<0.03). The mild/moderate group in comparison with control, showed significant blood eosinophilia (mean ± SD: 0.2 ± 0.1 & 0.1 ± 0.08 respectively, p=0.0001) and monocyteosis (mean ± SD: 0.5 ± 0.2 & 0.1 ± 0.01 respectively, p<0.0001).

Conclusions: MC activation with increased b-tryptase and sputum neutrophilic CP may reflect asthma severity.
Validation of an EHR Algorithm to Identify Adult and Pediatric Patients with Asthma in West Chicago

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RATIONALE: An electronic health record (EHR) algorithm to identify patients with asthma was developed. This algorithm was tested to identify asthma subjects and healthy controls among pediatric and adult patients.

METHODS: The EHR was queried from 1/1/2012 to 11/30/2014 at Rush University Medical Center (RUMC) and Cook County Hospital (CCH). Asthma cases required at least one meaningful clinical encounter with an asthma diagnosis (ICD-9 code 493.xx) and either a second encounter with an asthma diagnosis or current asthma medication prescription. Control patients required two meaningful encounters without an asthma diagnosis or asthma medication. A random sample of 100 children and 100 adults (50 asthma subjects, 50 controls) at each site were manually reviewed by two physicians. Agreement between the EHR algorithm and chart review was determined by kappa score, along with positive predictive and negative predictive values (PPV and NPV).

RESULTS: At RUMC, for the combined group, the agreement between algorithm classification and chart review was fair to good (κ = 0.51) with PPV = 75%, NPV = 76%. This was similar to that observed in the pediatric (κ = 0.68, PPV = 82%, NPV = 86%), and better to that observed in the adult (κ = 0.34, PPV = 68%, NPV = 66%) subgroups. At CCH, for the combined group, the agreement between the algorithm and chart review was excellent (κ = 0.81) with PPV = 84%, NPV = 97%. This was similar to that observed in the pediatric (κ = 0.80, PPV = 82%, NPV = 98%) and adult (κ = 0.82, PPV = 86%, NPV = 96%) subgroups.

CONCLUSIONS: The EHR algorithm demonstrated good to excellent positive and negative predictive values for identifying subjects with asthma in the combined age groups of the reviewed samples at both private and public hospitals in west Chicago.

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The Reference Value of Peak Expiratory Flow Rate of Children in China

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RATIONALE: The present study was established to determine the reference value and predicted equations of peak expiratory flow rate of healthy children in China.

METHODS: A school to school survey was carried out among the children aged 5 to 14 from five research centers of China: Guangzhou Suzhou, Chengdu, Xi’an and Beijing from Oct to Dec 2010. Finally, a total of 3169 children completed the survey and examination. Upon review of the questionnaire, children were excluded if they had: 1) a recent disease of the respiratory tract or a history of chronic respiratory disease; 2) a history of severe respiratory disease; 3) systemic disease with influence on the respiratory tract; 4) other significant disease with influence on the respiratory tract; 5) use of inhaled corticosteroids, bronchodilators or other medicines influencing the respiratory tract; and 6) household exposure to tobacco smoke.

RESULTS: 1. There were no significant differences of children’s height and weight between the five centers (both P > 0.05). 2. There was no significant difference between boys and girls in body height and weight. 3. In both boys and girls, home recorded PEF increased with height, age and weight (P < 0.001). 4. Home recorded PEF and hospital recorded PEF and FEV1 showed a very high correlation.

CONCLUSIONS: The correlation coefficients between home spirometer recorded PEF and height. The PEF values of Chinese children are similar with European and other Asian country.

Quantitative Validity of the Sgrq in Patients with Severe Asthma

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RATIONALE: The St George’s Respiratory Questionnaire (SGRQ) was developed for use in asthma as well as COPD, but there are limited data to demonstrate the psychometric properties of the SGRQ in patients with severe uncontrolled asthma.

METHODS: Psychometric properties of the SGRQ were tested using treatment-masked data from two clinical trials (MENSIA, SIRIUS) of mepolizumab, an anti-IL5 antibody, including: item and scale characteristics, reliability (test-retest and internal consistency), validity (convergent, discriminant and known groups), and responsiveness. Analyses were conducted on treatment masked data guided by an analysis plan developed post-hoc after study unblinding.

RESULTS: Internal consistency reliability was acceptable for the total score and all domains [r = 0.71 (symptoms) - 0.94 (total)]. Test-retest reliability was acceptable for the total score and 2 domains; the symptoms domain approached acceptable levels (r = 0.60-0.68). Construct validity was demonstrated with moderate to strong correlations with asthma symptoms score and the Asthma Control Questionnaire (ACQ-5) (r = 0.40-0.61 & 0.57 to 0.72, respectively); discriminant validity showed low correlations with FEV1 (% predicted), work absenteeism and nasal symptoms (r = 0.08-0.33, 0.01-0.34 & 0.02-0.33, respectively). Known groups validity was shown with significant differences in predefined groups of asthma control, baseline exacerbation history, exacerbation counts, and eosinophil counts. Mean SGRQ change score for ratings of mild improvement based on a patient global question were 3.4 and 7.1 counts, and eosinophil counts. Mean SGRQ change score for ratings of mild improvement based on a patient global question were 3.4 and 7.1

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667 Comparison of Clinical Usefulness Between Hypertonic Saline-Induced Sputum and Exhaled Breath Condensate in Asthma Patients

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RATIONALE: Exhaled breath condensate (EBC) and induce sputum are utilized in pathological analyses of asthma. However, there has been no report that directly compared cytokines and other components in EBC with that in induced sputum.

METHODS: The study was conducted in 104 Japanese adult patients with bronchial asthma (BA). EBC and induced sputum were collected at the same time and analyzed for 15 kinds of cytokines, chemokines, and chemical mediators using ELISA assays.

RESULTS: In the EBC, the proportion of data below the limit of detection (LOD) was 27% for histamine and more than 80% for 14 other variables. Particularly, all data were below LOD for TIMP-1, TGFB1, IL-4, etoxacin, IFN-γ, and IL-13. In the induced sputum, the proportion of data below LOD was more than 80% for IL-4 and IFN-γ, 60 to 80% for FGF, TIMP-1, PDGF AA, TGFB1, etoxacin, and MMP-9, 20 to 40% for TNF-α, IL-12, and IL-13, 14% for IL-5, and 4% for VEGF. The proportion of data below LOD was significantly higher in the EBC than in the induced sputum (p<0.05 – 0.001). Furthermore, observed values were generally higher in the induce sputum than in the EBC (p<0.05 – 0.001). In the analysis using FeNO and sputum eosinophil percentage as airway inflammation markers, VEGF in induced sputum was most highly correlated with inflammation in BA (p<0.05).

CONCLUSIONS: Cytokines, chemokines, and chemical mediators can be determined with higher accuracy in induced sputum than in EBC. Particularly, VEGF in induced sputum is important as a marker of airway inflammation.

668 Bronchodilator Reversibility Testing Methods By Practicing Allergists

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RATIONALE: Bronchodilator reversibility testing is used as a diagnostic test for asthma. This study seeks to gather information about methods of administration, type and amount of bronchodilator dose used, wait time before repeat spirometry, and compliance with American Thoracic Society (ATS) guidelines of four Albuterol doses and a wait time of 10-15 minutes before repeat spirometry in allergists’ offices.

METHODS: A questionnaire was approved and distributed by the American Academy of Allergy, Asthma, and Immunology (AAAAI) to all member allergists in North America and responses were collected over a three-week period.

RESULTS: Among 488 allergists who responded, 96.31% (n = 470) used bronchodilator reversibility tests. Albuterol, used by 93.90% (n = 462) of allergists, was the most common medication. However, 4.07% (n = 20) used non-recommended medications for reversibility testing. To administer medication, metered dose inhalers (MDI) with spacers were used by 59.34% (n = 289) of allergists, and without spacers by 24.64% (n = 120). Nebulizers were used by 58.52% (n = 285). Of those using MDIs, 23.21% (n = 81) delivered four puffs, 58.74% (n = 205) delivered two puffs and 10.32% (n = 36) delivered 1, 3, 6 or 8 puffs of medication, respectively. 63.01% (n = 307) of allergists waited 10-15 minutes before performing repeat spirometry, while 27.1% (n = 132) waited >15 minutes and 9.86% (n = 41) only waited <10 minutes.

CONCLUSIONS: The results indicate great variability in bronchodilator administration among allergists, and that a significant percentage of allergists do not follow the ATS guidelines for bronchodilator reversibility testing methods. Our data underscores the necessity of improved education on effective administration of bronchodilator tests in allergy practices.

669 Classification of Asthma in a Resident Based Primary Care Clinic

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RATIONALE: Asthma is a chronic inflammatory airway disease characterized by reversible airflow obstruction and bronchospasm. Its prevalence has increased significantly since the 1970s; as of 2011, 235 million people worldwide were affected, resulting in 250,000 deaths annually. The most common symptoms include: cough, wheezing, chest tightness, and shortness of breath. Asthma is clinically classified into four severity categories according to symptom frequency, FEV1, or peak expiratory flow rate. A reliable system for diagnosis and severity classification is essential to guide treatment and decrease death.

METHODS: Our study examined adherence to National Guidelines for asthma diagnosis and classification of disease severity in the University Hospital resident based primary care clinic. This was a retrospective chart review of consecutive patients seen for asthma between January-June 2013. RESULTS: 197 unique visits were reviewed using Epic EMR. 78% of patients were female and the mean age was 50 years (SD = 13). Categorization of asthma based on symptom severity was documented in 22% of notes. PFTs were documented in 30% of the patients. COPD was an accompanying diagnosis in 15% of the encounters; of these 76% had PFTs reported. Standardized clinical evaluation of weekly albuterol use, recent hospitalizations and presence of nighttime symptoms was documented in 26%, 17% and 11% of the notes, respectively.

CONCLUSIONS: It is evident that characterization of asthma is suboptimal in the resident primary care clinic. An implementation to improve classification of, and ultimately treat patients is developing an Epic SmartSet using applicable questions. Future studies include analyzing charts post-SmartSet implementation to assess for improvement.
Comparison of Non-Invasive Methods for Detecting Exercise-Induced Bronchoconstriction in Asthmatic Children

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RATIONALE: Non-invasive methods used to assess asthma include the measurement of fractional exhaled nitric oxide (FeNO), serum periostin levels, and the mannitol provocation test. Exercise-induced bronchoconstriction (EIB) is a distinct form of bronchial hyperresponsiveness (BHR), and is a cardinal feature of asthma. This study examined the utility of non-invasive methods in detecting EIB in asthmatic children.

METHODS: The study enrolled 41 asthmatic children between 6 and 15 years old. We measured FeNO and serum periostin levels and performed pulmonary function tests at baseline and mannitol inhalation. An exercise bronchoprovocation test was used for EIB diagnosis, the results of which were considered positive with a 15% or greater decrease in forced expiratory volume in 1 second (FEV1) after exercise.

RESULTS: Twenty six (63.4%) subjects with asthma showed positive exercise challenge tests. The maximum decrease in %FEV1 after exercise was positively correlated with FeNO (r = 0.468, p = 0.008), the response–dose ratio (RDR) to mannitol (r = 0.361, p = 0.046), and serum periostin level (r = 0.373, p = 0.039) in asthmatics with EIB. To discriminate between asthmatics with and without EIB based on non-invasive methods, receiver operating characteristic curve analyses were performed. No significant difference was observed among the area under the curve values for FeNO, RDR to mannitol, or serum periostin levels.

CONCLUSIONS: FeNO levels, BHR to mannitol, and serum periostin levels were significantly correlated with maximum decreases in %FEV1 after exercise. No significant difference was observed regarding the diagnostic properties of these methods for detecting EIB in asthmatic children.

Exhaled Nitric Oxide Utility in Predicting Asthma Exacerbations

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RATIONALE: Exhaled nitric oxide (eNO) has been shown to be a marker of eosinophilic inflammation in asthma. Prior studies have yielded mixed results regarding whether eNO levels are predictive of future asthma exacerbations. We hypothesized that there is an association between eNO level and asthma exacerbations, and that this association varies by FEV1.

METHODS: We conducted a retrospective chart review of 161 patients from a large allergy and asthma practice in Seattle. Patients were 18 years and older, had a diagnosis of asthma, and had undergone eNO testing between January 2012 and June 2014. Patients were stratified by FEV1 level: < 60%, between 60-80%, and >80%. eNO was modeled continuously rather than by choosing pre-determined cutoff values, as there is not an established clinically relevant threshold for eNO. Poisson regression models with robust standard errors were used to study the adjusted association between the number of exacerbations requiring prednisone and eNO. We controlled for FEV1, gender, height, BMI, smoking history, history of IgE-mediated allergies, allergic rhinitis, and positive inhalant skin tests.

RESULTS: There was no association between eNO levels and number of asthma exacerbations (p = 0.98). There was also insufficient evidence to conclude that the associations between number of exacerbations and eNO among individuals with FEV1 60-80% or FEV1 <60% differed from patients with FEV1 >80% (p = 0.06).

CONCLUSIONS: We did not find eNO levels to be a useful clinical marker in predicting risk of future asthma exacerbations, regardless of FEV1 level.

Association Between Asthma Control Test, Peripheral Eosinophil Counts, and Serum Total Immunoglobulin E Levels in Severe Asthmatics

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RATIONALE: There is a lack of published data surrounding the association between asthma control test (ACT) scores, absolute eosinophil counts, and serum total immunoglobulin E (IgE). This study aims to evaluate this association to better understand asthma phenotypes.

METHODS: The charts of 63 severe asthma patients at Montefiore’s Asthma Center (MAC) in the Bronx, NY were reviewed. Patient criteria included at least one asthma-related emergency department visit or asthma-related hospitalization within the last 12 months. The baseline ACT score, absolute eosinophil counts, and serum total IgE were analyzed and correlations were determined using the Spearman rank test. Patients using systemic corticosteroids in the 4 weeks prior to the ACT score collection were excluded.

RESULTS: Among the 63 patients, 17% were male, with a mean age of 50 years (SD = 15). Most of these patients were minorities (41% Hispanic, and 46% African-American). The median for ACT score was 10 (5 – 23), absolute eosinophil count was 200 (0 – 1700 cells/µL), and serum total IgE was 302 (9.7 – 4620 IU/mL). The mean time interval between the evaluation of ACT scores and blood collection was 10 days (SD = 15). ACT scores negatively correlated with absolute eosinophil counts (rho = -0.316, p = 0.012). There was no significant correlation between ACT scores and serum total IgE (rho = 0.065, p = 0.614).

CONCLUSIONS: Absolute eosinophil counts significantly and negatively correlated with ACT scores among MAC patients. Additional studies are needed to determine if this correlation might help to phenotype and further assess severe asthma patients.
673 Estimated Prevalence of AERD in Patients with Diagnosis of Asthma Identified with a Symptom-Based Assessment Questionnaire

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RATIONALE: The estimated prevalence of aspirin exacerbated respiratory disease (AERD) among asthma patients is 10-20%. There is no ICD-code for AERD. We sought to estimate AERD prevalence among asthma patients seen at Allergy, ENT, and Pulmonary Clinics at Montefiore Medical Center using a combination of specific diagnoses confirmed by a symptom-based questionnaire.

METHODS: Patients seen between 2008-2013 with a combination of ICD-9 diagnoses of asthma, nonsteroidal anti-inflammatory drugs (NSAID) allergy, and either nasal polyps or chronic rhinosinusitis were identified. A questionnaire to assess AERD-related symptoms was administered via telephone.

RESULTS: 4064 patients had ICD-9 diagnoses of asthma. Of these, 232 (7%) had ICD-9 diagnoses of NSAID allergy and either nasal polyps or chronic rhinosinusitis. One hundred forty-one patients agreed to participate in telephone interviews. The majority was female (82%), with mean age 52 (+/-SD 15). Sixty-five patients were categorized as likely having AERD based on reported asthma attacks with NSAID ingestion. The estimated AERD prevalence among asthma patients at Montefiore was 1.6%. Thirty-three patients (51%) with historically-diagnosed AERD reported frequent sinus infections, 31 patients (48%) had 21 sinus surgery, and 34 patients (54%) had poor or no sense of smell. Seventy-six patients reporting stomach pain, hives or angioedema, and no asthma symptoms after NSAID ingestion were identified as “not having AERD”.

CONCLUSIONS: The estimated low AERD prevalence among patients with asthma indicates that AERD is not a simple combination of diagnoses and is likely underdiagnosed. Introducing AERD-specific ICD code could raise awareness about this condition and lead to appropriate treatment choices (aspirin desensitization).

674 Asthma Control Test Composite Score May Not be Superior to Assessments of Rescue Inhaler Use for Predicting Severe Asthma Exacerbations

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RATIONALE: Current U.S. guidelines recommend the Asthma Control Test (ACT) for assessing disease control and selecting treatment. The ACT was initially validated based on concurrence with specialist opinion. The goal of this study was to prospectively assess the ACT and its component questions for their utility in predicting severe exacerbations.

METHODS: Study individuals were participants in the Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-ethnicity (SAPPHIRE) and had the following characteristics: age ≥18 years, physician diagnosis of asthma, and membership in a health system serving southeastern Michigan. Participants underwent a baseline evaluation that included the ACT. Severe asthma exacerbations, defined as the need for oral steroids, emergency room visit, or inpatient admission, were identified prospectively using pharmacy claims and patient encounters. Receiver-operator curves were used to assess predictive utility, and the area under the curve (AUC) was used for comparisons.

RESULTS: Two hundred thirty two (23.4%) of the 990 participants experienced an asthma exacerbation in the 6 months following their baseline evaluation. The ACT composite score had an AUC of 0.675. With the exception of the rescue inhaler use question, the composite ACT score was significantly better in predicting exacerbations when compared to the 4 other ACT questions. Pharmacy records of concurrent SABA MDI use were equally predictive of exacerbation when compared to the composite ACT score.

CONCLUSIONS: Our study demonstrates that while the ACT is predictive for exacerbations, the composite score may not be superior to assessing SABA rescue use alone when predicting risk of serious asthma exacerbations.

675 Leukotriene C4 Synthase Expression in Sputum Correlates with Disease Severity Amongst Patients with Different Clinical Phenotypes of Asthma

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RATIONALE: Amongst patients with asthma, clinical presentation and disease severity are well known to be heterogeneous. Recently, three distinct clinical phenotypes of asthmatic patients have been identified based on analysis of the sputum transcriptome. These have been classified as transcriptomic endotype of asthma (TEA) clusters 1-3, with clusters 1 and 2 consisting of patients with severe phenotypes and cluster 3 patients having relatively benign courses. We sought to characterize the expression of arachidonic acid metabolites as contributing factors to the pathophysiology of asthma in these TEA clusters.

METHODS: TEA clusters were identified through previously described methods. Expression of arachidonic acid pathway metabolites in sputum RNA samples was determined for patients in each TEA cluster using Affymetrix HuGene 1.0 ST gene arrays. Comparison of the average expression between TEA clusters was performed with student t-tests and Wilcoxon Rank-Sum tests.

RESULTS: Patients in different TEA clusters were noted to have statistically different levels of leukotriene C4 synthase (LTC4S) expression in the sputum. The level of LTC4S expression was significantly higher in TEA cluster 1 compared to TEA clusters 2 and 3. The expression of LTC4S was also significantly higher in TEA cluster 2 compared to TEA cluster 3.

CONCLUSIONS: Differences in the expression of LTC4S and, by extrapolation, the level of circulating leukotrienes in sputum appear to correlate with disease severity in patients with different phenotypes of asthma. Further investigation into the expression of inflammatory markers may help elucidate differences in the pathophysiology of asthma in these patients and aid in thoughtful implementation of therapeutic agents.
Cholinergic Modulation in Elderly Asthmatic Patients Compared to Young Asthmatic and Elderly Non-Asthmatic Patients

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RATIONALE: An increased parasympathetic activity may play a modulatory role in the pathogenesis of bronchial asthma. Early reports suggest a better effect of anticholinergic agents in elderly asthmatics. However, neurogenic influences have not been assessed in this population.

AIM: To compare measures of cholinergic modulation in elderly (EA) and young (YA) asthmatic patients and in elderly non asthmatic (ENA) patients.

METHODS: Twenty-two elderly (>60 years old; 10 EA and 12 ENA) and 15 younger (range 18 to 35 years) asthmatic patients had pulmonary function measurements and a 24h ECG Holter monitoring. Heart rate variability (HRV) was calculated during 3 time periods: 1) 24 hours, 2) daytime (between 8 AM and 8 PM) and 3) nighttime (between 12 AM and 6 AM). High frequency (HF) domain, the square root of the mean squared differences of successive RR intervals (rMSDD) and the proportion of interval differences of successive mean RR intervals >50 ms (pNN50) were calculated and used as parasympathetic activity indices.

RESULTS: Asthmatic patients showed similar asthma severity and were calculated and used as parasympathetic activity indices. Elderly asthmatics have increased daytime variability (HRV) was calculated during 3 time periods: 1) 24 hours, 2) nighttime (between 12 AM and 6 AM). High frequency (HF) domain, the square root of the mean squared differences of successive RR intervals (rMSDD) and the proportion of interval differences of successive mean RR intervals >50 ms (pNN50) were calculated and used as parasympathetic activity indices.

RESULTS: Asthmatic patients showed similar asthma severity and maintenance therapy needs. EA had more marked airway obstruction (FEV1/FVC, P = 0.03). Heart rate was higher in YA than EA (P = 0.002) and in all 3 groups during daytime compared to nighttime (P < 0.001). This was associated with higher parasympathetic indices during nighttime (rMSDD, pNN50) in YA (P = 0.002 and P = 0.0003, respectively) and ENA (P = 0.01 and P = 0.05, respectively).

CONCLUSIONS: Elderly asthmatics have increased daytime parasympathetic activity. This may contribute to the lower pulmonary function observed in this population.

Exacerbation Reduction in Severe Eosinophilic Asthma Based on Eosinophil Thresholds

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RATIONALE: Previous studies showed mepolizumab significantly reduces exacerbations in patients with severe eosinophilic asthma. This study assessed the effect of mepolizumab on the frequency of exacerbations in severe eosinophilic asthma based on different baseline blood eosinophil thresholds.

METHODS: A meta-analysis (GSK ID 204664) of two randomized, double-blind placebo-controlled studies (MEA112997/MEA115588) with mepolizumab or placebo plus standard of care given every 4 weeks in 1192 patients with severe asthma treated with high dose ICS with or without maintenance oral corticosteroids plus a controller, a history of >4 exacerbations in the previous year and evidence of eosinophilic inflammation. This post-hoc analysis was conducted using a negative binomial regression model, accounting for study. All mepolizumab doses were combined for this analysis.

RESULTS: The overall reduction in exacerbations with mepolizumab (N = 846) compared with placebo (N = 346) was 47% (95% CI: 38% to 56%, P < 0.001). The exacerbation reduction with mepolizumab compared with placebo based on a threshold ≥150, ≥300, ≥400 and ≥500 was 52% 59%, 66%, 70% respectively. The reduction in exacerbations with mepolizumab vs. placebo based on history of blood eosinophils ≥300 cells/µL in the past year and baseline blood eosinophils <150 cells/µL was 33%.

CONCLUSIONS: Mepolizumab significantly reduced the frequency of exacerbations by >50% at different thresholds ≥150 cells/µL. For patients with a baseline eosinophil count <150 cells/µL, clinically relevant reductions were observed in those with ≥300 cells/µL in the past year. These results support the use of blood eosinophils as a marker to predict exacerbation reduction with mepolizumab in severe asthma. Funding: GSK (NCT01000506, NCT01691521).

Baseline Sputum Parameters in Normals, Asthmatics, COPD, Atopics, Smokers and Ex-Smokers

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RATIONALE: Induced sputum is widely used in both research and industry-based clinical trials to evaluate changes in cellular and biochemical constituents in the central airways. Data is lacking however on baseline sputum parameters in large cohorts of healthy and diseased subjects.

METHODS: Uniform methods for induction (3, 4, 5%, 21 minutes) and processing (plug selection with DTT) were used on normals (N = 148), asthmatics (N = 97), COPD (N = 200), atopics (N = 195), otherwise healthy smokers (N = 43), atopic smokers (N = 45) and ex-smokers (N = 47). Endpoints examined included initial raw sample weight, selected plug weight, total and differential cell counts, cell viability, induction success, slide quality score and slide readability.

RESULTS: COPD subjects produced significantly less raw sputum (2667 mg) and selected plug material (1320 mg) but yielded significantly (p < 0.05) higher total cell counts (4.7 x 10^6 cells; 6420 cells/mg) and PMN levels (80%; 5831 pmn/mg) vs all other subject cohorts. Percent PMN levels in normals and asthmatics were equal (28%) but asthmatics had the lowest absolute PMN/mg count (259 PMN/mg) vs all subjects. Interestingly, COPD subjects demonstrated the highest and lowest % Eos (2.2%) and % Lym (0.3%), respectively vs all subjects. Cell viability was lowest among atopics (65%) and highest among COPD (78%). Asthmatics demonstrated the poorest ability to produce sputum (71% success rate) and smokers were the best (95%). Slide quality score and slide readability did not differ significantly among the subject cohorts analyzed.

CONCLUSIONS: Baseline sputum parameters differ among healthy and diseased subjects. These differences can inform important decisions regarding subject recruitment, study design and optimal application of sputum.
Bronchodilator Reversibility Testing Selection Criteria and Interpretation in Allergy Office Settings

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RATIONALE: Bronchodilator reversibility testing can be useful as a diagnostic aid for asthma. ATS guidelines for reversibility are defined as FEV1 of 12% and 200 mL above baseline values. However, use of these criteria in allergy practices has not been studied. This study seeks to gather information about selection criteria and interpretation of bronchodilator reversibility tests in allergy practices.

METHODS: An electronic survey was sent to North American allergists belonging to the American Academy of Allergy, Asthma, and Immunology (AAAAI). After a three week period, collected responses were analyzed.

RESULTS: 496 members of the AAAAI participated in the survey. Of allergists that use bronchodilator reversibility testing, most (95.7%) administered the test to a majority of new patients with asthma symptoms (99.36%). One-fourth of allergists (25.61%) administered the test to a majority of new patients without asthma symptoms (90.38%). 374 allergists (76.64%) administered the test to a majority of new patients with a history of asthma (95.51%). Over half of allergists (55.74%) administered the test to a majority of follow-up patients with asthma (92.31%). 13.9% of allergists use cut-off points other ATS guidelines for interpreting positive bronchodilator reversibility tests. After a negative test, most allergists’ treat empirically, generally with inhaled corticosteroids (42.56%) or order a provocation test (27.67%).

CONCLUSIONS: Bronchodilator reversibility tests are most commonly administered for diagnosing new patients with asthma. A significant number of allergists do not follow ATS guidelines for interpreting results. This emphasizes a need for improved education on the selection criteria and interpretation of bronchodilator reversibility tests among allergists.

Analysis of Salivary Micro-RNAs and Allergen Profile in Patients with Asthma

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RATIONALE: Salivary micro-RNAs (miRNAs) have un tapped potential as non-invasive biomarkers to diagnose and phenotype asthma. We previously demonstrated that miRNAs are differentially expressed in the saliva of asthmatics compared to non-asthmatics. We sought to determine whether these could be used as a tool to characterize phenotypic differences in asthmatics.

METHODS: After IRB approval, saliva was collected from asthmatics (n=26) and miRNAs were isolated by guanidium hydrochloride/phenol-chloroform extraction, reverse transcribed using a poly-A, 3’adapter system, and analyzed by quantitative real-time PCR. An unsupervised cluster analysis of miRNA expression was performed, using a panel previously found to be dysregulated in saliva of asthmatics (miR-200b, -146a, -92b, -330-5p, -200c, and Let7a). Two-tailed, unpaired T test (p<0.05 considered significant) was used to measure differences between clusters.

RESULTS: Two clusters of asthmatics were identified (group A, n=12 subjects; group B, n=14 subjects). Statistical differences were discovered between these groups for age (36.6±14.8 in Group A vs 51.8±13.6 in Group B, p=0.012), FEV1% predicted (92.3±13.6 in Group A vs and 67.5±24.1 in Group B, P=0.004), and total number of aeroallergen sensitivities (mean number of positive aeroallergen tests was 10.7±6.5 in Group A, and 5.21±4.0 in Group B, P=0.015). Eosinophil count was not statistically different (340±284 in Group A vs 378±251 in Group B, P=0.7609).

CONCLUSIONS: Group A was associated with lower salivary miRNA concentrations and contained subjects that were younger, had better lung function, and were more allergic. Salivary miRNAs may have utility in phenotypic analysis of asthmatics and require further study.

Efficacy and Safety of Albuterol Multidose Dry Powder Inhaler (MDPI) Versus Placebo in Children With Asthma

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RATIONALE: A chronic-dose study of the efficacy and safety of albuterol MDPI in children with asthma.

METHODS: This phase 3, double-blind, parallel-group, 3-week study (ABS-AS-303; NCT02126839) included children (aged 411 years) with asthma and predose FEV1 of 50%–95% of predicted. After a 14-day run-in period during which patients continued their current asthma therapy and received single-blind placebo MDPI, patients were randomized to albuterol MDPI, 90 mcg/inhalation, 2 inhalations 4 times daily (total daily dose, 720 mcg) or placebo for 3 weeks. Pulmonary function testing occurred at clinic visits on days 1 and 22. Efficacy and safety were evaluated by measuring area under the baseline-adjusted percent predicted FEV1 time curve over 6 hours postdose (PPFEV1.AUC0–6) and adverse events.

RESULTS: The full analysis set included 184 patients. Albuterol MDPI-treated patients experienced significantly (P<0.0001) greater improvements in PPFEV1.AUC0–6 over the 3-week study versus placebo recipients (least squares mean difference of 25% in favor of albuterol). The benefit of albuterol (mean change in PPFEV1) was evident 5 minutes after dosing and lasted several hours; maximal effect was noted 1–2 hours postdose. Albuterol MDPI was well tolerated.

CONCLUSIONS: Albuterol MDPI, administered chronically for 3 weeks, improved pulmonary function in pediatric patients significantly better than placebo. Clinical effects were evident within 5 minutes after dosing and were maintained for >2 hours. Four-times-daily administration was generally well tolerated in pediatric patients.

Effects of Roflumilast on Airway Hyperresponsiveness (AHR)

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RATIONALE: Roflumilast has been shown to treat asthma and chronic obstructive pulmonary disease (COPD) in patients via inhibiting phosphodiesterase 4 (PDE-4). Since its method of action remains poorly elucidated, we used a mouse model to explore its mechanism, hypothesizing that it would have a similar effect to its role in human patients.

METHODS: Whole body plethysmography (Penh) data on wild C57B1/6 mice (WT) were collected. Each experiment was set up so a sample of mice was either pre-exposed to room air, roflumilast, albuterol, IL-13, or a combination of them before they were exposed to increasing concentrations of methacholine (MCh). This allowed us to develop a dose response curve (DRC) quantifying the extent of airway hyperresponsiveness (AHR) under each condition.

RESULTS: Provocative dose percent increase (PDPi) was used to indicate a valid DRC for each treatment and to analyze the differences between treatments. The albuterol treated mice (202.53%) had lower PDPi than controls (256.57%). Interestingly, roflumilast-treated group had higher PDPi (451.53%) than controls and was partially reversed via albuterol (339.44%). Asthma and COPD conditions induced in mice by IL-13 did not show any signs of bronchodilation or bronchoprotection when treated with roflumilast or albuterol: 894.57% or 631.36% respectively—compared to IL-13 treated mice (319.24% at 48 hours and 387.02% at 72 hours). Although the time factor varied, it was clear that treatment with roflumilast or albuterol did not restore AHR back to normal conditions.

CONCLUSIONS: In conclusion, roflumilast does not cause bronchodilation or bronchoprotection in naive mice or airway inflamed mice—induced by IL-13.
Montelukast Is a Better Controller in Obese Atopic Asthmatics

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RATIONALE: The concomitant rise in the prevalence of asthma and obesity has suggested an association between the two. Two phenotypes of obesity-associated asthma exist; early-onset atopic and late-onset non-atopic asthma. Animal and human studies suggest involvement of leptin and leukotrienes in inflammatory pathways. We hypothesized that montelukast is a more effective controller of early-onset atopic asthma in overweight/obese (O) compared to normal (N) weight asthmatics.

METHODS: Mild to moderate persistent early-onset asthmatics on inhaled corticosteroids (ICS) were randomized in a double-blind controlled manner to receive montelukast (M) or placebo (P). Treatment with M was compared to P at week 24 for the primary outcome measure, Asthma Control Test (ACT) scores, and secondary outcome measures (spirometric measures, exhaled nitric oxide, total ICS dose, serum leptin and urinary leukotriene E4). Mean difference was calculated as M group minus P group with corresponding 95% confidence intervals.

RESULTS: The two treatment groups were comparable at baseline. At week 24, the O group, but not the N group, treated with M demonstrated a significantly higher ACT score than P (25.0 vs 15.7 respectively, p<0.01). ACT score differed significantly between M and P groups (24.5 vs 18.1 respectively, p<0.01), overall, but not for any other clinical or laboratory parameters assessed. There were no significant interactions between treatment group and weight subgroup for any parameters of interest.

CONCLUSIONS: Montelukast is a more effective controller medication among obese atopic early-onset compared to normal weight asthmatics. These data underscore the need to elucidate the underlying mechanism and individualize the management of obesity-associated asthma.

Feasibility of Using Treatment Response Thresholds for Lung Function and Asthma Symptom Variables As Indicators of Asthma Control in Patients with Moderate to Severe Asthma

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RATIONALE: Simple tools are needed in clinical practice for monitoring asthma control.

METHODS: This post hoc analysis (12-week study; NCT00652002) in moderate-to-severe asthma patients assessed the relationship between loss of asthma control (defined as withdrawal due to predefined asthma event during the treatment period) and response thresholds for lung function and symptoms. Response thresholds were based on mean changes from baseline during treatment period: ≥100-mL improvement in forced expiratory volume in 1 second (FEV1), ≥30-L/min improvement in evening peak expiratory flow (PEF), and ≥0.5-point decrease in asthma symptom score (4-point scale). Data were evaluated overall and by treatment (twice-daily budesonide [BUD]/formoterol [FM] pMDI 320/9 µg [n=107], BUD pMDI 320 µg [n=93], FM DPI 9 µg [n=98], or placebo [n=91]).

RESULTS: Overall, loss of asthma control was considerably more likely among non-responders (threshold not achieved) versus responders (threshold achieved) based on FEV1 (32.7% [n=72/220] vs 11.8% [20/169]), evening PEF (29.6% [89/301] vs 3.4% [3/87]), and asthma symptom score (27.9% [88/315] vs 5.4% [4/74]). These findings were consistent across treatments; however, loss of asthma control was less common with BUD/FM (nonresponders vs responders: FEV1 [15.4% vs 4.4%], PEF [14.0% vs 2.0%], symptoms [11.7% vs 0.0%] and BUD (FEV1 [21.6% vs 11.9%]; PEF [19.4% vs 6.3%]; symptoms [18.2% vs 12.5%]) versus FM (FEV1 [43.3% vs 18.4%]; PEF [38.6% vs 6.7%]; symptoms [41.0% vs 5.0%]) and placebo (FEV1 [41.4% vs 23.8%]; PEF [40.5% vs 9%]; symptoms [39.8% vs 12.5%]).

CONCLUSIONS: Findings confirm the feasibility of using specific response thresholds in monitoring asthma control during initiation of treatment. Supported by AstraZeneca, LP.
Dose-Ranging Efficacy and Safety Study of Albuterol Multidose Dry Powder Inhaler (MDPI) vs Albuterol Hydrofluoroalkane (HFA) and Placebo MDPI in Children With Asthma

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RATIONALE: Dose-ranging efficacy and safety study to evaluate albuterol MDPI and albuterol HFA relative to placebo in children with persistent asthma.

METHODS: A phase 2, multicenter, double-blind, double-dummy, single-dose, 5-period, crossover study (ABS-AS-202; NCT01899144) randomized pediatric patients (aged 4–11 years) with persistent asthma and prestudy FEV1 of 60%–90% of predicted normal to 1 of 10 treatment sequences containing albuterol MDPI (90 and 180 mcg), albuterol HFA (90 and 180 mcg), and placebo MDPI+placebo HFA. Efficacy was evaluated by measuring area under the baseline-adjusted percent-predicted FEV1-time curve over 6 hours postdose (PPFEV1AUC0-6), and safety was evaluated by adverse events.

RESULTS: The full analysis set included 61 patients. Albuterol MDPI and albuterol HFA significantly improved PPFEV1AUC0-6 vs placebo (Pd=0.0107). Improvement in PPFEV1AUC0-6 vs placebo with albuterol MDPI at 90 and 180 mcg was similar (21.2±4.87 [95%CI 11.60,30.81] and 22.6±4.87 [95%CI 13.00,32.20], •hour, respectively). Improvement with albuterol HFA 180 mcg was significantly [P=0.0226] greater vs albuterol HFA 90 mcg (23.7±4.85 [95%CI 14.13,33.23] and 12.5±4.85 [95%CI 2.93,22.05] •hour, respectively). All doses of albuterol were generally well tolerated.

CONCLUSIONS: Albuterol MDPI significantly improved pulmonary function vs placebo in children with asthma. Improvements for albuterol MDPI 90 and 180 mcg were similar; a dose-response effect was observed with albuterol HFA. Results suggest that relief of asthma symptoms in children may be managed adequately with albuterol MDPI (1–2 inhalations). No new safety concerns were noted with albuterol MDPI, and its safety profile is consistent with that of albuterol HFA.

Comparison of Treatment Modalities for Inpatient Asthma Exacerbation Among U.S. Pediatric Hospitals

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RATIONALE: Asthma is the leading cause of hospitalization in the pediatric population and impacts quality of life. Identifying the most effective therapies for severe asthma exacerbations requiring hospitalization based on length of stay (LOS) and Pediatric Intensive Care Unit (PICU) admission outcomes is not well established.

METHODS: We utilized the Pediatric Health Information System (PHIS) database, a national billing code database of 43 free-standing pediatric hospitals, to identify children ages 6-17 hospitalized for asthma from 2010-2014 to determine differences in use of asthma therapies in relation to LOS and PICU admission. All results were adjusted for illness severity based on diagnosis-related severity code.

RESULTS: 59,114 hospital admissions for asthma were evaluated. 60.8% were male with 31.0% White, 53.3% Black, 1.4% Asian, 0.2% Pacific Islander, 0.5% American Indian, and 11.4% Other races. Hispanic ethnicity comprised 16.9% of the population. Whites had 3% shorter LOS (p=0.04) and 18% fewer PICU admissions (p=0.006). American Indians and Other races had 54% (p=0.002) and 25% (p<0.001) fewer PICU admissions, respectively. Terbutaline was associated with 48% longer LOS (p<0.001) and higher risk of PICU admission (OR=4.32, p<0.001). Magnesium sulfate was associated with 29% longer LOS (p<0.001) and higher risk of PICU admission (OR=6.93, p<0.001). Heliox was associated with 24% longer LOS (p<0.001) and higher risk of PICU admission (OR=4.30, p<0.001).

CONCLUSIONS: Treatment with terbutaline, magnesium and heliox were each separately associated with longer LOS and risk of PICU admission, independent of severity of the admission. Future analysis will determine treatment-related outcomes based on regional treatment variations in the U.S.

Unsuccessful Aspirin Desensitization in Minority Patients with AERD: Association with Increased Eosinophilia and Sinus Surgery Timing

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RATIONALE: Aspirin desensitization is an effective long-term treatment for aspirin-exacerbated respiratory disease (AERD) but this has been insufficiently studied in minority populations.

METHODS: Outcomes of aspirin desensitization (650 mg twice daily) in AERD patients were assessed at four weeks by determining changes in the Asthma Control Test (ACT) and forced expiratory volume in one second (FEV1). RESULTS: Of 34 patients recruited, 29 self-identified as ethnic minorities (19 African-Americans, 10 Hispanics). Eleven were successfully desensitized (all 5 Caucasians and 6 minorities). Twenty-three patients either had no change in symptoms (2 African-Americans, 4 Hispanics) or had worsening of symptoms (14 African-Americans, 3 Hispanics) (p<0.01). Of the 17 patients who worsened on aspirin, 5 had persistent GI and respiratory symptoms and declined further desensitization. Twelve continued aspirin for up to 4 weeks. Their FEV1 decreased from 80% predicted (IQR 71-93) to 69% (IQR 46-88) (p=0.002), and ACT scores decreased from 17 (IQR 14-22) to 10 (IQR 6-14.5) (p=0.003). These changes were accompanied by increased peripheral eosinophilia from 0.6 μ/L (IQR 0.4-0.8) to 1.0 μ/L (IQR 0.7-1.6), p=0.01. In the desensitization failure group, there was a significant correlation between FEV1% decrease and increase in eosinophilia after the desensitization failure group, there was a significant correlation between FEV1% decrease and increase in eosinophilia after desensitization (r=0.74, p<0.01).

CONCLUSIONS: Aspirin desensitization in this minority population was less successful than in Caucasians. Desensitization-induced eosinophilia was associated with poorer asthma control. No ESS and ESS>6 months prior to desensitization was associated with unsuccessful treatment in minorities.
Once-Daily Tiotropium Respimat® Add-on to at Least Ics Maintenance Therapy in Patients with Symptomatic Asthma: Methodology of Modeling Analyses By Serum IgE and Blood Eosinophil Levels

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RATIONAL: Conventional subgroup analyses in late-phase clinical trials are often conducted by calculating relative treatment effects for each trial endpoint within subgroups defined by baseline characteristics. For continuous variables, selection of cut-off values by which to define subgroups is a matter of discussion and convention. To overcome this issue, modeling of tiotropium Respimat® treatment effects was performed for biomarkers, i.e. total serum IgE and blood eosinophils, in patients with moderate or severe symptomatic asthma.

METHODS: In 4 Phase III randomized, double-blind, placebo-controlled studies of tiotropium Respimat® add-on therapy in patients with moderate (2 replicate trials: NCT01172808/NCT01172821) or severe (2 replicate trials: NCT00772538/NCT00776984) asthma, total serum IgE and blood eosinophil data were collected at screening. Modeling was applied to pre-defined trial endpoints: asthma exacerbations (Cox regression); patient-reported outcomes, e.g. ACQ/AQLQ (logistic regression); and lung function expressed as trough and peak FEV1 (mixed-model repeated measures).

RESULTS: Rather than obtaining relative treatment effect estimates for each subgroup (e.g. hazard ratios, odds ratios, or mean differences, plus confidence intervals), modeling has the advantage that these estimates are calculated over the whole range of IgE and eosinophil values. The beneficial effect of tiotropium Respimat® in moderate and severe asthma was observed for all endpoints across a broad range of IgE and eosinophil values.

CONCLUSIONS: Modeling of treatment effects, while yielding results comparable with conventional subgroup analyses, provides a continuous profile of relative treatment effects without explicit reference to cut-off values conventionally used to define subgroups. All types of endpoint (time to event, binary, and continuous) can be modeled.

Monthly Triamcinolone Acetonide for Severe, Refractory, Life-Threatening Asthma in Children

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RATIONAL: Treatment modalities for severe, therapy-resistant asthma in children are not well studied. Triamcinolone acetonide has been described in adults, but pediatric data on its use is limited. At our institution, triamcinolone acetonide has been used recently for children who have demonstrated severe, life-threatening asthma refractory to NHLBI Guidelines step 6 therapy.

METHODS: Retrospective chart review for children treated with intramuscular triamcinolone acetonide (TA) was performed. The following data were extracted: medication history, hospitalizations per year before and during TA therapy, life threatening events (cardiac arrest, intubation, CPR, ECMO).

RESULTS: Fifty children with asthma exacerbations, ages 8-35months, were included in this study. The clinical scores and length of stay were not significantly different between the groups. Serum cortisol concentration was measured during the hospital stay. Results: Monthly injection of triamcinolone acetonide is a viable therapeutic modality for children with life-threatening severe refractory asthma.

Inhaled High Dose Budesonide Is As Effective As Systemic Corticosteroids for Children Under Three with Mild Asthma Exacerbations

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RATIONAL: Recurrent wheezing in children under three years of age is commonly associated with viral infections. The pathogen is different from that which causes allergen-induced asthma, usually in school-aged children. Both high-dose inhaled corticosteroids and systemic corticosteroids are efficacious in the treatment of children with allergen-induced asthma who have mild to severe exacerbations. The aim of this study is to compare the efficacy and safety of high-dose inhaled corticosteroids with systemic corticosteroids in children under three years of age with mild asthma exacerbations.

METHODS: A randomized controlled study of children admitted with mild asthma exacerbations was conducted from April 2013 to November 2014. Patients were divided into two groups and treated with either inhaled high dose corticosteroids (BIS, n = 30) or systemic corticosteroids (PSL, n = 20), nebulized budesonide 1.0mg/dose, twice daily, and prednisolone 0.5mg/kg iv, every eight hours. A clinical score, including wheezing and asthma symptoms, was recorded daily. Serum cortisol concentration was measured during the hospital stay.

RESULTS: Fifteen children with asthma exacerbations, ages 8-35months, were included in this study. The clinical scores and length of stay were not significantly different between the groups. Serum cortisol concentration was similar on admission (BIS 15.0μg/dL, PSL 17.2μg/dL, p>0.05), but there was a significant decrease in serum cortisol concentration in children receiving systemic corticosteroids after four days of treatment (BIS 17.0μg/dL, PSL 10.9μg/dL, p=0.036).

CONCLUSIONS: In hospitalized children under age three with mild asthma exacerbations, inhaled high dose corticosteroids are at least as effective as systemic corticosteroids, without suppressing serum cortisol levels.
Once-Daily Tiotropium Respimat® Add-on to at Least ICS Maintenance Therapy Demonstrates Improved Lung Function in Patients with Symptomatic Asthma, Independent of Serum IgE or Blood Eosinophil Levels

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RATIONALE: In adults with moderate or severe symptomatic asthma, once-daily tiotropium Respimat® add-on to at least ICS maintenance therapy has demonstrated lung-function improvements in conventional subgroup analyses, independent of serum IgE \( \geq 0 \) or >430 \( \mu \)g/L (equivalent to 179.2 IU/L) and blood eosinophils \( >0 \) or >600/\( \mu \)L (equivalent to 600/\( \mu \)L). We investigated whether these improvements in lung function were also observed in modeling estimates across a continuous range of IgE and eosinophil values following tiotropium Respimat® 5 \( \mu \)g add-on therapy.

METHODS: Four Phase III double-blind, placebo-controlled, parallel-group trials: PrimoTinA-asthma® (2×48-week trials; NCT00776984/NCT00772538; n=912) tiotropium Respimat® 5 \( \mu \)g or placebo Respimat® add-on to ICS (2800\( \mu \)g budesonide or equivalent) + LABA: MezzoTinA-asthma® (2×24-week trials; NCT01172808/NCT01172821; n=2100) tiotropium Respimat® 5 \( \mu \)g or placebo Respimat® add-on to ICS (400-800\( \mu \)g budesonide or equivalent). Patients had symptomatic asthma requiring treatment with at least ICS for \( \geq 2 \) weeks before screening; COPD was excluded. Post hoc mixed model with repeated measures modeling analyses of peak and trough FEV\(_1\) were performed across continuous ranges of IgE 0-2000\( \mu \)g/L and eosinophils 0-2.00×10\(^3\)/\( \mu \)L following treatment with tiotropium Respimat® 5 \( \mu \)g.

RESULTS: Tiotropium Respimat® 5 \( \mu \)g consistently improved peak and trough FEV\(_1\), compared with placebo, across all IgE and eosinophil ranges in all trials (mean difference >0).

CONCLUSIONS: Once-daily tiotropium Respimat® add-on to at least ICS improved lung function in patients with moderate or severe symptomatic asthma, independent of serum IgE or blood eosinophil levels. These results support the lung-function improvements previously reported from subgroup analyses using binary cut-offs of serum IgE \( \leq 2000 \mu \)g/L and blood eosinophils \( \leq 600 \times 10^3/\mu L \).

Controller Montelukast to Prevent Asthma-like Exacerbation in Preschool Children with Recurrent Wheeze

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RATIONALE: The effectiveness of montelukast for wheeze in young children has been suggested but still controversial. Recently, some evidences suggest the usefulness of early use of inhaled corticosteroids. However, the benefit of the treatment strategy with montelukast has not been proved.

Objective: To test whether montelukast for preschool children with recurrent wheeze prevents occurrence of severe asthma-like symptoms.

METHODS: A randomized, open-label study was performed in atopic children, 1 to 5 years old, with recurrent, beta2 agonist-responsive wheeze. The patients were eligible if frequency of the symptoms was more than once a month and less than once a week, mild severity, without any asthma controllers. The subjects were randomized to receive daily montelukast (MK) or no controller medication (NC) for 48 weeks. Primary outcome was number of unscheduled visits due to predefined severe asthma-like symptomatic exacerbation or severe wheeze with dyspnea and hypoxemia of SpO\(_2\) <92% that required systemic steroids or hospitalization.

RESULTS: Ninety-three children were enrolled. Forty seven patients were assigned to MK and 46 to NC. The number of the exacerbation episodes was significantly lower in MK group than in NC group, 0.9 and 1.9 times/year, respectively. The duration until the first exacerbation was significantly longer in MK group than NC group. The odds ratio for the exacerbation was 0.54 (95% CI: 0.34 – 0.87) with the treatment.

CONCLUSIONS: Montelukast may prevent progression of the disease from mild to severe phenotype in preschool-age children with recurrent wheeze.

53.5 % of patients with severe or difficult-to-treat asthma were atopic (VPC at TENOR I and TENOR II) versus 45.8% (38/83) of non-atopic patients were examined, as well as very poorly controlled (VPC) asthma based on National Heart, Lung, and Blood Institute asthma guidelines.

RESULTS: Of 317 patients with a specific IgE measure, the majority (n=231; 72.9%) had atopic asthma; 86 (27.1%) had non-atopic asthma. IgE geometric mean was 130.7 IU/mL and 14.1 IU/mL for atopic and non-atopic groups, respectively.

CONCLUSIONS: Atopic asthma was highly prevalent and more frequent than non-atopic asthma in TENOR II; however frequency of exacerbations and level of control were generally similar between the two subgroups.
Mometasone Furoate (MF) Improves Lung Function in Pediatric Asthma: A Dose-Ranging Study of MF Metered-Dose Inhaler (MDI)

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RATIONALE: The inhaled corticosteroid MF, as delivered via dry-powder inhaler (DPI) QD in the evening (PM), is approved in the US to treat pediatric asthma. This study evaluated 3 doses of MF as delivered via MDI, in children ages 5-11 yr with persistent asthma.

METHODS: This 12-week randomized, double-blind, placebo-controlled study included 5 arms: MF-MDI 50mcg BID, MF-MDI 100mcg BID, MF-MDI 200mcg BID, MF-DPI 100mcg QD PM and placebo, using a double-dummy design. The primary analysis assessed 3 doses of MF-MDI, vs placebo, on the change in % of predicted forced expiratory volume in one second (FEV1) from Baseline to Week-12; a secondary analysis compared MF-MDI 50mcg BID versus MF-DPI 100mcg QD PM. Adverse events (AEs) were monitored throughout the study.

RESULTS: All 3 doses of MF-MDI were superior to placebo on % of predicted FEV1, at Week-12; least-squares (LS) mean differences from placebo were 3.87 (P < 0.019), 6.29 (P < 0.001), and 5.34 (P = 0.001) percentage-points for MF-MDI 50, 100, and 200mcg BID, respectively. MF-MDI 50mcg BID was similar to MF-DPI 100mcg QD PM, though the LS mean difference of 1.39 (P = 0.368) numerically favored MF-MDI 50mcg BID. AE incidences were similar among all treatment groups. There were no reports of oropharyngeal candidiasis or dysphonia (which were AEs pre-specified for analysis) in the trial.

CONCLUSIONS: In children ages 5-11yr with persistent asthma, all three doses of MF-MDI (50mcg, 100mcg, and 200mcg BID) demonstrated significant improvement in FEV1 after 12 weeks of treatment. MF was generally well tolerated; no new safety concerns were identified in this trial.

Tiotropium Respimat® Add-on to at Least ICS Therapy Demonstrates Reduced Risk of Severe Asthma Exacerbation and Asthma Worsening in Symptomatic Asthma, Independent of IgE or Blood Eosinophil Levels

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RATIONALE: Once-daily tiotropium Respimat® add-on therapy has been shown, in conventional subgroup analyses, to reduce the risk of severe exacerbation and asthma worsening in patients with symptomatic asthma, independent of T2 phenotype (low and high) defined as total IgE ≤ or >430 µg/L and blood eosinophils ≤ or >0.6×10⁹/L. We further investigated treatment effects by modeling estimates of risk reduction across the whole continuous range of IgE and eosinophil values following tiotropium Respimat® add-on therapy.

METHODS: Four Phase III double-blind, placebo-controlled, parallel-group trials: PrimoTinA-asthma® (2× 48-week trials; NCT00776984/NCT00772558; n=912) tiotropium Respimat® 5 µg or placebo Respimat® add-on to ICS (≥200 µg budesonide or equivalent) + LABA; MezzoTinA-asthma® (2× 24-week trials; NCT01172808/NCT01172821; n=2100) tiotropium Respimat® 5 µg or 2.5 µg or placebo Respimat® add-on to ICS (400-800 µg budesonide or equivalent). Patients had symptomatic asthma, with at least ICS treatment for ≥2 weeks before screening; COPD was excluded. Post hoc Cox regression modeling was performed to investigate hazard ratios versus placebo Respimat® across continuous ranges of IgE 2-2000 µg/L and eosinophils 0.05-2.0×10⁹/L.

RESULTS: Overall, tiotropium Respimat® 5 µg and 2.5 µg reduced the risk of severe exacerbation and asthma worsening at all levels of IgE and eosinophils compared with placebo Respimat® (hazard ratio <1).

CONCLUSIONS: Once-daily tiotropium Respimat® add-on to at least ICS maintenance therapy reduces the risk of severe exacerbation and asthma worsening in patients with moderate or severe symptomatic asthma, independent of IgE or blood eosinophil levels. These results support the use of tiotropium Respimat® in both T2-high and T2-low patients.
**698 Differences in Oral Corticosteroid Prescribing Regimens for Asthma Exacerbations Between Primary Care and Specialty Pediatricians**

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**RATIONALE:** In the pediatric population, asthma exacerbations are a leading cause of Emergency Department (ED) visits and hospitalizations. Early treatment with systemic corticosteroids can help prevent the need for health care utilization. NHLBI asthma guidelines recommend oral corticosteroids for acute exacerbations, but offer a range of dosing regimens. There is a lack of data regarding corticosteroid prescribing regimens used for children with asthma exacerbations.

**METHODS:** We conducted a retrospective review of the electronic record from the primary care (PC), allergy/immunology and pulmonary outpatient clinics at a tertiary care pediatric hospital system for all patients (ages 6 months-21 years of age) with a diagnosis of asthma (ICD-9,493.xx) who were prescribed oral corticosteroids for asthma exacerbation between January 1 and December 31, 2014. Allergy/immunology and pulmonary clinics were aggregated into specialty clinics (SP) for purposes of comparison. Analyses were performed using chi-square.

**RESULTS:** In 2014, there were 2450 total outpatient prescriptions (PC=1030, SP=1420) of oral corticosteroids for asthma exacerbations. Mean age (PC=6.9 years, SP=7.2 years) and gender (PC Male=58%, SP=60%) were similar. Regimens differed significantly in regard to duration (<5 days; PC=1009/98%), SP=1363/96%; p<0.01. PC prescribed lower doses, with more courses <2mg/kg/day (n=180/17.5%) vs SP=167/11.8%; p<0.0001. PC prescribed more once daily regimens compared with SP (70%; n=730) vs 43%; n=613); p<0.0001. Rates of ED visits within 30 days of prescription were less in SP (4.58 visits/100 patients) compared with PC (7.18 visits/100 patients); p<0.01.

**CONCLUSIONS:** There is significant variation in treatment of asthma exacerbations in the outpatient setting between PC and SP pediatricians. Higher rates of ED visits were observed after prescriptions initiated by PC physicians. Standardization of corticosteroid regimens is important to help optimize clinical outcomes.

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**699 No Significant Growth Velocity Changes in Two Trials Evaluating the Potential Effects of Flunisolide HFA (Aerospan™) on Growth in Pediatric Patients with Mild-to-Moderate Asthma**

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**RATIONALE:** Two 1-year clinical trials were performed with flunisolide HFA, a small-particle inhaled corticosteroid with a built-in spacer, approved for the treatment of asthma in patients 6 years and older. Post-hoc analyses evaluated height changes and growth velocity changes from baseline after 52 weeks of treatment with flunisolide HFA 160 mcg BID (max approved dose in children 6 to 11).

**METHODS:** The first study was a double-blind, randomized 1-year safety study of flunisolide HFA and placebo in children 4 to 9 with mild-to-moderate asthma (n=218). The second study was an open-label, randomized, 1-year safety study of flunisolide HFA, inhaled beclomethasone (BDP) CFC, and inhaled cromolyn (negative control) in children 4 to 11 with mild-to-moderate asthma (n=206). Each study was analyzed similarly for growth velocity (via stadiometry assessments) over 1 year.

**RESULTS:** In the double-blind study, mean growth velocity was 6.01 cm/yr for flunisolide HFA versus 6.19 cm/yr for placebo, a non-significant difference (p=0.425). Distribution in height changes and growth velocity changes were similar between flunisolide HFA and placebo. In the open-label study, mean growth velocity was 6.2 cm/yr for the flunisolide HFA group versus 5.3 cm/yr for the BDP group (p=0.008) and 6.9 cm/yr for the cromolyn group (p=0.254). Distribution of height changes and growth velocity changes was similar between flunisolide HFA and cromolyn.

**CONCLUSIONS:** Two 1-year trials demonstrated that flunisolide HFA did not result in significant growth suppression in pre-pubescent pediatric asthma patients 4 to 11 years of age when compared to placebo or negative control.

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**700 Variation of in Vitro Glucocorticoid Response in Asthma**

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**RATIONALE:** Asthmatic patients show variable responses to glucocorticoids (GC). The GC lymphocyte stimulation (GCLS) assay has been used to assess GC response in vitro. There is limited information on the variability of this assay and how well it correlates with clinical response.

**METHODS:** GCLS results from 169 patients with asthma having evidence of expiratory airflow limitation and variability were analyzed. Log IC50 values (the amount of GC required to inhibit lymphocyte activation by 50%) for prednisolone, dexamethasone, budesonide and fluticasone were calculated; highest quartile values for each GC were considered as insensitive.

**RESULTS:** Mean (SD) log IC50 values for prednisolone, dexamethasone, budesonide, and fluticasone propionate were 1.59 (0.63), 0.68 (0.67), 0.06 (0.61), and -0.07 (0.66), respectively. 57% were pansensitive; 11% were insensitive to all GCs. 65% of patients were sensitive to fluticasone and budesonide; 15% were insensitive to both. 66% of patients were sensitive to prednisolone and dexamethasone; 16% were insensitive to both. Patients who were insensitive to all GCs were older [50.4 (19.4) vs. 34.4 (23.8) years, p=0.007], more obese [BMI 30.4 (8.0) vs. 26.1 (8.4) kg/m², p=0.04], and had worse airflow limitation [FEV1/FVC 64 (22) vs. 73 (13), p=0.02] compared to those who were pansensitive.

**CONCLUSIONS:** Variation in in vitro responses to GC exists. The association of steroid insensitivity and older age, obesity, and worse airflow limitation needs further investigation, as this may imply a need for increased doses of GC to overcome inflammation or airflow limitation in patients who are already susceptible to develop adverse effects.
701 Growth Effects of Concomitant Inhaled (ICS) and Intranasal (INCS) Corticosteroid (CS) Use in Children

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RATIONALE: One-year studies showed that older ICS and many INCS caused a ~1 cm growth effect in children with asthma and allergic rhinitis, respectively. However, there are no data on the growth effects of the concomitant use of ICS and INCS, which is very common in clinical practice.

METHODS: Single-center, randomized, placebo-controlled, 3-period cross-over study to evaluate the effect of: 1) Omnaris Nasal Spray 200 µg QD and Alvesco Inhalation Aerosol 80 µg BID (O/A); versus 2) Beconase AQ Nasal Spray 168 µg BID and QVAR Inhalation Aerosol 40 µg BID (B/Q); versus 3) Placebo Nasal Spray QD and Placebo Inhalation Aerosol BID (P/P) on short term growth (knemometry) and HPA axis function (12 hour overnight urinary cortisol) in pediatric subjects (6-15 years) with asthma and allergic rhinitis. Each treatment and washout period lasted 3 weeks.

RESULTS: Growth velocity in mm/week (mean, 95% CI) was 0.23 (0.04-0.41) for O/A (p = 0.033 versus P/P), 0.33 (0.14-0.51) for B/Q (p=0.16 versus P/P), and 0.51 (0.32-0.70) for P/P. The respective values for HPA axis function (mean cortisol/creatinine µg/mg, 95% CI) were 0.10 (0.05-0.15), 0.11 (0.06-0.16), and 0.14 (0.09-0.19) (p<0.05).

CONCLUSIONS: Combining an INCS with an ICS, even one which caused a growth effect in a robust 1-year study (Alvesco), produced a detectable signal of systemic steroid activity. Surprisingly, B/Q did not affect growth. More studies, including durations of 1-year and multiple years, need to be done to identify the true level of risk of concomitant therapy with ICS and INCS in children.

702 Resolution of T Cell Lymphopenia in a Term Infant with Absent TREC's on Newborn Screen

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RATIONALE: Screening for severe combined immunodeficiency (SCID) in the United States (US) using T-cell receptor excision circles (TRECs) began in 2008 and is currently operating in 26 US states*, the District of Columbia, and the Navaho Nation. This screening is facilitating early identification of SCID and other syndromes with T cell lymphopenia.

METHODS: TRECs screening performed by the Ohio Department of Health Laboratory.

RESULTS: SM is a term female whose newborn screen demonstrated no detectable TRECs x2. Initial flow cytometry revealed a CD3 count of 1171 cells/cu mm, CD4 count 979, CD8 count 192, CD19 606 and CD56/CD16 180. Initial CD3CD45RA was 70% and CD3CD45RO 28%. T cell function studies revealed normal nitrogen proliferation but low anti-CD3 proliferation. Repeat newborn screen at one month confirmed absent TRECs. TCR-v-beta repertoire was normal. Subsequent diagnostic workup for 22q deletion syndrome, HIV, ataxia telangiectasia and bare lymphocyte syndrome was negative. Next-generation SCID sequencing was also negative. IgG/AM levels were normal at 9 months. CD3, CD4 and CD8 counts normalized by 12 months, though anti-CD 3 proliferation remained low. Repeat newborn screen testing at one year revealed TRECS in the normal range. Patient is thriving and developing normally at 14 months with no recurrent or serious infections.

CONCLUSIONS: As more states adopt TRECs screening for SCID on the newborn screen, it is important to be aware that even some term infants with no detectable TRECs may have resolution of T cell lymphopenia and no evidence of a serious immune deficiency.
**Abstracts AB217**

**705** Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-Linked Syndrome (IPEX) Associated with Neurological Presentation

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**RATIONALE:** IPEX syndrome (Immune dysregulation, polyendocrinopathy, enteropathy x-linked syndrome) is characterized by autoimmune manifestations in multiple organs, particularly skin, gut, and endocrine systems. Mutations in the FOXP3 gene lead to dysfunction of T regulatory cells and an array of phenotypical manifestations. We present a child with previously undescribed neurological manifestations, very mild endocrinology and gastrointestinal symptoms, and severe pruritis leading to localized inguinal self-induced ulceration and genital enlargement.

**METHODS:** Whole Exome Sequencing performed by Gene Dx.

**RESULTS:** This patient presented at 22 months of age with decreased interactivity, anorexia with weight loss, and abnormal gait. He had regression of milestones including refusal to walk and talk, scattered erythematous plaques and extreme pruritis localized to the genital area, followed by a period of fevers without identified focus. Neurological symptoms slowly improved with a course of steroids. Multidisciplinary workup found no endocrinopathies, enteropathy, neurological or infectious etiologies. Hyperkeratotic psoriasiform hyperplasia without spongiosis on skin biopsy. IgE 9527, IgG 4 163, Normal IgM and IgA. Continued itching led to ulceration of the perineal area and penile enlargement. Three years after his initial presentation, whole exome sequencing for the diseases associated with elevated IgE revealed isolated heterozygous mutation for the R397Q mutation in the FOXP3 gene. Mother does not have the mutation and he has a brother with identical HLA typing for future bone marrow transplant.

**CONCLUSIONS:** IPEX presentation can be variable that this diagnosis should be considered in a male child with potential autoimmune neurological dysfunction if associated with immune deregulation and localized pruritic skin rashes.

**706** Novel Presentation of STAT1 Gain of Function (GOF) with Specific Antibody Deficiency without Fungal Infection

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**RATIONALE:** Patients with autosomal dominant (AD) STAT1 GOF mutations classically present with chronic mucocutaneous candidiasis (CMC). Severe disseminated fungal infections, hypogammaglobulinemia, herpes viral disease, and IPEX-like enteropathy have also been reported. We present a patient with a new presentation of AD STAT1 GOF.

**METHODS:** Retrospective chart and literature review were conducted. Whole exome sequencing of genomic DNA from the proband and both parents was performed. STAT1 phosphorylation/depshorylation were assessed by flow cytometry.

**RESULTS:** At 11 year old male with growth delay, requiring growth hormone, presented at 2 years of age with recurrent sinopulmonary infections despite prophylactic antibiotics, surgical interventions and then Ig replacement therapy. He had antibiotic related thrush only and no other fungal infections or autoimmune. He developed bronchiectasis and carried one CFTR mutation. Immune evaluation demonstrated absent IgA, normal IgG and IgM, poor specific antibody responses after vaccination, mild CD4+ T cell lymphopenia with an inverted CD4+:CD8+ ratio, decreased CD4+CD45RA+ T cells with normal lymphocyte proliferative responses to mitogens and Candida[IC1], and decreased memory B cells. Whole exome sequencing revealed a de novo single heterozygous STAT1 GOF mutation (c.C1154T;p.T385M, NM_007315). Flow cytometry studies confirmed hyperphosphorylation of STAT1 in monocytes when stimulated with IFN-γ and in NK cells and T cells after stimulation with IFN-α.

**CONCLUSIONS:** Although STAT1 GOF patients typically present with CMC, the disease presents heterogeneously. This case illustrates the roles genetic testing and biologic functional assays play in the diagnosis of a new clinical phenotype in a known genetic disease, which expands our knowledge of STAT1 biology in humans.

**707** Two Symptomatic Patients with Atypical Heterozygous Artemis Mutation Along with Other Mutations Including TACI, While Parents with an Isolated Heterozygote Mutation Were Asymptomatic

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**RATIONALE:** Most common mutation in Artemis deficiency is the deletion in exons 1-3; phenotypic variation is common with other mutations. Two unrelated gene mutations on different chromosomes encoding immune functions are rarely described. We report two cases with atypical heterozygous Artemis mutations, one patient with a missense mutation and other unassociated mutations on DCLREC1(Artemis) gene. Second patient with a heterozygous TACI (Chromosome 17) and a heterogeneous variant mutation on DCLRE1C (Chromosome 10). Both patients presented with hypogammaglobulinemia and recurrent infections. Parents are asymptomatic with the isolated mutations.

**METHODS:** Case description.

**RESULTS:** A 5 year old female with recurrent infections since age 2 months had low IgG, IgA and IgM, low CD4+ and high CD8+ percent of T cells and failed antibody responses to Pneumococcal polysaccharide and Conjugate vaccines, PPV23 and PCV13 respectively. Genetics revealed a missense mutation on exon 6 of the DCLREC1 gene: c.457G>A. G153R. Other mutations found on DCLREC1 reported as unlikely association.

A 2 year-old male presented with recurrent respiratory infections since age 6 months, had low serum IgG, failed antibody responses to PPV 23 and PCV 13 but normal lymphocyte subsets. Genetics revealed a variant mutation of the DCLRE1C gene of unknown significance: c.251G>C (p.S84C) and a heterozygous missense mutation of TNFRSF13B (TACI) gene associated with CVID type 2: c.310T>C (p.C104R). First patient’s mother with isolated similar heterozygous Artemis mutation and second patient’s mother and father with isolated TACI and Artemis mutations respectively are all asymptomatic.

**CONCLUSIONS:** Two Patients with heterozygote Artemis mutations associated with an unrelated gene mutation were immunodeficient while their parents with the isolated mutations were asymptomatic.
708 Detection of the 22q11 Deletion Using Dried Blood Spots and Digital PCR
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RATIONALE: 22q11.2 deletion syndrome (22q11DS) has an estimated prevalence of 1:3000. Infants with cardiac defects are frequently tested for 22q11DS at birth, but some are not diagnosed until adolescence. In SCID newborn screening approximately 29% of newborns with abnormal TREC have 22q11DS. NBS for 22q11DS may aid in early diagnosis.

METHODS: Primers for TUPLE and ZNF74 and FAM probes were used. RNAseP probe labeled with HEX, was the reference gene (2N). DNA was eluted from 2 or 3.2 mm blood spots punches into 40 μL. Normal cord blood and unaffected parents were controls. Samples from patients with 22q11DS, after consent. NdeI enzyme was added to digest DNA. Droplets were generated using an automated droplet generator (BioRad). Plate was sealed and was heated to 95°C for 10 minutes; 45 cycles of 95°C for 30 seconds and 60°C for 1 minute. Droplets were counted using Bio-Rad droplet reader. Copy number calculated using QuantaSoft (BioRad).

RESULTS: Copy number of both TUPLE and ZNF74, separately or multiplexed was accurately measured in all control and deleted patients. Copy number varied from 1000 to 20,000/20μL for 2 and 3 mm punches respectively. The target/RNAseP ratio was not affected. For multiplexed PCR, nondeleted patients had 4 copies of target genes (2 for RNAseP), deleted patients had 2 copies. One patient with a deletion of TUPLE alone had 3 copies.

CONCLUSIONS: Digital PCR provides an accurate and efficient way of detecting the 22q11 deletion using dried blood spots. Multiplexing this assay with TREC could make this a cost effective tool for NBS.

709 Newborn Screening for SCID Is Associated with a Shorter Interval from Diagnosis to Transplant
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RATIONALE: Severe combined immunodeficiency (SCID) is a serious, life-threatening condition for which universal newborn screening was recommended in 2010. Prompt diagnosis and hematopoietic stem cell transplantation (HSCT) is associated with increased survival. Previous studies have identified 3.5 months as an ideal timepoint for HSCT. We aim to report the impact of newborn screening on time to transplant in our cohort.

METHODS: We reviewed medical records of patients who received HSCT for SCID at The Children’s Hospital of Philadelphia between January 2010 and August 2015. We obtained data on mode of diagnosis and age at HSCT.

RESULTS: 19 SCID patients received HSCT for SCID at our center between January 2010 and August 2015. Six patients were diagnosed based on TREC newborn screen and received a HSCT at a median age of 2.95 months (range 0.9 to 3.9 months). Of these, 2 had family history (FH) of SCID/immunodeficiency. Two patients were diagnosed based on testing performed due to known FH of SCID (prenatal genetic testing n=1, flow cytometry and genetic testing within 24 hours of life n=1). Median age at transplantation for these patients was 0.65 months (range 0.6 to 0.7 months). The remaining 11 patients were diagnosed based on clinical history that prompted an immunodeficiency evaluation. Of these, none had prior FH of SCID/immunodeficiency. These patients underwent HSCT at a median age of 9.4 months (range 3.8 to 237.8 months).

CONCLUSIONS: Newborn screening or early diagnosis based on FH of SCID appears to reduce time to HSCT for patients with SCID.

710 Incongruent Phenotypic Expression of Autosomal Dominant Hyper IgE Syndrome (AD-HIES) in a Mother and Son
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RATIONALE: AD-HIES has multifarious effects on multiple systems. Although variable expressivity has been described, no reports detail the course of immediate family members with the AD type.

METHODS: Reviewed documented clinical course and studies conducted at WRNMMC and NIH.

RESULTS: Mother and son shared the 1909 G-A mutation in the SH2 domain of STAT3. They had near identical clinical courses from birth through infancy, including classic AD-HIES manifestations such as eczema and pulmonary infections; however, their courses subsequently diverged. The mother developed pneumatoceles and bronchiectasis and required a partial lobectomy by three years of age. Diagnosed with AD-HIES at 8 years old, she started SCIG. In early adulthood, her large pneumatoceles became chronically infected with aspergillus, mycobacterium abscesses, and stenotrophomonas. She underwent bilateral lung transplant at age 27 and developed a diaphragmatic aspergilloma resistant to standard antifungal therapies. Two years later, aspergilloma was identified involving her right pulmonary artery causing hypoxia. Isovaconazole led to improvement, but her lung function diminished requiring continuous oxygen. The patient’s son started replacement SCIG and prophylactic antibiotics by the first year of life. His pulmonary and cutaneous complications were mild after infancy. Although, he has small stature and characteristic AD-HIES facies, his course has been relatively benign on treatment.

CONCLUSIONS: This is the first reported case highlighting marked variable expressivity in AD-HIES of affected immediate family members. The divergent clinical courses may have been influenced by early diagnosis, initiation of SCIG and prophylaxis, and suggests that providers should consider early testing of AD-HIES patients’ offspring.

711 Prolonged Immune Suppression after Rituximab Use in Children
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RATIONALE: Rituximab is an anti-CD20 chimeric antibody that is used to treat B cell neoplasms and autoimmune disease. It induces the depletion of B lymphocytes in peripheral blood, with an average recovery time of 6-9 months. There is evidence that some patients have prolonged hypogammaglobulinemia and B-cell deficiency following Rituximab treatment (RT). We examined 10 children who received Rituximab to determine if there immune status fully recovered after treatment.

METHODS: A retrospective chart review was performed in 10 children that underwent RT for various autoimmune disorders. CBC, immunoglobulins, T and B cells were obtained at least 1 year after the last dose of Rituximab.

RESULTS: The mean follow-up time was 1-4 years. 20 % (2/10) patients had low IgG 1 year or more after the RT. 50% (5/10) patients had low IgM and one patient had low IgA. 50% (5/10) had low CD19 levels 2 years after the last Rituximab dose. 20% (2/10) also had low CD3, CD4 and CD8 levels up to two years after.

CONCLUSIONS: After RT, most patients have full recovery of B cells with no residual immune dysfunction. There is limited data in the literature regarding immune dysfunction after RT in children. In our patient sample, 8 children demonstrated some type of immune suppression 1 year or greater after treatment. Obtaining baseline studies prior to RT and close monitoring is important to differentiate RT-induced from an undiagnosed underlying immune dysfunction in these children.
A Case of Severe Combined Immunodeficiency (SCID) Due to Cartilage Hair Hypoplasia (CHH) with Normal Vaccine Responses and T-Cell Proliferation to Pokeweed Mitogen

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RATIONALE: SCID typically presents in infancy with severe infections and combined B- and T-cell deficiencies, T-cell proliferation to mitogens is usually severely reduced or absent and specific antibody responses impaired. We present a case of SCID at 15 months with normal T-cell proliferation to pokeweed mitogen (PWM) and protective antibody titers to vaccines.

METHODS: T-cell proliferation to mitogens performed by Mayo clinic. Antibody titers performed at St. Louis Children’s Hospital.

RESULTS: A 15 month female with short stature was hospitalized with 3 months of failure to thrive and diagnosed with norovirus. Prior infectious history included norovirus 2 months prior, enterovirus at 10 and 12 months, RSV complicated by pneumonia at 9 months, one episode of thrush, and one otitis media. WBC count and total IgG/M normal. IgA undetectable. Lymphocyte subpopulations (cells/mm3) showed lymphopenia (728); CD4 (95), CD8 (7), and B cell (262) cytopenias; and normal NK cells. CD4 recent thymic emigrants (9.1%; RR = 25.8-68%) and T-cell receptor excision circles (TREC) (500 copies; RR > 4168) were reduced. T-cell proliferation was normal to PWM (9.7%; RR = 3.5%) and reduced to phytohemagglutinin (11.3%; RR > 58.5%). Antibody titers to diphtheria, tetanus, H. influenza type B, and S. pneumoniae were protective. Patient was diagnosed with SCID and underwent stem cell transplant. Genetic testing confirmed the diagnosis of CHH, a rare cause of SCID.

CONCLUSIONS: SCID due to CHH may present after the first year of life with atypical lab findings, including normal responses to vaccines and proliferation to mitogens. The low positive threshold used for T-cell response to PWM can be falsely reassuring.

Idiopathic CD4 Lymphocytopenia: Immunologic Characteristics, Clinical Manifestations, and Disease Course

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RATIONALE: Idiopathic CD4 lymphocytopenia (ICL) is a heterogeneous disorder that confronts our specialty. Issues concerning diagnosis, treatment and long-term prognosis are common.

METHODS: Retrospective chart reviews were performed on four patients with a diagnosis of ICL to evaluate clinical features, laboratory variations, and disease course.

RESULTS: All patients were diagnosed with ICL based on at least 2 measurements of absolute CD4 count <300 cells/μL (normal range 490-1740 cells/μL). Median absolute CD4 count was 173 cells/μL (61-268 cells/μL). Median age at diagnosis was 66.5 years (44-72 years). One of four had an opportunistic infection at presentation: disseminated histoplasmosis. Autoimmunity with inflammatory arthritis and uveitis occurred in another. Anti-thyroid peroxidase antibodies were present in one patient without evidence of thyroiditis. The only malignancy was basal cell carcinoma of the skin in one patient. In addition to low CD4 T cells, CD19+ B cells and CD16+ NK cells were decreased in two and T cell proliferative responses were decreased in two. Specific antibody titers were decreased in one prompting therapy with gammaglobulin replacement.

CONCLUSIONS: ICL is a heterogeneous disease with variable presentation. Profoundly low absolute lymphocyte count or CD4 T cells did not correlate with severity of disease. Decreased NK cell quantities have reportedly been associated with more severe disease, but did not in our cohort. Autoimmune disease with presence of autoantibodies is closely associated with ICL and malignancy is a possible complication.

Efficacy of Recombinant Human Hyaluronidase-Facilitated Subcutaneous Infusion of Immunoglobulin G (IgG) (IGHy) in Patients with Primary Immunodeficiency Disease (PIDD): Infections over Time

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RATIONALE: IGHy provides protection against infections at similar doses and dosing intervals as intravenous IgG (IVIG). We report IGHy efficacy over time in patients with PIDD aged ≥16 years treated for up to ~3.5 years in the IGHy pivotal phase 3 study and its extension.

METHODS: Following a 3-month IVIG treatment period, patients received IGHy every 3 to 4 weeks for ~18 months, followed by up to an additional 21 months.

RESULTS: Of the 63 enrolled patients aged ≥16 (range 16–78) years, 61 were administered IGHy for up to ~3.5 years at the established dose. Rates of validated acute serious bacterial infections (VASBIs) and all infections were 0.01/patient-year (upper limit of 99% confidence interval [CI]: 0.01) and 3.05/patient-year (95% CI: 2.63–3.52), respectively. For the subset of patients completing IGHy through the extension study (n = 37), the infection rate/patient-year (3.18 overall) remained relatively constant (3.14 for months 1–12; 3.60 for months 12–24, and 2.70 for months 25–33.6). Over the course of IGHy treatment, serum trough levels of antibodies to Haemophilus influenzae, Clostridium tetani toxoid, and hepatitis B virus were protective.

CONCLUSIONS: In patients aged ≥16 years who were treated with IGHy for up to ~3.5 years, efficacy remained constant over time.

Incidence of Clinically Diagnosed DiGeorge Syndrome in Olmsted County, Minnesota

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RATIONALE: DiGeorge syndrome (DGS) is most commonly caused by a 22q11.2 chromosomal deletion, although more rare genotypes have been identified. With an estimated incidence of 1 in 4000 births the syndrome’s phenotype is highly variable. The aim of this study is to characterize the incidence of DGS.

METHODS: A retrospective study was conducted using the unique record linkage system in Olmsted County database using Rochester Epidemiology Project (REP).

RESULTS: There were a total of 17 subjects (6 males and 11 females) with clinically diagnosed DGS over the 10 year period. The overall incidence of DGS was 1.1/100000 person –years. The event rate was 5.2/10,000 births in Olmsted county over the 10 year period, which translates to 1/2000 children born in Olmsted county. The median age of diagnosis was 0.9 years with a median duration of follow up of 7 years. The prevalence of autoimmune cytopenia and thyroid dysfunction was 30%. 82% of the subjects had developmental delays. None of the subjects had IgE mediated reactions to food, 40% had allergic rhinitis and 38% had clinically diagnosed asthma/reactive airway disease.
Recurrent infections were common in this cohort (76%), with frequent tympanostomy tubes placement (65%) and hearing loss (68%).

CONCLUSIONS: This is one of the first population-based studies examining the incidence of DGS in Olmsted County. There is a higher than previously reported incidence of about 1/2000 births.

The patient’s age at diagnosis depends on the severity of their phenotype with cardiac defects being the most common reason for genetic identification earlier in life.

716 Local Adverse Reaction Rates Decreased over Time during Treatment with Recombinant Human Hyaluronidase-Facilitated Subcutaneous Infusion of Immunoglobulin G (IGHy) in Patients with Primary Immunodeficiency Disorders in the IGHy Phase 3 Studies

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RATIONALE: IGHy can be administered at similar doses/volumes and dosing intervals as intravenous immunoglobulin G (IgG) (IGIV) but, similar to conventional subcutaneous IgG, is associated with a lower risk of systemic and higher risk of local adverse reactions (ARs). We report local AR rates over time in patients with primary immunodeficiency disorders aged ≥16 years treated with IGHy for up to ~3.5 years in the IGHy pivotal phase 3 study and its extension.

METHODS: Following a 3-month IGIV treatment period, patients initiated IGHy on a dose ramp-up schedule and thereafter received IGHy every 3 (Q3W) or 4 weeks (Q4W) for ~18 months, followed by up to an additional 21 months. Local AR (temporally associated and/or causally related adverse events) rates were evaluated over time.

RESULTS: Of the 63 enrolled patients aged ≥16 (16–78) years, 61 were administered IGHy for up to ~3.5 years at the established dose. Overall, the local AR rate per infusion was 0.191; discomfort/pain was the most commonly reported local AR. Rates of ARs per infusion decreased over time: 0.28 (months 1–12), 0.15 (months 13–24), and 0.08 (months 25–33.6). The percentage of patients experiencing ≥1 local AR per infusion was highest during the dose ramp-up period (33.3–41.7% [Q3W] and 29.2–37.5% [Q4W]), and rapidly declined over time.

CONCLUSIONS: In adults treated with IGHy for up to ~3.5 years, rates of local ARs per infusion and the percentage of patients experiencing ≥1 local AR markedly declined over time.

717 Resolution of Primary Immune Defect in 22q11.2 Deletion Syndrome

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RATIONALE: 22q11.2 deletion is the most common microdeletion syndrome. It is associated with cardiac anomalies, hypocalcemia, characteristic facies and variable decrease in immunological parameters especially in T cell numbers. The objective of this study is to investigate the immunological changes over time.

METHODS: Forty-three medical records of 22q11.2 deletion syndrome patients were reviewed. Immunological parameters were evaluated every 6 months until they returned to normal level. Histories of infections were recorded. Kaplan-Meier survival curves were generated to depict the resolution of immune defect.

RESULTS: Forty-three patients, aged 4 to 222 months were studied. Twenty-three (53.5%) of them were female. Twenty-six patients exhibited decreased CD4 numbers. They returned to normal level in 15 (57.7%) patients. The median age of CD4 resolution was 31 months (range 3 – 204 months). T cell functions were abnormal in 3 patients. They returned to normal in all patients at median age 20 months (range 15–28 months). Six patients (13.9%) had abnormal serum immunoglobulin levels and they improved in 2 patients at 4 months and 12 months of age. The most common infection was pneumonia (69.8%). Eight patients (18.6%) did not have history of infection. BCG vaccination was administered in 42 patients at birth. Among 28 patients who had T cell defect, 2 of them developed BCGosis and disseminated BCG.

CONCLUSIONS: Immunodeficiencies in 22q11.2 deletion syndrome patients were T cell defect (65.1%) and decreased immunoglobulin levels (13.9%). The median age of CD4 resolution was 31 months.

718 Real-World Use of Recombinant Human Hyaluronidase-Facilitated Subcutaneous Infusion of Immunoglobulin G (IG) (IGHy) in Patients with Primary Immunodeficiency Disorders (PIDD)

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RATIONALE: IGHy (HYQVIA) was approved September 2014 in the US for the treatment of PIDD in adults. Data from a single-practice cohort was analyzed to understand IGHy treatment adoption.

METHODS: A chart review of patients in a private practice who initiated treatment with IGHy, or switched from intravenous IG (IGIV) or conventional subcutaneous IG (IGSC) to IGHy, was performed.

RESULTS: Between October 2014 and July 2015, 19 patients (aged 32–74 years; 68% female) began IGHy. IG replacement therapy before switching to IGHy included IGIV (n=2), IGSC (n=15), or none (n=2). Reasons for switching from IGIV were poor venous access (n=1) and desire to self-infuse (n=1). Reasons for switching from IGSC included desire for less frequent infusions (n=11), less needle sticks (n=2), systemic adverse reactions (ARs) (n=1), and non-adherence (n=1). Five patients, all of whom were among the first 9 treated with IGHy, switched back to IGIV (n=1); poor onboarding experience with training) or IGSC (n=4; local ARs [n=3]; preference for lower weekly IGSC volume [n=1]). Three of 4 patients who experienced IGHy as their first subcutaneously-administered IG currently remain on treatment. As the multidisciplinary care team gained expertise with IGHy, patient experience improved and patients opted to continue IGHy treatment. Care team key learnings included providing details on post-infusion site appearance, choosing proper needle length, and the option of adding a second infusion site.

CONCLUSIONS: In this real-world cohort, as the multidisciplinary care team gained experience with IGHy, patient retention improved. These data highlight the importance of an individualized patient infusion experience with IGHy.
719 Case Report of an Infant Female with X-Linked Chronic Granulomatous Disease Due to a De Novo Mutation in CYBB and Extremely Skewed X-Chromosome Inactivation (Lyonization)

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RATIONALE: Chronic granulomatous disease (CGD) is a primary immunodeficiency caused by mutations in any of the subunits of the NADPH oxidase all of which lead to an inability to generate reactive oxygen species, susceptibility to a narrow spectrum of organisms, and development of granuloma in those affected. X-linked CGD (CYBB) is the most common, occurring almost exclusively in boys. We describe a unique case of an infant female with X-linked CGD due to a de novo mutation in CYBB and extremely skewed X-chromosome inactivation (Lyonization).

METHODS: Retrospective chart review was performed.

RESULTS: Patient presented at 1 month age with Campylobacter gastroenteritis and Serratia marcescens heel abscess. At 3 months she developed bilateral cervical adenitis and retropharyngeal abscess secondary to Klebsiella oxytoca. Dihydrodrodamine assay was consistent with X-linked CGD and evaluation of CYBB revealed a heterozygous mutation in exon 5 (c.469C>T), which leads to premature truncation of the protein. Karyotype confirmed XX genotype and further analysis showed extremely skewed Lyonization (<1% superoxide producing granulocytes). Her father is unaffected and her mother’s evaluation was not consistent with carrier status suggesting a de novo mutation. Prophylaxis with TMP-SMX, itraconazole, and IFNγ ensued. The patient has been infection free for 6 months and under evaluation for hematopoietic stem cell transplant.

CONCLUSIONS: While there have been other reported cases of X-linked CGD in females, these cases still remain rare. A high index of suspicion is necessary for diagnosing CGD, especially in females. Determining the correct molecular defect can be difficult but provides valuable prognostic information.

720 Construction and Validation of a Health-Related Quality of Life (HR-QOL) Instrument for Patients with Primary Antibody Deficiency Disease

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RATIONALE: The development and validation of a disease-specific HR-QOL instrument has the potential to improve clinicians’ understanding of the QOL of PIDD patients, and allow the opportunity to optimize treatment.

METHODS: Subjects with X-linked agammaglobulinemia (12), or common variable immunodeficiency (64), age 16 and above (mean 40 yrs) were included for study. All subjects were receiving immunoglobulin replacement therapy either by IV or SC. Subjects were able to read and speak English. Each site obtained approval from their respective IRBs. A modified questionnaire of 28 questions was created for the validation phase that was created by immunologists, nursing, and feedback from patients. After informed consent, patients completed the survey instrument, and were asked to complete a second survey within 48-120 hrs at home. Item reduction was done based on item distribution, and Rasch analysis.

RESULTS: 214 surveys were collected on 76 subjects from 5 sites including demographic data. An interim analysis showed that a 3 point Likert-type scale was easier for patients to discriminate compared to a 5 point scale. A 28 item survey was reduced to 22 questions covering all of the SF-36 domains except body pain. Item reduction was based on those items from the Rasch analysis, disordered items, and lack of discrimination between the 3 point scale, and item overlap or duplication.

CONCLUSIONS: A PIDD specific HR-QOL survey questionnaire will provide clinicians with a tool for monitoring and evaluating Ig treatment in patients with PIDD.

721 Efficacy, Safety, Tolerance, and Pharmacokinetics of Human Immune Globulin Subcutaneous, 20% (IGSC 20%): Final Analysis of a Phase 2/3 Study in Patients with Primary Immunodeficiency Disease (PIDD) in North America

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RATIONALE: We report final results from a study of IGSC 20% in patients aged ≥2 years with PIDD in North America.

METHODS: Epoch 1 (13 weeks): immunoglobulin G 10% was administered intravenously (IGIV) at prestudy doses every 3-4 weeks (Q3W/Q4W). Epochs 2-4: IGSC 20% administered weekly (Epoch 2 [–12-16 weeks], 145% of the weekly equivalent Epoch 1 dose; Epoch 3 [12 weeks], dose adjusted per AUC assessments in Epochs 1-2; Epoch 4 [40 weeks], dose adapted individually per Epoch 3 IgG trough levels). Primary endpoint=validated acute serious bacterial infection (V ASBI) rate.

RESULTS: Seventy-four patients aged 3-83 years received IGSC 20% and 67 completed; no patient discontinued IGSC 20% due to a serious adverse event (SAE) or adverse reaction (AR). During IGSC 20% treatment (n=74), 1 V ASBI (rate=0.012/year; P=0.0001) was reported; the all-infection rate/patient-year was 2.41. Local ARs occurred in 23/74 patients (rate=0.022/infusion); all were mild (92.5%) and moderate (7.5%). In 4327 IGSC 20% infusions, median infusion rate was 60 mL/h/site, resulting in a <1h-median infusion time. A 30-59 mL volume/site was used in 67.4% of infusions, and 7.4% infusions employed a ≥60mL/site volume without tolerability issues. Overall, 84.9% of infusions were administered using ≤2 infusion sites; 99.8% were completed without slowing the rate or interrupting/stopping administration. Ratio of geometric means of AUC time for IgG with individualized IGSC 20% treatment over IGIV 10% Q3W/Q4W was 109% (90% CI=1.0394-1.1336).

CONCLUSIONS: In patients treated with IGSC 20%, VASBI and infection rates were low, and infusions—most administered using ≤2 sites—were well-tolerated at relatively high infusion rates.
Importance of Identifying Pathogenic Causes of Infection in Lung Abscess in Chronic Granulomatous Disease

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RATIONALE: To demonstrate the importance of identifying pathogens in patients affected with Chronic Granulomatous Disease (CGD).

METHODS: Background: Patients affected with CGD are known to have increased susceptibility to catalase-producing pathogens. The five best characterized disease-causing-organisms in these patients include S. aureus, Nocardia, Serratia, Burkholderia, and aspergillus. Especially in recent years, numerous other pathogens have also been identified, including rare species of fungi and unusual bacteria. Implications of identification are extensive and often help direct specific therapies.

RESULTS: Presentation: A 22 year old male with X-CGD with prior history of numerous infections including Nocardia pneumonia, MRSA liver abscess, serratia cellulitis and anterior mediastinal lymphadenitis presented with cervical lymphadenitis. CT of the neck and chest demonstrated a new 11x16 mm right middle lobe lung lesion. This had not been present on imaging 3 months prior, and developed while on prophylactic voriconazole and Bactrim, albeit with suboptimal adherence. Biopsy of the nodule led to identification of Cladophialophora bantiana. This organism is known to cause potentially severe and fatal disease, with reported cases spreading to the CNS with risk of cerebral phaeohyphomycosis.

CONCLUSIONS: Cladophialophora bantiana is yet another organism causing serious morbidity in CGD patients that can be difficult to treat, require multiple antifungal agents and even lesion resection. Our patient did not respond to amphotericin and voriconazole. This case emphasizes the importance of identifying the pathogen causing an infection whenever possible in CGD patients – to target therapy, direct need for antimicrobial prophylaxis, assess for co-infections, and be aware of other potential co-morbidity risks such as dissemination.

Successful Lung Transplant for Bronchiectasis in an Adult Male with Autosomal Recessive Chronic Granulomatous Disease with a Novel NF1 Gene Mutation

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RATIONALE: Chronic granulomatous disease (CGD) is a rare immuno-deficiency curable at a young age by stem cell transplant (SCT). To our knowledge this is the first reported lung transplant (LT) performed in a patient with CGD.

METHODS: PubMed search was conducted for combinations of CGD and LT.

RESULTS: At 19 months of age, this Trinidadian male had his first respiratory infection which required prolonged hospitalization and antibiotic treatment. Thereafter he was hospitalized frequently during childhood for respiratory infections. At 27 years of age, biopsy of a large mastoid abscess revealed granulomas. CGD was initially diagnosed with a Nitroblue Tetrazolium test. A CBC was normal except for elevated monocytes. Lymphocyte subsets, HIV testing, and cystic fibrosis screening were normal. IgA level was slightly elevated at 725mg/dL. Additionally, he developed bronchiectasis necessitating tracheostomy at 28 years of age despite standard treatment. Genetic testing [performed by Gene Dx (Gaithersburg, MD)] revealed heterozygous autosomal recessive CGD with a novel missense mutation of the NF1 gene (p.His51Pro or c.152A>C). While on chronic systemic steroids and oxygen, spirometry showed FEV1 16% predicted and FVC 30% predicted. At age 32, he underwent a successful double LT with alemtuzumab induction and immunosuppression with tacrolimus, mycophenolate and prednisone. Pathology demonstrated necrotizing granulomas without acid fast bacilli. Eighteen months post-transplant the patient continues to tolerate LT.

CONCLUSIONS: LT may be a viable option in patients with CGD. Future areas of research should focus on the viability of solid organ transplantation as a bridge to curative SCT in patients with secondary organ damage.
Prevalence of Primary Immunodeficiency (PID) in a Tertiary Center 1995-2015

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RATIONALE: Hematopoietic stem cell transplantation (HSCT) for severe combined immunodeficiency (SCID) and other selected primary immunodeficiencies (PID) is becoming standard of care. Delayed diagnosis prior to transplant significantly worsen outcome. Our study aims to describe children with PID who underwent HSCT and investigate their outcome.

METHODS: We performed a retrospective analysis of children with PID who underwent HSCT and investigated their outcome. Most patients had multiple infections prior to transplant. Outcomes varied among patients with different primary diagnosis. Additional studies are needed to study the outcomes of HSCT in PID patients.

CONCLUSIONS: Twenty-Four patients with PID underwent HSCT between 1995-2015. Of those, 13 patients had SCID, 3 had Wiskott-Aldrich syndrome, 2 had CD40-ligand deficiency, 3 had HLH, 2 had CGD, and 1 had Chediak-Higashi syndrome. Infections were reported in all patients before transplantation, more than half of the patients had multiple infections prior to transplantation. Viral antibody screen pre-HSCT showed that 70% were positive for CMV, 35% were positive for EBV, and 30% were positive for HHV6. The incidence of acute GVHD grade 1 or 2 was 22%, and 19% for grade 3 or 4 at 100 days. Chronic GVHD at 2 years was reported in 1 patient. T-cell recovery was noted in more than 90% of patients. Discontinuation of immunoglobulin replacement was possible in 17 out of 18 living patients. Second transplant was done for 3 patients.

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CONCLUSIONS: We describe a cohort of patients with PID who underwent HSCT. Most patients had multiple infections prior transplant. Outcomes varied among patients with different primary diagnosis. Additional studies are needed to study the outcomes of HSCT in PID patients.
Immune and Clinical Assessment in a Cohort of Pediatric Hispanic Patients with Partial DiGeorge Syndrome: An Institutional Review

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RATIONALE: DiGeorge syndrome (DGS) is the result of microdeletions of chromosome 22q11.2, resulting in a highly variable phenotype. Since limited clinical information is available, the purpose of this study was to characterize the immunologic status of a cohort of Hispanic DGS patients.

METHODS: We studied 50 Hispanic patients diagnosed with DGS (64% confirmed using FISH), ages 0–21 years old (27 females and 23 males, mean age of diagnosis 4.1 ± 2.1 years) by retrospective medical record review. Immune studies including lymphocyte subsets, mitogen proliferation, serum immunoglobulins and specific antibody response, and other clinical data were recorded.

RESULTS: Nine patients (18%) had normal T and B lymphocyte numbers, and normal total serum immunoglobulins. Twenty six patients (52%) had decreased T cells (both CD4+ and CD8+). Both T and B lymphocytes were affected in five (10%) patients. Five patients (10%) had decreased vaccine titers, two patients (4%) had hypogammaglobulinemia, and two patients (4%) had reduced, but not absent, proliferative response to mitogens. No patients had complete DGS. A variety of pre-diagnosis infections were found in 20% of patients. Post-diagnosis infections were present in 52%, the majority Otitis Media (28%). Prophylactic antibiotics were given to 20% of the patients. Cardiac malformations were common (82%). Other affected systems included: endocrine (48%), gastrointestinal (54%), and neurologic (56%). Developmental disorders included speech delay (78%) and learning disabilities (54%).

CONCLUSIONS: Hispanic patients with partial DGS had diminished T lymphocyte numbers and hypogammaglobulinemia, similar to those previously described in the literature.

Removal of Immunosuppression Unmasks a Case of Autoimmune Lymphoproliferative Syndrome (ALPS)

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RATIONALE: ALPS is a disorder of lymphocyte homeostasis most commonly caused by defects in the FAS apoptotic pathway. Common features include lymphoproliferation, autoimmune cytopenias, and immunodeficiency. Variable penetrance leads to under-diagnosis. We present a child with ALPS whose diagnosis was confounded by the use of immunomodulatory therapies.

METHODS: Retrospective chart review was performed.

RESULTS: This patient had multiple congenital anomalies concerning for CHARGE syndrome (esotropia, pre-auricular pits, coarctation of the aorta), recurrent mild infections, failure-to-thrive, and onset of severe thrombocytopenia at 1 year. However, mutations in CHD7 and 22q11 were excluded. Thrombocytopenia was idiopathic and recalcitrant to corticosteroids, IVIG, rituximab and vincristine, but stabilized at 4 years following initiation of mycophenolate mofetil (MMF). Evaluation at 6 years showed profound hypogammaglobulinemia (IgG 47mg/dL, IgA <7mg/dL, IgM 25mg/dL) and non-protective vaccine titers, 5 years post rituximab. Monthly replacement gammaglobulin was initiated. With IVIG, thrombocytopenia improved, and so MMF was weaned. Within a few months, she developed massive splenomegaly (19cm), and large mediastinal lymphadenopathy. Evaluation for lymphoma was unrevealing. Laboratory assessment showed elevated vitamin B12 (1298pg/mL), elevated double negative T cells (98cells/µL), and elevated B220+ double negative T cells (79%), all consistent with ALPS. Genetic evaluation is pending. Once malignancy was excluded, MMF was re-started; lymphadenopathy and splenomegaly improved.

CONCLUSIONS: Medications administered for symptomatic palliation can unintentionally mask aspects of the presentation and obscure recognition of ALPS. MMF is an effective immunosuppressive agent in treating ALPS related lymphoproliferation.

Wiskott-Aldrich Syndrome in a Two-Month-Old Boy Presenting with Intussusception and Normal-Sized Platelets

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RATIONALE: Wiskott-Aldrich Syndrome (WAS) is an X-linked disorder caused by mutations in the WAS protein gene. Clinical manifestations are variable and frequently the diagnosis is delayed. We report a case with a unique presentation to highlight the importance of maintaining a high index of clinical suspicion when evaluating an infant with early onset thrombocytopenia and bloody stools.

METHODS: None.

RESULTS: Two-month-old boy who presented with a one-month history of intermittent fussiness and hematochezia, presumed secondary to cow’s milk protein allergy. He was otherwise well and thriving. Physical exam was normal, other than rectal bleeding and seborrheic dermatitis. Initial labs showed anemia, decreased platelets of normal size, normal white cell count with eosinophilia, no inflammatory markers and normal stool cultures. Ultrasound identified intussusception that was successfully reduced with Gastrografin enema. He then developed fever with tachypnea and was found to have staphylococcus bacteremia and cytomegalovirus viremia. Quantitative immunoglobulins, T & B cell subsets and neutrophil oxidase burst assay were normal. Lymphocytes proliferated briskly to mitogens but not antigens. NK cell function was absent. Gene sequencing identified a hemizygous c.336delC variant in the WAS gene resulting in complete absence of lymphocyte WAS protein expression.

CONCLUSIONS: More than 300 gene variants have been described in WAS. Mutations leading to absent WAS protein expression are associated with profound immunodeficiency and/or hemorrhagic disease, resulting in decreased survival. In cases like the one presented herein, prompt diagnosis and molecular identification are key, since early bone marrow transplantation can be curative.
**Abstracts AB225**

**732 Reversible Hypogammaglobulinemia Due to Dimethyl Fumarate**

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**RATIONALE:** Dimethyl fumarate (DMF), used in relapsing multiple sclerosis (MS) and in psoriasis, may cause lymphopenia and has been implicated in rare cases of progressive multifocal leukoencephalopathy (PML). Suppression of CD3, CD4, CD8 and CD19 cells, in some instances profound, has been described in association with DMF exposure. Investigations of the effect of DMF on serum immunoglobulin levels have not been published previously.

**METHODS:** Serial total IgG levels and T-cell subsets were monitored in a 56 year-old female MS patient referred for immunologic evaluation following 22 months of DMF treatment after it was discontinued because of lymphopenia.

**RESULTS:** Total serum IgG levels, as well as CD4, CD8, and total lymphocyte counts normalized after 5 months of serial observation (IgG from 529 to 706 mg/dL, CD4 from 164 to 338 /µL, CD8 from 88 to 266 /µL, lymphocyte count from 400 to 900 /µL) following discontinuation of DMF. Sinusitis was noted near the nadir of immunosuppression.

**CONCLUSIONS:** We believe this is the first reported case of hypogammaglobulinemia due to DMF. Resolution of hypogammaglobulinemia in the same time-frame as resolution of T-cell suppression after discontinuation of DMF (5 months), and absence of other known causes of transient hypogammaglobulinemia in this patient support a causal relationship; DMF should be recognized clinically as a potential cause of hypogammaglobulinemia. Further investigation of the extent of immunosuppressive effects from DMF and their clinical relevance may be warranted.

**733 Systemic Hypersensitivity to G-CSF in a Healthy Donor Followed By Successful Drug Challenge Allowing Stem Cell Donation**

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**RATIONALE:** Suspected anaphylaxis after first dose of G-CSF in healthy donors has been reported 3 times. Prior cases had shortness of breath, tachycardia and hypotension within 40-90 minutes. All cases received epinephrine and no further G-CSF doses. We describe a woman with systemic G-CSF hypersensitivity who underwent successful drug challenge and donated stem cells.

**METHODS:** Graded challenge with G-CSF.

**RESULTS:** A healthy 43-year-old Ecuadorian female volunteered for sibling stem cell donation. She had incidental eosinophilia (620-1000 eosinophils/µL) and IgE of 144 IU/ml. Twenty minutes after her subcutaneous G-CSF injection, she reported throat tightness, dyspnea and wheezing, diaphoresis, nausea, dimming vision and headache. Heart rate was 130, and blood pressure 110/80. She remained alert, though anxious and received oxygen, albuterol nebulizer and diphenhydramine (25 mg orally). Symptoms resolved within 10 minutes except for residual headache. Several features of her reaction were inconsistent with IgE mediated anaphylaxis. She had a first dose reaction (without presumed allergic sensitization), normal blood pressure, lack of skin and mucosal findings, and rapid recovery without epinephrine. She received a graded dose challenge with 10% of her 960 ug dose (10ug/kg), followed 30 minutes later by 90% of her dose. She remained well for 1 hour, and completed the remaining G-CSF course without incident concluding in stem cell harvest.

**CONCLUSIONS:** We believe this is the first reported case of G-CSF drug challenge in a healthy donor. Distinguishing anaphylaxis from non-IgE mediated systemic reactions after G-CSF may allow selected donors the option for drug challenge to explore safety of continued therapy with G-CSF.
**736 Comparison of the Effect of Aspirin and Heparin with or without Intravenous Immunoglobulin in Treatment of Recurrent Abortion with Unknown Etiology: A Clinical Study**

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**RATIONALE:** Abortion is the most common complication of pregnancy, defined as spontaneous expulsion of products of conception before 24 weeks of pregnancy or termination of pregnancy with a fetus weighing <500 g. The aim of this study was to compare the efficacy of intravenous immunoglobulin (IVIG) in combination regimens with aspirin and heparin versus aspirin and heparin combination alone in women with idiopathic recurrent abortion.

**METHODS:** This randomized, clinical trial was performed at Imam Khomeini Hospital in Sari-Iran between March 2010 and March 2013. Sixty people were randomly allocated into two groups. The control group was treated by subcutaneous enoxaparin 40 mg daily up to 24 weeks associated with aspirin 80 mg daily up to 37 weeks of gestation. The intervention group received IVIG 200 mg/kg/monthly up to 24 weeks of gestation with enoxaparin and aspirin for the same therapeutic period and the same dose as the control group.

**RESULTS:** Three patients (10%) in the intervention group had abortion and 25 (90%) had live births with mean birth weight 3.5 ± 0.9 kg. Four patients (13%) in the control group had abortions, and 28 (87%) had live births with birth weight 3.4 ± 1.2 kg (P = 0.74). The difference was not statistically significant.

**CONCLUSIONS:** It seems that employing the heparin and aspirin combination therapeutic regimen is appropriate for idiopathic abortions and avoids the high cost of IVIG use and its complications.

**737 Comparison of the Efficacy and Safety of Three Intravenous Immunoglobulin Brands in Pediatric Patients with Primary Immunodeficiency**

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**RATIONALE:** Patients with primary immunodeficiency disease who have hypogammaglobulinemia need to receive regular immunoglobulin therapy. Each year our hospital changes the brand of IVIG due to government policy. We question how the different brands influence either the trough level of IgG or the rate of infection. The aim of the study was to evaluate the trough levels of IgG and the infection rates of three IVIG brands.

**METHODS:** This was a retrospective study of the past three years to compare the efficacy of three IVIG brands (Liv-gamma, Gammarass and IV-globulin SN) at Songklanagarind Hospital in primary immunodeficiency patients. The medical records of patients who received regular doses of the three brands of IVIG every 3-4 weeks were reviewed. Each brand had a one-year treatment period. The data collected included the patient characteristics, trough levels of IgG, infections during treatment and adverse effects.

**RESULTS:** The data of ten primary immunodeficiency patients were collected. Different trough levels of IgG were found in all three brands at visit 6 (Liv-gamma 857.8 mg/dL, Gammarass 821.9 mg/dL, IV-globulin SN 1051.3 mg/dL) (P = 0.01). There were no statistical differences in the infection rates among the three brands (Liv-gamma 22%, Gammarass 11%, IV-globulin SN 33%). Adverse reactions occurred in only one patient who received Gammarass.

**CONCLUSIONS:** The results confirmed that different IVIG brands influenced the trough levels. But the infection rates were in discordance with the trough levels. Maybe there were other factors that influenced the infection rates such as the constancy of the trough levels. This should be evaluated further.

**738 Effectiveness of Subcutaneous IgG Supplementation in a Patient with Myotonic Dystrophy**

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**RATIONALE:** Myotonic dystrophy (MyD) is an autosomal dominant neuromuscular disease associated with a variety of systemic abnormalities including low concentrations of serum IgG. Optimal management of hypogammaglobulinemia in patients suffering from MyD still needs to be defined. In primary immunodeficiencies, lower total weekly SCIG doses are required to achieve equivalent serum IgG levels than with monthly IVIG therapy.

**METHODS:** Intravenous immunoglobulin supplementation and measurement of trough/steady-state serum IgG levels were reviewed. No infections were reported.

**CONCLUSIONS:** Subcutaneous once-weekly IgG administration appears to be more effective than once-monthly IVIG regimen in a patient with high IgG catabolism.

**739 A 17-Year-Old Male with a Small Bowel Neuroendocrine Tumor (NET): Flushing Differential Diagnosis**

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**RATIONALE:** NETs are heterogeneous neoplasms originated from cells with a secretory function, extremely rare in children. Small bowel NETs are related to serotonin hypersecretion causing flushing, diarrhea, abdominal pain, bronchoconstriction and heart involvement (carcinoid syndrome); unusual symptoms in kids. We present a 17-year-old male with this pathology.

**METHODS:** Clinical, 5-hydroxyindoleacetic acid (5-HIAA), CT-scan, biopsies.

**RESULTS:** The patient was admitted to the allergist because he presented evanescent non-pruriginous erythematous lesions after eating. He described other symptoms: conjunctival injection, warmth and diaphoresis after the lesions disappeared. Other circumstances like strong emotions, standing and valsalva triggered the symptoms. He denied abdominal pain, diarrhea, cough or wheezing. We triggered the symptoms by asking him to eat; after 5 minutes he presented an evanescent flushing in the face, trunk and extremities for 12 minutes. Given the characteristics of the lesions, we discarded the diagnosis of urticaria or food allergy. We asked for 24-hour urinary 5-HIAA: 42.6 mg (<10 mg/24 hours). The CT showed thickening of the distal ileum and multiple lesions on both hepatic lobules. Colonoscopy revealed a prominent ileocecal valve with a mammillated and eroded lesion. Hepatic and intestinal biopsies: well-differentiated grade 2 primary NET of the ileocecal valve with hepatic metastasis. He started ocreotide and underwent a wide hepactectomy and right hemicolectomy.

**CONCLUSIONS:** This is one of the few reports of carcinoid syndrome in children associated to high 5-HIAA levels. Additionally the patient had an atypical presentation: flushing involved the extremities, very advanced disease and was very young. It shows a differential diagnosis of flushing that should be considered by allergists.
Diagnosis of Multicentric Castleman’s Disease: An Evaluation of a Patient with Polymyogamopathy

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RATIONALE: Multicentric Castleman’s Disease (MCD) is a rare lymphoproliferative disorder characterized by an inflammatory state as well as nonspecific symptoms such as fever and night sweats. Diagnosis is crucial as untreated MCD is associated with high mortality rates. In this case study, we discuss how an initial workup revealed polymyogamopathy leading to an eventual diagnosis of MCD.

METHODS: Open lung biopsy performed Yale Thoracic Surgery and pathology performed by Yale Pathology.

RESULTS: Our patient was a 51 year male with a chronic cough associated with recurrent fevers and lymphadenopathy. An immunological workup revealed polymyogamopathy with an IgA of 700, IgG of 4790, and IgE of 1204. He also had a very elevated CRP of 19.2. The broad differential for polymyogamopathy includes malignancies, chronic infections, and vasculitides. An elevated VEGF of 1200 indicated that the most likely diagnoses were MCD and IgG4 disease. A subsequent open lung biopsy showed plasmacytosis, which supported both diseases. However, absence of definitive obliterative arteritis, along with the patient’s age and severe inflammatory state, led to the diagnosis of MCD.

CONCLUSIONS: MCD is a difficult diagnosis given the broad differential of polymyogamopathy. Clinical history and lab findings such as CRP, IgA level, and IL-6 may be used to point towards MCD. However, in our case study, a biopsy was needed to produce a definitive diagnosis as characteristic findings helped differentiate MCD from IgG4 disease.

Case Series of Tolerability of SCIG in Young Adults with Ataxia Telangiectasia

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RATIONALE: Some patients with Ataxia Telangiectasia (AT) require gamma globulin therapy for hypogammaglobulinemia or poor specific antibody production. Little information regarding tolerability of SCIG in AT patients, even with skin disease, is available.

METHODS: Three patients with AT and poor antibody response to specific antigens presented for evaluation. One patient was a 17 year old male with active sarcoid skin disease, advanced neurological degeneration, chronic EBV and respiratory infections. The second patient was a 17 year old female with AT and scoliosis. The third patient was a 21 year old with AT and recurrent warts. All patients had poor response to protein and polysaccharide vaccines.

RESULTS: The first patient had a pre-treatment IgG level of 293 mg/dL. He was started on IVIG 500 mg/kg/month. He received three doses of IVIG and transitioned to weekly subcutaneous gamma globulin therapy at a dose of 125 mg/kg/week, his one month post-treatment level was 633 mg/dL. The second patient had a pre-treatment IgG level of 118 mg/dL. She received five doses of IVIG at 500 mg/kg and transitioned to a weekly subcutaneous dose of 125 mg/kg/week with a one month post-treatment level of 906 mg/dL. Both patients tolerated the infusions well without premedication. The third patient had normal IgG of 1121 mg/dL, with poor response to vaccines. She was started on subcutaneous dose of 125 mg/kg/ week. None of the patients had any skin changes or significant site reactions to SCIG.

CONCLUSIONS: Young adult patients with Ataxia Telangiectasia and poor vaccine response tolerated use of 20% subcutaneous gamma globulin.
743 A Recombinant Cystatin from Ascaris Lumbricoides Has Immunomodulatory Effects

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RATIONALE: Helminthiasis may ameliorate inflammatory chronic diseases, such as inflammatory bowel disease (IBD) and asthma. Information about immunomodulators from Ascaris lumbricoides, the most common human helmint worldwide is scarce, but could be important considering the co-evolutionary relationships between helminths and humans. We sought to evaluate the potential immunomodulatory effects of a cystatin from A. lumbricoides on an acute model of IBD.

METHODS: From an A. lumbricoides cDNA library we obtained an E. coli produced recombinant cystatin (rAl-CPI). Protease activity inhibition was tested on cathepsin B and papain. Immunomodulatory effects were evaluated at two doses, administered intraperitoneally (0.5 and 0.25 μg/g) on mice with chemically induced (4% Dextran Sodium Sulphate, DSS) - IBD. Body weight, colon length, disease activity index (DAI), histological inflammation score, myeloperoxidase (MPO) activity and gene expression of six cytokines in colon tissue were analyzed.

RESULTS: rAl-CPI showed biological activity. The treatment with rAl-CPI significantly reduced DAI, MPO activity and inflammation score, without toxic effects. Also, IL-10 (p=0.0001) and TGFβ (p=0.001) gene overexpression was observed in rAl-CPI treated (both concentrations) compared to DSS-exposed animals and healthy (PBS) group. Furthermore, a significant reduction of IL-6 (p=0.001) and TNFα (p=0.01) expression, key mediators of IBD, was observed. Although lower expression of IL-1β and IL-12 was detected, it was not statistically significant.

CONCLUSIONS: rAl-CPI reduces the inflammation in a mouse model of IBD, probably by increasing the expression of anti-inflammatory cytokines and reducing pro-inflammatory ones. The usefulness of this recombinant protein in respiratory inflammation should be further investigated.

744 IL-33 Is Selectively Expressed By Esophageal Basal Layer Epithelial Cells during Allergic Inflammation

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RATIONALE: Recent studies on the pathogenesis of allergic disorders have focused on the involvement of innate cytokines produced by epithelial cells that promote the development of Th2 cell immunity. Herein, we focused on the involvement of the innate cytokine IL-33 in eosinophilic esphagitis (EoE). We aimed to test the hypothesis that IL-33 has increased expression in the epithelium in EoE.

METHODS: Quantitative real-time PCR (qRT-PCR), immunohistochemistry (IHC), immunofluorescence (IF), and flow cytometry were performed on esophageal biopsies of patients with inactive and active EoE or control individuals.

RESULTS: IL-33 mRNA was increased (2-fold; p = 0.045) in active EoE biopsies compared to control biopsies. While IL-33 protein was not present in the esophageal epithelium in control individuals and in patients with inactive EoE, IL-33 protein was detected in the epithelium of patients with active EoE and was limited to the nuclei of the cellular layer in direct contact with the basement membrane between papillae. These IL-33-positive cells were characterized by low expression of podoplanin and p75 by both IF and flow cytometry. In contrast, IL-33-negative basal layer epithelial cells expressed high levels of podoplanin and p75. Further analysis revealed that the IL-33-positive cells co-express E-cadherin, keratin 5 and keratin 14, but not the proliferation marker Ki67.

CONCLUSIONS: IL-33 is selectively present only during active EoE disease in the most basal layer in a quiescent population. We propose that IL-33 is likely involved in disease pathogenesis.

745 CXCR4/SDF-1 Axis Promotes EMT Mediated Fibrosis in Eosinophilic Esophagitis (EoE)

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RATIONALE: Epithelial-Mesenchymal Transition (EMT) is associated with series of events that losses epithelia characteristics and acquire properties of mesenchymal cells, via N-cadherin, and de-polarized cytoskeletal arrangements such as Vimentin. EMT processes are earlier reported in eosinophilic esophagitis (EoE); however the mechanism of EMT induction in EoE is clearly understood. Herein, we tested the hypothesis that CXCR4/SDF-1 axis may be operational in the induction of EMT in EoE.

METHODS: Accordingly, histological detection of esophageal fibrosis by Masson’s trichrome stain tissue section; pro-inflammatory and pro-fibrotic cytokines levels by performing ELISA and CXCR4/SDF1 and associated signaling molecules by Western Blot analyses.

RESULTS: DOX induced IL-13 overexpressed mice showed induced SDF-1 and CXCR4 proteins in the esophagus compared to no-DOX exposed mice. Additionally, we observed CXCR4 protein is also induced in vitro in primary esophageal epithelial cells (PEEC) following IL-13 exposure along with TGF-β and TGF-β and N-cadherin levels reduces in IL-13 treated PEEC following the treatment CXCR4 antagonist AMD070. Furthermore, we observed that the levels of mesenchymal marker N-cadherin, TGF-β and Vimentin are induced and epithelial marker E-cadherin is reduced in the esophagus of IL-13 transgenic mice exposed to DOX food compared to no DOX treated mice. Notably IL-13 overexpressed mice show all the characteristics feature of EoE.

CONCLUSIONS: Taken together, we show that CXCR4/SDF-1 axis is involved in EMT process as IL-13 treated primary esophageal epithelial cells and in DOX regulated IL-13 transgenic mice show induced CXC4/ SDF1 and CXCR4 antagonist treatment to IL-13 treated PEEC down regulates profibrotic and EMT associated proteins.
Half Cow’s Milk-Induced Food Protein Induced Enterocolitis Syndrome (FPIES) Require Amino Acid Feeding

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RATIONALE: FPIES is mainly related to cow’s milk and manifests as a chronic digestive disease or in its acute form with potentially life-threatening vomiting/diarrhea/dehydration. The objective of this study is to characterize the clinical features of cow’s milk-induced FPIES in children.

METHODS: A cohort of patients with FPIES was constituted in French Children’s Hospitals (Necker, Paris – Lenval, Nice). Data were collected from medical records including all patients referred for an acute episode of FPIES, and divided into 2 groups according to their tolerance of extensively hydrolysed formula (eHF) or their need to be fed an amino acid formula (AAF).

RESULTS: 49 children were enrolled. Chronic had occurred in 36 (73%), after a median period of 10 days following introduction of milk-based formula. In the whole group, the acute episode occurred at a median age of 4 months. Allergy testing was rarely positive: patch test 21 (51%), skin prick tests 3 (8%), specific IgE 13 (30%). Recovery was observed in 19 (40%) at a median age of 31 months. The eHF group comprised 24 (49%) infants and the AAF one 25 (51%). They exhibited the following significant or trend towards significance differences: number of hospitalizations before diagnosis per patient 0.9 vs 2.7 (p=0.02), age of FA diagnosis 4.5 months vs 2.8 (p=0.04), food tolerance acquisition 54% vs 24% (p=0.02), associated FA 4% vs 4% (p=0.0002).

CONCLUSIONS: Half infants with milk-induced FPIES do not tolerate eHF, and need to be fed with an AAF, a condition associated with a delayed diagnosis.

Investigation of Periostin and TARC Levels in the Search for a Non-Invasive Biomarker in Children and Adults with Eosinophilic Esophagitis

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RATIONALE: Eosinophilic esophagitis (EoE) is an allergic inflammatory disease of the esophagus. An intracellular protease called calpain-14 (CAPN14) has been shown in a previous genome-wide association study (GWAS) to be most highly associated with EoE and is up-regulated in EoE esophageal biopsies. In this study, we investigated the localization of CAPN14 in human esophageal epithelial cells.

METHODS: Immunofluorescence (IF) and biochemical fractionation were performed on transduced immortalized human esophageal epithelial cells (EPC2) stably overexpressing CAPN14 grown in submerged culture. Fractionation was also performed on untransduced EPC2 cells grown at the air-liquid interface (ALI) and on primary esophageal epithelial cells grown in submerged culture.

RESULTS: CAPN14 was readily detectable in whole cell lysates from transduced, but not untransduced, EPC2 cells. Fractionation revealed ~77% of CAPN14 to be in the cytosolic fraction, with ~7% percentage detectable in the membrane and ~16% in the nuclear fractions in human esophageal epithelial cells grown in submerged culture. However, following differentiation into a stratified squamous epithelium, endogenous CAPN14 was mainly localized in the nucleus.

CAPN14 was mainly localized in the nucleus. IF staining of phorbol-12-myristate-13-acetate (PMA) and ionomycin treated esophageal epithelial cells in monolayer culture showed CAPN14 to undergo changes following a shift from the cytoplasmic to nuclear compartments and then to the plasma membrane after 30 and 180 minutes, respectively.

CONCLUSIONS: CAPN14 is localized to the cytoplasm, membrane, and nucleus in human esophageal epithelial cells. Following cellular activation (PMA/ionomycin), CAPN14 shows a dynamic distribution, most notable by its presence in the nucleus, consistent with a key cellular function, yet to be described.
RESULTS: We compared age-matched healthy controls with 40 EoE patients at baseline. Thirty patients were also studied after treatment. Among EoE patients, 159 genes were differentially expressed with a minimum of two-fold expression change compared with healthy controls. By comparison with controls, EoE patients had over expression of genes involved in cell cycle and inflammation and under expression of cytotoxic/NK cell and platelets/red blood cell related genes. In EoE treated patients, a high proportion of cytotoxic/NK cell genes were over expressed. Although the signature was faint, hierarchical clustering revealed two groups of EoE patients with distinct transcriptional profiles.

CONCLUSIONS: EoE patients showed differences in gene expression patterns compared with healthy controls that are modified following treatment suggesting that they may be functionally significant. Further studies are needed to understand the significance of two distinct groups of EoE patients.

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RATIONALE: Eosinophilic esophagitis (EoE) is diagnosed in patients with symptoms of esophageal dysfunction associated with predominant eosinophilic inflammation. Traditionally, attention has been directed toward IgE-mediated immediate-type food allergies, but environmental allergies may also play an important role. Th2 inflammation, implicated in EoE immunopathogenesis, is shared by many atopic conditions. The objective of this project was to contribute to the limited literature on the prevalence of environmental sensitization in adults with EoE.

METHODS: We conducted a retrospective chart review from multiple allergy clinics in five Canadian cities for patients diagnosed with EoE. Demographics, skin prick tests (SPT), and treatment data were collected and reviewed.

RESULTS: A total of 182 patients (male:female ratio of 2:1, p-value < 0.01; 35±16 years) were diagnosed with EoE. Food sensitization was identified on SPTs in 47% of patients (peanuts=22%, tree nuts=27%, milk=12%, soy=12%, seafood=11%, egg=9%, vegetables=8%, wheat=5%, meat=6%, seeds=5%, fruits=4%, oats=2%). Environmental sensitization was detected in 85% of patients (tre=66%, grass=62%, ragweed=62%, dust mites=59%, cat=56%, mould=32%, dog=21%, cockroach=16%). Most patients had both environmental and food sensitization (43%) or environmental sensitization only (42%). Few had food sensitization only (8%) and some were negative to both food and environmental allergens (18%). Most patients were on PPIs (77%) or inhaled/swallowed corticosteroids (73%).

CONCLUSIONS: Environmental allergens had a significantly higher prevalence than food sensitization. Comorbid atopic conditions like environmental allergies should be optimized, as there are trends in early clinical and basic research which suggest environmental allergies may contribute to EoE. The mechanism of EoE requires further study.
**CONCLUSIONS:** This is the first EoE registry that we are aware of in British Columbia. Children referred to the BC Children’s Hospital EoE clinic with biopsy-proven EoE were approached to join our longitudinal EoE registry. After parents consented, data on clinical characteristics and management were recorded. Descriptive statistics and Mann-Whitney-U tests examined differences between groups given that our data was not normally distributed.

**RESULTS:** Among 63 patients assessed between July/2012 and August/2014, the majority (84%) were male, and median age at diagnosis was 5.8 years (IQR = 6.6). Forty-six percent (29) had allergy testing previously, of which 21% had had more than 1 food trigger and 46% (12) had experienced anaphylaxis.) Almost one-third (29%) had atopic dermatitis, 29% had allergic rhinitis, and 24% had asthma. Most were white (71%) or South Asian (25%). Among 19 (30%) patients on dietary intervention for EoE, cow’s milk (32%) and egg (21%) were the most commonly restricted foods. Most (62%) were from the Vancouver area where median time from symptom onset to diagnosis was 1.3 years (IQR = 1.1) versus 2.8 years (IQR = 4.5) for those outside the Vancouver area (p<0.05).

**CONCLUSIONS:** This is the first EoE registry that we are aware of in British Columbia. The underlying factors for longer delays outside the Vancouver area need to be further explored in order to evaluate the potential need for improved EoE service access outside of the Vancouver area and better awareness of EoE presenting symptoms across British Columbia.

**Rationale:** To assess clinical and demographic characteristics of children with eosinophilic esophagitis (EoE) in a new multidisciplinary allergy and gastroenterology clinic serving British Columbia.

**Methods:** Children referred to the BC Children’s Hospital EoE clinic with biopsy-proven EoE were approached to join our longitudinal EoE registry. After parents consented, data on clinical characteristics and management were recorded. Descriptive statistics and Mann-Whitney-U tests examined differences between groups given that our data was not normally distributed.

**Results:** Among 63 patients assessed between July/2012 and August/2014, the majority (84%) were male, and median age at diagnosis was 5.8 years (IQR = 6.6). Forty-six percent (29) had allergy testing previously, of which 21% had had more than 1 food trigger and 46% (12) had experienced anaphylaxis.) Almost one-third (29%) had atopic dermatitis, 29% had allergic rhinitis, and 24% had asthma. Most were white (71%) or South Asian (25%). Among 19 (30%) patients on dietary intervention for EoE, cow’s milk (32%) and egg (21%) were the most commonly restricted foods. Most (62%) were from the Vancouver area where median time from symptom onset to diagnosis was 1.3 years (IQR = 1.1) versus 2.8 years (IQR = 4.5) for those outside the Vancouver area (p<0.05).

**Conclusions:** This is the first EoE registry that we are aware of in British Columbia. The underlying factors for longer delays outside the Vancouver area need to be further explored in order to evaluate the potential need for improved EoE service access outside of the Vancouver area and better awareness of EoE presenting symptoms across British Columbia.

**Presence of Food Allergy Alters the Presentation of Pediatric Eosinophilic Esophagitis**

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**Rationale:** A transition from food allergy (FA) to eosinophilic esophagitis (EoE) after immunotherapy has been described, yet the pathophysiologic interaction between these diseases remains unclear.

**Methods:** Utilizing a database-approach that captures clinical, medical, and laboratory data, we characterized a cohort of pediatric EoE patients to determine the prevalence of EoE+FA (as defined by history and detection of food-specific IgE by SPT and/or serologic testing) and differences in presentation compared to EoE-FA by McNemar’s test.

**Results:** We found that 58 (29%) of our EoE patients had evidence of FA, suggesting FA may be more prevalent in EoE than previously appreciated. The EoE+FA cohort was significantly younger than EoE-FA (6.06 versus 8.13 years), suggesting EoE manifests earlier when FA is present. 74.6% of the EoE-FA cohort had allergic rhinitis, versus only 44% of the EoE-FA (p<0.0001). EoE+FA subjects could be easily identified due to dramatically higher IgE to multiple foods, including milk, egg, soy, wheat, peanut, and tree nuts, and an increased likelihood for positive skin prick tests. Further characterization revealed that EoE+FA subjects presented with significantly more dysphagia (15/40 versus 21/87 reported, p<0.0001), gagging (14/40 versus 8/87, p<0.0005), and chest pain (5/40 versus 10/87, p<0.05) and surprisingly significantly more rings on EGD and eosinophils on biopsy (p<0.05, respectively).

**Conclusions:** Our findings suggest a subtype of EoE in which IgE-mediated food allergy may impact aspects of EoE. Importantly, while these patients could be identified based on measures of food allergy, several measures of EoE were more pronounced, including both local esophageal features and incidence of symptoms.
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**Aeroallergen, Food and Panallergen Sensitization Patterns in Eosinophilic Esophagitis Patients**

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**RATIONALE:** Eosinophilic Esophagitis (EoE) has been etiologically associated with egg, milk, and wheat allergy. Non-traditional allergens are being increasingly identified in EoE. We aimed to identify sensitization patterns to aeroallergens and food, and associations with pan-allergens, in an EoE population.

**METHODS:** A case-series analysis of skin test results from 66 EoE patients meeting IRB study criteria was performed. Associations between sensitization to pan-allergens, profilin/PR-10 and sensitization to aeroallergens and foods were determined via Chi-square tests. Entomophilous plant extracts (Locust; profilin, Alfalfa; PR-10, and non-native Ailanthus; profilin) were used as pan-allergen markers.

**RESULTS:** 73% of our EoE patients (aged 2-73 years; mean ± SD = 16 ± 16 years; 56% male) were sensitized to both aeroallergens and food. 18% were sensitized solely to aeroallergens and 1.5% solely sensitized to food. 86.4% patients were pansensitized (>3 aeroallergens). Overall, patients were sensitized to an average of 20.4 (SD = 14.9) aeroallergens and 6.3 (SD = 6.5) foods. Sensitization to egg (12/60, 20%), milk (8/62, 13%) and wheat (4/58, 7%) was less than anticipated, and sensitization to unique, pan-allergen containing foods: mustard (14/56, 25%), sunflower (15/25, 60%), garlic (12/45, 27%), and corn (12/46, 26%) was observed. Sensitization to unusual foods, along with legumes and tree nuts, was significantly associated with sensitization to PR-10 (p < 0.05) and profilin pan-allergen markers.

**CONCLUSIONS:** Novel findings in our EoE population included: 86.4% of patients were sensitized to aeroallergens and increased sensitization to unique foods was associated with sensitization to pan-allergens. Increased research into pan-allergen sensitization and cross reactivity to food maybe warranted in highly aeroallergen-pansensitized EoE patients.

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**Serum IgG4 Antibodies in Pediatric Subjects with Eosinophilic Esophagitis Treated with Cow’s Milk Elimination Diet or Swallowed Fluticasone: High Levels of Specific IgG4 to Cow’s Milk Components Despite Low to Negative IgE Antibodies**

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**RATIONALE:** High titer IgG4 antibodies to relevant food allergens have been reported in adults with eosinophilic esophagitis (EoE). Responsiveness to cow’s milk elimination diet alone (i.e., without swallowed steroid) has been demonstrated in children with EoE mediated by this food, including those with <0.35 IU/mL of IgE antibodies to cow’s milk. Here we investigate serum IgG4 levels to cow’s milk components among pediatric EoE patients in relation to IgE antibodies and the results of cow’s milk elimination.

**METHODS:** ImmunoCAP for specific IgE antibodies to cow’s milk and IgG4 antibodies to cow’s milk components Bos d 4 (alpha-lactalbumin), Bos d 5 (beta-lactoglobulin), Bos d 6 (bovine serum albumin; BSA), and Bos d 8 (caseins) were performed on sera collected before and after treatment with either cow’s milk elimination diet or fluticasone. 

**RESULTS:** In subjects treated with cow’s milk elimination diet, a reduction in IgG4 antibodies to alpha-lactalbumin, beta-lactoglobulin, BSA, and caseins was observed. Diet nonresponders (n = 39) had higher levels of IgG4 antibodies to cow’s milk components at baseline compared to responders (n = 69). There was a general increase in allergen-specific IgG4 antibodies in subjects with low to negative serum IgE to cow’s milk (i.e., <0.35 IU/mL). Conversely, serum IgG4 antibodies to cow’s milk components decreased, irrespective of treatment, in subjects with ≥0.35 IU/mL of IgE to cow’s milk.

**CONCLUSIONS:** The results indicate that IgG4 antibodies are often present in sera with low to undetectable IgE to the same protein, and that the response to cow’s milk avoidance is unrelated to IgE antibodies to cow’s milk components.

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**Food-Specific IgG4 Is Associated with Eosinophilic Esophagitis**

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**RATIONALE:** Current forms of allergy testing are unreliable for identifying triggers of eosinophilic esophagitis (EoE). Recent data suggests EoE is IgG4-associated. We hypothesized that food-specific IgG4 (FS-IgG4) is associated with active EoE and may elucidate dietary triggers.

**METHODS:** Prospectively collected esophageal biopsies and plasma from 20 EoE subjects (newly diagnosed) and 10 non-EoE controls were tested for total IgG4 (T-IgG4) and FS-IgG4 using ELISA. After 6-8 weeks of empiric dietary elimination, responder status in EoE subjects was determined by repeat biopsy (diet responders (DR) vs. non-responders (NR)). TRIGGERS were identified in DR by elimination, reintroduction, and biopsy. Follow-up samples were available for 14 EoE subjects (DR = 8, NR = 6). Comparisons were made between EoE subjects vs. non-EoE controls and DR vs. NR.

**RESULTS:** Median esophageal T-IgG4 and FS-IgG4 (ng/ml) were significantly elevated in EoE subjects vs controls (total: 1,847 vs 469, p = 0.008; peanut: 4.05 vs 0.01, p = 0.003; soy: 2.12 vs 0.01, p < 0.001; egg white: 61.4 vs 2.88, p < 0.001; casein: 55.8 vs 0.67, p < 0.001; wheat: 19.9 vs 1.1, p < 0.001). Esophageal FS-IgG4 correlated with plasma FS-IgG4 for all foods (r > 0.5). DR demonstrated significant decreases in esophageal T-IgG4 (p = 0.04) and had lower T-IgG4 following dietary elimination compared to NR (673.6 vs. 1,793, p = 0.03). Importantly, esophageal FS-IgG4 to known triggers also declined significantly in DR (p = 0.02).

**CONCLUSIONS:** Elevated T-IgG4 and FS-IgG4 are associated with active EoE and decline in response to dietary elimination.

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**Abstracts**

**FEBRUARY 2016**
Identification of Food Sensitivity in Adult Eosinophilic Esophagitis Patients Lacks Clinical Utility

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RATIONALE: Evaluation of IgE mediated food sensitivity is frequently performed for EoE patients. However, the clinical relevance of identifying IgE mediated sensitivity to foods is not clear. We sought to determine whether EoE patients with food sensitivity represent a phenotype of EoE with distinct clinical features.

METHODS: An IRB approved retrospective chart review identified 724 adults with a diagnosis of EoE seen at the University of Wisconsin Hospital and Clinics through the year 2013. Individual patient charts were reviewed to capture disease severity, endoscopy results, pathology results, allergy testing, medical management and patient outcomes.

RESULTS: 257 out of the 724 adult patients met clinical criteria for EoE and were evaluated in the allergy clinic. 93% of those patients had skin prick testing and/or serum IgE done to foods. The prevalence of food sensitization to at least one food was 53%, with peanut being the most common food sensitivity (52%), followed by soy (36%). Patients with food sensitivity were more likely to report concomitant asthma, allergic rhinitis, eczema and/or food allergy compared to non-food sensitive patients. Other clinical characteristics, including symptoms, disease severity, endoscopic findings, peripheral eosinophilia, and patient reported outcomes did not differ between food sensitive and non-food sensitive patients. Additionally, there was no significant difference in outcomes for food sensitive patients treated with food avoidance compared to food sensitive patients treated without food avoidance.

CONCLUSIONS: Food sensitive adult EoE patients are not phenomenally different than non-food sensitive patients. We did not observe any clinical utility for identifying food sensitivity in adult EoE patients.

Patch Test and Immediate Hypersensitivity Tests to Foods in Pediatric Patients with Eosinophilic Esophagitis

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RATIONALE: Eosinophilic Esophagitis (EoE) is a combined IgE mediated immediate hypersensitivity and Type IV hypersensitivity reaction for which the evaluation includes skin prick test (SPT) and/or specific IgE (sIgE); and patch test (PT) respectively. We compared the positivity of these tests to foods singly or in combination in pediatric patients with biopsy proven EoE.

METHODS: We conducted a retrospective chart study of 17 pediatric patients with biopsy proven EoE. Data analyzed include PT, SPT, and sIgE levels to 25 specific foods (425 total patches placed).

RESULTS: Of 17 patients, 9 were female and 13 had a history of atopy (asthma, allergic rhinitis and/or atopic dermatitis). Sixteen of 25 foods were positive on PT and 9 were negative. Of those with a positive PT, 3 (19%) (wheat, white potato and peanut) were positive in both PT and SPT and/or sIgE; and 13 (81%) were SPT negative with normal sIgE levels. Four foods (barley, green beans, squash, and lamb) were negative in all testing modalities used.

CONCLUSIONS: The majority of foods that were positive on PT (81%) were negative to SPT or sIgE. When used in combination PT, SPT, and sIgE may yield more positive results than individually. Certain foods are more likely to have negative results in all modalities of testing and may not have utility in identifying food hypersensitivity in pediatric EoE.

Amino Acid-Based Diet Induces Histological Remission, Reduces Clinical Symptoms and Restores Esophageal Mucosal Integrity in Adult Eosinophilic Esophagitis Patients

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RATIONALE: The pathophysiology of eosinophilic esophagitis (EoE) is mainly driven by food allergy, whereby an increase in mucosal permeability might facilitate transepithelial allergen flux in the esophagus. Studies on the effect of elemental diets in adults are scarce and unpalatability makes adherence challenging. The aim of this study was to assess the effect of a ready-to-drink amino acid-based formula (Neocate, Nutricia) on eosinophilic inflammation and to study its effect on the integrity of esophageal mucosa. Additionally, adherence to this formula was evaluated.

METHODS: In this prospective study 21 adult patients with active EoE were included. Patients underwent endoscopy before and 4 weeks after dietary treatment. Clinical, endoscopic and histological responses, along with the mucosal integrity of the esophagus were evaluated, using electrical tissue impedance in vivo and transepithelial electrical resistance and molecule flux through esophageal biopsies in Ussing chambers.

RESULTS: Peak eosinophil count decreased significantly after the diet from 40 to 9 per high power field (p<0.001). In total, 17 (81%) of the included patients completed the diet. 12 (71%) patients showed complete histological response (≤5 eosinophils) and another 4 (24%) patients showed partial histological response (≤25% decrease). Symptoms decreased substantially and 15 patients (88%) became completely asymptomatic (p<0.001). A strong improvement of endoscopic signs was observed (p<0.000). Esophageal permeability decreased and mucosal resistance increased significantly (p<0.05).

CONCLUSIONS: This study strongly indicates that in adults with EoE, a ready-to-drink amino acid-based diet reduces eosinophilic inflammation, induces clinical remission and restores the esophageal mucosal integrity. Patient’s adherence to this diet is better than previously described.
761 Successful Treatment of Eosinophilic Gastroenteritis with a Multiple-Food Elimination Diet

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RATIONALE: Dietary restriction therapies for eosinophilic gastroenteritis (EGE) have been shown to be effective in some studies. We analyzed the effectiveness of a multiple-food elimination diet (MFED), an empiric diet preferentially devoid of the six most common food allergens—milk, soy, egg, wheat, peanuts/tree nuts, and shellfish/fish (6-FED)—and other the patient’s historically causative foods for the treatment of EGE.

METHODS: Three patients with EGE who were diagnosed on the basis of gastrointestinal symptoms and eosinophil infiltration of the gastrointestinal mucosa (>20 eosinophils/high-power field) and were treated with a MFED (for a total of four times) followed by reintroduction of those eliminated foods without systemic steroids at our hospital between 2010 and 2014 (for a total of four times) followed by reintroduction of those eliminated foods without systemic steroids at our hospital between 2010 and 2014 were included. Clinical data, including imaging and histological findings, and eosinophil, albumin, immunoglobulin G (IgG), and hemoglobin levels before and after the MFED were retrospectively reviewed and compared.

RESULTS: Before the MFED, all patients had a low serum IgG level. A before and after the MFED were retrospectively reviewed and compared. and eosinophil, albumin, immunoglobulin G (IgG), and hemoglobin levels and imaging or histological findings; a decrease in the eosinophil level; and an increase in the albumin, IgG, and hemoglobin levels after the MFED. The causative foods identified in the reintroduction phase were cow’s milk and wheat in two patients and soybean and hen’s eggs in one patient each.

CONCLUSIONS: The MFED may be a promising alternative treatment to improve clinical findings and laboratory data in patients with EGE.

762 Long-Term Safety and Efficacy of Reslizumab in Children and Adolescents with Eosinophilic Esophagitis: A Review of 477 Doses in 12 Children over 7 Years

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RATIONALE: To evaluate the long term safety and efficacy of reslizumab (RSZ), a monoclonal humanized antibody to interleukin-5, in pediatric patients who have received the drug through participation in a randomized controlled trial (RCT), followed by an open-label extension (OLE), and ongoing treatment on a compassionate use (CU) basis.

METHODS: Records of patients who received RSZ in our center were reviewed. Patients received RSZ 2 mg/kg (or placebo) every 4 weeks as part of the RCT from March 2008 to October 2009, OLE from July 2008 to January 2012, and CU from January 2012 until July 2015. Labwork, history, and examinations were conducted every 12 weeks. Biopsy results were compared from baseline (prior to RCT) and at the most recent evaluation. Adverse events (AE) were recorded.

RESULTS: 12 patients entered the RCT at our center. 6 patients completed the OLE. 4 received RSZ through CU. Between the RCT, OLE, and CU periods, patients received 477 doses of RSZ (mean 40, range 2-89). No serious AE were attributed to RSZ in any phase of administration. No clinically significant laboratory abnormalities were identified. Symptoms improved on treatment: dysphagia (42% vs 9%); abdominal pain (58% vs 0%); heartburn (18% vs 0%); vomiting (67% vs 33%); reflux (58% vs 0%). Mean esophageal eosinophil count improved on treatment (33 eos/hpf vs 3).

CONCLUSIONS: RSZ appears to be safe in children with eosinophilic esophagitis over 7 years of experience. Symptoms and eosinophil count improved in our patients treated with RSZ.

763 Quality of Life in Eosinophilic Esophagitis

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RATIONALE: Eosinophilic esophagitis (EoE) is a chronic immune-mediated, eosinophilic disease. Although change in histology as well as symptom scores following implementation of different treatment modalities have been explored previously, major patient-oriented outcome measures such as quality of life (QoL) have not been well examined in EoE. QoL issues in patients with EoE are distinct and potentially as devastating as those faced by the general food allergy community. We hypothesize that QoL is significantly impeded in patients with EoE.

METHODS: The Goryeb Children’s Hospital Department of Gastroenterology recruited one patient to date between the age of 5-18 for a prospective quality of life study. The PedsQL™ as well as the EoE-specific Pediatric QoL Inventory was administered to the child and parent. Active enrollment of patients is currently ongoing. We plan to have at least 20 subjects by the annual meeting. Data will be compared with QoL measurements from healthy controls as obtained from the 2005 study by Youssif, et al.

RESULTS: Physical and social functioning was not significantly affected with patient reported overall score of 0 (never have problems with) in each category. While emotional functioning mildly diminished, the most significantly affected category was school functioning with the patient stating that it is often hard to pay attention in school and he often forgets things.

CONCLUSIONS: Health related quality of life is an important outcome in clinical trials, clinical improvement strategies and population-based health assessment. We hope to further explore it within the world of EoE at the completion of this study.
764 Long-Chain Polysaturated Fatty Acid Intake in Children with Eosinophilic Esophagitis

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RATIONALE: Omega-3 fatty acids, α-linolenic (ALA), docosahexanoic (DHA) and eicosapentaenoic acid (EPA) are important immune modulators. The role of these fatty acids in atopic conditions is well established. To date, their role in eosinophilic esophagitis (EoE) has not been investigated. Elimination diets are common therapy for EoE, and depending on the diet prescription, may exclude omega-3-rich foods such as nuts (ALA) and seafood (DHA & EPA) from the diet. In this study we aim to compare omega-3 fatty acid intake of EoE patients following restricted diets to the general population of a similar age range.

METHODS: Three-day food records were collected from new patients (n=78) seen at the Cincinnati Center for Eosinophilic Disorders and analyzed by a registered dietician. Each patient had a confirmed EoE diagnosis based on 2011 consensus guidelines. Mean ALA, DHA and EPA intake was compared to age-matched reference data from the National Health and Nutrition Examination Survey (NHANES) by unpaired t-test.

RESULTS: In this cohort of EoE patients (n=78), dietary intake of ALA (mean=0.50g), DHA (mean=0.02) and EPA (mean=0.007g) were lower than reference data from NHANES (n=8604), with ALA (mean=1.4g; p=0.0043; 95% CI: 0.288-1.519), and DHA (mean=0.07 g; p=0.0001; 95% CI: 0.045-0.055) but not EPA (mean=0.03g; p= 0.031; 95% CI: 0.002-0.044) reaching significance.

Only 1 of 78 subjects was taking an omega-3 supplement.

CONCLUSIONS: Children with EoE have lower intake of omega-3 fatty acids than national-survey controls and therefore may benefit from a referral to a registered dietician for nutritional assessment.

765 Food Allergy in Infancy Is Associated with Dysbiosis of the Intestinal Microbiota

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RATIONALE: Food allergy is a major public health concern. The role of the intestinal microbiota in food allergy is increasingly being appreciated.

METHODS: Food-allergic (history of immediate hypersensitivity to food with positive food-specific skin and/or serum IgE) and healthy control infants < 12 months of age were enrolled. Stools samples were collected and detailed health, environmental and dietary questionnaires were completed serially every 4 months. Bacterial DNA was extracted and the V4 region of the bacterial 16s rRNA gene was sequenced using the Illumina MiSeq instrument.

RESULTS: 137 infants (52 food-allergic and 85 controls) were enrolled. There were significant differences in fecal microbiota between the 2 groups. At the phyla level, there was decreased relative abundance of Firmicutes and Proteobacteria, and increased relative abundance of Bacteroidetes in food-allergic babies. These differences could be traced down to altered abundance of taxa at the genus level. Differences for food-allergic babies 1-6 months of age included decreased abundances of genera in Bacteroidetes (Parabacteroides and Alistipes) and Firmicutes (Blautia, Clostridium, Subdoligranulum, Veillonella, Staphylococcus and Enterococcus) and increases in other Firmicutes (Sarcina and Cellulosilyticum). Differences for food-allergic babies 7-12 months of age included decreased abundances of genera in Bacteroidetes (Parabacteroides, Alistipes, and Prevotella), Firmicutes (Eubacterium, Clostridium and Ruminococcus), and Proteobacteria (Campylobacter), and increases in other Firmicutes (Dorea) and Proteobacteria (Parasutterella).

CONCLUSIONS: Our data supports the presence of a gut microbial signature in food allergy. Evaluation of a larger group (500 subjects) and longitudinal follow-up for 3 years with fecal microbiota analysis and questionnaires every 4 months is in progress.

766 Peanut Sensitivity in Children Is Highlighted By Increased IL-13 Production and Cyp11a1 Expression

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RATIONALE: The pathobiology of peanut allergy is focused on IgE-mediated reactions. Genetic factors and critical pathways contribute to the risk of developing such reactions. The steroidogenic enzyme Cyp11a1 has been linked to development of allergic disease and IL-13 has been shown to play a role in IgE-mediated intestinal peanut allergy in mice. Activation of Cyp11a1 enzymatic activity was shown to be essential for IL-13 production and for development of peanut-induced intestinal anaphylaxis in mice.

METHODS: Human PBMCs from peanut-allergic children and healthy controls were isolated and stimulated with anti-human CD3/anti-CD28 for 48 hours. Cell supernatants were collected and cytokines measured by ELISA. Cyp11a1 expression levels were monitored by real-time PCR and protein expression in cells was detected by immunohistochemistry. Peanut allergy was confirmed in all patients with a clinical history of reaction and/or evidence of sensitization (positive skin prick test or specific IgE) by double-blind, placebo-controlled oral food challenges to peanut protein.

RESULTS: Following activation, PBMCs from patients with peanut sensitivity had significantly increased production of IL-13 compared to controls but IFNg levels were similar between groups. Cyp11a1 protein and mRNA levels were significantly increased in PBMCs from patients with peanut sensitivity compared to controls.

CONCLUSIONS: Cyp11a1 mRNA and protein expression and levels of IL-13 from activated T cells were significantly increased in peanut-allergic subjects, implicating this pathway in peanut-induced disease. Targeting this pathway may be an effective alternative or adjunct to oral immunotherapy in the future.

Supported by Siemens, MW by Crawford Charitable Lead Unitrust, CS by fellowship from Monsanto.
CONCLUSIONS: These data suggest that GLA was efficacious in this rodent peanut allergy model and may have utility in a range of allergic diseases.

769 Identification of Japanese Apricot Pea maclein As a New Allergen Related to Food-Dependent Exercise-Induced Anaphylaxis Due to Japanese Apricot: Cross-Reactivity to Pru p 7

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RATIONALE: In previous research, we identified peach pea maclein (Prn p 7) as an allergen related to systemic reactions in peach allergy. We hypothesized that Japanese apricot (JA) pea maclein may be a new allergen related to food-dependent exercise-induced anaphylaxis (FDEIA) due to JA.

METHODS: Seven patients (M:F=2:5, mean age 28.6 yrs) diagnosed with JA allergy based on relevant clinical history, positive skin test and/or challenge test were enrolled. To evaluate the allergenicity of the purified JA pea maclein, we performed ELISA and IgE-immunoblotting using the patients’ sera with JA pea maclein. ELISA with nPrn p 7 was conducted. Using ImmunoCAP, we measured specific IgE levels against peach, rPrn p 1, rPrn p 3, and rPrn p 4. We also performed basophil activating tests (BATs) for JA pea maclein. To investigate the cross-reactivity between JA pea maclein and Pru p 7, we performed ELISA inhibition tests.

RESULTS: Exercise after intake of JA was followed by the onset of allergic reactions in six patients’ self-reports and one patient’s challenge test. The ELISA and IgE-immunoblotting using JA pea maclein showed positive reactions in six (85.7%) and seven (100%) patients, respectively. The positivity for specific IgE against peach, rPrn p 1, rPrn p 3, rPrn p 4 and nPrn p 7 was 57.1%, 0%, 0%, 0% and 85.7%. JA pea maclein induced basophil CD203c expression in all four patients who underwent BATs. In all four patients who underwent ELISA inhibition tests, IgE binding to pea maclein inhibited binding to the other.

CONCLUSIONS: Pea maclein is a causative allergen of FDEIA due to JA, and is a cross-reactive allergen between JA and peach.

770 Effects of Pressure and Temperature Processing on the Allergic Reactivity of the Chestnut

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RATIONALE: Nuts are one of the principal causes of anaphylactic fatal reactions caused by food. It has been observed that temperature and pressure processing of food, may have the effect of reducing the allergenicity of this food, like nuts, and may be useful to control this allergenic risk. We hypothesized that food processing, in this case boiling and autoclave, could modify chestnut allergenicity.

METHODS: 17 patients allergic to chestnut were retrospectively evaluated between 2004 and 2014. The diagnosis was made by prick-prick, chestnut specific-IgE, and in all patients (except cases of anaphylaxis) oral challenge with chestnut. We measured the binding capacity of IgE in the unprocessed and processed extracts by thermal treatment (boiling and autoclave). Then we determined the effect of thermal and pressure processing over the binding capacity of IgE of each allergen by Immunoblotting.

RESULTS: We observe, in the majority of the serums, one or more bands in approximate 25 KD. They also appear in many of the samples, one of more bands of around 50 KD. Both disappear with the first boiling in many cases.

CONCLUSIONS: The different treatments significantly reduce the allergenic capacity of the proteins that appear in westerns of these patients. It does not seem that any treatment increases the allergenicity of the chestnut in these cases.
Cross-Reactivity Among Peanut and Tree Nut Allergens

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Rationale: Significant information exists on the sequences and structural details of the IgE based responses to peanut allergens. Much less work has been done to explain such a high degree of cross-reactivity among various nuts. We have developed computational and experimental approaches to identify common epitopes that could contribute to cross-reactivity.

Methods: IgE and IgG4 immunanalysis of allergen proteins and peptides were performed using antibodies and sera from patients with confirmed peanut and tree nut allergy. The protein extracts of these samples were all normalized according to protein content and subjected to SDS-PAGE. Spot blot, microarray and western blot analysis with sera from multiple patients. Antibody or IgE-reactive bands were identified using mass spectroscopy. Potentially cross-reactive peptides were identified computationally and with peptide-microarray analysis.

Results: Previously unknown IgE and IgG4 epitope maps for multiple nut allergens were developed. IgE cross-reactivity was seen at both protein and peptide levels of the different nuts. Several proteins that showed cross-reactivity with various antibodies were observed, excised, and shown to be previously identified allergens in the corresponding nut extracts. Previously unidentified, strongly cross-reactive peptides and peptide motifs with various levels of sequence identity were found to be cross-reactive often in proteins that are not in the same protein families (Piam).

Conclusions: Extensive IgE cross-reactivity was seen between peanuts and tree nuts within the known major allergen protein families. However, previously unidentified cross-reactive proteins seem to also exist. Novel IgE epitopes and peptide motifs were identified that could account for cross-reactivity.

Walnut Food Allergenic Extracts

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Rationale: Total protein extractability and IgE binding are useful methods for determining potency of allergenic extracts. These techniques were applied to investigate various production methods for walnut food extracts.

Methods: English walnut food extracts were made to evaluate source material, defatting, extraction fluid, and processing. Protein content was determined by Bradford and SDS-PAGE. IgE binding was determined by immunoblotting and microtiter plate ELISA titration using sera from tested by Bradford and SDS-PAGE. IgE binding was determined by immunoblotting and microtiter plate ELISA titration using sera from patients with confirmed peanut and tree nut allergy. The protein extracts of these samples were all normalized according to protein content and subjected to SDS-PAGE. Spot blot, microarray and western blot analysis with sera from multiple patients. Antibody or IgE-reactive bands were identified using mass spectroscopy. Potentially cross-reactive peptides were identified computationally and with peptide-microarray analysis.

Results: Walnut food extracts can show a more than 100 fold variability in total protein depending on the extraction process. Aqueous extraction greatly improves the extractability of protein. Total protein correlated to material, defatting, extraction fluid, and processing. Protein content was determined by Bradford and SDS-PAGE. IgE binding was determined by immunoblotting and microtiter plate ELISA titration using sera from patients with confirmed peanut and tree nut allergy. The protein extracts of these samples were all normalized according to protein content and subjected to SDS-PAGE. Spot blot, microarray and western blot analysis with sera from multiple patients. Antibody or IgE-reactive bands were identified using mass spectroscopy. Potentially cross-reactive peptides were identified computationally and with peptide-microarray analysis.

Conclusions: Extensive IgE cross-reactivity was seen between peanuts and tree nuts within the known major allergen protein families. However, previously unidentified cross-reactive proteins seem to also exist. Novel IgE epitopes and peptide motifs were identified that could account for cross-reactivity.

Study of Relevant Allergens in Children and Adults with Lentil Allergy in a Population of Madrid Compared to Those with Allergy to Lentil and Peanut

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Rationale: Legumes are the sixth leading cause of Food Allergy, being Lentil the most frequently involved in the Mediterranean.

Aim: To analyze Allergy to Lentil and the relation with Peanut allergy.

Methods: We studied 1,375 patients (368 children/1,007 adults) from 2012-2014. Allergological evaluation: clinical history, skin test, sIgE (immunoCAP) and OFC were performed.

Results: Twenty-one children and 10 adults were allergic to Lentil, and 6 children and 4 adults to Lentil and Peanut. Group 1: symptoms after the introduction of Lentil (1-2 yo); Group 2: occasionally Lentil tolerance (3-19 yo); Group 3: well-established tolerance (20-51 yo). Positive results by molecular allergens in patients with URT/AE and ANAP by Lentil: Allergic to Lentil: Group 1 (n=7): Ara h1: 57%; Ara h2: 43%; Ara h3: 0%; Pru p3: 0%. Group 2 (n=8): Ara h1: 50%; Ara h2: 12%; Ara h3: 0%; Pru p3: 25%. Group 3 (n=4): Ara h1: 50%; Ara h2: 50%; Ara h3: 0%; Pru p3: 50%. Allergic to Lentil and Peanut: Group 1 (n=1): Ara h1: 100%; Ara h2: 100%; Ara h3: 0%; Pru p3: 0%. Group 1 (n=1): Ara h1: 100%; Ara h2: 100%; Ara h3: 0%; Pru p3: 100%.

Conclusions: In this study molecular analysis results indicate that there is no recognition and/or low cross reactivity. Ara h1 is most frequent in those patients with URT/AE to Lentil, and Pru p3 in those with ANAP. No differences have been found in patients allergic to Lentil and allergic to Lentil and Peanut, but further studies are needed with more patients.

Cross-Reactivity Among Cereal Grains

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Rationale: Cross-reactivity among cereal grains is only reported when wheat is involved. We assess three cases of severe anaphylaxis and cross-reactivity to sunflower, oat and rye.

Methods: Patient 1 had colic, vomiting, urticaria and angioedema, 20 minutes after eating 7 grain’s bread with tuna and mayonnaise. Patient 2 presented itching after using moisturizer with oatmeal. Years later, 15 minutes after ingestion of milk, fruits and mixed cereals, he developed urticaria, angioedema, and vomiting. Patient 3, experienced angioedema minutes after eating 7 grain’s bread with tuna and mayonnaise. Patient 1 had colic, vomiting, urticaria and angioedema, 20 minutes after eating 7 grain’s bread with tuna and mayonnaise. Patient 2 presented itching after using moisturizer with oatmeal. Years later, 15 minutes after eating 7 grain’s bread with tuna and mayonnaise. Patient 3, experienced angioedema minutes after eating 7 grain’s bread with tuna and mayonnaise.

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All abstracts are strictly embargoed until the date of presentation at the 2016 Annual Meeting.

AB238 Abstracts

**775 Sensitization Profile of Individuals to Shellfish in the Chesapeake Bay Area**

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**Rationale:** There is limited information on the demographics of adults at risk for shellfish allergy. Past surveys suggest more women are affected. We examined the frequency of serologic sensitization in adults tested for shellfish allergy at a major clinical reference laboratory.

**Methods:** Shellfish-specific IgE antibody levels were analyzed by ImmunoCAP in serum from 2538 Chesapeake Bay residents who were evaluated from 2010-2015. The frequency of positive tests (e.g., >0.1 kUa/L) and IgE antibody ranges were determined across gender and age distributions.

**Results:** A total of 2165 tests were ordered for subjects >18 years old (Range 18-88 yo). IgE antibody responses to crustacean allergens (shrimp, crab, and lobster, n = 1341) were tested more often than those to mollusks (clam, oyster, scallop, mussel, n = 824). 33% of all tests were positive. While females were tested more (n = 1446 tests vs n = 719 tests males), males had a higher rate of positivity (47.71% vs 27.39% in females x2 = p < 0.01). For all shellfish allergens, the range of IgE antibody measured was higher in males. The median IgE (kUa/L) for males (M) and females (F) were: shrimp (M)1.16, (F)0.41; crab (M)1.44, (F)0.50; lobster (M)1.29, (F)0.48; clam (M)0.50, (F)0.57; oyster (M)0.46, (F)0.33; scallop (M)0.36, (F)0.29; mussel (M)0.23, (F)0.45; with the medians higher in females for clam and mussel.

**Conclusions:** The results support that adult males have a higher frequency of positive IgE antibody results for all species of shellfish. This supports a difference in exposure or gender bias in the acquisition of sensitization, which contrasts with 2 previous surveys.

**776 Removing Peanut Allergen Ara h 1 from Peanut Extracts Using p-Aminobenzamidine**

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**Rationale:** Ara h 1 is one of 3 major allergens in peanut. Removing Ara h 1 from a peanut extract may produce a hypoallergenic peanut extract for immunotherapy and other purposes.

**Methods:** Peanut extracts were treated overnight with and without 10 mM p-aminobenzamidine (pABA, a protease inhibitor) in the presence of 1% glutaraldehyde, pH 8.5. Various amino acids (e.g., glycine, lysine, phenylalanine, and histidine) with functional groups similar to pABA. Data on IgE binding indicated an absence of Ara h 1 in the treated extract. By contrast, residual Ara h 1 and other soluble protein polymers besides Ara h 1/2/Ara h 6 were seen in the extracts treated without pABA but with glutaraldehyde. The soluble protein polymers were recognized by IgE antibodies. Treatment with various amino acids provided the same results.

**Conclusions:** Treatment with pABA in the presence of glutaraldehyde resulted in a peanut extract that contained no Ara h 1 but did contain Ara h 2/Ara h 6. Total IgE binding was reduced as a result. The pABA method thus appears to have a potential for the production of hypoallergenic peanut extracts.

**777 Impacts on Rice Allergic Proteins with Different Methods of Food Processing**

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**Rationale:**Our aim is to provide rich diet methods for rice allergic patients by observing the impacts on rice allergic proteins with different methods of food processing.

**Methods:** We selected the food processing methods which the local people commonly used, boiling, steaming, microwave heating, yeast fermentation and distiller’s yeast fermentation carried on the processing of rice. The allergen protein was extracted, then the electrophoresis, observed and analyzed the allergenic protein changes after the treatments with different processing methods.

**Results:** There are eight bands (16, 26, 33, 38, 49, 55, 72, 98KD) appeared in the raw rice extract; The 16 KD band is the most obvious. There are two bands (16, 98KD) and a fuzzy area between 26-38KD appeared in the boiled rice extract. There are five clear bands (16, 26, 38, 72, 98KD) appeared in the steamed rice extract; Moreover, the 26KD band is clearer compared with raw rice extract. There is only one band, 33KD band, clearer and wider compared with raw rice extract, and a fuzzy area between 55-98KD appeared in the microwave heated rice extract. There is no band and fuzzy area in yeast fermentation extract. There is only one band, 33KD band, appeared in the distiller’s yeast fermentation extract, its definition is similar to the rice clearer.

**Conclusions:** There are different damages to rice allergic protein after different processing methods. And also new proteins generate in the processing process. The yeast fermentation is the best appropriate rice processing method to the rice-allergy patients.

**778 Co-Sensitization Patterns of Crustaceans and Mollusks**

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**Rationale:** Food allergy is complicated by the lack of knowledge regarding what potentially cross-reactive foods must be removed from a diet after an initial reaction to another food. The frequency of co-sensitization among mollusks and crustaceans, however, is not well known. In addition, frequencies of co-sensitization within the Mollusca phylum are not well known.

**Methods:** This retrospective, cross sectional study was performed at a pediatric tertiary care center. Following approval by the hospital’s IRB, de-identified Immunocap data from January 2009-June 2011 were obtained from the hospital’s laboratory computer system. Specific IgE antibodies to 7 crustaceans and bivalves (shrimp, lobster, crab, clam, mussel, scallop, and oyster) as well as milk (used as a control) were obtained. Co-sensitization was measured via Spearman Correlation Coefficients.

**Results:** Intra-crustacean co-sensitization, as previously reported, was high with an average correlation of 0.889. The highest co-sensitization correlation was between lobster and crab (0.942, p<0.0001). The average intra-bivalve correlation was 0.866 and the highest correlation was between scallops and clams (0.940, p<0.0001). The co-sensitization between crustaceans and bivalves ranged from 0.735 (lobster/oyster, p<0.001) to 0.881 (lobster/clam, p<0.0001) with an average of 0.824.

**Conclusions:** Our results suggest that there is high co-sensitization within the bivalves as well as significant, albeit slightly less, co-sensitization between crustaceans and bivalves.
779 A Retrospective Study of Clinical Shrimp Allergy in the Setting of Shrimp, Cockroach and Dustmite Sensitization

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RATIONALE: The protein that commonly causes shrimp allergy, tropomyosin, is also found in cockroach and dust mite (DM). The presence of clinical shrimp allergy and immunologic sensitization amongst these allergens is underreported and therefore merits further investigation.

METHODS: A retrospective chart review was conducted on patients ages 5 through 80 with allergy clinic visits from Jan 2012 through Jun 2015. Data was collected on shrimp, cockroach, and dustmite sensitization based on IgE skin prick (Dermapak®) or in-vitro (immunoCAP®) testing. A history of clinical reactivity to shrimp was recorded to determine the prevalence of shrimp allergic symptoms in the presence of shrimp, cockroach or DM sensitization.

RESULTS: Of 171 patients analyzed, 46 (27%) was sensitized to shrimp, 77 (45%) to cockroach, 89 (52%) to DM, 31 (18%) to SH+/CR+/DM+, and 2 (1.2%) to SH+/CR-/DM-. Clinical shrimp allergy was reported by 57% (26/46), 34% (26/77), and 34% (30/89), respectively, with sensitization as compared to 17% (21/124, p<0.0001), 22% (21/94, p=0.10), and 21% (17/82, p=0.06) without sensitization to shrimp (OR=6.4, 95% CI 3.0-13.6, p<0.0001), cockroach (OR=0.6, 95% CI 0.2-1.5, p=0.29), and DM (OR=1.1, 95% CI 0.5-2.5, p=0.76), respectively. Shrimp allergy was reported in 51% vs. 86% (p=0.12) with SH+/CR+ vs. SH+/CR- and 56% vs. 60% (p=1.0) with SH+/DM+ vs. SH+/DM-.

CONCLUSIONS: Shrimp sensitization was the only predictor that is significantly associated with clinical shrimp allergy. Cockroach or DM sensitization was not found to significantly increase the odds of having a history of clinical shrimp allergy.

780 Natural Variability of Allergen Levels in Soybeans Across North and South Americas from Five Growing Seasons

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RATIONALE: Soybean is one of eight foods that, as a group, are responsible for more than 90% of all food-induced allergies. Although exposure to allergenic proteins from these foods is key for developing sensitization of atopic populations and eliciting allergic reactions in sensitized consumers, the natural variability of the levels of specific allergenic proteins is unknown.

METHODS: Using validated enzyme-linked immunosorbent assays (ELISAs), seven soybean allergens were quantified from 624 conventional soybean seed samples with 41 different varieties, which were grown on 26 different field locations over five different years. Variance Component Analysis (VCA) was used to determine the impact factors on allergen levels.

RESULTS: Seven soybean allergen levels ranged from six (Gly m 6) to 19 fold (Gly m 4) over five growing seasons. VCA demonstrated that the environmental conditions had the largest impact on allergen levels.

CONCLUSIONS: Atopic individuals are exposed to variable levels of soybean allergenic proteins.

781 Quality of Life and Feeding Difficulties Associated with Childhood FPIES and IgE-Mediated Food Allergies

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RATIONALE: Food allergies are a growing public health concern. There is little information about the impact of childhood FPIES on quality of life and feeding difficulties. The primary goal of this survey was to compare these outcomes in children with FPIES versus IgE-mediated food allergy.

METHODS: Anonymous surveys were administered online to the parents of children with FPIES and IgE-mediated food allergy. The quality of life survey (adapted from Cohen et al, 2004) included 17-questions that were scored from 1 (not troubled) to 7 (extremely troubled); maximum possible score was 119 per family. The feeding survey (adapted from the Montreal Children’s Hospital feeding scale) included 14-questions and was scored from 1 (not difficult) to 7 (very difficult); maximum possible score was 98 per affected child.

RESULTS: Sixty-one responses to the FPIES survey and 131 responses to the IgE-mediated food allergy survey were analyzed. The median quality of life score for families with at least one child with FPIES was 78 compared to a median score of 70 for families with at least one child with IgE-mediated food allergy, p=.015. The median feeding difficulties score for children with FPIES (n=69; 8 families with 2 affected children) was 48 versus 31 for children with IgE-mediated food allergy (n=155; 27 families with 2 and 7 families with 3 children), p<0.0001.

CONCLUSIONS: Parents of children with FPIES report significantly lower quality of life and greater feeding difficulties in their children compared to IgE-mediated food allergy. FPIES may have a higher impact on the families than IgE-mediated food allergy.

782 Case Series of 5 Patients with Anaphylaxis to Hemp Seed Ingestion

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RATIONALE: Hemp, (C. sativa) is an annual herbaceous weed of the family Cannabinaceae that produces flowers, leaves and seeds. Hemp seeds are added to cereals, granola, and pressed to produce oil. Leaves of C. sativa are known for their psychoactive effects due to tetrahydrocannabinol (THC). Hemp seed contains negligible THC content. There are very few reports on hemp seed allergy. We aim to present the clinical features and the diagnostic approach in 5 patients with anaphylaxis to hemp seed.

METHODS: Epicutaneous skin prick testing (SPT) was performed to hemp seed in all patients as well as a healthy control. A positive test was defined as 3 mm greater than the negative saline control.

RESULTS: There were 4 (80%) males and 1(20%) female, ranging in age from 13-40 years (mean age 25 years). 80% were atopic. All patients presented to an emergency room with anaphylaxis shortly after ingestion of hempseed. 60% of patients received isolated anti-histimine, 20% received isolated epinephrine, and 20% received both treatments. All were prescribed an epinephrine autoinjector. All had positive SPTs to fresh hemp seed, with an average wheal size of 10.3mm (3/5 patients).

CONCLUSIONS: We present one of the first case series of pediatric and adult patients with anaphylaxis to hemp seed ingestion. This allergy appears to manifest later in life as anaphylaxis. Allergists should be aware of the potential allergenicity of hemp seed, especially with the increasing commercial availability of foods containing hemp seed and its derivatives.
783 The Clinical Prehistory of Food-Protein Induced Enterocolitis Syndrome (FPIES)

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RATIONALE: Misdiagnosis and delays in diagnosis for children with Food Protein-Induced FPIES is common. We evaluated the diagnostic itinerary of FPIES children before the correct diagnosis.

METHODS: A retrospective assessment of clinical records of 23 children diagnosed with FPIES was performed.

RESULTS: Between August 2012 and July 2015, twenty-three children (14 males and 9 females) were diagnosed with FPIES (mean age at onset: 9.99 months with exclusion). The diagnosis was made in seven cases at the first clinical food reaction. In the remaining 16 children, the mean time lapse between the first episode and the diagnosis was 10.02 months. The diagnosis was made in seven cases at the first clinical food reaction. In the remaining 16 children, the mean time lapse between the first episode and the diagnosis was 10.02 ± 9.99 months with an average of three events (SD 1.58) before the proper identification. Specialists consulted for differential clinical suspect included:

- Gastroenterologist (Mecckels diverticulum, intussusception, pyloric stenosis, gastroenteritis, celiac disease, megaloclon, congenital microvillus atrophy) in 9/23 cases;
- Cardiologist (congenital cardiopathy) in 6/23;
- Neurologist (seizures, intracranial hemorrhage) in 6/23;
- Infectious disease specialist (sepsis) in 6/23;
- Pediatric Surgeon (pyloric stenosis) in 4/23;
- Endocrinologist (adrenal insufficiency, diabetes insipidus) in 4/23;
- Dietician (Enteral nutrition) in 4/23;
- Anesthetist (hypotension, tachycardia, arrhythmia, hyperpye) in 3/23;
- Metabolic disease specialist (acidosis, Hereditary Fructose Intolerance) in 3/23;
- Nephrologist (urinary infection) in 3/23;
- Immunologist (IPEX, primary immunodeficiency, hypogammaglobulinaemia) in 2/23;
- Haematologist (Anemia, methemoglobinemia) in 2/23;
- Geneticist (Genetic syndrome) in 2/23.

CONCLUSIONS: Delay in FPIES identification incurs costs of specialist consultations, unnecessary (often-painful) procedures and the experience of multiple episodes. Educational training courses on FPIES for hospital-based pediatricians may reduce the diagnostic delay.

784 Factors Affecting the Attainment of Tolerance Status in a Cohort of Food Protein-Induced Enterocolitis Patients

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RATIONALE: The natural history of food protein-induced enterocolitis syndrome (FPIES) is not well understood. We sought to examine factors which may influence time to and age of tolerance in our single-centre, tertiary cohort.

METHODS: A retrospective cohort study of children with FPIES (using pre-defined criteria) who underwent observed food challenges (OFC) at The Children’s Hospital at Westmead from 1995-2015 was undertaken. Categorical and non-parametric analyses were performed.

RESULTS: We identified 67 OFCs on 59 infants with FPIES (median age at OFC = 20 months), 14 (26%) reacted on OFC. Common food triggers were grains (n=37), cow’s milk (CM) (n=26), soy (n=12) and egg (n=12). There was no significant difference in sex, comorbid atopy, time between initial episodes and OFC or age at OFC between reactors and tolerant children.

Of children with grain-FPIES, 90% (34/37) were tolerant at OFC (median age at OFC = 20 months; median time from initial episode = 14 months). 88% of children with CM-FPIES (33/36) and 92% with soy-FPIES (11/12) were tolerant at OFC (median age at OFC = 19 and 21 months; median time from initial episode = 15 months and 21 months, respectively). By comparison, only 66% of children with egg-FPIES (8/12) and 50% (3/6) with fish-FPIES were tolerant at OFC (median age at OFC = 36 and 47 months; median time from initial episode = 33 and 34 months, respectively).

CONCLUSIONS: Most children with FPIES from our cohort attained tolerance earlier than 3-4 years. Certain foods were associated with a longer time to tolerance. Well-designed prospective studies are required to ensure children with FPIES do not undergo unnecessary prolonged dietary exclusion.

785 Economic Impact of Childhood Fpies and IgE-Mediated Food Allergies

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RATIONALE: FPIES can result in repeated emergency room visits and extensive dietary modifications. Health-care costs for the families with children with FPIES have not been studied before. The primary goal of this survey was to determine the economic impact of FPIES compared to IgE-mediated food allergies (IgE-FA).

METHODS: Anonymous survey was administered online to the parents of children with FPIES and IgE-FA. The economic impact survey (adapted from Gupta al., 2013), assessed direct medical, out-of-pocket, and indirect costs.

RESULTS: Sixty-one FPIES responses and 131 IgE-FA responses were analyzed. In the past year, children with FPIES had 436 outpatient visits, 36 emergency room visits, and 18 hospitalizations versus 290 outpatient visits, 33 emergency room visits, and 2 hospitalizations for children with IgE-FA allergies. Out-of-pocket health-related costs were $7233 per child with FPIES, compared to $5029.8 per child with IgE-FA, P <0.001. The largest expense for FPIES families was special diets, $2583.4 per child, while for the IgE-FA families the largest expense was education and supervision, $1531 per child. In the past year, FPIES families missed an average 8.4 days of school and/or work versus average 4.8 days missed school and/or work days for IgE-FA families, P =0.007. However, four FPIES families stated they had to give up their job in order to look after their child and reported an average salary loss due to FPIES as $75,000/family.

CONCLUSIONS: Childhood FPIES and IgE-FA result in significant self-reported direct and indirect costs for health care systems and families.
Plasma Cytokine/Chemokine Profiles in Non-IgE-Mediated Gastrointestinal Food Allergy

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RATIONALE: Reports of non-IgE-mediated gastrointestinal food allergy (non-IgE-GI-FA) cases have increased in recent decades. We previously reported that the antigen-specific cytokine secretion profile of PBMCs from non-IgE-GI-FA patients is Th2-predominant. Also, massive eosinophilia was observed in approximately 70% of biopsy specimens from those non-IgE-GI-FA patients. However, it remains unclear how lymphocytes are recruited to the GI tract in those patients and to the skin in IgE-mediated food allergy (IgE-FA) patients. We examined plasma cytokine/chemokine levels in order to elucidate the Th2-predominant pathogenesis shared by non-IgE-GI-FA and IgE-FA and to identify differences in lymphocyte recruiting factors between non-IgE-mediated and IgE-mediated allergies.

METHODS: We recruited 42 pediatric non-IgE-GI milk allergy patients together with 10 IgE-dependent milk allergy patients, and obtained written informed consent. Plasma samples were obtained before the resolution of the GI symptoms. Plasma cytokine/chemokine levels were measured by multiplex assay.

RESULTS: Similar levels of plasma Th2 and Th17 cytokines (IL-5, IL-13 and IL-17) were observed in non-IgE-GI-FA and IgE-FA. The MCP-2/CCL8 level was significantly higher, whereas the MMP-1/CCL4 level was significantly lower, in non-IgE-GI-FA compared with IgE-FA.

CONCLUSIONS: Our results suggest that the mechanisms of lymphocyte recruitment in non-IgE-mediated allergy may be distinct from those in IgE-mediated allergy, although both allergy types have a similar Th2-predominant pathogenesis. Further studies are required to elucidate the molecular and cellular mechanisms underlying release of these chemokines from the affected tissues.

Clinical Characteristics of Non-IgE-Mediated Gastrointestinal Food Allergy: Analysis of Nation-Wide Web-Based Online Patient Registry

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RATIONALE: Cases of non-IgE-mediated gastrointestinal food allergy (non-IgE-GI-FAs) have increased dramatically in Japan since 2000. The most recently determined incidence rate was 0.21%. We established a nation-wide Web-Based Online Patient Registry in order to elucidate the clinical characteristics of non-IgE-GI-FAs.

METHODS: Pediatricians all over Japan registered 718 patients from December 2009 through April 2014. We investigated 362 patients whose age at onset was less than 12 months and who fulfilled at least 4 of Miceli Sopo’s 5 diagnostic criteria. Clinical symptoms, signs, laboratory data and responses to treatments were analyzed.

RESULTS: Based on the initial symptoms, the patients were classified into 4 clusters according to our previous study (JACI 2011). Ninety-two patients were classified as food-protein-induced enterocolitis syndrome (FPIES) with bloody stool (Cluster 1), 69 were FPIES without bloody stool (Cluster 2), 67 were food-protein-induced enteropathy (Cluster 3) and 131 were food-protein-induced colitis (Cluster 4). Patients in Cluster 1 showed significantly earlier onset (median: 8 days after birth). Serious complications (ileus, intestinal perforation, etc.) were observed in 6.1% of the total patients, and the highest rate (13%) was in Cluster 1 patients. Milk-specific IgE was detected in 17% of the total population, with the lowest rate (5%) in Cluster 4 patients. Amino acid-based formula reduced the symptoms most effectively in all clusters.

CONCLUSIONS: FPIES with bloody stool was characterized by earlier onset and the highest incidence of serious complications among the 4 clusters of non-IgE-GI-FAs. Early diagnosis and treatment seem to be essential for infants with FPIES with bloody stool.
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RATIONALE: The overall impact of specialty consultation for patients with chronic spontaneous urticaria (CSU) has never been reported. The objective of this study was to assess the impact of allergist/immunologist evaluation of CSU patients on filled prescriptions of corticosteroids.

METHODS: We conducted an interrupted times series analysis using prescription data from Truven Health Analytics MarketScan, a nationwide claims database, for patients with dates of service between January 1, 2010 and December 31, 2012. CSU patients were identified using a previously validated ICD-9-CM coding algorithm. Eligibility for cohort inclusion was further limited to continuously enrolled patients with incident cases of CSU and incident evaluations by an allergist. The monthly oral steroid burden in the 12 months before and after the date of allergy/immunology evaluation was compared.

RESULTS: 635 patients met inclusion criteria. In the twelve months preceding allergy evaluation, total oral steroid prescriptions, measured in prednisone equivalents, increased by 1,579 mg per month. Steroid prescriptions peaked at 31,145 mg in the 30 days prior to the date of allergy evaluation. Prescriptions filled on the date of evaluation were excluded due to an artificial alignment of refills. In the twelve months after specialty consultation, prescriptions dropped by 1,580 mg per month, representing a significant treatment effect (p=0.0003). The initiation of second-line immunomodulators, particularly cyclosporine, hydroxychloroquine and dapsone, was similarly associated with significant decreases in filled corticosteroid prescriptions.

CONCLUSIONS: The evaluation of patients with CSU by an allergy/immunology specialist is associated with a marked decrease in corticosteroid prescriptions, possibly due to the introduction of immunomodulating agents.

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RATIONALE: Physical urticaria/angioedema syndromes (PUs) are commonly encountered. PUs are identified by a history of physical triggers provoking symptoms, and diagnosed by provocation testing; however, positive/negative likelihood ratios (LR) have not been established for challenge procedures recommended in recent guidelines (J Allergy Clin Immunol 2014;133:127). We conducted a systematic review to determine the diagnostic utility of practical office procedures recommended for three common PUs: dermatographia (DERMATO), cholinergic urticaria (CU), and delayed pressure urticaria/angioedema (DPUA).

METHODS: Literature searches were conducted up to May 13, 2015, on EMBASE, MEDLINE, PubMed and SCOPUS databases. We included studies for PUs with diagnostic challenge testing compared to a reference standard (Ann Intern Med 1994;120:667-676). Two authors independently appraised study quality, extracted and analyzed data.

RESULTS: A total of 2505 citations were identified, of which 1875 were not relevant. None of the 108 studies of DPUA or 307 of DERMATO satisfied our inclusion criteria. Of 215 studies of CU, 4 of small size, with 33 CU patients, were accepted as fulfilling criteria. Patient data were combined: methacholine intradermal challenge compared to exercise challenge (reference standard) was associated with a sensitivity = 24.2%. Data were not sufficient to calculate specificity or positive/negative LR.

CONCLUSIONS: We were unable to identify studies of sufficient methodologic quality to calculate positive/negative LR to recommend diagnostic challenges for PUs. Limited data imply that methacholine intradermal challenge is associated with a low sensitivity for CU. There is a need for well-designed studies to aid the clinician in interpretation of diagnostic challenges for patients with DERMATO, CU, and DPUA.

CONCLUSIONS: Distinct managerial, clinical, QoL and attitudinal differences exist between refractory and non-refractory CIU patients in the US. This information is valuable in informing best clinical practice and appropriate new interventions for both patient types.

METHODS: We conducted an interrupted times series analysis using prescription data from Truven Health Analytics MarketScan, a nationwide claims database, for patients with dates of service between January 1, 2010 and December 31, 2012. CSU patients were identified using a previously validated ICD-9-CM coding algorithm. Eligibility for cohort inclusion was further limited to continuously enrolled patients with incident cases of CSU and incident evaluations by an allergist. The monthly oral steroid burden in the 12 months before and after the date of allergy/immunology evaluation was compared.

RESULTS: 635 patients met inclusion criteria. In the twelve months preceding allergy evaluation, total oral steroid prescriptions, measured in prednisone equivalents, increased by 1,579 mg per month. Steroid prescriptions peaked at 31,145 mg in the 30 days prior to the date of allergy evaluation. Prescriptions filled on the date of evaluation were excluded due to an artificial alignment of refills. In the twelve months after specialty consultation, prescriptions dropped by 1,580 mg per month, representing a significant treatment effect (p=0.0003). The initiation of second-line immunomodulators, particularly cyclosporine, hydroxychloroquine and dapsone, was similarly associated with significant decreases in filled corticosteroid prescriptions.

CONCLUSIONS: The evaluation of patients with CSU by an allergy/immunology specialist is associated with a marked decrease in corticosteroid prescriptions, possibly due to the introduction of immunomodulating agents.
792 A Randomized Trial of Icatibant in ACE-Inhibitor–Induced Angioedema

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RATIONALE: Angioedema induced by treatment with angiotensin-converting-enzyme (ACE) inhibitors is estimated to occur in up to 0.68% of patients receiving ACE inhibitors and usually are located in the upper airway and the head and neck region. There is no approved treatment for this potentially life-threatening condition. The study objective was to evaluate the effectiveness and safety of the selective B2-receptor-antagonist icatibant in the treatment of this condition.

METHODS: Patients (n = 30) who had been diagnosed with ACE-inhibitor-induced angioedema of the upper aerodigestive tract were randomly assigned to treatment with 30 mg of subcutaneous icatibant or to the current off-label standard therapy consisting of intravenous inhibitor-induced angioedema of the upper airway and the head and neck region. There is no approved treatment for this potentially life-threatening condition. The study objective was to evaluate the effectiveness and safety of the selective B2-receptor-antagonist icatibant in the treatment of this condition.

RESULTS: The median time to complete resolution of edema was 8.0 hours with icatibant as compared to 27.1 hours with standard therapy (P = 0.002). Three patients receiving standard therapy required rescue intervention with icatibant and prednisolone; 1 patient required tracheotomy. Significantly more patients in the icatibant group than in the standard-therapy group showed complete resolution of edema within 4 hours after treatment (5 of 13 vs. 0 of 14, P = 0.02).

CONCLUSIONS: Among patients with ACE-inhibitor-induced angioedema, the time to complete resolution of edema was significantly shorter with icatibant than with combination therapy with a glucocorticoid and an antihistamine. Icatibant therefore seems to be an effective and safe therapeutic option in patients suffering from ACE-inhibitor-induced angioedema.

793 Safety of a C1 Esterase Inhibitor Concentrate in Pregnant Women with Hereditary Angioedema: Findings from the International Berinert Patient Registry

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RATIONALE: Increased estrogen levels during pregnancy can exacerbate hereditary angioedema (HAE), yet disease and treatment ramifications have not been well studied in pregnant women. Using data from the international Berinert patient registry, we analyzed outcomes of pregnancies exposed to plasma-derived, pasteurized, nanofiltered C1-Inhibitor concentrate (pnfC1-INH; Berinert/CSL Behring) during routine HAE management.

METHODS: This observational registry, conducted between 2010 and 2014 at 34 US and 7 European sites, gathered data on 318 subjects and 15,000 pnfC1-INH infusions. Whenever possible, subjects who used pnfC1-INH during pregnancy were followed to term to assess neonatal outcomes and maternal adverse events (AEs).

RESULTS: The registry database included eleven pregnancies in ten subjects who were using pnfC1-INH for HAE attack treatment and/or prophylaxis. Eight pregnancies concluded in the birth of a healthy baby. Of the remaining three pregnancies: one (16-year-old subject) was voluntarily terminated at 9 weeks gestation; a second (30-year-old subject, previous miscarriage) ended as a first-trimester spontaneous abortion one week after the subject’s last pnfC1INH infusion and was considered unrelated to pnfC1INH treatment; the third occurred in a 30-year-old subject who exited the registry approximately two months before her due date with no further follow-up, although no AEs or complications were recorded up to that point. Five of these subjects had no AEs during registry participation; the remaining 6 had no AEs that were considered related to pnfC1-INH.

CONCLUSIONS: Berinert administration during pregnancy was generally safe and not associated with any treatment-related AEs. In all registry pregnancies followed to term, the birth of a healthy baby was reported.

794 Novel Association of GAD65-Positive Autoimmune Inner Ear Disease with Autoimmune Urticaria

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RATIONALE: Acute autoimmune sensorineural loss or autoimmune inner ear disease (AIED) is characterized by bilateral, progressively worsening asymmetric hearing loss that usually improves with early immunosuppressive therapy. The disease shares a T-cell mediated pathology with Muckle-Wells Syndrome (MWS), a rare autosomal disorder characterized by urticarial rash and steroid-resistant deafness. AIED was postulated to be an autoimmune disorder, and a large subset of patients with this disease express antibodies to the 68kD antigen/HSP70. Other associated autoantibodies can be directed against collagen, endothelial, or cochlear antigens.

METHODS: We evaluated a 56 year old female with acute onset of progressive hearing loss in the left ear and fluctuant loss in the right ear. Audiograms demonstrated compatible losses. Serology was negative for ANA but was positive for antibodies to 68kD antigen/HSP 70. The patient also developed recurrent bouts of urticaria and angioedema, with very high titters of antibody to the high affinity IgE receptor anti-FceRI. The hearing loss responded to intratympanic steroids, while the urticaria improved with histamine and leukotriene inhibition.

RESULTS: This patient demonstrates a novel association of autoimmune urticaria with autoimmune sensorineural deafness. AIED has not been described in association with chronic autoimmune urticarial (characterized by detectable antibodies targeting FceRI on mast cells and basophils). However both disorders tend to occur with increased frequency in patients with autoimmune “proclivity”. Several autoantibodies may coexist in these patients- such as ANA, RF, ANCA, and cardiolipin and thyroid antibodies.

CONCLUSIONS: The pathogenesis and roles of IgE and TNF-alpha in these diseases and novel approaches to therapy need further evaluation.
RATIONALE: Chronic spontaneous urticaria (CSU) is defined as the occurrence of almost daily wheals and itching for at least 6 weeks, with no obvious cause. Specific laboratory tests should be carried out to discover the suspected cause. Our aim was to investigate the possible significance of patch test (PT) which depends on type IV and delayed type I hypersensitivity with common allergens in diagnosis of CSU.

METHODS: Fifty patients having CSU were selected from Allergy and Clinical Immunology outpatient clinic of Ain Shams University Hospitals, with 50 healthy controls. Blood and immunological tests were done to exclude known causes of chronic urticaria. (PT) was done using common aeroallergens, food, chemicals, metals and drug allergens.

RESULTS: The patch test results were positive in 22(44.0%) of case group with 36(6%) positivity among the control group. The sensitivity to the PT was 44%, the specificity was 94%, the positive predictive value was 88% and the negative predictive value was 63%. Most of patients showed positivity to mixed group of allergens. PT was positive in 42.9% to food allergens, 18.4% to drugs, 26.5% to chemicals and 24.5% to aeroallergens.

CONCLUSIONS: Patch test showed satisfactory results to be used in diagnosing chronic spontaneous urticaria as it show high specificity and predictive values in comparison to control.

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The Role of Component Resolved Diagnostics for Assessing Hidden Allergens of Idiopathic Urticaria in Childhood

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RATIONALE: Acute idiopathic urticaria (AIU) in childhood is a common condition in childhood. However, the exact causing factors and physiopathology remains unknown. The serum profile of IgE antibodies to those allergen components differs, between patients due to local variation of allergen exposures. The aim of this study was to evaluate hidden allergens of AIU in childhood by using the component resolved diagnostics (CRD).

METHODS: Seventy four children with AIU were recruited from Hanyang University Guri Hospital for last 5 years. There were no positive results from allergy skin prick or serum test, but some of them showed positive food related history and food challenge tests. We applied CRD including pathogenesis-related protein family number 10 (PR-10) and non-specific lipid transfer proteins (nsLTP) for evaluating hidden allergens of AIU.

RESULTS: There were no evidences with allergic skin and serum test for subjects. Twenty-four children of 74 subjects presented positive CRD results including PR-10 (apple (nMal d 1) 1, hazelnut (rCon a 1) 5, peach (rPru p 1) 4, peanut (rAra h 8) 4, kiwi (nAct d 8) 3, birch (rBet v 1) 4, alder (rAln g 1) 1), nsLTP (peach (nPru p 3) 4, hazelnut (rCor a 8) 3, mugwort (nArt v 3) 2), profilins (rBet v2) 3 children.

CONCLUSIONS: IgE sensitization to storage proteins in peanut, tree nuts or seeds is regarded as an important risk marker for severe systemic reactions. IgE sensitization to PR-10 or nsLTP may be shown to be the important allergen components for systemic reaction including AIU in childhood.

Use of a C1 Esterase Inhibitor Concentrate in Elderly Patients with Hereditary Angioedema: Findings from the International Berinert® (C1-INH) Registry

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RATIONALE: Treatment of hereditary angioedema (HAE) in elderly patients is not well characterized. A large international patient registry evaluated the use of plasma-derived, pasteurized, nanofiltered C1-inhibitor concentrate (pnfC1-INH, Berinert®/CSL Behring) in patients of all ages.

METHODS: This observational registry, conducted from 2010-2014 at 34 US and 7 European sites, gathered prospective (post-enrollment) and retrospective (pre-enrollment, if available for 2009) usage and adverse event (AE) data on subjects treated with pnfC1-INH. Data from subjects ≥65 years of age were compared with those in adults 17 to <65 years of age.

RESULTS: The registry documented 1701 pnfC1-INH infusions in 27 elderly subjects (maximum age 83 years). A total of 1511 HAE attacks treated with pnfC1-INH administration were reported among 25/27 (92.6%) elderly subjects. Among elderly subjects, mean ± SD (8.8 ± 4.1 IU/kg) and median (6.4 IU/kg) pnfC1-INH doses were lower than those reported for 252 adults (12.9 ± 6.2; 12.5 IU/kg, respectively). Nineteen AEs occurred in 8 of 23 (34.8%) elderly subjects with prospective data (safety set), for rates of 0.83 events/subject and 0.02 events/infusion, similar to corresponding rates in adults (0.91 and 0.03, respectively). None of the AEs were considered related to pnfC1-INH and all but two events (prostatectomy; GI bleeding) were mild or moderate in severity. There were four serious adverse events (prostatectomy; urinary tract infection requiring hospitalization; transient ischemic attack; and GI bleeding).

CONCLUSIONS: These findings suggest a high degree of safety with pnfC1-INH administration in elderly HAE patients and reveal a pattern of lower weight-based dosing in elderly versus non-elderly adults.

Role of Urinary N-Methylhistamine in Chronic Urticaria

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RATIONALE: Histamine is thought to play an important role in chronic urticaria (CU) as evidenced by its detection in urtiacral lesions and symptomatic treatment of CU with anti-histamines. However, there are limited studies evaluating the utility of urinary n-methylhistamine (uNMH) in chronic urticaria. We analyzed associations between uNMH and clinical features of patients with CU.

METHODS: This was a retrospective review of 33 CU patients seen at Mayo Clinic between 8/30/13 and 4/22/15 that had uNMH measured around the time of their first visit. Clinical features were derived from a standard questionnaire and associated laboratory tests were reviewed.

RESULTS: NMH values in all subjects were essentially within the normal range [55 to 208 mcg/g Cr, median 125 mcg/g Cr]. There was no significant age or gender difference in uNMH excretion. Subjects in the study had hives for a median of 40 weeks [interquartile range (IQR) 16 weeks to 160 weeks]. We noted a significant and moderate negative correlation (-0.56) between uNMH levels and duration of urticaria (P=0.0006). We also found a difference in uNMH excretion in patients with angioedema [median 135 mcg/g Cr, IQR 58 – 119] compared to those without angioedema [median 75.5 mcg/g Cr, IQR 113 - 160] (P=0.02).

CONCLUSIONS: Reduction of uNMH excretion with increasing duration of urticaria may be a reflection of histaminergic ‘burn out’ and increased NMH excretion in angioedema suggests a greater histamine burden in this subset of patients. Larger studies aimed at deriving algorithms based on biomarker excretion to predict response to therapy and disease evolution may be beneficial.
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**Anakinra Syndrome-Associated Chronic Urticaria with Reliably Responsive to Icatibant**

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**RATIONALE:** Hereditary angioedema (HAE) with normal C1-esterase inhibitor (C1-INH) is subdivided into factor XII mutation or of unknown origin (U-HAE). The diagnosis is based on recurrent edema (eg skin swellings, tongue swelling), family history, and normal C1-INH. U-HAE is presumed when factor XII mutation is absent. Here we present a 65 year old male with suspected U-HAE, who has a 30-year history of recurrent upper airway swelling, family history, and normal C1-INH. He initially responded to empiric C1-INH. However, he seemed to have developed resistance to C1-INH, requiring rescue therapy with icatibant.

**METHODS:** A log method was used to collect information on attack intensity, anatomical location, number of doses, onset of relief, time until complete resolution. Hospital records and patient-reports were collected for each treatment received through the ED.

**RESULTS:** Initially the patient responded to C1-INH treatment. Within the first year, 2 attacks required treatment with multiple doses of C1-INH to achieve symptoms resolution. By February 2015, despite multiple C1-INH doses, the patient was intubated and admitted to ICU for tongue swelling with throat involvement, which resolved slowly over 4 days. In April 2015, icatibant was used for treatment in the ED when on tongue swelling occurred because he was unresponsive to C1-INH. Swelling began to subside within 1 hour of the icatibant administration. Since then, the patient has had many documented swellings that have not responded to C1 but have responded to icatibant.

**CONCLUSIONS:** Icatibant can be an effective treatment for suspected U-HAE when treatment response with intravenous C1 esterase inhibitor is inadequate.

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**A Case of Successful Treatment of Autoinflammatory Syndrome-Associated Chronic Urticaria with Anakinra**

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**Aspirin Desensitization in Two Patients with Refractory Urticaria, Positive Chronic Urticaria Index, and Elevated Mast Cell Mediators**

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**Reliably Responsive to Icatibant**

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**RATIONALE:** Autoinflammatory syndrome is characterized by various systemic inflammatory symptoms and cutaneous urticarial rashes. Systemic disease-associated chronic urticaria may be often difficult to treat with usual anti-urticarial medications. We report a case in which autoinflammatory syndrome-associated chronic urticaria was successfully treated with IL-1 receptor antagonist, anakinra.

**METHODS:** Anakinra 100 mg was subcutaneously injected on a daily basis.

**RESULTS:** A 69-year-old man suffered from pruritic urticarial rash for 9 years. It aggravated episodically and accompanied high fever, arthralgia, leukocytosis, elevated C-reactive protein and erythrocyte sedimentation rate. The episodes lasted over one week. A subpleural nodule with pleural effusion was detected. Neutrophilic and eosinophilic inflammation was found on skin biopsy. The cutaneous lesions were unresponsive to various kinds of anti-histamines, systemic glucocorticoids, colchicine, cyclosporine, dapsone, or methotrexate that have been administered in the recent 3 years. A dramatic response however, has been observed after a daily administration of anakinra. We assume that the case might have adult onset TNF receptor-associated periodic syndrome.

**CONCLUSIONS:** Anakinra could be effective in cases of corticosteroid- and other immunomodulator-refractory chronic urticaria, particularly in urticaria patients with suspected autoinflammatory syndrome.
CONCLUSIONS: Although angioedema is a common diagnosis made by Allergy & Immunology specialists, many mimics exist. When hereditary angioedema is ruled out, as it was in our two patients, the question of secondary etiology versus angioedema-mimic arises. In the two patients, angioedema-like presentations were initially attributed to ACE-inhibitor exposure, but they were subsequently found to have more plausible etiologies mimicking angioedema.

CONCLUSIONS: Mimics of Angioedema

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RATIONALE: Allergy & Immunology specialists are often consulted for the clinical question, “Does this patient have angioedema?” Our goal was to identify mimics of angioedema, which should be considered when confronted with a patient who presents with possible angioedema.

METHODS: Cases of presumed angioedema in a large, urban teaching hospital were reviewed. Atypical clinical and laboratory features were identified.

RESULTS: Two patients with presentations concerning for angioedema but unrevealing work-ups were identified. Patient 1, a 49-year-old man, presented in 2013 with laryngeal and epiglottal edema in the absence of urticaria or tongue swelling, but with airway compromise requiring intubation. He had several similar subsequent presentations. C1 esterase and C4 levels were normal. He was ultimately found to have SVC syndrome with subclavian stenosis, which is the likely etiology of his presentation. Patient 2, a 65-year-old man, presented in 2014 with dysarthric speech and tongue swelling. He, too, had normal C1 esterase and C4 levels. He was ultimately diagnosed with myasthenia gravis to which his angioedema-like picture was attributed. Both of these patients’ angioedema-like presentations were initially attributed to ACE-inhibitor exposure, but they were subsequently found to have more plausible etiologies mimicking angioedema.

CONCLUSIONS: Assessment of Inhibitory Antibody Formation in Subjects with Hereditary Angioedema Treated with Plasma-Derived C1-Esterase Inhibitor Concentrate (Berinert®)

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RATIONALE: Limited data are available regarding C1-esterase inhibitor (C1-INH) administration and anti-C1-INH antibodies. This study assessed the incidence and relevance of antibody formation during treatment with pasteurized, nanofiltered plasma-derived C1-INH (pnC1-INH; Berinert®/ CSL Behring) in subjects with hereditary angioedema with C1-INH deficiency (C1-INH-HAE).

METHODS: In this multicenter, open-label study, subjects with C1-INH-HAE (≥ 12 years of age) were given pnC1-INH 20 IU/kg per HAE attack that required treatment and followed for 9 months. Blood samples were taken at baseline (day of first attack) and Months 3, 6, and 9 and analyzed for inhibitory (c1-INHab) and non-inhibitory anti-C1-INH antibodies (niC1-INHab).

RESULTS: The study included 46 subjects (69.6% female; mean age, 38.9 y; all Caucasian) who received 221 on-site pnC1-INH infusions; most subjects received ≥5 infusions. No subject tested positive (titer ≥1:50) for iC1-INHab at any time during the study. Thirteen (28.2%) subjects had detectable niC1-INHab in ≥1 sample. Nine (19.6%) subjects had detectable niC1-INHab at baseline; three of these had no detectable antibodies post-base. Of 10 (21.7%) subjects with ≥1 detectable result for niC1-INHab post-base, 6 had detectable niC1-INHab at baseline.
CONCLUSIONS: Hereditary angioedema (HAE) due to C1-inhibitor deficiency or dysfunction is a rare disease characterized by recurrent episodes of edema with an estimated frequency of 1:50,000 in the world population without racial or gender differences. We present an update of the frequency reported in Colombia of patients diagnosed with HAE, as result of an ongoing project of the first Colombian record of this disease.

METHODS: A questionnaire on the diagnosis, treatment and current control of patients with HAE, was completed by allergists and immunologists (n = 14) of Colombia.

RESULTS: 44 patients with confirmed diagnosis of HAE were reported. The average age of onset of symptoms was 23 years old, with an average age at diagnosis of 37 years. 88.23% with positive family history for the disease. 62% of patients are currently in maintenance treatment: 48% with danazol, tranexamic acid 12.07%; 38.9% of patients used Icatiban for disease. 62% of patients are currently in maintenance treatment: 48% with danazol, tranexamic acid 12.07%; 38.9% of patients used Icatiban for disease. 62% of patients are currently in maintenance treatment: 48% with danazol, tranexamic acid 12.07%; 38.9% of patients used Icatiban for disease. 62% of patients are currently in maintenance treatment: 48% with danazol, tranexamic acid 12.07%; 38.9% of patients used Icatiban for disease. 62% of patients are currently in maintenance treatment: 48% with danazol, tranexamic acid 12.07%; 38.9% of patients used Icatiban for disease. 62% of patients are currently in maintenance treatment: 48% with danazol, tranexamic acid 12.07%; 38.9% of patients used Icatiban for disease. 62% of patients are currently in maintenance treatment: 48% with danazol, tranexamic acid 12.07%; 38.9% of patients used Icatiban for disease. 62% of patients are currently in maintenance treatment: 48% with danazol, tranexamic acid 12.07%; 38.9% of patients used Icatiban for disease.

CONCLUSIONS: HAE is a rare disease but that could cause death by an acute attack, therefore it is important that the patients have the appropriate rescue therapy. This data has been achieved thanks to the collaboration of colombian allergists who have shared their patient medical records for the national HEA statistical data.

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Refined Method for Collection of Plasma Samples to Evaluate the Role of Plasma Kallikrein in Various Disease States

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RATIONALE: Examination of plasma biomarkers of contact system activation is challenging due to inadvertent activation during blood collection and processing. We examined the utility of specialized blood collection tubes in assessing levels of cleaved high-molecular-weight kininogen (cHMWK) in plasma from healthy subjects and those with Types I/II hereditary angioedema (HAE), idiopathic angioedema or HAE with normal C1-INH (HAEnc1).

METHODS: To avoid artificial activation of the contact pathway during blood sampling, the study used standardized blood collection techniques and custom tubes containing protease inhibitors. Blood samples were collected from healthy subjects and disease subjects (during periods of disease quiescence and flare) to assess the percentage of cHMWK using a Western blot assay.

RESULTS: In healthy subjects, levels of cHMWK were stable (<5%) at RT for at least 24 hours following blood collection into custom tubes but were elevated (12%) in plasma samples obtained from a commercial vendor, demonstrating the importance of optimizing blood collection techniques when examining contact pathway activation. cHMWK percentages were clearly elevated at baseline in subjects with HAE (n = 21) compared to healthy controls (n = 26) but not in plasma from subjects with idiopathic angioedema (n = 4) or HAEnc1 (n = 5), suggesting limited plasma kallikrein activity, although not excluding a role of contact pathway activation during acute attacks in those disorders.

CONCLUSIONS: A refined method for collection of plasma samples for evaluation of contact system activation has been developed which prevents cleavage of HMWK ex vivo.

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Hydroxychloroquine As a Steroid-Sparing Agent in an Infant with Chronic Urticaria

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RATIONALE: In adults, hydroxychloroquine is one anti-inflammatory steroid-sparing agent used to treat chronic idiopathic urticaria (CIU) refractory to antihistamines. Whether hydroxychloroquine is safe and effective for antihistamine-refractory CIU in children is unknown.

METHODS: We present an infant with resolution of antihistamine-refractory CIU following treatment with hydroxychloroquine and concomitant discontinuation of steroids.

RESULTS: A 9-month-old male infant presented with a 5-month history of recurrent unprovoked urticaria and angioedema of the hands and feet refractory to high-dose H1 and H2 antihistamines and leukotriene antagonists. Physical examination revealed diffuse pleomorphic urticaria and marked dermatographism. Laboratory testing demonstrated an elevated platelet count (534,000/microliter) and C-reactive protein (CRP, 2.0 mg/dL). Serum tryptase, C3, C4, and Clq were normal. Antinuclear, anti-thyroid, and anti-IgE receptor antibodies were negative; cow’s milk specific IgE was undetectable. Skin biopsy showed perivascular lymphocytic infiltrate, perivascular to interstitial eosinophils, no neutrophilic infiltrate or evidence of urticarial vasculitis. Symptoms were moderately well controlled by adding oral prednisolone (0.65 mg/kg) every other day but rebounded if steroids were tapered further. Hydroxychloroquine 2mg/kg/day was initiated and uptitrated to 6 mg/kg/day over 3 months, and platelet count and CRP normalized. Adverse reactions included diarrhea that resolved with dose modification. After 3 months of hydroxychloroquine (at age 12 months), prednisolone taper was initiated. Prednisolone was discontinued by age 14 months without recurrence of urticaria or angioedema.

CONCLUSIONS: While further study is needed, we demonstrate that hydroxychloroquine can be a safe and effective treatment for antihistamine-refractory CIU in children, leading to down-titratin and subsequent cessation of systemic steroid therapy.
811 CRTh2 and Aspirin/NSAID Intolerance in Chronic Spontaneous Urticaria

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RATIONALE: A significant fraction of patients with chronic spontaneous urticaria (CSU) develop Aspirin/NSAID intolerance during clinical disease, leading to the avoidance of such medications even when indicated for cardiac disease prevention. Reduced surface expression of the PGD2 receptor, CRTh2, is observed on basophils and eosinophils in CSU subjects. We compared clinical and cellular features in CSU subjects with and without Aspirin/NSAID intolerance.

METHODS: We recruited adult CSU subjects (n=18). We obtained detailed histories, complete blood counts, and disease activity surveys from all subjects. We examined basal expression of CRTH2 via flow cytometry. Basophils and eosinophils were gated using scatter and specific markers. Data are reported as Median Net MFI (± SEM), and were analyzed using Mann-Whitney Test.

RESULTS: 5/18 patients reported histories of Aspirin/NSAID intolerance. CSU patients with Aspirin/NSAID intolerance showed lower median UAS7 scores (16.5 ± 12.06 vs 25.5 ± 10.96) and subcomponent hives scores (7.3 ± 8.112 vs 15.5 ± 6.453). The median MFI (± SEM) for basophil CRTh2 expression trended lower in CSU patients in Aspirin/NSAID intolerance (171.9 ± 81.21 vs 245.4 ± 80.11). Eosinophil CRTh2 and PGD2-induced eosinophil shape change were similar. There was no correlation between CRTh2 expression, CBC eosinophil percentage, and UAS7 scores.

CONCLUSIONS: CSU subjects with self-reported histories of Aspirin/NSAID intolerance had lower UAS7 scores. CRTh2 expression trended lower on basophils from CSU subjects with Aspirin/NSAID intolerance. Levels of eosinophil CRTH2 expression were similar. These findings suggest that functional differences may exist in the CRTH2 pathway in a subset of CSU subjects with Aspirin/NSAID intolerance.

812 Differential Expression of Micro-RNAs in Circulating Blood of Chronic Idiopathic Urticaria Patients with Hives

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RATIONALE: Chronic idiopathic urticaria (CIU) is a complicated skin disease with unknown trigger factors. MicroRNAs (miRs), which are snippets of mRNAs occurring during mRNA degradation, have been shown to be active in cellular regulation. The goal of this pilot study is to examine whether miRs may be involved in the regulation of CIU or as a biomarker for CIU.

METHODS: CIU patients were recruited during doctor’s visit for treatment. Four groups of 3 patients each were selected: Active hives with positive chronic urticaria (CU) Index results; Active hives with negative CU Index; Positive CU Index but no active hives; and Negative CU Index with no active hives. MicroRNAs were isolated from plasma and analyzed using miR microarray technology to determine the amount of each of the 2567 known human miRs.

RESULTS: Those transcripts which show statistically significant differences between groups (p value <0.01), including those that have low signals but show greater than two-fold differences, are listed. miR-2355-3p, 2355-5p, 29c-5p and 4264 are of particular interest because they are uniquely expressed in patients with active hives with and positive CU Index. We also compared patients with active hives to those without hives, and found 12 miRs (3691-3p, 6799-3p, 3180, 3187-3p, 6799a-5p, 6800-3p, 1184, 205-5p, 4733-5p, 1910-5p, 4649-5p, 302c) which are differentially expressed.

CONCLUSIONS: We have identified 16 miRs which are differentially expressed in CIU. Further study is needed to confirm these findings and to investigate the source genes from which they originate and the potential target genes on which they might act.

813 Improvement of Chronic Urticaria with Vitamin D Repletion Is Associated with Baseline Markers of Autoimmunity

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RATIONALE: Several studies indicate a relationship between vitamin D deficiency and chronic urticaria (CU). The role of autoimmunity in this association has not been explored. We examined improvement in CU symptoms and markers of autoimmunity based on vitamin D status and correction.

METHODS: The urticaria activity score (UAS) and urticaria-specific quality of life index (CU-Q2oL) were assessed at initial and follow-up visits for 17 adult patients with CU. Initial 25-hydroxy vitamin D levels were checked and repleted according to current guidelines. ANA and anti-IgE receptor antibody levels were measured at baseline and follow-up time points.

RESULTS: Eight subjects were vitamin D deficient, 6 were insufficient, and 3 were sufficient. Initial and follow-up mean UAS were 3.67 to 0.75, 3 to 1.75, and 2.5 to 1.5 for the deficient, insufficient, and sufficient groups respectively. Initial and follow-up mean CU-Q2oL scores were 43.67 to 2.67, 35 to 10.25, and 42 to 51.5 for the deficient, insufficient, and sufficient groups respectively. IgE receptor antibody was positive in 4/7 deficient subjects, 2/6 insufficient subjects, and in no sufficient subjects. 1:160 ANA titers were in 3/7 deficient subjects, in no insufficient subjects, and in no sufficient subjects.

CONCLUSIONS: Vitamin D deficient and insufficient CU subjects demonstrated greater evidence of autoimmunity and follow-up improvement of CU symptoms with vitamin D repletion. The relationship between Vitamin D deficiency and CU may be mediated through an autoimmune mechanism. A larger study to confirm the observed trends is underway to examine these preliminary findings.

814 Cytokine and Estrogen Stimulation of Endothelial Cells Augments Activation of the Surface-Bound Prekallikrein-High Molecular Weight Kininogen Complex: Implications for Hereditary Angioedema (HAE)

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BACKGROUND: When the prekallikrein-high molecular weight kininogen complex (PK-HK) is bound to endothelial cells, prekallikrein is stoichiometrically converted to kallikrein due to release of heat shock protein-90 (Hsp90).

RATIONALE: Since attacks of hereditary angioedema can be related to infection or to estrogen we questioned whether estrogen or cytokine stimulation of endothelial cells could augment release of Hsp90 and prekallikrein activation. We also tested release of pro-inflammatory cytokines, uricokinase (UK) and tissue plasminogen activator (TPA).

METHODS: Cells were stimulated with agonists and Hsp90, UK, and TPA were measured in the culture supernatants by ELISA. Activation of the PK-HK complex was measured employing pro-pherarg-p-nitroanilide reflecting kallikrein formation.

RESULTS: Hsp90 release was stimulated with optimal doses of estradiol, IL-1, and TNFa (10ng/ml) from 15 min to 120 min. TPA release was not augmented by any of the agonists tested but UK was released by IL-1, TNFa and thrombin (positive control) but not estrogen. Augmented activation of PK-HK was seen with each agonist that releases Hsp90. Addition of 0.1 molar factor XII relative to PK-HK leads to rapid formation of kallikrein; factor XII alone does not autoactivate.

CONCLUSIONS: Interleukin-1, TNFa, and estrogen stimulate release of Hsp90 and augmentation of the PK-HK complex. IL-1 and TNFa stimulate release of uricokinase which can augment fibrinolysis.

CLINICAL IMPLICATION: Attacks of angioedema in patients with HAE may be initiated by use of estrogen or infection. Cytokine or estrogen stimulation of endothelial cells and activation of the PK-HK complex may contribute to this process.
Clinical Features of Patients with Hereditary Angioedema with Normal C1 Inhibitor: A Study of Seventy-Four Brazilian Individuals Belonging to Nine Unrelated Families

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RATIONALE: Hereditary angioedema (HAE) is an autosomal dominant disorder, characterized by episodes of swelling of face, extremities and larynx, and attacks of abdominal pain. The majority of patients with HAE present mutations in the gene coding for C1 inhibitor (C1-INH); in addition, mutations in the gene coding for coagulation factor XII (FXII) have been described in patients with normal C1-INH (HAE-FXII). Our aim was to analyze clinical features of Brazilian patients with HAE-FXII.

METHODS: Seventy-four individuals from 9 unrelated families were studied. Index cases presented clinical features of HAE-FXII. Mutations were detected by allelic discrimination and sequencing of exon 9 of F12 gene. All patients and relatives completed a questionnaire assessing clinical characteristics and severity of disease.

RESULTS: Missense mutation c.983C>G (p.Trh328LYS) in F12 gene was identified in 46 subjects (31 female,15 male). Twenty-nine subjects (22 female,7 male) presented symptoms of HAE, including 16 with severe (all female), 6 moderate (2 female, 4 male) and 7 mild (2 female, 5 male) symptoms. Abdominal attacks were predominant (69%), followed by swelling of face (62%), limbs (59%), upper respiratory tract (24%) and genitalia (14%). Seventeen were asymptomatic (9/31 female, 8/15 male). Mean age at onset of symptoms was 20 years, and maternal to paternal transmission of c.983C>G: A mutation was 1.25:1.

CONCLUSIONS: Our HAE-FXII patients were mainly women, presenting more severe symptoms than men. Predominant symptoms were abdominal pain, and swelling of face and limbs. Age at onset of symptoms was in keeping with reports from other areas of the world. Maternal transmission of mutation was slightly higher than paternal transmission.

C1-Esterase Inhibitor Concentrate for Acute Laryngeal Hereditary Angioedema (HAE) Attacks: Different Treatment Response Based on Dosing Regimen?

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RATIONALE: For acute treatment of hereditary angioedema (HAE) attacks, international consensus guidelines recommend plasma-derived C1-inhibitor concentrate (pdC1-INH) both at fixed and body weight-adjusted doses. Since fast response to treatment with a single dose is paramount for potentially life-threatening laryngeal HAE attacks, we compared available efficacy data with different pdC1-INH dosing regimens.

METHODS: We performed an indirect, descriptive comparison of treatment response with pdC1-INH at fixed doses of 500 or 1000 IU and body weight-adjusted doses of 20 IU/kg, using data from clinical studies with 1000 IU Cinryze® and 500 or 1000 IU and 20 IU/kg Berinert®. Data were compared descriptively, using a Kaplan-Meier analysis, and by a Wilcoxon test.

RESULTS: Median time to onset of symptom relief (95% confidence interval [CI]) was 15 minutes (14; 25) with 20 IU/kg Berinert (N=48), 30 minutes (30; 40) with 500 IU Berinert (N=48), and 45 minutes (30; 75) with 1000 IU Cinryze (N=82) (per-attack analysis). A similar difference was seen in a per-patient analysis, with significantly shorter median average time to onset of symptom relief with 20 IU/kg compared with fixed pdC1-INH doses (26 versus 43 minutes; p=0.019). No re-dosing was needed with body weight-adjusted dosing, while a second dose was used in up to 62% of attacks treated with 1000 IU.

CONCLUSIONS: Available data suggest body weight-adjusted dosing with pdC1-INH at 20 IU/kg as preferred treatment choice over fixed dosing to ensure optimal treatment response for acute laryngeal HAE attacks.

Subcutaneous Icatibant for the Treatment of Acute Attacks of Hereditary Angioedema: Comparison of Self-Administration to Administration at a Medical Facility

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RATIONALE: Hereditary angioedema (HAE) is a life-threatening disorder characterized by recurrent angioedema. Icatibant, a subcutaneous bradykinin-B2-receptor antagonist, is an effective on-demand therapy. Data outside the United States (US) suggest that self-administration is well-tolerated and patient-preferred compared to administration by healthcare professionals at medical facilities (HCP-administration) [Aberer 2014, Fernandez-de-Reijas 2015].

METHODS: Subjects ≥18 years old with HAE Type I or II were enrolled in a prospective, multi-center study in the US evaluating icatibant self-administration for HAE attacks. The first two attacks were treated at medical facilities. Subjects were instructed on self-administration during icatibant treatment for the second attack. Subjects self-administered icatibant at home for all subsequent attacks. Patient characteristics, timing of attack and icatibant treatment, initial improvement of symptoms, and complete symptom resolution were evaluated.

RESULTS: Nineteen patients received icatibant for 78 distinct HAE attacks. HAE attack duration (attack onset to complete symptom resolution) was significantly shorter with self-administration (n=49, 377±73 minutes) than HCP-administration (n=29, 735±133 minutes, p=0.003). Median time to treatment was significantly shorter with self-administration (30±33 minutes) than HCP-administration (167±93 minutes, p=0.01). Time from icatibant injection to initial symptom improvement and complete symptom resolution were comparable between self-administration and HCP-administration. Improvements in Visual Analogue Score and Patient Symptom Score from pre-treatment to 4 hours post-injection were also comparable. There were no serious adverse events (AEs) related to icatibant or discontinuations due to AEs with self-administration or HCP-administration.

CONCLUSIONS: Icatibant self-administration was comparable to HCP-administration in a prospective, multi-center study, shortening HAE attack duration with no difference in safety or treatment outcomes.
**818 Targeting Factor 12 (F12) with a Novel RNAi Delivery Platform As a Prophylactic Treatment for Hereditary Angioedema (HAE)**

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**RATIONALE:** A significant medical need exists for improved prophylactic treatment options for Hereditary Angioedema (HAE). Factor 12 (F12) autoactivation in the absence of C1 inhibitor (C1INH) initiates the pathway that leads to bradykinin-mediated edema. We hypothesized that an RNA interference (RNAi) based approach for reducing liver F12 production using our Dynamic Polyconjugate (DPC)™ delivery platform may provide a new prophylactic therapy for HAE.

**METHODS:** Highly specific and mouse/human/non-human primate (NHP) cross-reactive RNAi triggers were designed in silico and screened for F12 knockdown activity in vitro and in wild type mice. Structure activity relationship (SAR) studies of the most active RNAi triggers identified optimal modifications enabling lead identification. This lead RNAi trigger was further tested for activity and safety in NHPs. Disease-modifying activity in relevant disease-specific mouse models was also explored.

**RESULTS:** Screening of in vitro-active F12 RNAi triggers in wild type mice identified those triggers that exhibited significant and sustained knockdown of serum F12 levels. SAR studies allowed identification of a lead RNAi trigger that demonstrated >97% maximum knockdown after a single 2 mg/kg dose. A multi-dose study in NHPs using 2 mg/kg monthly doses showed >90% sustained knockdown of serum F12 levels without toxicity. NHPs in these studies showed changes in coagulation measurements consistent with F12 deficiency. Studies in mice showed reduced FeCl3-induced thromboembolism consistent with the expected physiological effects of F12 knockdown. Studies in C1INH-deficient mice (HAE model) are currently in progress.

**CONCLUSIONS:** Delivery of a potent F12-specific RNAi trigger by DPC™ offers potential for a novel, infrequently-dosed prophylactic treatment for HAE.

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**819 Relationship Between Drug Exposure and Clinical Response Observed in the Phase 1b Study of DX-2930 in Subjects with Hereditary Angioedema**

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**RATIONALE:** DX-2930 is a human monoclonal antibody inhibitor of plasma kallikrein in development for the prevention of hereditary angioedema (HAE) attacks. Data from the phase 1b study of DX-2930 in HAE subjects was analyzed to characterize the relationship between drug exposure and clinical response.

**METHODS:** Subjects with Type I/II HAE were randomized to receive 2 subcutaneous doses of DX-2930 on Days 1 and 15 in dose groups of 30, 100, 300 or 400 mg (n= 4, 5, 11, 1) or placebo (n= 13). A post-hoc modified efficacy analysis was conducted that included 1 subject who received only one dose of DX-2930 and 1 subject who did not have HAE Type I/2. The incidence of HAE attacks was evaluated in relation to drug exposure over time in subjects receiving the full dose regimen of DX-2930.

**RESULTS:** In the modified efficacy analysis, from Day 8 to 50 in comparison to placebo, the 300 and 400 mg DX-2930 groups had a 100% (P<0.0001) and 95% (P=0.0022) reduction in attacks, respectively. Placebo-treated subjects reported HAE attacks throughout the study (9 subjects, 65 HAE attacks). In the 300 and 400 mg dose groups, HAE attacks were reported prior to or just after initial dosing. When drug levels were high (Day 8 to 50), all but 1 subject was attack free. As drug levels waned, attacks re-emerged. No safety signal correlating with drug exposure was observed.

**CONCLUSIONS:** HAE attacks substantially decreased or were eliminated during periods of notable drug exposure.

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**820 C1 Inhibitor for Routine Prophylaxis in Patients with Hereditary Angioedema: Interim Results from a European Registry Study**

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**RATIONALE:** Human plasma-derived C1 inhibitor (C1 INH) is used for routine prophylaxis against hereditary angioedema attacks. We evaluated interim data from a European registry to characterize the use of C1 INH in the real-world setting.

**METHODS:** This is an ongoing, prospective, multi-center, observational study (NCT01541423). The analysis included data from patients enrolled for 23 months between May 2012 and May 2015 and who received C1 INH for ≥ 21 months.

**RESULTS:** Data from 45 patients were categorized according to the frequency of doses received: intensified routine prophylaxis (every 1 or 2 days; n=14 [31.1%]), routine prophylaxis (every 3 or 4 days; n=39 [86.7%]), and prolonged-interval prophylaxis (every 5 to 7 days; n=15 [33.3%]). Due to an individual and adaptive treatment approach, 42.2% of patients received more than one dose regimen. An interval of 28 days was considered an interruption in dosing; patients had a median of 5.5 dose interruptions. Patients received intensified, routine, and prolonged-interval regimens for a median of 20.5, 197.0, and 47.0 days, respectively. The median attack frequency was 4.8, 1.4, and 4.0 attacks per month. Overall, 69.7% of attacks occurred on the day of the next expected dose; 45.7% of these were “mild”.

**CONCLUSIONS:** In the real-world setting, patients decreased the dosing interval of C1 INH during periods when they were having more frequent attacks and frequently interrupted their dosing regimen. Attacks occurred most often on the day the next dose was due, suggesting that delaying a prophylaxis dose, even by only a few hours, may leave patients vulnerable to an attack.
METHODS: This phase 1b multi-center, double-blind study randomized 25 subjects with Type 1 or 2 HAE to receive 2 subcutaneous doses of DX-2930 on Days 1 and 15 in dose groups of 30, 100, 300 or 400 mg (n = 4, 5, 11, or placebo (n = 13). Blood samples were obtained prior to and following study drug administration (Days 1, 8, 22, 64, 92, 120). The ability of DX-2930 to inhibit pKal in FXIIa-activated citrated plasma was assessed using Western blot for 2-chain HMWK.

RESULTS: In FXIIa-activated samples mean 2-chain HMWK levels were significantly reduced and essentially normalized in the 300 and 400 mg dose groups on Days 8 and 22, and on Days 8, 22 and 50, respectively, when compared to placebo-treated subjects. Treatment with 300 or 400 mg DX-2930 also attenuated 2-chain generation to levels at or below that observed in healthy individuals. Levels of 2-chain HMWK did not differ from pre-dose plasma samples in samples collected on Days 64, 92 or 120 following DX-2930, which correspond to periods of low drug exposure.

CONCLUSIONS: DX-2930 inhibits pKal in a dose and time-dependent manner in HAE patients.
823  
**Gender Analysis of Icatibant-Treatment Outcomes of Acute Angioedema Attacks in Patients with Hereditary Angioedema Type I and II: Results from the Icatibant Outcome Survey**

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**RATIONALE:** The Icatibant Outcome Survey (IOS) is an international, observational study monitoring the safety and effectiveness of icatibant in a real-world setting. We report a gender-based analysis of baseline (BL) characteristics and icatibant-treatment outcomes in patients with HAE type I or II enrolled in IOS.

**METHODS:** Patient characteristics and icatibant-treatment outcomes were recorded at clinic visits. Descriptive retrospective analyses by gender were performed on data collected from July 2009–April 2015.

**RESULTS:** At IOS entry, 596 patients (353 female, 59.2%) reported BL data. Icatibant was used to treat 2245 angioedema attacks in 415 patients with 240 females (57.8%) reporting 1419 attacks (63.2%). Females reported a significantly higher annual attack frequency at BL (median: 7.5 vs 6.3; p=0.025) and more frequent abdominal and multiple location attacks. Complete treatment outcome data were available for 219 patients who had 831 attacks, including 136 females (62.1%) who had 481 attacks (57.9%). Respectively, the median time to icatibant administration in females vs males was 2.0 vs 1.0 hours (p=0.075), the median time to symptom resolution was 5.0 vs 6.5 hours (p=0.882) and the median attack duration was 10.0 vs 8.3 hours (p=0.420). For attacks treated with a single icatibant injection, C1 INH rescue use was higher in males (13.3%) than females (5.9%).

**CONCLUSIONS:** Female HAE/III patients enrolled in IOS reported significantly more annual angioedema attacks at IOS entry than male patients. No significant gender difference in icatibant treatment outcome was observed in this real-world observational study, however male patients used C1 INH more frequently as rescue medication.

824  
**Radial Immunodiffusion Method for Evaluation of C1-Esterase Inhibitor Function**

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**RATIONALE:** To examine the frequency of abnormal C1-esterase inhibitor (C1-inh) function in samples with low C1-inh level during a 2 year period at a single Canadian centre that utilizes radial immunodiffusion (RID) for C1-inh function, as opposed to the chromogenic assay.

**METHODS:** Retrospective analysis of all C1-inh function samples submitted to a tertiary lab and analyzed via RID and turbidimetry methods.

**RESULTS:** 1438 samples were assessed for C1-inh function from July 2013 - June 2015. 558 were assessed for C1-inh function and levels. Of these, 545 (97.7%) had normal C1-inh function and level and 1 (0.18%) had abnormal C1-inh function and a low level. Nine (1.6%) had normal C1-inh function and a low level. Of these, 3 had levels <50% of the lower limit of normal, consistent with possible hereditary angioedema (HAE) type II.

**CONCLUSIONS:** C1-inh function should be abnormal when C1-inh level is less than 50% of the lower limit of normal. Three samples (7%) with C1-inh level less than 50% of normal had normal C1-inh function, indicating the RID technique may result in falsely normal C1-inh function.
**827 C1-INH Therapy in ACEi/ARB Acquired Angioedema**

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**RATIONALE:** Angiotensin Converting Enzyme Inhibitors (ACEI) are a common cause of Emergency Room presentation for angioedema. Although no treatment guidelines exist, C1 esterase inhibitor concentrate (C1-INH) is used on an off label basis for management of ACEI I acquired angioedema (ACEI AAE). We are evaluating the efficacy of C1-INH in management of ACEI AAE.

**METHODS:** This is a retrospective chart review of treatment with C1-INH therapy for ACEI AAE. The primary end point is defined as time to symptom resolution from start of C1-INH. Exclusion criteria is angioedema from any other cause.

**RESULTS:** 8 patients, from 3 academic sites, were identified through Allergy Service consultation data and records from Diagnostic Services Manitoba, Canada from 2010-2015. Less than 20 hours from time of C1-INH infusion to resolution of angioedema was defined as a positive response to treatment. 6/8 patients required endotracheal intubation prior to initiation of C1-INH. 4/8 patients had resolution of angioedema between 12-13.5 hours (median 12.75) and no recurrence. One patient had transient symptom resolution in 14 hours, however, recurrence of angioedema required re-intubation.

**CONCLUSIONS:** Our findings demonstrate a therapeutic response with C1-INH therapy for ACEI AAE. The primary end point is defined as time to symptom resolution from start of C1-INH. Exclusion criteria is angioedema from any other cause.

**828 Oral Intake of Anti-Hangover Substance Increases Metabolizing Capacity of Aldehyde Dehydrogenase 2 in Rat Model: New Therapeutic Potentials for Chronic Itch?**

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**RATIONALE:** Aldehyde dehydrogenase 2 (ALDH 2) metabolizes acetaldehyde, the major cause of alcohol hangover symptoms. It also detoxifies endogenous cytotoxic aldehydes, such as 4-hydroxynonenal. Oxidative stress promotes lipid peroxidation of cellular membrane, leading to the accumulation of reactive aldehydes that contribute to itch signaling via mast cell degranulation and the activation of TRPA1 on sensory neuron. A variety of anti-hangover products are commercially available, however, almost none of them has been proven to show enhanced metabolizing capacity of ALDH 2 in a live subject. We aimed to test a specific product of interest.

**METHODS:** An anti-hangover product (KISLip, Pico Entech, Korea) was examined by in vitro & in vivo experiments to measure the amount of NADH formation which is generated through catalytic conversion of acetaldehyde. Powder sample was used as the experimental substance. In-vivo examination tested the ethanol and acetaldehyde level in blood of rats with oral infusion of substance before or after ethanol intake.

**RESULTS:** The activities of alcohol dehydrogenase & aldehyde dehydrogenase within the anti-hangover substance were 1.84 unit/g and 0.28 unit/g, respectively. The oxidation capacities in experimental rats were dose-dependently increased after substance gavages. Particularly, the cases with oral intake of substance 220 mg/kg after 1hr of ethanol intake have shown more meaningful and obvious decreases in acetaldehyde level in blood.

**CONCLUSIONS:** Oral intake of anti-hangover substance has significantly enhanced aldehyde-metabolizing capacity in rat model, potentially suggesting increased ALDH 2 capacity within circulation and detoxifying ability of 4-hydroxynonenal.

**829 Tamoxifen, a Trigger Factor of Hereditary Angioedema with Normal C1-INH with a Specific Mutation in the F12 Gene (HAE-FXII)**

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**RATIONALE:** In hereditary angioedema with normal C1 inhibitor with a specific F12 mutation (HAE-FXII) various trigger factors are known. Tamoxifen is a selective estrogen-receptor modulator (SERM) used in the treatment of breast cancer.

**METHODS:** A patient with a trigger factor hitherto unknown for angioedema attacks of HAE-FXII is reported.

**RESULTS:** In a now 71 year-old women the family history was negative for angioedema. At age 23 she had three lip swellings during the second and third trimester of her second pregnancy. At age 25 she took an estrogen-containing oral contraceptive for three month and developed another lip swelling. Then she was symptom-free until the age of 68. At the age of 67 a breast carcinoma was diagnosed. The patient underwent surgery and radiation therapy. Subsequently she received tamoxifen for a period of 36 months. Under tamoxifen the patient had 12 severe tongue swellings, partly associated with swelling of the floor of the mouth and the pharynx. Six of the swellings made a hospital stay necessary, two of them an ICU stay. During the last 4 months of the tamoxifen medication the swellings occurred every 3 weeks. The patient had normal values for C1-INH function and protein and C4 in plasma. In the F12 gene the mutation p.Thr328Lys was found. The diagnosis of HAE-FXII was established. After discontinuation of tamoxifen the patient immediately became symptom-free. Since then the patient had no further swellings, for one year until now.

**CONCLUSIONS:** Tamoxifen can cause severe angioedema attacks in patients with HAE-FXII.

**830 An Investigational RNAi Therapeutic Targeting Factor XII (ALN-F12) for the Treatment of Hereditary Angioedema**

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**RATIONALE:** Hereditary angioedema is a genetic disorder caused by a defect in the C1-inhibitor gene that results in poor control of contact pathway activation and bradykinin generation. Excessive bradykinin generation increases vascular permeability and is ultimately responsible for the episodes of swelling characteristic of hereditary angioedema. We hypothesized that the use of RNA interference (RNAi) to target factor XII would reduce contact pathway activation and prevent excessive bradykinin generation.

**METHODS:** A subcutaneously administered small interfering RNA (siRNA) targeting factor XII (ALN-F12) was developed and initially tested in dose response and durability studies in mice. This compound was subsequently evaluated in a bradykinin-driven mouse model of vascular permeability. Animals received a single subcutaneous injection of either saline or 0.1, 0.3, 1, or 3 mg/kg of ALN-F12. One week later animals received the angiotensin converting enzyme (ACE) inhibitor captopril and Evans Blue dye via tail vein injections. Dye was extracted from tissue and blood samples to determine vascular permeability.

**RESULTS:** A single subcutaneous administration of ALN-F12 led to potent, dose-dependent, and durable inhibition of factor XII. A single dose of 1 mg/kg resulted in >80% reduction of factor XII with effects durable for over 2 months. Similarly, administration of ALN-F12 resulted in dose-dependent reduction in ACE inhibitor induced vascular permeability, with doses >0.3 mg/kg resulting in normalization of vascular permeability to control levels.

**CONCLUSIONS:** These data suggest that the use of an RNAi therapeutic to inhibit factor XII is a potentially promising approach for the prophylactic treatment of hereditary angioedema.
Are Angiotensin Converting Enzyme Inhibitors the Main Elicitors of Tongue Angioedema?

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RATIONALE: ACE-I has been considered main elicitor in angioedema of the tongue (AET) but its real implication is undetermined.

METHODS: A retrospective-descriptive study including patients diagnosed with AET at the Emergency Department (ED) Jan-2013 to Dec-2014 at the third level Hospital was conducted.

RESULTS: 300.300 Patients were attended at the ED. 513 were identified with angioedema. (Incidence 0.17%) 70 had AET. (13%) Mean age: 60 DS +/-20.07. Median 64, with no gender differences. 32 (51.52%) had recurrent episodes. In 44 patients (62.85 %) the AET was isolated, 17 (24.28%) was accompanied by facial angioedema (eye lid, lips or cheeks), 10 (14.28%) had pharyngolaryngeal involvement. 16 patients (22.85%) had breathing or swallowing difficulties and one required intubation. ACE-I were responsible for the AET in 24 patients (34.28%), other drugs were suspected in 12 (17.14%), foods 7 (10%), unknown in 26 (37.14%) and others 1 (1.42%). AET was isolated in 54.2% of the ACE-I-induced AE, compared to other drugs in the rest of the patients. 47 cases were later studied at the Allergy Department. They were classified as histaminergic 21 (45.65%), no histaminergic 24 (52.17%). There were 2 cases of inflammatory edema. On the first group foods were involved in 3 (15%) and 18 (85%) were considered idiopathic. In the second group the most common cause identified was ACE-I 21 (87.5%), followed by hereditary AE 2 (8,33%) and idiopathic AE 1 (4.16%).

CONCLUSIONS: ACE-I was the cause of a third of the AET, being responsible for 87.5% of the non-histaminergic episodes. Most of the histaminergic AET were idiopathic.

Skin Prick Testing Alone Is Not a Good Predictor of Allergy Symptom Severity in Grass Allergic Patients

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RATIONALE: Skin prick tests (SPT) are a useful initial diagnostic tool for assessing allergic response. The Environmental Exposure chamber (EEC) is used to expose subjects to controlled, natural levels of allergen in order to evaluate their allergic response. We wanted to determine if the SPT could predict patient’s symptom severity in the EEC.

METHODS: A study involving 152 patients was analyzed to determine correlations between SPT and maximum TSS. Subjects underwent a screening visit where a panel of SPT were performed including three different grass allergen extracts (5-grass mix, Meadow fescue grass, and Rye grass) and were exposed to grass pollen in the EEC at a concentration of 3500 ± 500 grains/m3 for 6 hours, over 3 consecutive days. Total symptom scores (TSS) were obtained at scheduled intervals.

RESULTS: Correlation analysis revealed a weak correlation between the 5-grass mix SPT and the symptom severity (r²=0.31). A correlation of r²=0.34 was identified when comparing the Meadow Fescue grass SPT to the maximum TSS. This also shows a weak correlation between the SPT and TSS. Finally, the eye grass showed the weakest correlation of r²=0.29 between the SPT and maximum TSS.

CONCLUSIONS: This analysis demonstrates that the SPT is correlated with symptom severity. The value is less than 0.5, indicating SPT alone cannot be used as a predictor of allergic response when exposed to allergen. Overall, enrolling subjects in allergic rhinitis clinical trials based on SPT alone may not be suitable and additional clinical response assessment such as EEC exposure should be done for eligibility.

Quality of Life in Patients during Oral Immunotherapy for Food Allergy

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RATIONALE: Quality of life (QOL) of patients with food allergy improves following oral immunotherapy (OIT) but may be adversely affected by the treatment process itself.

METHODS: Parents of children aged 4-12 years undergoing OIT for milk, peanut and egg allergies were recruited. Patient demographics and clinical histories before OIT; and their treatment course, including dose escalation rate, reactions and treatments required were recorded. The Food Allergy Quality of Life Questionnaire-Parental Form (FAQ-LQ-PF) was completed at the beginning and following 5 months of treatment. Patients with improved (reduction of >0.5 points), unchanged (reduction/increase of <0.5 points) and diminished (increase of >0.5 points) FAQ-LQ-PF scores were compared using Chi test and One-way Anova.

RESULTS: Of the 108 patients recruited, 18 were excluded, either because of incomplete questionnaires (n=17), or treatment failure (n=1). Of the remaining 90 patients (milk; n=48, peanut; n=37, egg; n=5), 46 were in the dose escalation phase and the remains were in maintenance (full dose; n=37, and partial dose; n=7). Patients with improved (n=32), unchanged (n=39) and diminished (n=19) total score on the FAQ-LQ-PF did not differ in pre-OIT clinical histories, tolerated dose at treatment initiation, course of treatment (reactions, epinephrine use, rate of dose escalation) or stage of treatment. Patients with improved FAQ-LQ-PF total score had a significantly diminished score at baseline (4.36) compared to those with unchanged score (3.56, p=0.016) and decreased score (2.75, p<0.001).

CONCLUSIONS: Patients with diminished QOL before OIT benefit significantly during treatment. Those whose QOL is minimally affected at baseline might benefit from better preparedness for OIT.

Impact of Parent-Reported Food Allergies on Children’s Growth and Quality of Life of the Caregivers

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RATIONALE: Some caregivers who believe their children have food allergies avoid feeding certain foods to their children without proper allergy tests. Such actions, made without a proper diagnosis, can negatively impact children’s health and impose unnecessary burden on the caregivers. In this study, we hypothesized that parent-reported allergies without proper diagnosis can result in higher stress levels for the caregivers, and might deter the children’s growth.

METHODS: An observational cross-sectional study was performed in 200 children aged less than five years, who have parent-reported food allergies. The caregivers’ Quality of Life (QoL) was evaluated by two questionnaires - the Food Allergy Quality of Life-Parental Burden (FAQ-PB) and the Scale of Psychosocial Factors in Food Allergy (SPS-FA). The growth of the children was evaluated by their weight-for-age and length/height-for-age percentiles.

RESULTS: Among the caregivers, 30% expressed worry that their children might be allergic to some foods, and 30% were concerned about leaving their children in others’ care. According to the QoL scores, caregivers whose children underwent Oral Food Challenges (OFC) were significantly less stressed, while caregivers whose children had multiple food allergies and had experienced at least one anaphylactic reaction were significantly more stressed. Regarding the children’s growth, the distributions of both weight-for-age and length/height-for-age percentiles were normal in the 50th percentile range, showing no significant differences from the general population.

CONCLUSIONS: Parent-reported food allergies could put caregivers under high stress, but the OFC test could reduce stress among anxious, over-parenting caregivers. Parent-reported food allergies did not result in the diets that deterred children’s growth.
**835 Food Allergy and Health-Related Quality of Life in a Racially Diverse Sample**

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**RATIONALÉ:** Food allergy (FA) prevalence and health-related quality of life (HRQoL) may differ among demographic groups, but most studies have focused on predominantly Caucasian populations. This study characterizes FA and HRQoL among a racially diverse sample.  

**METHODS:** An online survey assessed demographics, perceived risk of allergen exposure, perceived severity, FA worry, and HRQoL. (Food Allergy Quality of Life– Parental Burden questionnaire) among 103 caregivers recruited from the pediatric allergy clinic at Children’s National Medical Center.  

**RESULTS:** Caregivers were 8.7% Hispanic, 44.4% Caucasian, 26.2% African American, 8.7% Asian American, and 9.7% Non-Hispanic Other. Mean child age was 5.28 years (SD = 4.35); mean FA number was 2.85 (SD = 1.95). Prevalence of individual FAs were comparable among racial/ethnic groups; there were no significant differences in FA number, p > .05. Controlling for age, Asian Americans reported a significantly higher perceived risk of allergen exposure than African Americans, F(4, 92) = 2.89, p < .05. After controlling for age, there were no significant differences in perception of FA severity, FA worry, or HRQoL among racial/ethnic groups, p > .05, but notably, American Americans reported the highest perceived FA severity. African Americans were most worried, and Hispanics reported the worst HRQoL.  

**CONCLUSIONS:** Results from a diverse allergy clinic indicate no racial/ethnic differences regarding FA prevalence. Variations regarding FA perceptions and HRQoL were apparent. Additional research is needed with larger, diverse samples to further elucidate patterns of FA perceptions and HRQoL among racial/ethnic groups.  

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**836 Anxiety and Depression in Adults with Primary Immunodeficiencies (PID’s)—How Much Do These Patients Experience and What Factors May Increase Patients’ Risk?**

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**RATIONALÉ:** Primary Immunodeficiency (PID) is a rare group of disorders that manifest similarly with infection, neoplasms, allergic and autoimmune diseases and are treated with injectable medications. Often the burden of disease and cost of management is excessive and premature death is not uncommon. In light of above features of PID, it was our objective to survey our cohort to assess for additional morbidity from depression and anxiety.  

**METHODS:** We used an investigator-administered survey, the Hamilton Depression Rating Scale and the Hamilton Anxiety Rating Scale, after IRB approval, to determine the extent of anxiety and depression, as compared to the general public, that our PID patients experienced. The differences between groups were tested using Wilcoxon Rank Sum tests, Kruskal Wallis tests, and Chi-square tests.  

**RESULTS:** Patients with PID had significantly increased depression compared to normal populations, as assessed by the Hamilton Depression Rating (HAM-D) scale. Risk factors associated with significantly elevated HAM-D scores included: not driving, intravenous immunoglobulin therapy (vs. subcutaneous), nurse-administered therapy (vs. self-administered), having unpleasant side effects from therapy, previously attempting suicide, and having family members with reported anxiety and/or depression. Anxiety was also significantly increased in our cohort. Risk factors for significantly elevated HAM-A scores included: having poor health, an unhealthy diet, lack of refreshing sleep, and family members with reported anxiety and/or depression.  

**CONCLUSIONS:** Depression and anxiety add to the morbidity of PID; patients should be assessed for depression and anxiety, and treatment or referrals should be initiated to improve our patients’ quality of life and outcomes.  

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**837 The Arietta Study: Exploring Severe Asthma Biomarkers in a Real-World Setting**

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**RATIONALÉ:** As the heterogeneity of asthma is increasingly recognized, and targeted treatment options emerge, the role of asthma biomarkers in patient selection, monitoring and risk-prediction will be important. However, the prognostic value of these biomarkers in a real-world clinical setting remains unknown. Here, we outline the design of a multicenter, prospective, longitudinal non-interventional study that aims to assess the relationship between biomarkers and asthma-related health outcomes in a real-world setting.  

**METHODS:** The study will enroll ~1200 adult patients with severe asthma (GINA steps 4–5) from ~160 sites in 21 countries, who will have regular follow-ups over 52 weeks (NCT02537691). Enrollment criteria include adults with asthma requiring daily inhaled corticosteroid (~500 mcg fluticasone propionate or equivalent) and >1 second controller. Key biomarkers assessed include FeNO, serum peroxisomal, blood eosinophil count and serum IgE. Data on pulmonary function, symptoms and quality of life, exacerbations, asthma-related healthcare utilization and safety events will also be collected. During the study, patients’ treatment regimens are not pre-specified. The primary outcome is the rate of asthma exacerbations from baseline to Week 52 in patients with high periostin (~50 ng/mL). Enrollment criteria include adults with asthma requiring daily inhaled corticosteroid (~500 mcg fluticasone propionate or equivalent) and >1 second controller. Key biomarkers assessed include FeNO, serum peroxisomal, blood eosinophil count and serum IgE. Data on pulmonary function, symptoms and quality of life, exacerbations, asthma-related healthcare utilization and safety events will also be collected. During the study, patients’ treatment regimens are not pre-specified. The primary outcome is the rate of asthma exacerbations from baseline to Week 52 in patients with high periostin (~50 ng/mL). Secondary analyses will examine the longitudinal relationship between different asthma biomarkers and clinical outcomes.  

**RESULTS:** The first patient was enrolled in August 2015. Data is expected to be available in 2018.  

**CONCLUSIONS:** This unique real-world study will address crucial unanswered questions regarding asthma biomarkers, their prognostic value, and ultimately help guide clinicians to a more targeted therapeutic approach to severe asthma.
Pharmacodynamic Model to Predict Ocular Itching Outcomes at 24 Hours Post-Treatment with Olopatadine (0.7% or 0.2%)

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Rationale: Simulate 24-hour ocular itching assessments between olopatadine 0.2% and 0.7% treatments, in patients with high baseline itching severity.

Methods: A differential odds model characterized individual and population olopatadine ocular itching using 2 completed CAC trials. These trials graded itching from 0 (no itching) to 4 (unbearable itching). Both vehicle and olopatadine reduced baseline itching. A one-compartment KPD\(E_{max}\) model was used to model the effect of Olopatadine. The baseline itching severity was significant in the model, affecting both overall itching and magnitude of effect. This model simulated the proportion of patients achieving 24-hour itching control with olopatadine 0.7% increased over olopatadine 0.2% (from 5% to 14% more control). This prediction was validated model population olopatadine ocular itching using 2 completed CAC trials. These trials graded itching from 0 (no itching) to 4 (unbearable itching). Both vehicle and olopatadine reduced baseline itching. A one-compartment KPD\(E_{max}\) model was used to model the effect of Olopatadine. The baseline itching severity was significant in the model, affecting both overall itching and magnitude of effect. This model simulated the proportion of patients achieving 24-hour itching control with olopatadine 0.7% increased over olopatadine 0.2% (from 5% to 14% more control). This prediction was confirmed with retrospective clinical data analysis.

Conclusions: The model predicted both mean scores and proportions of patients in itching categories. With increasing baseline severity, % population with 24-hour control for Olopatadine 0.7% increased over Olopatadine 0.2% (from 5% to 14% more control). This prediction was confirmed with retrospective clinical data analysis.

Three and a Half Years of Multi-Allergen Subcutaneous Immunotherapy Is Associated with a 50% Reduction in Asthma Symptom Scores

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Rationale: Allergen immunotherapy is effective in improving allergic asthma1. Few studies assess efficacy of multi-allergen subcutaneous immunotherapy (SCIT) in relation to asthma.

Methods: After institutional review board approval and informed consent, a real world, single center observational study from an academic center in Pennsylvania was conducted. Sixty-three subjects with asthma and allergic rhinitis diagnosed by skin prick puncture, plus or minus intradermal testing or by immunocap testing were followed for up to 5 years. Average subject age was 33.5 years with 67% female. Immunotherapy treatments were conducted per immunotherapy practice parameters as published in the Journal of Allergy and Clinical Immunology5. Subjects on average were treated with a combination of 15 allergens.

Results: The average ACQ score for the group at initiation of immunotherapy was 1.02. A 50 percent average reduction in ACQ scores was achieved by year 3.5.

Conclusions: Multi-allergen SCIT is effective in improving asthma symptoms. A subset of subjects were non-responsive to therapy. Further work is necessary to address nonresponsiveness to allergen immunotherapy.

AGM– Antibiotic Allergies in General Medicine

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Rationale: We aimed to determine the prevalence of Antibiotic Allergy (AA) labels in a cohort of general medical inpatients to describe the nature of AA, accuracy of recording and feasibility of an oral re-challenge study.

Methods: Multi centre, prospective non-interventional study conducted at Austin Health and Alfred Health, from May 18th to June 5th, 2015. Baseline demographics, medical and allergy history, infective diagnosis and antimicrobial prescribing data was collected from admission and electronic medical records of all general medical inpatients. A survey to clarify allergy history was undertaken for patients with AA, followed by correlation with description in electronic and admission record. A hypothetical oral re-challenge in a supervised setting was offered to patients with a low allergy phenotype (uncomplicated rash or non-immune mediated adverse reaction).

Results: Of the 453 inpatients, 23.62% had an AA label. Of these patients 162 allergy labels were recorded, 34% were for penicillin and 21% had a mis-match in documentation between electronic and medical record. 37% of the AA labels were for ‘rash’ or non-immune mediated reactions. 32% of AA labels were unknown reactions and 36% occurred > 10 years previously. Fifty-four percent of AA patients were willing to be re-challenged, 31% exhibiting a low risk allergy phenotype.

Conclusions: AA prevalence in general medical inpatients was 23.62%, 34% of antibiotic allergy labels toward penicillin. A large proportion of AA labels were non-immediate reactions, many of which were potentially amenable to re-challenge. A direct oral antibiotic re-challenge study in carefully selected low risk allergy phenotypes may be feasible.

Hemolysis Associated with IVIG Therapy

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Rationale: Intravenous immunoglobulin (IVIG) is used for treatment of various immune diseases. Although IVIG is known to contain antibodies to A and B antigens, these antibodies do not typically mediate clinically significant haemolysis. Our patient, with blood type A, developed symptomatic haemolysis soon after receiving multi-dose IVIG for treatment of interstitial lung disease.

Methods: Hemoglobin (Hg), LDH, total bilirubin (TB), haptoglobin, reticulocyte count (RC) and a DAT were evaluated prior to IVIG infusion and for two weeks after infusion.

Results: Prior to our patient’s IVIG infusion, his Hg was 14.3g/dL. His other hemolysis labs were unremarkable. He received 5 infusions of IVIG (each 35g) over the course of 3 days. Three days after his last IVIG infusion, his labs showed a drop in Hg to 11.4g/dL, an increase in LDH to 574u/L, TB 2.9mg/dL, haptoglobin <10mg/dL, RC 3.3%, with a positive DAT for IgG. Anti-A,B was identified in the eluate. Ten days post-IVIG infusion, he was hospitalized with worsening dyspnea. His Hg nadir was 7.9g/dL with reticulocytosis of 12.4%. He improved without blood transfusion.

Conclusions: It is important for physicians to be aware that hemolysis may result after IVIG infusion. If a blood transfusion is required, it is generally recommended to transfuse type O RBCs, as these cells would be impervious to circulating anti-A,B from the IVIG. The role of titering lots of IVIG for anti-A,B is not currently established in clinical practice, as hemolysis is rare and appears to be largely dependent on recipient factors.
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RATIONALE: Assess the quality of life in patients with chronic urticaria (CU) through the questionnaire - Chronic Urticaria – Quality of Life Questionnaire (CU-Q2oL).

METHODS: This cross-sectional study assessed patients with chronic urticaria followed up in a tertiary hospital. The CU-Q2oL contains 23 questions, with scores from 1 (no complaints) to 5 (many complaints). We consider the scores ≥ 3 as poor quality of life. They were classified into two groups: A – those patients who respond to antihistaminics (AH1), and B – others medications beyond the AH1. We considered the difference between (B-A) ≥ 1 in each question, as relevant. The groups were assessed about the duration of disease ≥ 10 years.

RESULTS: Sixty-one patients participated in the study, of these, 58 (95%) were female and the mean age was 41 years. The average of the CU-Q2oL score was 72.5 for group B and 57.2 for group A. When we evaluated the time of disease ≥ 10 years, group A had 37% comparing to group B, 56%. The difference between groups B and A ≥ 1 was observed for the following issues: 3, 15, 17, 19, 20, 21.

CONCLUSIONS: These results showed that the group with recalcitrant CU (group B) had urticaria for a longer time and a higher score for CU-Q2oL. Among the issues, those that were more important were related to social relationships, diet and side effects of medicines.

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RATIONALE: To evaluate and compare skin test reactivity of sublingual immunotherapy tablets (SLIT) based solutions to commercial grass and ragweed extracts (CE).

METHODS: Sixteen subjects with allergic rhinitis consented to allergy skin testing with aqueous preparations of Grastek® and Ragwitek®; Timothy grass and short ragweed extract from three commercial suppliers, fish extract and SLIT excipients. Grastek® and Ragwitek® were diluted to similar concentrations found in CE for prick and intradermal testing. Intradermal testing was performed only when prick tests were negative. Intradermal test results were combined with prick test results. Results from CEs were compiled into a composite index via majority classification. Fleiss’ Kappa and non-parametric bootstrap confidence intervals were computed for CE and SLIT versus the CE composite index, yielding measures of agreement between CEs themselves and the CE composite index and SLIT, respectively.

RESULTS: Though the number of subjects is small, Kappa suggests strong agreement amongst the three CEs as well as between the CE composite index result and the analogous SLIT (Grass CEs: κ=0.92 [0.71–1.0]; Grass index vs Grastek®: κ=0.87 [0.58–1.0]; Ragweed CEs: κ=0.92 [0.63–1.0]; Ragweed index vs Ragwitek®: κ=1.0 [NA]). The bootstrap confidence intervals do not include 0 in all but one case, suggesting that Kappas are significantly different from 0.

CONCLUSIONS: This study shows statistically significant skin test reactivity to aqueous solutions of Grastek® and Ragwitek® comparable to CE. Skin test reactions of each CE were consistent with each other; the skin test reaction of Grastek® and Ragwitek® were consistent with each CE.
846 Correlation of Symptom Scores, Nasal Airflow, and Nasal Resistance in Dust Mite Sensitized Allergic Rhinitis Children

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RATIONALE: Nasal obstruction is a major troublesome symptom in children with allergic rhinitis (AR). The severity nasal obstruction can be subjectively assessed by symptom score. Objective assessment involves measurement of peak nasal airflow (PNIF) and total nasal resistance. This study was to determine the correlation of total nasal symptom score (TNSS), PNIF, and total nasal resistance in children with AR.

METHODS: Forty four children with dust mite sensitized AR, age 7-18 years old were challenged with Der p. TNSS including nasal congestion, nasal itching, sneezing, and rhinorrhea were assessed at baseline. PNIF and total nasal resistance measured by rhinomanometry were recorded at baseline and after dust mite nasal provocation test.

RESULTS: A total of 40 children with positive NPT were enrolled. The mean aged was 12.2 ± 2.4 years (62.5% were male). Mean of baseline TNSS was 2.28 (± 1.36 SD). Median (range) TNSS at baseline was 2.23 (1.06-3.11) points out of maximum of 12 points. Baseline PNIF was significantly correlated with TNSS (r = -0.466, p = 0.002), nasal congestion (r = -0.541, p = 0.001), rhinorrhea (r = -0.453, p = 0.003), baseline total nasal resistance (r = -0.483, p = 0.002), and total nasal resistances after positive NPT (r = -0.361, p = 0.022). Baseline symptom score of rhinorrhea was significantly correlated with total nasal resistance (r = 0.358, p = 0.023), but there were no correlation of other symptom score or TNSS and total nasal resistance.

CONCLUSIONS: PNIF correlates better than total nasal resistance assessed by rhinomanometry. PNIF may be an easy and useful tool to evaluate nasal obstruction in children with AR.

847 An Exploratory Analysis of the Correlation Between Erythema Size and Total Nasal Symptom Scores in the Environmental Exposure Unit

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RATIONALE: Traditionally, wheal size has been used in studies conducted in the Environmental Exposure Unit (EEU), and other Controlled Allergen Challenge Facilities (CACF), for determining participant’s eligibility. It has been suggested anecdotally, however, that erythema diameter in the ‘wheat and flare’ reaction may be more indicative of allergic response than wheal size. The goal of this analysis was to examine the relationship between the longest measured length of skin prick test (SPT) erythema to the Total Nasal Symptom Score (TNSS) achieved in the EEU after both 2 and 3 hours of ragweed pollen exposure during the first Priming Visit and the first 2 hours during a Baseline Challenge Visit.

METHODS: This analysis was part of a larger study involving the EEU and ragweed allergic participants. From the original data set collected of 222 randomized subjects we isolated 142 subjects who attended at least one priming visit (initial pollen exposure visit to activate allergic rhinitis symptoms) and had SPT erythema data to ragweed on file. The TNSS scores achieved at 2hrs on the Baseline Challenge day were also analyzed. Spearman’s correlation analysis of these data was performed using GraphPad Prism 6.0.

RESULTS: The correlation analysis showed no significant correlation between TNSS and erythema at the Priming Visit at 2hr (r = 0.309) and 3hr (r = 0.279) or the Baseline Visit at 2hr (r = -0.113).

CONCLUSIONS: Although it has been suggested that erythema may be a valuable predictor of allergic responsiveness in a CACF study, the correlation analysis performed has shown that erythema may not relate well to TNSS and further study may be warranted.

848 Patient-Reported Symptoms Induced By Allergic and Non-Allergic Triggers in Randomized Controlled Trials of MP-AzeFlu (Dymista) in Seasonal Allergic Rhinitis (SAR) Patients

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RATIONALE: MP-AzeFlu is an intranasal formulation of fluticasone propionate (FP) and azelastine HCl (AZE) in a single delivery device for the treatment of SAR. However, many individuals with SAR also report symptoms in response to non-allergic triggers. In NDA registration studies, which found that MP-AzeFlu was superior to monotherapy with FP and AZE in treating SAR, a rhinitis questionnaire was used to identify specified patient demographic and clinical characteristics.

METHODS: Upon enrollment, patients (n=3398) completed a questionnaire that elicited information on age at symptom onset, parental history, types of symptoms experienced, symptoms induced by allergic and non-allergic triggers, and response to previous medications.

RESULTS: Patients were on average 37.3 years old with a mean age at onset of allergic symptoms at 15.6 years. Stuffy nose (94.4%) was the most frequently reported nasal symptom and itchy/watery eyes (93.6%) was the most common ocular symptom. Temperature changes (71.4%), tobacco smoke (60.8%), perfumes (56.4%), and cleaning products (37.9%) were the most frequently reported non-allergic triggers, and more than 90% of patients reported symptoms in response to at least one non-allergic trigger. Less than 16% of patients reported a big effect from previous medications, including intranasal corticosteroids, oral antihistamines, and intranasal antihistamines.

CONCLUSIONS: A large proportion of SAR patients reported symptoms in response to non-allergic triggers suggesting a high percentage of patients with SAR had a non-allergic component (mixed rhinitis). The efficacy of MP-AzeFlu in this study population suggests that, in addition to SAR, MP-AzeFlu may also be effective for treatment of patients with mixed or non-allergic rhinitis.
**849** Relationship Between Nasal Symptom Scores, IgE Class and Skin Prick Test (SPT) Size in the Environmental Exposure Unit (EEU) – Relevance of IgE Class and Spt Diameter

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**RATIONALE:** The requirement for minimum allergen-specific IgE (sIgE) levels in clinical trials involving novel allergen therapies has been increasing in both EEU type studies and traditional field trials. The impact of sIgE Class (traditionally divided into 6 classes) and/or SPT wheal size on Total Nasal Symptom Score (TNSS) when exposed to allergen in the EEU are not fully characterized.

**METHODS:** Participants with grass-induced allergic rhinitis (AR) and a SPT wheal to rye grass ≥3mm than negative control were included. Four consecutive daily 3HR rye grass pollen exposures in the EEU generated AR symptoms. Different classes of sIgE and SPT wheal sizes were compared to TNSS over time sIgE testing was performed by Phadia. Data were analyzed via GraphPad Prism 6.0.

**RESULTS:** On average, participants with higher sIgE or larger SPT wheals achieved a higher TNSS. Significant differences were seen in mean TNSS scores between certain classes of sIgE or wheal diameters (e.g. TNSS by sIgE Class 0 vs. Class 3 days 2,3,4 respectively; p<0.05) (Day 2 TNSS by wheals 3-5mm vs. 8-9mm,10-12mm,13mm+ respectively; p<0.05). TNSS did not correlate with sIgE or SPT directly, however. Correlation was noted between sIgE and SPT (r<0.61; p<0.0001). On the 3rd EEU challenge, however, there were no significant differences between the TNSS scores of the various classes of sIgE (two-way ANOVA with Bonferroni correction).

**CONCLUSIONS:** Statistically significant differences in TNSS are shown between different classes of sIgE or SPT wheal size after 1, 2 or 3 consecutive exposure days in the EEU. Most significant differences, however, are lost after a 3rd consecutive exposure.

**850** Efficacy of MP-AzeFlu in the Treatment of Postnasal Drip and Rhinorrhea in Patients with Seasonal Allergic Rhinitis (SAR)

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**RATIONALE:** The objective of this analysis was to evaluate MP-AzeFlu (Dymista), an intranasal formulation of azelastine HCL (AZE) and fluticasone propionate (FP) in a single delivery device, for the treatment of postnasal drip (PND) and rhinorrhea in patients with SAR.

**METHODS:** A total of 3389 patients with PND severity assessments and 3392 with rhinorrhea assessments were analyzed from three 2-week, double-blind, placebo- and active-controlled studies comparing MP-AzeFlu to FP and AZE monotherapy. Treatments were administered 1 spray per nostril bid (AM and PM); total daily doses of FP and AZE were 200 mcg and 548 mcg, respectively. The primary efficacy variable was change from baseline in the 12-hour reflective total nasal symptom score (rTNSS), which included nasal congestion, sneezing, itchy nose, and rhinorrhea scored twice daily (AM and PM) on a 4-point (0-3). Change from baseline in PND was evaluated in a similar pre-specified analysis.

**RESULTS:** MP-AzeFlu was statistically superior (P<.05) to FP, AZE, and placebo for improving overall rTNSS in all studies. MP-AzeFlu was also statistically superior to FP (P<.05) and AZE (P≤.001) for improving PND and rhinorrhea in a meta-analysis of the three studies. Statistical or numerical improvements favoring MP-AzeFlu vs. FP and AZE were seen on each day of the 14-day study periods for each nasal symptom.

**CONCLUSIONS:** Results of these analyses demonstrated that MP-AzeFlu significantly improved the overall complex of nasal symptoms of SAR, including PND, compared to monotherapy with either FP or AZE.

**851** Clinical Utility of FeNO in Preschool Children with Allergic Rhinitis

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**RATIONALE:** Studies on FeNO levels in preschool children with allergic rhinitis (AR) are lacking. The aim of this study was to compare FeNO levels in preschool children (3-7 years) having atopic current AR and atopic healthy children.

**METHODS:** This is a general population-based, cross-sectional survey of 1757 preschool children in Korea. Those with physician-diagnosed asthma were excluded. A modified International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire was used. Current AR was defined as having nasal symptoms within the last 12 months and physician-diagnosed AR.

**RESULTS:** Children with atopic current AR had significantly higher geometric mean levels of FeNO compared with those in non-atopic current AR (12.43; 95% CI, 7.31-21.3 vs. 8.25; 95% CI, 5.62-12.10, P=0.008) as well as non-atopic healthy children (8.58; 95% CI, 5.51-13.38, P=0.013). FeNO levels were higher in children with atopic current AR compared with those of atopic healthy (12.43; 95% CI, 7.31-21.13 vs. 9.78; 95% CI, 5.97-16.02, P=0.121). Total serum IgE levels and eosinophil percentage were significantly higher in children with atopic current AR compared with those with non-atopic current AR.

**CONCLUSIONS:** FeNO level was higher in preschool children having atopic current AR, which suggests that FeNO level can be a useful diagnostic biomarker in these children.
**LOCAL Allergic Rhinitis: Entopy or Spontaneous Response?**

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**RATIONALE:** The existence of a “local” allergic rhinitis was prosed on the basis of the detection of nasal IgE in the absence of a systemic sensitization. Nevertheless, the significance of this phenomenon remains partially unclear. We assessed the presence of mucosal nasal IgE in patients with ascertained allergic rhinitis, nonallergic rhinitis with inflammation and in healthy controls.

**METHODS:** Consecutive patients with a well ascertained rhinologic diagnosis (clinical history, skin prick test, specific IgE assay, nasal endoscopy, nasal cytology) underwent an immunoenzymatic measurement of specific IgE to grass, cypress, parietaria and olive in nasal scrapings.

**RESULTS:** Fifteen patients with allergic rhinitis, 12 with nonallergic cellular rhinitis and 14 healthy subjects were studied. The patients with allergic and nonallergic rhinitis had significantly more nasal symptoms versus the control subjects. A systemic sensitization (assessed by skin test and CAP RAST) was obviously more frequent in allergic rhinitis. Nasal IgE could be found equally present in the three groups (86%, 33%, and 50% positive, respectively), even more frequently in the controls than in nonallergic rhinitis patients. No difference among the single allergens was detected. Among the 26 nonallergic patients (cellular rhinitis+controls) nasal IgE were positive in 11.

**CONCLUSIONS:** According to the results, the presence of nasal IgE against allergens seems to be a non-specific phenomenon, since they are present also in non allergic rhinitis and in healthy subjects. It can be hypothesized that the mucosal IgE production is part of a spontaneous immune response.

**Reduction of Substance-P Mediated Neuronal Hyper-Reactivity By Dymista™ (Azelastine & Fluticasone) Correlates with Decreased Cough-Frequency in Non-Allergic Rhinitis**

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**RATIONALE:** Nonallergic triggers have been demonstrated to activate Ca2+ channels on sensory nerve endings resulting in release of neuuropeptides, e.g. Substance P (SP) resulting in marked vasodilation and vascular permeability leading to nasal congestion and rhinorrhea. Clinical evidence supports the benefits of fluticasone and Azelastine in NAR. The purpose of this study was to compare the effect of Dymista™ (Azelastine+Fluticasone) to placebo on reducing NP levels in nasal lavage fluid (NLF) and improving clinical symptoms before and after exposure to cold dry air (CDA) in an environmental exposure chamber.

**METHODS:** In a double-blinded, placebo-controlled study, 30 NAR patients randomized to Dymista (n=20) or Placebo (n=10) treatment groups were initially (Pre-Rx visit) exposed to CDA (~14°C, ~1 hr) and again two-weeks post treatment (Post-Rx visit); NLFs were collected pre-and post-CDA exposure at each visit. Enzyme immunoassays were used to measure SP levels in NLF. Association of CDA-induced cough-counts with log-normalized SP ratio (post/pre-exposure) was determined by correlational and linear regression analysis.

**RESULTS:** Log(SP)-ratio differed significantly between Dymista-Post-Rx vs. Dymista-Pre-Rx samples (est. = -0.739, p<0.00004) and Dymista-Post-Rx vs. Placebo-Post-Rx (est. = -0.748, p=0.00051). Within the Dymista-group CDA-induced cough-counts post-Rx visit were significantly decreased (p=0.0003) and correlated with a reduction in the Logi(SP)-ratio (Spearman rho = 0.33, p=0.03).

**CONCLUSIONS:** Dymista may have a significant clinical effect in NAR by reduction in SP secretion. Larger clinical studies are warranted to demonstrate the clinical effect of Dymista in the NAR treatment.

**Comparison of Commercial Cat and Dog Extracts in Skin Prick Testing and Protein Electrophoresis**

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**RATIONALE:** Many different cat and dog allergens are available commercially for testing and treatment. We aimed to study differences in skin prick testing (SPT) reactivity in a pool of patients to two cat extracts [Cat Hair 10,000 BAU/mL (Greer Labs) and AP Cat Pelt 10,000 BAU/mL (Hollister-Stier)] and two dog extracts [AP Dog Hair-Dander (Hollister-Stier) and Dog Hair & Epithelia (Allergy Labs)]. We hypothesized that similarities or differences in reactivity could be explained by a comparison of extract protein profiles which were elucidated using electrophoresis.

**METHODS:** Data was collected from skin testing results of 260 consecutive patients tested to both cat extracts and 334 consecutive patients tested to both dog extracts since December 2014. A positive skin test result was defined as 3 mm greater than the skin test response to the negative saline control. Electrophoresis was then performed on a number of commercially available cat and dog extracts.

**RESULTS:** We found that only 60% of patients with a positive SPT to cat had a positive skin test to both commercial cat extracts and only 51% of SPT positive dog patients were positive to both dog extracts. Conversely, cat and dog allergic patients were skin test positive to only one of two extracts in 40% and 49% of cases, respectively. Electrophoresis illustrated major differences in protein composition for cat and dog extracts among products from different manufacturers.

**CONCLUSIONS:** Variable protein composition among commercial cat and dog extracts may explain inconsistencies in skin prick testing when using extracts from different manufacturers.
Cytokine Profiles in Monosensitized and Poly-sensitized Allergic Rhinitis Patients Treated with Sublingual Immunotherapy

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RATIONALE: Cytokines induce allergic inflammation leading to respiratory allergy. This study assesses intracellular cytokine profiles in patients receiving Sublingual immunotherapy (SLIT).

METHODS: 60 adult patients with allergic rhinitis 19 to 46 years old, who received SLIT for two years with standardized allergen extracts (Sevapharma) were studied. Group 1 included 30 patients receiving monotherapy with a mixture of grasses I or Artemisia. Group 2 included 30 patients, receiving combination therapy of a mixture of grasses I or Artemisia and mixture of house dust mites or indoor moulds. The control group included 30 healthy subjects. CD4+T-cells were assayed for intracellular cytokines after stimulation with PMA plus ionomycin.

RESULTS: CD4+T-cells (IL-4+ cells, IL-5+ cells, IL-13+ cells, or IL-17+ cells) were significantly increased before SLIT compared to controls but were reduced after the 2nd year of SLIT. IFN-γ+ cells increased after the 2nd year of SLIT. Comparing CD4+cells before and after SLIT in patients of Group 1, IL-4+ was reduced from 0.91 to 0.3; IL-17+ reduced from 0.75 to 0.38; IL-5+ reduced from 4.71 to 2.05; IL-13+ reduced from 4.9 to 1.58 and IFN-γ+ cells increased from 13.37 to 18.85. In Group 2, IL-4+ cells were reduced from 0.75 to 0.28; IL-17+ reduced from 0.5 to 0.2; IL-5+ reduced from 6.11 to 1.88; IL-13+ reduced from 4.95 to 2.06 and IFN-γ+ increased from 14.53 to 18.65.

CONCLUSIONS: Reduction of IL-4+, IL-17+, IL-5+ and IL-13+ CD4+T-cells and increase of IFN-γ+ CD4+T-cells demonstrated that SLIT can modulate immune responses in mono- and poly-sensitized patients.

Validation and Verification of Grass Allergen Challenge in the Allergen BioCube (ABC)

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RATIONALE: Grass allergy can be difficult to study in field trial due to unreliable exposure patterns and poor correlations between skin test response and severity of nasal symptoms. To overcome these challenges, the Allergen BioCube (ABC) was validated for the delivery of Timothy grass allergen in a uniform manner to a capacity of 25 subjects inducing a clinically meaningful rhinitis response.

METHODS: Twenty five subjects were screened and 14 were enrolled with SPT wheel > 5mm, and no symptoms at the screening Visit 1. Visits 2, 3, 4 and 5 consisted of 3 hour exposures to 4000+/− 450 grains per cubic meter of timothy pollen in consecutive days. PNIF, PEFR, serum specific IgE and clinician graded Nasal Inflammation Score (NIS) were captured. The study was conducted out of season.

RESULTS: The average baseline Total Nasal Symptom Score (TNSS) of 0.36 increased to 6.7 ±2.7 after three hours at Visit 2. This response persisted at Visit 3, 4, and 5 with averages of 6.2 ± 3.4, 5.5 ± 3.5, and 5.5 ± 3.5, respectively. From this population 50% of subjects reached a TNSS > 6 by Visit 5. Similarly the NIS increased to a grade of 3.7 ± 1.6 by Visit 5.

CONCLUSIONS: The Allergen BioCube creates a clinically meaningful level of rhinitis in a controlled environment which can be used to evaluate the efficacy of therapies without the concern of a poor natural season and within shorter timelines.

Contrast Agent Reduces Allergic Rhinitis Symptoms

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RATIONALE: We hypothesized that the contrast agent iodixanol, as Nasapaque nasal solution, was effective in reducing nasal allergy symptoms.

METHODS: This clinical trial enrolled 73 adult subjects with seasonal allergic rhinitis and positive ragweed skin tests. After priming at earlier visits, treatment efficacy (Nasapaque or placebo) was assessed at Visit 4 (90 minutes ragweed exposure in Ora’s Allergen BioCube® [ABC]) followed by treatment and additional 7.5 hours ABC exposure) and at Visit 5 (treatment 30 minutes before 3 hours ABC exposure). The primary efficacy endpoint was total nasal symptom score (TNSS, 0-12 scale) assessed at multiple time points pre- and during exposure. Mean TNSS differences between active and placebo treatment groups and change from baseline/pre-treatment differences were calculated (1-sided t-test, alpha = 0.10).

RESULTS: Subjects treated with Nasapaque (N = 36) had lower TNSS scores and greater change from baseline than placebo (N = 37) subjects. Onset of action for Nasapaque was as early as 15 minutes (mean Δ from baseline -3.2; treatment difference -0.9, 80% CI -1.6 to -0.2, p = 0.0602). Statistically significant differences were seen as late as 4.25 hours post-treatment (mean Δ from baseline -4.1; treatment difference -0.9, 80% CI -1.7 -0.1, p = 0.0754). Visit 4 3-hour post-treatment mean TNSS scores were 3.9 (Nasapaque) and 5.0 (placebo); -1.1 difference, 80% CI -2.0, -0.02, p = 0.0625. Visit 5 results also indicated greater efficacy with Nasapaque treatment, which was safe and well tolerated.

CONCLUSIONS: Nasapaque nasal solution is effective in reducing nasal allergy symptoms. Further evaluations of efficacy are warranted.

Three Complementary Pathways Characterize the Suppressive Properties of Epit-Induced Tregs

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RATIONALE: Epitope-specific immunotherapy (EPIT) demonstrates clinical efficacy and induces significant Foxp3+ Tregs in mice. In addition, adoptive transfer of EPIT-induced Tregs protects mice from anaphylaxis and further sensitizations (bystander effect). Nevertheless, mechanisms of action of EPIT-induced Tregs are not clearly elucidated. This study analyzed the suppressive properties of EPIT-induced Tregs in specific/bystander conditions.

METHODS: Milk-sensitized BALb/c mice were treated or not with milk EPIT. Tregs (CD4+CD25+ T cells) from EPIT, Sham or non-sensitized groups and effector T cells (CD4+CD25+) from milk or peanut sensitized mice were sorted and co-cultured for 4 days at different ratios, using allergen stimulation with milk or peanut stimulation. Presence of EPIT-induced Tregs was assessed by flow cytometry. Supernatants were also collected to quantify cytokine secretion.

RESULTS: Effector T cells proliferate up to 82.5%-92.5%, respectively with milk or peanut stimulation. Presence of EPIT-induced Tregs significantly inhibited effector T cells proliferation in specific or bystander conditions (68-71% of proliferation, i.e. 20%-25% proliferation inhibition) compared to Sham or non-sensitized Tregs. Interestingly, blocking CTLA-4 and TGF-b antibodies were also tested to determine whether EPIT-induced Tregs act via cytokines or by cell-contact dependent mediation. Suppression was analyzed by tracking divided CD4+CD25+ with CFSE by flow cytometry. Supernatants were also collected to quantify cytokine secretion.

CONCLUSIONS: EPIT-induced Tregs inhibited effector T cell proliferation with the same potency in specific and bystander conditions. Suppression induced by EPIT-induced Tregs might use 3 complementary pathways: a low availability of IL-2, TGF-b secretion and CTLA-4 cell contact mediation.
SEM4A Contributes Eosinophilic Phenotypes in Asthma and Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

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RATIONALE: We previously reported that the class IV semaphorin SEM4A was critical for Th1/Th2 regulation and that eosinophilic airway inflammation was enhanced in SEM4A-deficient mice. However, the role of SEM4A in eosinophils and human eosinophilic airway inflammation is still unknown.

METHODS: We compared serum SEM4A levels in patients with asthma and CRSwNP vs healthy individuals by enzyme-linked immunosorbent assay (ELISA), and examined SEM4A expression in nasal polyps by immunohistochemistry. We cultured bone marrow cells from Wild Type mice (WT mice) and SEM4A-deficient mice with recombinant IL-5, and evaluated the recovery of the bone marrow-derived eosinophils (BMDEos). In addition, we determined the number of eosinophils in the spleen from WT mice or SEM4A-deficient mice.

RESULTS: Levels of SEM4A were significantly elevated in sera from patients with asthma and CRSwNP than healthy individuals. (mean±SEM 3588±840 and 2403±618 versus 445±214). We found that SEM4A was strongly expressed in eosinophils in the nasal polyps by immunohistochemistry. BMDEos and the number of splenic eosinophils from SEM4A-deficient mice were significantly lower than those from WT mice (mean±SEM 2.14±0.23×10^7 versus 1.41±0.10×10^7, 5973±189×10^6 versus 4100±750×10^6, respectively).

CONCLUSIONS: Our results suggested that SEM4A had trophic functions for eosinophils in human and mice. SEM4A may promote eosinophil survival and disease activity in patients with asthma and CRSwNP.

Treatment of Persistent Blepharitis and Keratoconjunctivitis with Intraocular and Topical Use of Tacrolimus 0.03% Ointment

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RATIONALE: To report a case of persistent blepharitis and keratoconjunctivitis despite the oral use of corticosteroids treated at last with topical and intraocular use of tacrolimus 0.03% ointment.

METHODS: A male patient, aged 42, presented with persistent blepharitis and limbic keratoconjunctivitis in both eyes. The patient had previously received several treatments (such as topical: steroids and cyclosporine and per os: methylprednisolone, median dose: 32mg, for one year), with no improvement. Clinically he showed blepharitis with burning, itching, abnormally greasy tearing and severe keratoconjunctivitis (tingling, itching, pain in some cases, thick mucous secretions and atomic dermatitis on the eyelids). Because of poor response to initial management, we started treatment with intraocular and topical use of tacrolimus 0.03% twice a day.

RESULTS: A week later, the patient appeared with significant clinical improvement. Four weeks later they were no signs of blepharitis and keratoconjunctivitis. Tacrolimus was successfully tapered. There were no side effects.

CONCLUSIONS: Intraocular and topical use of tacrolimus 0.03% ointment may be considered an additional treatment option for keratoconjunctivitis.

Demonstrating the Repeatability of the Nasal Allergen Challenge Protocol Utilized By the Allergic Rhinitis – Clinical Investigator Collaborative (AR-CIC)

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RATIONALE: The Allergic Rhinitis – Clinical Investigator Collaborative (AR-CIC) has optimized a Nasal Allergen Challenge (NAC) model for studying AR pathophysiology and evaluating novel therapies. We sought to evaluate the repeatability of the NAC protocol.

METHODS: Nine ragweed allergic participants were enrolled out of season. The nasal cavity was washed with saline and diluent control delivered intra-nasally; participants were excluded if their Total Nasal Symptom Scores (TNSS), recorded 15 minutes following each step, were >2. The lowest allergen concentration was delivered and TNSS and Peak Nasal Inspiratory Flow (PNIF) recorded 15 minutes later. Participants qualified if a TNSS≥8 and PNIF reduction≥50% were achieved; otherwise the next higher allergen concentration, (4-fold increase), was administered until criteria were met. Participants returned 21-28 days later for a NAC visit (NAC1), and received an allergen challenge concentration equal to all doses delivered at screening, including the qualifying concentration. TNSS/PNIF were recorded at 15 minutes, 30 minutes, 1 hour, hourly up to 12 hours, and at 24 hours following NAC. A second NAC visit (NAC2) was conducted 21-28 days after NAC1.

RESULTS: Participants experienced an initial peak in TNSS at 15 minutes (mean=8.0 NAC1; 7.33 NAC2) followed by gradual decline. PNIF changes mirrored TNSS findings, decreasing to a nadir at 30 minutes following NAC, followed by a gradual return to near-baseline. Both NAC visits had similar results, with no statistical difference (two-way ANOVA with Bonferroni corrections and paired t-tests).

CONCLUSIONS: The AR-CIC’s NAC protocol reliably reproduces clinical results, ensuring that any change would be purely due to medication under investigation in a clinical trial setting.

Patients’ Knowledge and Attitude about Allergic Immunotherapy

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RATIONALE: Allergic immunotherapy (AIT) is currently the only immune-modifying treatment for allergic disease. The clinical efficacy of AIT for the treatment of allergic rhinitis and bronchial asthma is well documented. However, many factors including inconvenience, cost, side effects, and adherence influence the initiation and persistence with AIT. We sought to evaluate the AIT practice pattern and patients’ attitude and behavior about AIT.

METHODS: We conducted a retrospective analysis of medical records of 157 patients received AIT, and compared the clinical characteristics between conventional (CIT) and rush immunotherapy (RIT). A total of 80 were performed a questionnaire survey.

RESULTS: Of 157 patients, 105 (66.9%) were treated with CIT, and 52 (33.1%) with RIT. Frequent hospital visits was the main reason for start RIT. There were no significant differences in allergic diseases, allergens in immunotherapy, and the frequency of adverse reactions during build-up phase. The rate of noncompliance during build-up phase was higher in CIT than RIT (26.7% vs 3.8%). More than half of the patients (67.5%) initiated AIT according to the physician’s recommendation. RIT, initiation of AIT by oneself, longer duration and less allergens of AIT were associated with better treatment satisfaction.

CONCLUSIONS: A majority of patients initiated AIT by the physician’s recommendation and showed good treatment satisfaction. Adequate education of patients would improve the effectiveness of AIT.
Characteristics of Systemic Reactions in the Setting of Modified Environmental Rush Immunotherapy (Protocol MERIT)

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RATIONALE: Conventional allergen immunotherapy is efficacious in allergic rhinoconjunctivitis. However, low adherence has been a significant barrier, whereas rush immunotherapy offers quicker efficacy and may improve adherence. However, there have been concerns for increased risk of systemic reactions. We hypothesize that there are specific characteristics that distinguish patients who develop systemic reactions in the setting of modified environmental rush immunotherapy (MERIT).

METHODS: We conducted a retrospective analysis of demographic and clinical data from adult patients seen in an outpatient university allergy clinic from January 2005- January 2015 who underwent MERIT. We specifically focused on patients who underwent MERIT and developed systemic reactions at any time during their allergen immunotherapy.

RESULTS: Preliminary results from evaluation of 22 patients demonstrated no difference in gender (11 male/11 female), with median age of 30.5 years, and median BMI of 24.9. There was no difference in coexistence of asthma (11 asthmatic/ 11 non-asthmatic). The most common allergens in the immunotherapy serums were cat (21/22) and dust mite (20/22). All patients manifested grade I or II WHO reactions, 8/22 had systemic reactions on more than 1 occasion, and the majority of reactions (15/22) occurred during build up phase, after MERIT was completed.

CONCLUSIONS: Our preliminary data suggests that patients undergoing MERIT develop grade I or II systemic reactions during therapy. This does not seem to be associated with gender or asthma history but allergy serum containing dust mite and cat is seen more frequently in those with systemic reactions. Further comparisons to subjects undergoing MERIT without systemic reactions are underway.

Co-Seasonal Initiation of Allergen Immunotherapy: A Systematic Review

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RATIONALE: It is unclear if allergen immunotherapy (AIT) can be safely initiated during pollen season (co-seasonal initiation [CSI]) because of a potential increased risk of systemic reactions. Publications reporting the safety of subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) CSI were systematically reviewed to validate or invalidate the perception of increased safety risk.

METHODS: PubMed, EMBASE, Ovid, LILACS, and Cochrane Library databases were searched without limits for studies of any design reporting SCIT or SLIT CSI for pollen allergen. Congress abstracts were included.

RESULTS: Nineteen eligible studies were identified; 8 SCIT (n=947 subjects total; n=340 double-blind placebo-controlled [DBPC]) and 11 SLIT (n=2,668 subjects total; n=565 DBPC). Study characteristics and safety reporting were heterogeneous. No epinephrine administrations were reported. Discontinuation frequencies were ≤5.6% and ≤10% with SCIT and SLIT CSI, respectively. In DBPC SCIT studies, systemic allergic reaction frequency was ≤7.1% with CSI and ≤6.1% with placebo; no systemic allergic reactions with CSI were reported in retrospective studies. In SCIT studies, serious treatment-related adverse event (TRAE) frequency with CSI ranged from 0%–2%; besides local reactions no severe AE were reported. In DBPC SLIT studies, systemic allergic reaction frequency was ≤2% with CSI and ≤0.55% with placebo; no systemic allergic reactions with CSI were reported in a retrospective study. Overall, 2 serious TRAEs with SLIT CSI were reported. Severe AE frequency in SLIT studies was ≤7.7% for CSI and ≤1.9% with placebo or non-CI. S.

CONCLUSIONS: No increased safety signal was observed with SCIT or SLIT CSI; however, additional data with standardized regimens and doses are needed.

Adherence to Topical Medications for Chronic Rhinosinusitis: Medication Possession Ratio and Description of Adherence Barriers

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RATIONALE: Topical medication is a cornerstone of therapy for chronic rhinosinusitis (CRS) and adherence to these medication regimens is not well described in the literature. Understanding topical medication adherence will help guide further efforts at medical management of CRS.

METHODS: Patients with physician-diagnosed CRS on topical medications other than saline alone were recruited from an Allergy Clinic. Claims data were obtained from patient pharmacies for the 6 months prior to enrollment and medication possession ratio (MPR) was calculated. A telephone survey was conducted to assess barriers to adherence using an adaptation of the Brief Medication Questionnaire (BMQ). Patients were defined as non-adherent if they self-reported missed doses for one or more days in the week prior to survey.

RESULTS: Thirteen patients, age 35 to 77, were enrolled. Based on data obtained from the BMQ, 61.5% were non-adherent to their medications in the past week. The mean 6-month MPR; however, based on pharmacy refill data, was 81.5%. Three of the thirteen patients were unsure whether the medication was effective indicating a belief barrier. Approximately half of patients were positive for recall barrier; most patients with recall barriers reported the medication as inconvenient to use or time-intensive to prepare. Access barriers were present in five patients with reasons including expense and inability of the preferred pharmacy to provide the specific medication.

CONCLUSIONS: Adherence to topical medications for CRS is low. Attempting to identify and decrease belief, recall, and access barriers is crucial for management of CRS.

Prediction and Classification of Allergenicity within Protein Families

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RATIONALE: The finding that allergens belong to a relatively limited number of protein families provides a unique opportunity to identify the allergen specific motifs (ASMs) that are not present on innocuous proteins from the same family. We derived quantitative physical-chemical descriptors of aligned amino acid sequences and three-dimensional (3D) structures of the allergens within the same family. This approach should allow more accurate predictions of the allergenic potential of proteins within our environment.

METHODS: Unique clusters of protein sequences from the pectate lyase family to identify ASMs. The residues in ASMs were then compared to those in Jun α 1 and other allergens in the pectate lyase family to identify ASMs. The residues in ASMs were then compared to those in the predicted conformational epitopes on Jun α 1. The structure-function relationships will be validated by synthesizing mutated Jun α 1 and expressing in a tobacco mosaic virus system and testing for alterations in IgE and monoclonal antibody binding.

CONCLUSIONS: Our new computational analyses will establish a quantitative platform for identifying proteins that cross-react with known allergens and potential allergenicity of proteins that are being introduced into our environment. This approach will also allow us to identify hypoallergenic derivatives that could be used for rapid and safe immunotherapy.
Characterising Unintended Effects of Genetic Modification on Expression of Gluten Proteins Involved in IgE-Mediated Allergies and Coeliac Disease Using Proteomics

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RATIONALE: Wheat gluten proteins are responsible for triggering coeliac disease (CD) and IgE-mediated allergies and consequently are included in allergenicity risk assessment of novel foods (including GMOs). Understanding the unintended effects of new technology on gluten protein allergens will support the risk assessment process. Untargeted proteomic profiling approaches have much to offer in understanding such effects.

METHODS: A wheat gluten protein database was built with potential coeliac toxicity and IgE-reactivity assessed using in silico epitope mapping. Gluten proteins were extracted from untransformed and GM wheat lines. Proteomic profiling was performed using data independent analysis. Data were processed and searched against a complete gluten database and additional IgE-mediated allergy proteins.

RESULTS: The distribution of celiac toxic and IgE-epitopes was assessed in different gluten protein sub-types. The α-gliadins had the highest density of celiac toxic motifs, followed by the γ-gliadins. Proteomic profiling of wild-type and GM lines showed many gluten proteins not expressed in wheat seeds. Semi-quantitative analysis allowed differences in wild-type and GM lines to be identified with over-expression of HMW subunits of glutenin. Changes observed in expression of wheat gluten proteins and their implications for allergenicity risk assessment process are discussed.

CONCLUSIONS: Proteomic profiling of gluten proteins allows unintended effects of genetic modification to be assessed. Such evidence-based approaches help inform how the benefits of novel foods, including GM and food processing procedures are realised for the population whilst still protecting the allergic consumer.

Association of Peripheral Blood Naïve and Memory T Cells Markers from Immigrants to Brooklyn Who Develop Asthma/Allergies with Family History of Cancer

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RATIONALE: Immigrants to Brooklyn from regions of low allergy/asthma prevalence who develop asthma and allergy have a less robust Th1 responses than those who remain healthy. We determined whether this profile extends to history of familial malignancies, as malignancies are most likely associated with defecte immune surveillance of cancer.

METHODS: Immigrants to Brooklyn (Chinese and Hispanic, n=112) with self-reported asthma and/or seasonal allergies and controls (asthma/allergy, n=57; control, n=55) had blood drawn for determination of total serum IgE (fluoroimmunoenzyme assay) and concurrent peripheral blood leukocyte memory markers: stem cells (CD35+), CD4+ and CD8+ T cells: naïve (CD4+, CD8+), CD45RO-CD62L+CD11a+, and CD28- memory (CD28-CD45RO+) (flow cytometry, LSR Fortessa, BD). The history of cancer in first-degree relatives was obtained. Chi-square test and Pearson correlations were calculated.

RESULTS: Those with asthma/allergies had significantly higher levels of IgE (p=0.016). Increased percent of naïve T cell significantly associated with decreased percent of memory T cells for the following subsets: asthma/allergy CD4+ and CD8+ (p=0.008 and 0.001, respectively) and control CD4+ (p=0.003). No significant association was found for control memory CD8+ cells (p=0.25).

There was no difference in total number of malignancies in control vs. allergy subjects (n=13,13, p=ns), paternal cancer (n=5,5, p=ns), and self, sibling, or children (p=ns). However, maternal cancer was reported by only 1 control but by 6 allergic subjects (p=0.057).

CONCLUSIONS: Taken together, our findings suggest that a lack of robust Th1 responses in immigrants who develop allergic disease may be genetic and extend to defective cancer immune surveillance.

Clinical Characteristics of NSAID Drug Allergies and Predictive Value of the History for Oral Drug Challenge Outcomes

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RATIONALE: NSAID allergies are among the most frequently reported drug allergies and have significant implications for patients.

METHODS: We conducted chart reviews and phone interviews of patients seen in our Drug Allergy Clinic from 2009-2014 who underwent an oral drug challenge for a self-reported NSAID allergy.

RESULTS: 41 NSAID challenges in 35 patients were reviewed, 37 challenges were negative. The majority of patients were female (86%), of Hispanic ethnicity, and ages 41-60. Most reported one single episode of NSAID allergy and at least one other allergic reaction to an unrelated medication. The most frequent reaction was urticarial alone (34% of patients) followed by angioedema (22% of patients) and most reactions took place within 5 hours of ingesting medication. Of patients with urticarial rash alone, 0 patients had positive challenge. Of patients with angioedema alone, 10% had positive challenge, and of patients with both, 46% had positive challenge. On follow up calls, 18 patients were reached, and 16 participated. Of these patients, 9 were tolerating the medication and 7 were not taking medication at all. Of patients currently not taking the medication, one third developed delayed adverse reaction after challenge (angioedema and vomiting), one third developed a repeated adverse reaction on re-exposure (angioedema), and the rest were afraid of trying the medication at home.

CONCLUSIONS: A history of urticarial rash attributed to NSAIDs was most likely associated with a negative challenge. Despite negative oral challenge in the office to NSAIDs, only 60% of patients continued to safely take the medication.
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**Rationale:** T helper (Th) 2 cytokines promote the development of an allergic inflammatory response in allergic individuals. Th1 cytokines can counterbalance the Th2 immune response and aid in treatment of allergic diseases. The goal of this study was to evaluate the potential of using Glucopyranosyl Lipid A (GLA), a synthetic TLR4 agonist, to modify Th1/2 cytokine responses to grass pollen allergen in PBMC from allergic donors.

**Methods:** Peripheral blood mononuclear cells (PBMC) were collected from 12 subjects with allergy to Timothy grass pollen and cultured with grass pollen *Phleum pretense* extract (10 μg/mL), with or without GLA (1 μg/mL) for 6 days. Cytokine production was measured by ELISA and Luminex assays.

**Results:** The levels of Th2 cytokines, IL-5 and IL-13, were significantly decreased in the presence of GLA. IL-5 was 213 ± 72 pg/mL in the allergen alone group vs. 322 ± 140 pg/mL in the allergen plus GLA group (p < 0.02). IL-13 was 635 ± 140 pg/mL in the allergen alone group vs. 384 ± 179 pg/mL in allergen plus GLA group (p = 0.006). Th1 cytokines, IFNγ and IL-12, were significantly increased in the presence of GLA. IFNγ was 1008 ± 378 pg/mL in the allergen alone group vs. 48 ± 48 pg/mL in allergen plus GLA group (p = 0.001). IL-12p40 was 126 ± 48 pg/mL in allergen alone group vs. 898 ± 179 pg/mL in allergen plus GLA group (p = 0.0004). Anti-IL12 neutralizing antibody inhibited GLA-induced IFNγ significantly (p = 0.0002).

**Conclusions:** GLA can decrease grass pollen extract induced Th2 cytokines and increase Th1 cytokines. These results support testing of GLA in pollen-allergic patients in the setting of desensitization.

**AB266 Abstracts**

**870 TLR4 Agonist GLA Modifies Th1/Th2 Cytokine Profiles in PBMC from Patients with Pollen Allergy**

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**Rationale:** Allergy to cockroach is a significant problem in some urban areas. Termites are within the order Blattodea and are evolutionarily related to cockroaches. We evaluated the ability of proteins from the Subterranean Formosan termite (*Coptotermes formosanus*) to cross-react with cockroach allergens.

**Methods:** Genomic and expressed sequence termite libraries were searched for homology to cockroach allergens using Blast 2.2.21 software. Whole termite extracts were analyzed by mass-spectrometry and probed with anti-cockroach antibody IgG, scFv, and human IgE from cockroach allergic patients by immunoblot and ELISA.

**Results:** Sequencing results indicate greater than 60% homology between predicted termite proteins and cockroach allergens including Bla g 3, Bla g 6, Bla g 7, Bla g 8, and Per a 9. Termite peptide sequences were matched to those of Bla g 7, Bla g 8, and Per a 9. Immunoblot and ELISA testing with IgG and IgE antibodies to cockroach allergens revealed cross-reaction to termite proteins. In particular, anti-cockroach allergen antibodies were reactive to putative termite homologs of hemocyanin (Bla g 3) and tropomyosin (Bla g 7).

**Conclusions:** We demonstrate that there is significant sequence homology between cockroach allergens and termite proteins, and we have identified termite orthologs for several cockroach allergens. We show that termite proteins cross-react with antibodies to cockroach allergens, including the termite hemocyanin (Bla g 3) and tropomyosin (Bla g 7) homologs. This research could have important consequences to the diagnostic and therapeutic allergy fields.
873 Prediction and Identification of Korean Pine (Pinus koraiensis) Vicilin As a Food Allergen

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RATIONALE: Pine nut allergy cases have been reported, but pine nut allergens remain to be identified and characterized. Korean pine nut is one of the major varieties of pine nuts that are widely consumed. Vicilins belong to one of a few protein families that contain more than 85% of the known food allergens of plant sources. Korean pine vicilin (Pinkv) is likely to be a food allergen.

METHODS: Korean pine vicilin was purified from pine nuts. It was also expressed in E. coli and purified. The recognition of the native and recombinant Pinkv by sera from three individuals with pine nut allergy was analyzed by Western blot.

RESULTS: While one of the sera contained very low level of IgE specific to any particular pine nut protein, 66% of the sera recognized both the pine nut purified from nuts and recombinant Pinkv, although they recognized different natural fragments of the native protein.

CONCLUSIONS: Although more studies with additional patient sera are required for it to be officially defined, Korean pine vicilin is likely to be a bona fide food allergen. Two of the available patient sera each recognized a single linear IgE epitope located at the boundaries of the natural Pinkv fragments.

874 Anti-Atherosclerotic Vaccination with T-Cell Peptides Is Most Effective in Reducing Plaque in the Thoracic Aorta

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RATIONALE: We previously demonstrated T-cell peptides derived from murine ApoB100 were used to vaccinate against atherosclerosis, possibly via a mechanism akin to allergy immunotherapy. Here, we studied whether different portions of the aorta responded more readily to vaccination than others.

METHODS: 15-mer peptide sequences spanning ApoB100 were synthesized and screened for ability to bind tightly to MHC class II. Candidate peptides (CP3, CP6, CP101 - CP103) were used to vaccinate female ApoE KO mice using 50 mcg of peptide+CFA subcutaneously in the inguinal area at 8 weeks of age. Western diet was started at 10 wks of age. Repeated boosters with 25 mcg peptide+IFA were administered intraperitoneally at age 12, 16, 20 and 22 weeks. Mice were sacrificed at age 23 weeks and organs were harvested for analysis. PBS and irrelevant peptide were used as controls.

RESULTS: CP3 was 30% protective in the aortic arch, nearly 50% protective in the thoracic aorta (p<0.05), and trended toward significant protection in the abdominal aorta. CP6 was 50% protective in the thoracic aorta (p<0.05). CP101 - P103 were three additional candidate peptides that were tested which conferred similar degrees of atheroprotection, most notably in the thoracic aorta (50% protection, p<0.05).

CONCLUSIONS: Vaccination with peptide fragments from murine ApoB100 confer the greatest amount of atheroprotection in the thoracic aorta. The consequences of these regional differences will need to be elucidated before atheroprotective vaccination can proceed to human trials.

875 The Sensitization Model and Correlation of Bermuda Grass and Timothy Grass Pollen Allergen in Respiratory Allergic Diseases Patients in Southern China

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RATIONALE: Study on the sensitization model and correlation of Bermuda and Timothy grass allergen in allergic patients in Southern China.

METHODS: 258 cases of patients with allergic diseases, including 92 asthma patients, 78 allergic rhinitis patients, 88 rhinitis with asthma. Serum sIgE of Bermuda, Timothy and Japanese hop were determined by UnitCAP. If the Bermuda-sIgE were positive, sIgE of Cyn d1, Phl p1, Phl p4, peanut, Ara h1, Ara h8, birch, Bet v1 and CCD were tested.

RESULTS: The sensitization rate of Bermuda, Timothy and Japanese hop in 258 cases were 22.5%, 13.6% and 9.3% respectively. 53.4% (31/58) Bermuda-sIgE positive patients were sensitized to Cyn d1. 100% (35/35) timothy-positive patients were sensitized to Phl p4, but only 17.1% (6/35) were positive to Phl p1. 41.4% of Bermuda-sIgE positive patients were Japanese hop sIgE positive. 56.9% (33/58) Bermuda-positive patients were sensitized to peanut. Ara h1 were positive in 3 patients. 32.8% (19/58) were sensitized to birch. Phl p4 was the main component of timothy. CCD had good correlations with grass pollen, peanut and birch allergens, indicated wide cross-reactions between them were caused by carbohydrate cross-react determinants.

CONCLUSIONS: The sensitization rate of Bermuda, Timothy and Japanese hop were 22.5%, 13.6% and 9.3% in Southern China. Bermuda sIgE positive patients were sensitized to timothy, peanuts, CCD and birch and Japanese hop in different degree. Phl p4 was the main component of timothy. CCD had good correlations with grass pollen, peanut and birch allergens, indicated wide cross-reactions between them were caused by carbohydrate cross-react determinants.

876 Structural, Serological, and Genomic Analyses of the Major Mite Allergen Der p 23

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RATIONALE: Der p 23 was recently identified in a European population as a major allergen and potentially a chitin binding protein. This study sought to determine the structure of Der p 23, and assess the importance of Der p 23 among other Dermatophagoides allergens in a North American population.

METHODS: The structure was analyzed by X-ray crystallography and NMR. IgE binding to Der p 23, Der p 1, Der p 2, Der p 5, Der p 7, and Der p 8 was measured by ELISA. Allergen expression levels were estimated using RNA-seq data from D. farinae.

RESULTS: Der p 23 is a small, globular protein, stabilized by two disulfide bonds, that is structurally related to allergens that contain carbohydrate binding domains such as Blo t 12. Functional assays failed to confirm chitin binding by Der p 23. Despite a high prevalence of Der p 23, (83% versus 87% and 85% for Der p 1 and Der p 2, respectively), the anti-Der p 23 IgE levels were relatively low. The RNA expression level of Der f 23 is the lowest of the major allergens. Expression levels of Dermatophagoides allergens do not correlate with their reported prevalence of IgE sensitization.

CONCLUSIONS: Der p 23 accounts for a small percentage of the IgE response to mite allergens, which is dominated by Der p 1 and Der p 2. The prevalence and amount of specific IgE to Der p 23 and Der p 2 are disproportionately high compared to other more abundant Dermatophagoides allergens.
All abstracts are strictly embargoed until the date of presentation at the 2016 Annual Meeting.

**877 A Role for Glycans in Bla g 2 Cockroach Allergen-Induced Allergic Responses**

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**RATIONALE:** Exposure to German cockroaches is associated with IgE sensitization to cockroach allergen and increased risk for allergic asthma. Recombinant peptide-based cockroach allergens have been produced that are associated with allergic responses, however, little is known about other cockroach allergen factors that contribute to allergic responses. We sought to identify additional/novel components in cockroach extract (CRE) that contribute to the induction of cockroach sensitization and asthma.

**METHODS:** Profiling of N-linked glycans on purified Bla g 2 was performed by MALDI-TOF mass spectrometry. The binding capacity of serum IgE antibodies to glycan from individuals with positive reactivity to Bla g 2 (n = 22) was detected by ELISA. Glycan-induced histamine release in human basophils was examined.

**RESULTS:** N-linked hybrid- and complex-type di-fucose modified glycans with mannose-, galactose-, and/or N-acetyl glucosamine-terminated moiety on Bla g 2 was identified by mass spectrometry. Of five selected individuals with strong reactivity to Bla g 2, four showed a significant reduction in IgE binding to deglycosylated Bla g 2 compared to native Bla g 2. Furthermore, Bla g 2 deglycosylation reduced histamine release in passively sensitized human basophils as compared to Bla g 2 (6.0 ± 0.5% vs 12.0 ± 1.1%, p < 0.019). Interestingly, our initial study suggests that glycan alone appears to prevent spontaneous histamine release in basophils.

**CONCLUSIONS:** Our studies heighten the potential involvement of glycans in cockroach allergen-induced sensitization and asthma. However, further studies are clearly needed to expand upon this observation.

**878 Are Dust Mite Allergens More Abundant or More Stable Than Other Dermatophagoides Pteronyssinus Proteins?**

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**RATIONALE:** It is frequently reported that allergens are more abundant and/or more stable proteins than other proteins. However, numeric comparisons on a genomic and proteomic scale are lacking.

**METHODS:** Dermatophagoides pteronyssinus (DP) expression levels were analyzed by RNAseq to assess the relative abundance of all transcripts. Thermodynamic stabilities of proteins in a DP extract were assessed using a mass spectrometry- and chemical denaturation-based strategy.

**RESULTS:** Allergens are among the more highly expressed genes in DP. However allergens are not the most abundant, nor are the allergens a majority of the highly abundant genes. The thermodynamic stabilities of the 919 DP proteins assayed here were on average similar to those previously measured in other eukaryotic species. The 21 DP allergens identified trend toward greater stability than the remaining 898 proteins, but in general the allergens are not exceptionally stable; e.g. Der p 1’s stability is close to the mean. Der p 2 is greater than two standard deviations from the mean, however about 50 other non-allergens were also as stable as Der p 2. When considered together, high abundance and high stability increase the likelihood that a protein is an allergen, however it is not predictive.

**CONCLUSIONS:** Allergens are among the more abundant and more stable proteins in DP. However, these features are not unique. In DP extract, commonly used for immunotherapy, the 898 non-allergic proteins assayed had similar abundance and stability profiles to the 21 known allergens assayed. Abundance and stability do not completely account for the allergenic nature of some proteins.

**879 Ligand Binding Preferences of Pathogenesis-Related Class 10 (PR-10) Allergens**

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**RATIONALE:** Many PR-10 proteins are associated with allergens when inhaled or ingested. One proposed function of these proteins is delivering bio-active compounds to wounds and/or the developing plant. We examined ligand binding to seven known PR-10 allergens. Ligand binding could well affect allergens' function in vivo allergens' function.

**METHODS:** We generated pure, recombinant Ara h 8.01, Ara h 8.02, Cor a 1.02, Cor a 1.04, Que a 1.02, Que a 1.03 and Bet v 1.01 from peanut, hazelnut, white oak and birch respectively. Twenty three putative ligands were tested for binding using a fluorescence assay.

**RESULTS:** All of the proteins bound apigenin, daidzein, genistein, quercetin and resveratrol. Que a 1.03 bound the widest array of ligands including several fatty acids. Preliminary structural studies show changes in protein structure with ligand binding.

**CONCLUSIONS:** Our results support the theory that these PR-10 allergens’ function in vivo is as a delivery vehicle for bio-active compounds. Now that we have identified biologically-relevant ligands we will test the possibility that binding them to PR-10 proteins may influence allergic potential.
Molecular and Immunological Characterization of Gamma Gliadins As Major Allergens in Wheat Food Allergy

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RATIONALE: Wheat gluten proteins provoke IgE-associated allergy (i.e., food allergy and wheat-dependent exercise-induced anaphylaxis) as well as T cell-mediated hypersensitivity (i.e., celiac disease). Here, we aimed to characterize wheat gamma gliadins regarding their molecular, structural and immunological properties in detail.

METHODS: Five recombinant wheat gamma gliadins were expressed in Escherichia coli cells, purified to homogeneity, characterized by means of SDS-PAGE, mass spectrometry, gel filtration, circular dichroism, and their allergenic activity was studied by RAST-based IgE dot blotting as well as rat basophil β-hexosaminidase release assay. IgE epitope mapping was performed with synthetic overlapping peptides spanning the gamma gliadin sequence.

RESULTS: Wheat gamma gliadins react with IgE antibodies from 62% of wheat food allergic patients and exhibit strong allergenic activity by basophil activation. Gamma gliadins represent proteins with high degree of sequence identity and form strong protein aggregates under reducing and non-reducing conditions. According to circular dichroism analysis, recombinant gamma gliadins represent unfolded proteins. Immunodominant IgE epitopes were identified on the N-terminus indicating that IgE recognition does not require fold and is directed against linear epitopes. Thus, gamma gliadins can be considered as typical class I food allergens which sensitize generally via the gut such as several allergens originating from other food sources.

CONCLUSIONS: Recombinant gamma gliadins representing major wheat food allergens may be used for diagnosis and immunotherapy of wheat food allergy.

Assessing the Impact of Lipids on the Allergenic Potential of Peanuts Using a Germ-Free Murine Model of Food Allergy

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RATIONALE: Published studies have reported that lipid components in some foods interact with specific proteins to enhance their allergenicity. Peanuts have high lipid content and are potent allergenic sources with a number of allergenic proteins including the potent allergen Ara h 2. Therefore we compared clinical responses in mice sensitized with extracts of defatted and non-defatted peanut flour.

METHODS: Extracts were prepared from defatted and non-defatted raw peanut flour. Protein concentrations were measured by Lowry assay and Ara h 2 by immunoblotting. Germfree (GF) C3H/HeN mice were sensitized with defatted or non-defatted extracts by intraperitoneal injection (IP) each week with alum adjuvant. Mice were challenged (week 4) IP with 500 mg of Ara h 2 or peanut extract (without alum). Rectal temperatures were recorded and clinical scores assigned 30 minutes after challenge. Sera were collected for analysis of mMCP-1 and specific IgE.

RESULTS: Ara h 2, the peanut allergen of interest was present in significant amounts in both defatted and non-defatted peanut extracts. Sensitized mice had statistically significant clinical reactions and temperature drops compared to controls. However, differences in post-challenge clinical scores and reductions in body temperatures between sensitization groups were not statistically significant between the mice sensitized with full-fat vs. defatted peanut extracts.

CONCLUSIONS: In this study, defatting did not have a significant effect on the sensitization potential of peanut extracts of raw peanut as measured by challenges with peanut extract or Ara h 2 in GF mice. Future work will assess the impact of lipids on the sensitizing potential of roasted peanuts.

Dynamics of Regulatory T Cell-Mediated Control of Antigen Responses and Autoimmune Neuroinflammation

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RATIONALE: Despite the indispensable contribution of regulatory T cells (Tregs) for maintenance of immune homeostasis and prevention of autoimmune disease, little is known about their cellular dynamics during suppression of T cell priming and neuroinflammation in experimental models of multiple sclerosis.

METHODS: Transgenic mice carrying fluorescent proteins in a cell-specific manner allow simultaneous imaging of complex interactions. Using two-photon microscopy, we characterize the behavior of Tregs during antigen-specific T cell priming in lymph node and, using the myelin oligodendrocyte glycoprotein (MOG) model of experimental autoimmune encephalomyelitis (EAE), during autoimmune demyelination in spinal cord.

RESULTS: Under steady-state conditions, Tregs exist as two non-overlapping populations that explore the T-zone and the B cell follicle. In the T-zone, Tregs migrate more rapidly than conventional T cells (Tconv) and interact with both resident dendritic cells (DC) and Tconv. During an antigen-specific immune response, Tregs interact with antigen-induced DC:Tconv clusters. Blocking CTLA4-4 reduces Treg:Tconv interaction times, increases the volume of DC:Tconv clusters, and subsequently enhances Tconv proliferation in vivo. In the EAE model, Th17 cells mediate neuroinflammation and Tregs promote remission. During EAE, Tregs home to sites of ectopic lymphoid structures in spinal cord where they actively interact directly with Th17 cells engaging APCs.

CONCLUSIONS: Our results demonstrate a role of altered cellular choreography, mediated by Tregs through CTLA4-based interactions, to reduce Tconv:DC clustering during helper T cell priming. Our study of cellular competition-based immunoregulation provides the first visualization of Treg suppression of Tconv cell priming and of neuroinflammatory cell interactions in spinal cord during EAE.
883 Prostaglandin I2 Receptor (IP) Signaling Increases Regulatory T (Treg) Cell Induction and Function and Renders T Effector (Teff) Cells More Susceptible to Treg-Mediated Suppression

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RATIONALE: Regulatory T (Treg) cells are pivotal in suppressing immune responses and maintaining tolerance. Prostacyclin I2 (PGI2) signaling through the I prostanoid (IP) receptor has anti-inflammatory effects and inhibits Th2-mediated cardinal features of asthma. We reported that PGI2 inhibits dendritic cell function and Th2 cytokine production; however, the effect of PGI2 on Treg cell function is not known.

METHODS: Naive CD4+ T, Teff, and Treg cells were isolated from the spleens of BALB/c WT and IPKO mice. To induce iTreg differentiation, CD4+ cells were cultured with anti-CD3, IL-2 and TGF-B for 6 days. Teff and CFSE+ Teff were stimulated with anti-CD3 and anti-CD28 for 3 days. The percent inhibition was calculated as follows: [(proliferation at ratio/proliferation Teff only)*100].

RESULTS: Naive CD4+ cells from IPKO mice exhibited significantly decreased iTreg cell induction compared to naive CD4+ cells from WT mice. There was a significant increase in splenic Treg cell numbers in IPKO mice compared to WT mice. Treg cells from IPKO mice had significantly decreased suppressive function compared to Treg cells from WT mice, and Teff cells from IPKO mice were less susceptible to Treg-mediated suppression compared to Teff cells from WT mice.

CONCLUSIONS: Endogenous PGI2-IP signaling increases iTreg cell induction and Treg cell function, and renders Teff cells more susceptible to Treg-mediated suppression. These results suggest a possible mechanism by which PGI2 inhibits airway inflammation during allergic asthma.

884 T-Cell Epitope Optimization to Maximize Allergic Donor Responses

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RATIONALE: Peptide T-cell epitopes have been considered as alternatives to allergen extracts in Allergy Immunotherapy (AIT). In order to design effective therapies, it is important to know the contribution of peptide length and sequence on T cell recognition.

METHODS: We cultured PBMCs from grass allergic patients with Phl p extract and tested for cytokine production after restimulation with 15-mer peptide epitopes. We systematically lengthened these 15-mers to 20-mers and compared the cytokine responses they elicited as a function of the position of the 15-mer within the 20-mer and the composition of the added flanking residues which either matched the pollen sequence or were completely mismatched.

RESULTS: We found that the lengthened 20-mers elicited higher responses in allergic patients than the 15-mers they were derived from, and that a greater number of allergic patients mounted significant responses to them. This effect was especially pronounced when the epitope was flanked on both sides by amino acids and therefore “protected”. We also found that lengthened peptides with mismatched flanking residues did not elicit as high responses as peptides that were sequence matched.

CONCLUSIONS: Our findings suggest that longer peptides maximize allergic T-cell responses, by two effects: First, the flanking residues on either side of the epitope seem to protect it from proteolysis. Second, addition of residues that match the pollen sequence may generate additional epitope registers in the peptide thereby increasing the likelihood of MHC binding and T-cell recognition. These results can be utilized for choosing peptides to include in AIT.

885 Regulatory T Cell Immunophenotype Is Influenced By Food Allergy Status

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RATIONALE: The development and maintenance of regulatory T cell (Treg) populations may be important in the pathogenesis of food allergy. We hypothesize that children with food allergy have decreased number or function of Treg cells. These differences may be influenced by age and the presence of concomitant atopic dermatitis.

METHODS: Peripheral blood mononuclear cells (PBMC) of 136 children (50 without atopic disease and 86 with food allergy) were stained and analyzed by flow cytometry for surface (CD25, CD127) and intracellular (Foxp3) markers of Treg cells. Cells were further phenotyped to assess homing (CCR6), memory (CD45RO) and TCR Vb expression. ANOVA, simple and multivariable linear regression were performed to assess differences in cell populations while controlling for possible confounders.

RESULTS: We found no difference in the bulk Treg cell population (CD25+CD127+ Foxp3+/CD4+) in food allergic versus non-atopic children (p=0.944). In unadjusted analysis, food allergic children had increased CD45RO+CD25+CD127+ Foxp3+ cells (p=0.045) and CD45RO+CD25+CD127+ CCR6+ cells (p=0.053) compared to non-atopic children. In adjusted analysis, food allergic children had more CD45RO+/CD25+CD127+ (p<0.001), CD45RO+ CD25+CD127+ CCR6+ (p=0.001) and CD45RO+ CD25+CD127+ FoxP3+ (p<0.001) cells compared to non-atopic children. Additionally, in adjusted analysis, food allergic children had a trend of increased Vb(3,5)+/CD25+CD127+ FoxP3+ cells.

CONCLUSIONS: Food allergic children have increased memory Treg cells and gut-homing memory Treg cells compared to non-atopic children. Food allergic children also have increased staphylococcus-responsive Treg cells compared to non-atopic children. These findings suggest phenotypic differences in Treg cell subsets that may be important in the pathogenesis of food allergy. Naive Treg cells may be important to maintain oral tolerance.
886 Recognition of Bla g T Cell Antigens Variies As a Function of Allergic Asthma Versus Rhinitis

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RATIONALE: German cockroach (Bla g) antigens have been defined by IgE reactivity. Less information is known regarding targets of cockroach CD4+ T cell responses, and potential differences as a function of allergic disease.

METHODS: To thoroughly map Bla g-derived T cell epitopes, cockroach extract was subjected to proteomic and transcriptomic analysis. PBMC from Bla g-sensitized subjects, with (n = 55) or without (n = 17) asthma, and non-Bla g-sensitized controls with Bla g-unrelated rhinitis (n = 55) or without (n = 17) asthma, were analyzed. To characterize different T helper cell functionalities of allergen-specific T cells, overlapping peptides from known allergens and novel antigens were assayed for their capacity to induce IL-5, IFNγ, IL-10, IL-17, and IL-21 production in PBMC.

RESULTS: T cell responses in PBMC for 20 known and novel Bla g antigens (NBGA) were detected. This represents a >10-fold increase in cockroach-specific T cell targets compared to what has been reported in the literature to date. Cytokine responses of cockroach-sensitized individuals were predominantly Th2-polarized (IL-5), with higher response magnitude in patients with diagnosed asthma. Strikingly, the dominant antigens were different in asthmatic subjects (Bla g9 and 11) as compared to non-asthmatic sensitized (Bla g4, and the novel antigen NBGAS).

CONCLUSIONS: Asthmatic and non-asthmatic sensitized individuals exhibit similar functionality (predominantly Th2 polarized responses). Asthmatic individuals exhibit higher levels of cytokine producing T cells and different patterns of immunodominance. Moreover, many T cell epitopes identified here may present attractive targets for the development of a peptide-based cockroach-specific immunotherapy approach that circumvents IgE reactivity and any associated adverse reactions therefore rendering it suitable for asthmatics.

887 Substance P (subP) Suppresses Induction of Specific Memory IgE Responses By PBMC of Ragweed Sensitized IgE+ Humans, but NOT CD4+IL4+ or CD8+CD60+IL4+ T Cells or IL-4

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RATIONALE: Transmagnetic/electrical stimulation of human/rat left temporo-parieto-occipital cortex increases levels of the neuropeptide subP and CD4+ T cells in blood while suppressing ongoing IgE responses; this was prevented by cutting rat spinal cord at T2 or thymectomy. SubP suppresses murine memory IgE responses in vivo/vitro. The signaling molecule p38MAPK is associated with IL-4 and CD4+ and CD8+CD60+ T cells, IL-4 and 5 other cytokines (not IL-13) are required for human memory IgE responses. The role of subP in suppression of human CD4+IL4+, and CD8+CD60+IL4+ T cells, p38MAPK and memory IgE responses was investigated.

METHODS: We determined the numbers of (1) CD4+IL4+, and CD8+CD60+IL4+ T cells and subP receptor+ (NK-1R) leukocytes in blood of ragweed sensitized humans (n = 6); (2) CD45+, CD4+CD3+, CD8+CD60+, CD19+, CD16/56+, and CD14+ cells expressing p38MAPK in PBMC ± 15-30 min incubation with PMA ± subP; and (3) the effect of subP on specific memory IgE responses by PBMC cultured for 0-12 days ± ragweed antigen ± subP ± antibodies to subP receptors (flow cytometry; ELISA) (data expressed as % T cell subsets, % total lymphocytes or monocytes, ng/ml).

RESULTS: SubP did not affect CD4+IL4+, or CD8+CD60+IL4+ T cells but suppressed CD45+p38MAPK+ lymphocytes (70%) (including CD4+, CD8+, CD19+, CD16/56+ p38MAPK+ cells), and specific memory IgE responses, with antibodies to subP receptors reversing this effect. Monocytes, B and NK cells were subP receptor+ but T cells were not.

CONCLUSIONS: Substance P suppresses specific memory IgE responses by acting on monocytes, B cells or NK cells, but not on T cells or IL-4.

888 Non-Atopic Individuals Exhibit a Distinct Immune Reactivity Patterns in Response to Timothy Grass Pollen in and out-of-Season

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RATIONALE: Timothy grass (TG) pollen is one of the most frequent aero-allergens causing symptoms ranging from mild rhinitis to severe asthma in allergic individuals.

In this study, we were interested in assessing and characterizing changes in seasonal TG-specific T cell responses.

METHODS: Peripheral blood mononuclear cells (PBMC) from allergic and non-allergic donors were obtained either during or out of TG pollen season. Cells were stimulated either with TG extract or a pool of previously identified Phl p-derived immunodominant T cell epitopes.

RESULTS: T cell responses from in-season allergic subjects were found to be associated with higher levels of IL-5 and IL-10 compared to out-of-season donors. Strikingly, non-atopic donors exhibited an opposing pattern in immune reactivity compared to allergic patients, with immune responses being significantly lower in-season compared to out-of-season.

TRANSCRIPTOMIC analysis of allergen-specific T cells defined genes modulated in concomitance with allergen exposure and inhibition of responses in non-allergic donors.

CONCLUSIONS: Magnitude and functionality of T-helper cell responses are differentially regulated in-season versus out-of-season in allergic and non-allergic subjects. Cohort-specific and opposing modulation of immune responses can be observed in atopic versus non-atopic individuals following antigen stimulation during the pollen season. Seasonal immune-downregulation in non-allergic donors indicates that healthy individuals react with an active suppression of responses following antigenic stimulation during the pollen season. This differential seasonal modulation may reflect the enactment of specific molecular programs associated with health and allergic disease.
Pulmonary MicroRNA Expression Profiles Associated with Subchronic Aspergillus fumigatus Exposure

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RATIONALE: The role of small noncoding RNAs involved in pulmonary immune responses to fungi has not been elucidated. The study objective was to evaluate microRNA (miRNAs) profiles in murine lungs and to evaluate potential biomarkers to evaluate fungal exposure. Furthermore, altered miRNAs may serve as biomarkers.

RESULTS: Approximately 28% and 50% of miRNAs were altered 24 and 48 hours following the final exposure when comparing viable to the nonviable and air control groups. MiR-23b-3p, known to regulate genes involved in the IL-13 and IL-33 responses, was identified as having the largest decreased change. MiR-30c-5p and miR-29a-3p, both of which are involved in the IL-13 and IL-33 responses, respectively. Examination of the miRNA profile post-fungal exposure demonstrated a large number of altered miRNAs. Our findings support previously reported immune responses following A. fumigatus exposure. Furthermore, altered miRNAs may serve as potential biomarkers to evaluate fungal exposure.

Critical Genetic Virulence and Epidemiological Information

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RATIONALE: Despite the enormous medical burden caused by respiratory viruses in asthma subjects, the specific genetic variations that influence transmission, virulence, and pathogenesis are poorly understood for most viruses. We aimed to develop a clinical test that would detect infections and identify viral genetic variations that might influence these critical processes.

METHODS: We developed the UNM ResVir Panel, a hybridization-based method to target and enrich complete coding sequences from 12 respiratory viral families, representing more than 34 virus subtypes, and more than 100 virus strains. We have now evaluated 123 viral nasopharyngeal swabs obtained for clinical purposes. The samples are sequenced in a high-throughput, multiplexed, rapid manner on the Illumina MiSeq. This information is used to determine specific viruses, construct nearly complete genome sequences, assess viral gene expression, detect genetic variation, and conduct phylogenetic analysis.

RESULTS: We have identified more than 150 viral infections from clinical nasopharyngeal swabs representing 8 of 12 viral families targeted, including 27 co-infections and multiple viruses missed by current clinical testing. Concordance of viruses detected with clinical PCR testing is >90%, and importantly this targeted RNA sequencing approach can be successfully conducted on very low quantities (<5 ng) of poor quality RNA (RIN <1.0) in a rapid (~72 hours) and low cost manner.

CONCLUSIONS: Evaluation of viral pathogens by targeted RNA sequencing provides important information about clinical viral isolates currently not detected by clinical testing that may impact clinical severity of illness and inform clinical management.
Comparison of Different Protocols for the Induction of Experimental Allergic Rhinitis Mice

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RATIONALE: Experimental models of allergic rhinitis using different protocols were compared.

METHODS: BALB/c mice group 1 were intraperitoneally (i.p.) sensitized with 25 μg/mouse of ovalbumin (OVA) together with Al(OH)3 three times in four week intervals and challenged by 12 intranasal applications (INAs) with 25 mg/mL OVA on consecutive days. Group 2 mice - same protocol with 50 mg/mL. Group 3 mice - OVA by INAs (12 days) with 25 mg/mL and in a two week interval with OVA by two series of INAs (25 mg/mL) during 12 days. Group 4 mice were sham sensitized (i.p.) and challenged by INAs with PBS. After the last challenge sneezing was counted for 5 min. Hyper-responsiveness to methacholine was measured and nasal tissues were removed for histology. Serum anti-OVA IgE, IgG1, IgG2a antibodies were detected by ELISA.

RESULTS: Group 1 showed maximum sneezing. Highest anti-OVA IgE was observed in groups 1 and 2. Highest levels of anti-OVA IgG1 were observed after the third sensitization in group 3. The level of anti-OVA IgG1 was very high in groups 1, 2, 3. Anti-OVA IgG2a had significantly increase in Groups 1, 2, 3. AHR in groups 2 and 3 was significantly higher than group 4. Mild histological changes were found in group 3, moderate in group 1 and severe in group 2.

CONCLUSIONS: i.p. allergen injections together with adjuvant and intranasal allergen challenge with 25 μg/mouse of allergen is the most appropriate for induction of mouse model of allergic rhinitis.

A Three Part Over the Counter Intervention Induces Remission or Improvement in Chronic Oropharyngeal Candidiasis

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RATIONALE: Oropharyngeal candidiasis is a painful condition with frequent relapses. Antibiotic containing oral products may be a risk factor favoring Candida over other species.

METHODS: In 8 patients with oropharyngeal candidiasis demonstrated by physical examination or direct laryngoscopy, we assessed use of antibiotic containing oral care products, inhaled corticosteroids, systemic antibiotics, and the presence of immune suppression. We then discontinued antibiotic containing oral care products, added daily liquid probiotic antibiotics, and the presence of immune suppression. We then discontinued antibiotic containing oral care products in 8 patients with oropharyngeal candidiasis demonstrated by physical examination or direct laryngoscopy, we assessed use of antibiotic containing oral care products, added daily liquid probiotic antibiotics, and the presence of immune suppression. We then discontinued antibiotic containing oral care products, added daily liquid probiotic antibiotics, and the presence of immune suppression. We then discontinued antibiotic containing oral care products, added daily liquid probiotic antibiotics, and the presence of immune suppression.

RESULTS: Antibiotic containing toothpaste use was present in 100% of our cases, with triclosan being the most common antibiotic (88%). Use of inhaled corticosteroids (50%), immune suppression (25%) and recent systemic antibiotic use (25%) were also common. 50% of patients achieved resolution of oropharyngeal candidiasis by intervention alone and 50% achieved remission with addition of antifungal medication. 100% reported symptomatic reduction with the intervention. Continuing the intervention, 4 out of 8 patients were able to tolerate subsequent oral antibiotic exposure without recurrence of oropharyngeal candidiasis, 1 had symptoms return with lower severity, and 3 have not yet required antibiotics. Importantly, two patients who had lived with >2 years of persistent daily candidiasis achieved remission without antifungal treatment.

CONCLUSIONS: Use of antibiotic containing oral care products is common in patients with oropharyngeal candidiasis. Cessation of antibiotic containing oral care products along with addition of probiotic kefir yogurt and rinses with dilute baking soda helps achieve remission or symptom reduction.
Alterations in the Gut Microbiome of Patients with Food Allergy

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RATIONALE: Alterations in the diversity and composition of the human gut microbiota have been observed in patients with atopic diseases. We explored the association of the gut microbiome with food allergy (FA) in the pediatric population.

METHODS: 12.5 ng of isolated DNA from fecal samples from 29 children with FA (peanut, milk, and/or egg allergy) and 10 healthy, non-atopic controls (C) were amplified using primers specifically for the V3-V4 region of the 16S rRNA gene which is unique to bacteria. The Mann-Whitney U-test was used for comparison of continuous variables between the two groups. All analyses were carried out using SAS V9.3.

RESULTS: FA and C subjects both had a median age of four years. The phylogenetic differences showed that an increased proportion of Actinobacteria when compared to C (median=1.4% vs 0.55%; p=0.04). Actinobacteria class was more abundant in subjects with FA compared to C (median=1.4% vs. 0.28%; p<0.02). At the family level, Alcaligenaceae was significantly less abundant in subjects with FA (median=0% vs. 0.63%; p<0.01) while Bifidobacteriaceae was significantly more abundant in subjects with FA (median=1.11% vs. 0%; p<0.02). Sixteen genera were identified in C while 21 genera were identified in patients with FA.

CONCLUSIONS: Differences in the gut microbiome in children with food allergy and healthy controls exist and may contribute to the pathogenesis of food allergy or be an association due to other factors. Further studies with larger sample sizes are needed to clarify these observations.

Th17/Treg Disregulation in Allergic Asthmatic Children Is Associated with Elevated Notch Expression

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RATIONALE: Notch signaling pathway is critically involved in the differentiation of T helper (Th) cells, key players in the pathogenesis of allergic diseases. We hypothesized that in children with allergic asthma, there is dysregulation of Th17 and Treg cells in peripheral blood. Furthermore, such change may be mediated by overexpression of Notch. METHODS: Thirty-five patients with allergic asthma and thirty-five healthy control children were selected. Asthma was diagnosed according to the criteria of Global Initiative for Asthma (GINA). Their allergy status was confirmed by the presence of dust mite specific IgE via ImmunoCAP. Peripheral blood mononuclear cells (PBMC) were obtained from study and control groups. Flow cytometry was used to detect Th17 and Treg cells using specific antibodies (CD4, CD25, Foxp3 and IL-17A). Quantitative real-time polymerase chain reaction (QRT-PCR) was used to measure the expression of Notch1 mRNA. The correlations among Notch1 mRNA expression, the percentage of Th17 cells, and Th17/Treg ratio were calculated.

RESULTS: Th17 and Treg cells were significantly increased and decreased, respectively, in children with allergic asthma than in healthy control (P<0.01). At the same time, mRNA level of Notch1 was elevated in children with allergic asthma compared to healthy controls (P<0.01). The mRNA expression of Notch1 was positively correlated with the percentage of Th17 cells (r=0.775, P<0.01) and Th17/Treg ratio (r=0.698, P<0.01).

CONCLUSIONS: Children with allergic asthma showed dysregulation of Th17/Treg cells in peripheral blood. Such change is accompanied with overexpression of Notch1, indicating the role of Notch signaling pathway in allergic asthma of children.

The Effect of Age on Airway Inflammation in Older Versus Younger Patients with Asthma

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RATIONALE: Although older patients (>60 years) with asthma suffer increased morbidity and mortality, the characteristics of airway inflammation in this population are not well established to explain these differences.

METHODS: To compare airway inflammation in young (20 to 40 years of age) vs older patients with asthma, induced sputum from younger (n=39) and older (n=36) inner-city asthmatics was collected and accessed for cell count differentials, Treg cells and cytokine protein expression. To control for the effect of aging itself, which, by itself, may be associated with increased systemic inflammation, sputum was collected from younger (n=23) and older (n=19) non-asthma subjects as well. Asthma history and health-care utilization, current medications, degree of airflow obstruction and reversibility, asthma control (ACT), asthma-related quality of life (mini-AQLQ), atopy, and co-morbidities were obtained.

RESULTS: Older asthmatics had significantly elevated sputum neutrophils (23.4±5% vs. 11±2.5%, p<0.001), eosinophils (8.3±1.9% vs.3.4±2.01%, p=0.02), IL-6, TNF-α, GM-CSF, IL-1β, IL-27, and increased Treg cells (CD3+CD4+Foxp3+CD127low) (12.4% vs 9.89, p=0.2) compared to younger patients with asthma.

CONCLUSIONS: These findings indicate that the pattern of airway inflammation in asthma is different in older patients, and is a pattern typically associated with a decreased responsive to inhaled corticosteroids. This data may possibly explain a greater risk for morbidity and mortality in older patients with asthma and further point to the need to identify treatments directed towards the characteristics of inflammation seen in this age group.
899 Eosinophilia-Associated Coronary Artery Vasospasm in Patients with Aspirin-Exacerbated Respiratory Disease

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RATIONALE: Eosinophilia is known to be associated with coronary artery vasospasm that does not respond to conventional vasodilator treatment but does respond to eosinophil-suppressing treatment. The prevalence of eosinophilia-associated coronary vasospasm in patients with aspirin-exacerbated respiratory disease (AERD), an inflammatory disease characterized by blood and respiratory tissue eosinophilia, is unknown. We observed that some patients with AERD report angina-type chest pain that responds to corticosteroid therapy. We sought to understand the cause of and determine the most appropriate treatment for such chest pain.

METHODS: A retrospective chart review of patients with AERD followed at Brigham and Women’s Hospital was performed. Patients who reported chest pain were assessed for presence of cardiac risk factors, eosinophilia, and chest pain response to conventional and unconventional treatments.

RESULTS: One hundred fifty three patients were reviewed: 10 had a history of angina-like chest pain. Eight of the 10 patients had undergone aspirin desensitization and initiated high-dose aspirin; of those, 6 reported an increase in the frequency or severity of chest pain while on high-dose aspirin with improvement after aspirin discontinuation or dose reduction. Most patients had no traditional cardiac risk factors but did have significant eosinophilia. Their chest pain did not improve with typical anti-anginal treatments but did respond to corticosteroid therapy.

CONCLUSIONS: Though uncommon, patients with AERD can develop eosinophilia-associated coronary artery vasospasm, which is occasionally worsened by high-dose aspirin. AERD patients who present with chest pain, particularly if they are on high-dose aspirin, should be screened for eosinophilia as early treatment with corticosteroids could be life saving.

900 Airway but Not Blood Type 2 Innate Lymphoid Cells (ILC2s) from Asthmatic Patients Are Steroid-Resistant, Which Is Induced By IL7R-Alpha Ligands

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RATIONALE: The ILC2 is a new type 2 immune cell. We previously reported that the ILC2 frequency was increased in the airways in asthma. Its response to steroids is unknown.

METHODS: ILC2s were isolated from bronchoalveolar lavage and blood from asthmatic patients and disease controls and analyzed by flow cytometry and ELISA as described previously (Christianson et al, JACI 136:59; 2015).

RESULTS: Culture of human blood ILC2s (lin-CRTH2+IL7Rα+) from asthmatic patients with dexamethasone (dex) (10^{-7}M) inhibited IL5+ILC2s by 77±12% (N=16). In contrast, culture of BAL cells with dex inhibited IL5+ILC2s by only 21±14% (N=10) suggesting a relative steroid resistance. Two IL7Rα ligands–IL7 and TSLP induced steroid resistance in IL5+ILC2s in vitro. In contrast, IL2-, IL25- and IL33-treated ILC2s remained steroid sensitive. Dex increased IL7Rα expression by 171±16% in ILC2s and reduced the threshold for IL7- and TSLP-induced STAT5 activation by half. IL7 and TSLP increased the expression of PLZF (ZBTB16), a transcriptional repressor/activator. Both STAT5 and PLZF are known to interact with the glucocorticoid receptor and block its nuclear function. We observed sustained STAT5 phosphorylation in IL7/TSLP but not IL2/IL33-stimulated ILC2s. Inhibition of STAT5 by Tofacitinib reversed steroid resistances of ILC2s. TSLP was elevated in BAL from select asthmatic patients, which negatively correlated (r=-0.62) with dex-inhibition of BAL IL5+ILC2.

CONCLUSIONS: Airway but not blood ILC2s from asthmatic patients are relatively steroid-resistant, which is induced by IL7 and TSLP, and is mediated by sustained STAT5 signaling and heightened PLZF expression. STAT5 inhibitors and anti-IL7/TSLP modalities are likely to benefit steroid-resistant asthma.

901 Mast Cell-Derived PAI-1 Promotes Airway Inflammation and Remodeling in a Murine Model of Asthma*****

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RATIONALE: We previously reported that plasminogen activator inhibitor-1 (PAI-1) promotes airway remodeling in a murine model of asthma and mast cells (MCs) are an important source of PAI-1 in asthmatic airways. In this study, we hypothesized that MC-derived PAI-1 plays a major role in airway remodeling.

METHODS: MC-deficient C57BL/6J-Kitw-sh/w-sh mice reconstituted with bone marrow cultured MCs (BMMCcs) from PAI-1−/− and wild type (WT) mice. These mice were sensitized and challenged with ovalbumin (OVA) or phosphate buffer saline (PBS) exposure for 4 weeks. Airway hyperreactivity was measured by a whole body plethysmography after the final OVA challenge. After sacrificing the mice, bronchoalveolar lavage fluids (BALF) and lung tissues were collected. Tissues were embedded in paraffin, sectioned, and processed with H&E, PAS and trichrome staining.

RESULTS: The numbers of total inflammatory cells and eosinophils in BALF from PAI-1−/− BMMC-reconstituted Kitw-sh/w-sh mice were significantly decreased compared with those from WT BMMC-reconstituted Kitw-sh/w-sh mice following OVA challenge (12.26±4.00 vs 25.06±10.42, p<0.01 and 1.44±0.80 vs 3.10±0.69, p<0.01, respectively). In addition, PAI-1−/− BMMC-reconstituted Kitw-sh/w-sh mice showed decreased goblet cell hyperplasia and peribronchial collagen deposition compared with WT BMMC-reconstituted Kitw-sh/w-sh mice following OVA challenge. Airway hyperresponsiveness of PAI-1−/− BMMC-reconstituted Kitw-sh/w-sh mice was significantly decreased compared to that of WT BMMC-reconstituted Kitw-sh/w-sh mice with OVA challenge.

CONCLUSIONS: This study demonstrates that MC-derived PAI-1 promotes airway inflammation, goblet cell hyperplasia and peribronchial collagen deposition in a murine model of asthma, suggesting MC as a major source of PAI-1 and MC-derived PAI-1 as a novel therapeutic target for airway remodeling in asthma.
Predicting Optimal Timing of Halting IVIG Therapy after HSCT for SCID

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RATIONALE: Significant practice variation suggests the optimal approach to halting antibody replacement after hematopoietic stem cell transplantation (HSCT) for severe combined immunodeficiency (SCID) is currently undefined.

METHODS: We retrospectively studied all patients undergoing HSCT for SCID at our center between 1995 and 2014 with thorough B cell flow cytometric analyses. B cell subsets, humoral immunity and engraftment were compared between patients who successfully discontinued IVIG on first attempt and those who failed.

RESULTS: Of 21 eligible patients, 20 remain alive (follow up range 0.7 to 32 years). Ten patients stopped IVIG successfully on first attempt, while 6 failed (3 were subsequently successful). 5 patients never trialed off IVIG. The 10 successful transitions on initial halt had higher IgM than the six who failed in the 9 months prior to halting IVIG or 3 months after halting. Patients who failed in the 9 months prior to halting IVIG or 3 months after halting had lower switched-memory B cells (SwBm) or IgA levels. Patients who failed in the 9 months prior to halting IVIG or 3 months after halting had lower switched-memory B cells (SwBm) or IgA levels.

CONCLUSIONS: The 10 successful transitioners on initial halt had higher IgM than the six failed (3 were subsequently successful). 5 patients never trialed off IVIG. The 10 successful transitions on initial halt had higher IgM than the six who failed in the 9 months prior to halting IVIG or 3 months after halting, without higher switched-memory B cells (SwBm) or IgA levels. Patients able to remain off IVIG trended towards higher SwBm and IgM at 18 months (both p = 0.07), with significantly higher SwBm, IgM, and B cell engraftment 5+ years post transplant (n = 13, p = 0.006, 0.007 and 0.04 respectively). Nine patients currently receive IVIG: 4 with X-SCID, one each with Artemis and JAK3.

Use of Rabies Virus Vaccine As a Neoaantigen to Evaluate Humoral Immune Function in Patients with Primary Immunodeficiency Disorders Receiving Immunoglobulin Replacement Therapy

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RATIONALE: Rabies virus vaccine has been proposed for evaluation of specific antibody response in patients with primary immunodeficiency disorders (PIDs), especially in the setting of intravenous immunoglobulin (IVIG) replacement therapy. More data are needed to define the appropriate protocol and safety of the test.

METHODS: We investigated specific antibody response to rabies immunization in 11 patients with predominate antibody deficiency and combined immunodeficiency disorders, compared to 9 healthy controls. All participants received Purified Vero Cell Vaccine 0.5 ml intramuscular regimen on day 0, 3, 7 and 14. Rabies neutralizing antibody(RNab) titers were measured at day 0, 14 and 28 after vaccination.

RESULTS: The geometric mean titers of RNab in PIDs patients were significantly lower than healthy controls at day 14 (1.19 IU/mL, range 0–6.16 IU/mL) vs 4.75 IU/mL (range 2.18-19.15); p = 0.03) and day 28 (2.09 IU/mL range 0–10) vs 10 IU/mL(range 2.19–24.84); p = 0.03). Most patients had RNab titers above 0.5 IU/mL(acceptable protective level) by day 14 after vaccination, except patients with X-linked agammaglobulinemia. There was no adverse event associated with vaccine administration.

CONCLUSIONS: We propose the protocol using rabies vaccine as a neoaantigen to evaluate humoral immune function in PIDs patients receiving IVIG. The protocol used in our study is safe and elicits antibody response that can discriminate between healthy subjects and those with PIDs on day 14 and more obviously on day 28.
905 Outcomes for Umbilical Cord Blood Transplantation in Severe Combined Immunodeficiency Disorders: Ten-Year Experience

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RATIONALE: Severe combined immune deficiency (SCID) is a lethal disorder of infants. Patients who undergo genotypic HLA-matched bone marrow transplantation have improved survival. Some patients are unable to find a suitable donor and may undergo umbilical cord blood transplantation (UCBT).

METHODS: A retrospective chart review was performed on the 10 patients with SCID who underwent UCBT between 1996-2005 at Cardinal Glennon Children’s Medical Center at Saint Louis University. We analyzed patient survival as well as T-cell, B-cell, NK-cell subsets and function, and infections prior to and post-transplant at months 3, 6, 12, 24, 60 and 120.

RESULTS: Eight of ten patients were alive 10 years post-transplantation. One patient died 19 days after transplant from cardiac arrhythmia and presumed cardiomyopathy. The other patient died 32 days after transplant from graft versus host disease of the gut and adenovirus sepsis. Immune studies for the cohort prior to UCBT had mean Absolute Lymphocyte Count (ALC) of 1634/mm^3; CD3+ 15.3%, 784 cells/mm^3; CD4+ 12%, 497 cells/mm^3; CD8+ 8.7%, 300 cells/mm^3; CD20+ 4.3%, 515 cells/mm^3 and CD56+ 19.6%, 239 cells/mm^3. Immune studies 10 years after UCBT had mean ALC of 2603/mm^3; CD3+ 70.3%, 1797 cells/mm^3; CD4+ 41%, 1042 cells/mm^3; CD8+ 27.6%, 718 cells/mm^3; CD20+ 11.5%, 383 cells/mm^3 and CD56+ 13.9%, 364 cells/mm^3. Immune reconstitution.

CONCLUSIONS: Patients with SCID who do not have a suitable bone marrow donor and undergo unrelated UCBT have good and sustained immune reconstitution.

906 Newborn Screening for Severe Combined Immune Deficiency with T Cell Receptor Excision Circle Assay in Mississippi 2012 – 2014

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RATIONALE: Severe combined immunodeficiency (SCID) is a life-threatening genetic disorder with severe deficiency of T-cells. SCID patients have severe viral, fungal and bacterial infections early in life, and is fatal by 1-2 years of life if not treated. Hematopoietic stem cell transplantation is most successful for SCID prior to 3.5 months of age. Early detection and treatment of SCID is imperative to prevent mortality.

METHODS: The state of MS began newborn screening (NBS) for SCID on all newborns in January 2012. Standard heel-stick blood Guthrie cards are used to measure T cell receptor excision circles (TRECs) by real-time polymerase chain reaction (PCR). Real time quantitative PCR assay for human beta actin gene was also used to monitor the integrity of the sample and the success of DNA extraction. All patients with presumptive positive screens were sent for immunologic testing. We report the results for the first 3 years of SCID screening in MS.

RESULTS: In 2012, 37,613 newborns were screened for SCID; 4 had presumptive positive screens, and 1 had SCID. In 2013, 38,696 newborns were screened for SCID; 7 screens were presumptive positive, and 1 patient had SCID. For 2014, 37,828 infants were screened for SCID; 7 had presumptive positive screens, and 2 (fraternal twins) had SCID. The present incidence of SCID in Mississippi is approximately 1 out of 28,500.

CONCLUSIONS: With NBS, we now know the incidence of SCID is more common than previously reported. Incidence of SCID in MS is higher than the national average of 1.58,000 found by newborn screening.

907 Eosinophil Mediators in Nasal Washes Obtained during Experimental Infections with Rhinovirus-16 in Subjects with and without Asthma

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RATIONALE: Rhinovirus (RV) infections frequently cause asthma exacerbations in children and young adults. Mechanisms, including the capacity of RV to stimulate Th2 related responses, remain unclear.

METHODS: Twelve subjects (ages 19-33) were inoculated with RV 16 (dose = 300 TCID_50). They included 7 allergic-asthmatics (AA; total IgE levels 596-1989 IU/mL), and 5 non-atopic controls without asthma (total IgE levels 5 to 42 IU/mL). Eosinophil mediators (ECF [Phadia AB] and EDN [MBL International Corporation]) were measured by ELISA in nasal washes (NW’s) obtained before and during the infection. The results were analyzed in relation to symptoms.

RESULTS: Both ECP and EDN peaked by day 3, paralleling cold symptoms over the first 4 days of the infection. Cumulative values derived from morning NWs during the first four days were significantly higher among AA subjects than controls (ECP: GM = 416 ng/mL and 16.8 ng/mL, respectively, p < 0.05; EDN: GM = 1320 ng/mL and 260.6 ng/mL, respectively, p < 0.05). Compared to baseline values (determined before inoculation), mediator values in NW’s increased 20-fold for ECP and 16.6-fold for EDN by day 3 in the AA subjects. By comparison, ECP and EDN levels increased 2.6-fold and 4.7-fold, respectively, among controls.

CONCLUSIONS: The increase in eosinophil mediators (ECP and EDN) in nasal washes after RV inoculation was significantly greater in the allergic asthmatics than controls, but the results indicate that RV may also have the capacity to stimulate a Th2 related eosinophil response in the non-allergic, non-asthmatic host.
908 Tracking and Characterizing Human B-Cell Responses in Rhinovirus Infection

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Rationale: Human rhinoviruses (RV) account for 31 million estimated cases of the common cold per year within the US, and trigger disease exacerbations in allergic asthmatics. Adaptive immunity to RV does not provide durable protection owing partly to considerable diversity of RV strains. Here we describe circulating lymphocytes in the context of RV infection, exploring factors that determine the quality of the humoral response.

Methods: Mass cytometry was used to capture fluctuations in discrete B-cell populations during an experimental RV-16 infection in allergic asthmatics. The findings were used to inform the design of an antigen-specific fluorescence-based flow cytometry panel in order to further interrogate the B-cell compartment in relation to RV infection.

Results: B-cell antigen-specificity was validated in blood from control subjects and atopicus using fluorescent tetramers of tetanus toxoid and Der p 1, respectively. We readily identified naïve B-cells (IgD+), plasmablasts (CD20-, CD38+), and 2 discrete memory populations that differentially expressed the follicular-homing marker, CXCR5. Whereas CXCR5-memory cells expressed CD27 and diverse isotypes, their CXCR5-counterparts were CD27lo, expressed the transcription factor T-bet, and lacked IgM. This latter phenotype disappeared from the blood in conjunction with memory T-cells during the acute phase of RV infection, while plasmablasts that primarily expressed IgA were expanded.

Conclusions: Our findings are consistent with the presence of pre-existing memory B-cells that are poised for reactivation by cognate antigen stimulation, potentially with or without T-cell help. Further work is necessary to determine the B-cell mechanisms that promote virus-neutralizing activity, including how T-cells might instruct the protective-ness of antibodies produced.

909 Induction of Airway BAFF during Upper Respiratory Infections in Patients with Asthma

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Rationale: Epithelial cells produce B-cell activating factor of the TNF family (BAFF) upon interferon stimulation. BAFF promotes B cell development and antibody production. We hypothesized that BAFF increases in airways during upper respiratory infections (URI) and may vary among patients with asthma (AS), allergic rhinitis (AR), and healthy controls (HC).

Methods: Nasal lavages and induced sputum supernatants were collected from AS, AR, and HC patients on days 2 (range 1-3) and 6 (5-7) during URI and at baseline >42 days later. BAFF was measured using ELISA kits.

Results: 70 subjects (mean±SD age 34.4±10.6 years, 71% females). 66% AS, 16% AR, and 18% HC had URI caused mostly by HRV (44%) and CoV (13%). No virus was detected in 24% of URI. Compared to baseline, nasal BAFF increased on day 2 (mean±SE=113±13 vs 83±7pg/ml,p=0.015), but not on day 6 (97±6 vs 93±5 pg/ml,p=0.56) versus baseline in all subjects. The increase on day 2 was similar in AS subjects and controls (AR+HC) (31.2±16 vs 28.5±16,p=0.35). Nasal BAFF on day 2 in all subjects correlated inversely with cold symptom severity (r=-0.30,p=0.046). Sputum BAFF was detectable in only 29% of samples. With low power, we found no significance in the increases during URI (Day 2 x baseline: 43±27 vs 5±3, p=0.18) in all subjects, or between AS vs controls on day 2: (35±19 vs 6±3,p=0.15). In AS subjects, nasal BAFF on day 2 was non-significantly inversely correlated to severity of chest symptoms (r=-0.29, p=0.22).

Conclusions: Nasal BAFF, a reflection of interferon response, increases during URI and correlates with less severe airway symptoms.
911 Rapid Quantification of Juniperus Pollen Proves Overlapping Pollen Seasons

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RATIONALE: Microscopic analysis of air samples fails to determine the pollen season overlap between various species with morphologically similar pollen such as members of the Cupressaceae and Poaceae. Previously, we showed it was possible to use PCR to identify Juniperus ashei pollen from air samples. The present study was undertaken to determine if qPCR could be used to determine airborne pollen counts for three Junipers species and define the pollen season overlap.

METHODS: The atmosphere in Tulsa, OK(USA) was monitored with a Burkard sampler and analyzed by microscopy using standard methods. A second Burkard sampler was used from 2013 to 2015 for molecular analysis; 109 samples were tested with species-specific primers and probes designed for J.ashei, J.pinchnotii and J.virginiana. Numbers of pollen grains obtained from microscopy were compared with numbers obtained from qPCR by Spearman correlation coefficient.

RESULTS: Cupressaceae pollen was detected in the Tulsa atmosphere from October through April. The qPCR counts for total Juniperus pollen showed a significant correlation with the microscope counts, R=0.92, p<0.001. Quantitative PCR data showed overlapping pollen seasons. In the fall, the data indicated five days (in two years) with both J.pinchnotii and J.ashei pollen. Similarly, in January and February eight days (in two years) indicated both J.ashei and J.virginiana pollen in the air.

CONCLUSIONS: This approach is a rapid method to identify and quantify specific pollen types and the pollen season overlap where species and genera cannot be distinguished by microscopy. Defining the exact pollen season will be a benefit for patients sensitive to pollen from specific taxa.

912 11q13 Is an Allergic Risk-Locus That Increases EoE Risk and Increases LRRC32 Expression

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RATIONALE: Eosinophilic esophagitis (EoE) is an antigen driven Th2-mediated inflammatory disease. We previously demonstrated the presence of IL-9+ eosinophils and T cells in the pediatric EoE esophagus. Group 2 innate lymphoid cells (ILC2s) are activated by IL-9 to produce IL-5 and IL-13. As IL-9+ eosinophils and T cells in the pediatric EoE esophagus. Group 2 innate lymphoid cells (ILC2s) are activated by IL-9 to produce IL-5 and IL-13. As IL-13 treatment showed a significant correlation with the microscope counts, R=0.92, p<0.001. Quantitative PCR data showed overlapping pollen seasons. In the fall, the data indicated five days (in two years) with both J.pinchnotii and J.ashei pollen. Similarly, in January and February eight days (in two years) indicated both J.ashei and J.virginiana pollen in the air.

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CONCLUSIONS: This approach is a rapid method to identify and quantify specific pollen types and the pollen season overlap where species and genera cannot be distinguished by microscopy. Defining the exact pollen season will be a benefit for patients sensitive to pollen from specific taxa.

913 Group 2 Innate Lymphoid Cells and IL-9 Receptor Are Increased in Active Eosinophilic Esophagitis

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RATIONALE: Eosinophilic esophagitis (EoE) is an antigen driven Th2-mediated inflammatory disease. We previously demonstrated the presence of IL-9+ eosinophils and T cells in the pediatric EoE esophagus. Group 2 innate lymphoid cells (ILC2s) are activated by IL-9 to produce IL-5 and IL-13. As IL-5 and IL-13 are key regulators of EoE and abundantly expressed by ILC2s, we hypothesized that IL-9 and ILC2s are important in EoE pathogenesis.

METHODS: Flow cytometry and immunohistochemistry experiments were performed to determine the level of IL-9 receptor (IL-9R) expression and numbers of ILC2s in proven pediatric EoE biopsies. ILC2s were identified as CD45(+) Lineage(-) CRTH2(+) lymphocytes. Active disease was identified as eosinophilic biopsies with >15 eos/hpf despite proton pump inhibitor treatment. Eosinophilic submucosal lymphoid aggregates were isolated from normal organ donors and used in vitro to assess the effects of IL-9 on ILC2s.

RESULTS: Flow cytometric analysis of EoE biopsies revealed higher levels of ILC2s in biopsies from patients with active disease compared to inactive disease (0.20% ± 0.15 vs. 0.04% ± 0.04, p=0.005). Active EoE biopsies had increased IL9R high-positive cells compared to inactive biopsies using immunohistochemistry and image analysis (n=22, p=0.002) and eosinophilic ILC2s from EoE subjects displayed decreased IL-9R expression. Additionally, lymphoid aggregates were capable of responding to IL-9 with increases in ILC2s following treatment with IL-2 and IL-9 in vitro as compared with isolated IL-2 treatment (81.2 ± 9.4 vs 323.8 ± 27.4 cells per well, p<0.0001).

CONCLUSIONS: Our data supports that IL-9 may play a mechanistic role in EoE pathogenesis, possibly through expansion of ILC2s.
Loss of SPINK7 in Esophageal Epithelial Cells Unleashes a Pro-Inflammatory Response Characterized By Excessive Cytokine Production and Loss of Barrier Function

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Rationale: The serine peptidase inhibitor kazal-type 7 (SPINK7) is markedly down-regulated in eosinophilic esophagitis (EoE), an inflammatory TH2 type immune disease of the esophagus. We hypothesized that SPINK7 has a key role in the propagation of EoE.

Methods: We used an in vitro system of human esophageal epithelial cells that were subjected to air-liquid interface (ALI) to induce squamous cell differentiation. Cells were stably transduced with either non-silencing control or SPINK7 shRNAs. The integrity of the epithelium was examined by barrier function assays complemented by histological and ultrastructural analyses and immune-fluorescence of junctional proteins. Protease activity, transcriptional alterations and identification SPINK7's downstream targets were assessed. Last, cytokines and chemokines secretion was analyzed after SPINK7 gene silencing.

Results: We determined that depletion of SPINK7 results in transcriptional alterations including down-regulation of other SPINKs and unleashes trypsin-like serine protease activity. In vitro, SPINK7 inhibits the serine protease-kallikrein 5 that is known to be involved in the regulation of the skin barrier. Furthermore, we demonstrated that SPINK7 gene silencing is sufficient for induction of architectural alterations in junctional complexes and a profound loss of the “zipper-like” structures in between the epithelial cells that characterize the healthy esophageal epithelium and is missing in EoE. These alterations followed by impaired barrier function. In addition, loss of SPINK7 induces a series of pro-inflammatory cytokines and Chemokines.

Conclusions: We suggest that deficiency of SPINK7 results in uncontrolled proteases activity which is a novel checkpoint for regulating pro-inflammatory esophageal epithelial responses.

Eosinophilic Esophagitis Is a Trait of Netherton Syndrome

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Rationale: Netherton syndrome (NS) is a rare autosomal recessive skin disease due to loss of LEKTI, a protein expressed in stratified epithelia, with severe skin inflammation and constant allergic manifestations. This study assessed whether eosinophilic esophagitis (EoE) could occur during NS.

Methods: Routine upper gastrointestinal endoscopies with systematic biopsies of the proximal, medial and distal esophagus were performed and analyzed in 9 patients (4 girls, 5 boys; median age 5.6 [1-15] years) with digestive manifestations and characteristic NS. Standard stains and LEKTI immunostaining (using a monoclonal antibody specific for LEKTI, Santa Cruz Biotechnology) were performed on esophageal samples, in NS and non NS-control patients: 5 with EoE and 10 without EoE. According to international consensus, diagnosis of EoE was affirmed when >15 eosinophils/HPF were present in at least one sample. Patients are followed in the referral centre MAGEC, Necker-Enfants Malades Hospital (Paris, France) and included in the French cohort of allergic patients (Arsene, French Health Minister registry DC-2009-955), implying parents written consent.

Results: EoE was found in 4/9 (44%) NS patients. Among the 5 NS patients without EoE, all but one patient were systematically fed with the conventional “6-food” elimination diet (SFED) used in EoE treatment strategy. Esophageal LEKTI immunoreactivity was negative in 8/9 (89%) NS patients, contrasting with positivity in all control patients (with or without EoE).

Conclusions: EoE appears to be a major feature of NS. Further research is needed to try to prevent the development of EoE in NS patients.
917 Dimer Levels May Identify Chronic Urticaria Patients Who Would More Likely Fail H2 Blockers or Omalizumab

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RATIONALE: Several studies support that activation of the extrinsic coagulation pathway occurs in patients with chronic urticaria (CU). It has been suggested that elevated plasma levels of D-dimer may also correlate to the clinical severity of CU. Our purpose was to determine whether or not plasma D-dimer should be studied as a marker for treatment failure to H2 blockers and/or omalizumab. Identifying patients who would likely fail the traditional initial line of therapies in the early stages of their presentation may advance them to the next line of therapies sooner, and spare them unnecessary treatments or prolonged disease activity.

METHODS: Six patients with chronic urticaria (by skin biopsy and clinical criteria) where studied; their response to antihistamines and omalizumab, as well as serum D-dimer levels (by ELISA) and other laboratories were recorded.

RESULTS: All but one of our CU patients who had failed both H2 blockers and omalizumab (n=6) had significant D-dimer elevation during a flare of their urticaria (mean = 2670 ng/mL, median = 3295 ng/mL, normal reference <600 ng/mL). Patients with CU but who responded to H2 antihistamines and/or to omalizumab, and who had D-dimer coincidently checked for other concerns during an urticarial flare (n=4), did not have elevations in D-dimer (mean = 336 ng/mL, median = 342 ng/mL).

CONCLUSIONS: Though CU patients with a normal D-dimer may also fail first line therapies, this study suggests that CU patients with significantly elevated D-dimer may be more likely to fail first line therapies, and that further study of D-dimer and other laboratory indicators of complement activation should be studied as markers for first line treatment failure in CU.

918 Sonographic Assessment of Optimal Needle Length for Epinephrine Autoinjectors in Infants and Toddlers

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RATIONALE: Epinephrine auto-injectors (EAI) represent the standard of care for the treatment of anaphylaxis. Injections are most effective if epinephrine is delivered intramuscularly, whereas intramuscular injection may be harmful. The current needle length for pediatric EAI is 12.7 mm, however, the ideal needle length for infants and toddlers weighing 7.5 to 15 kg is unknown.

METHODS: Infants and toddlers weighing 7.5-15 kg, recruited from two North American ambulatory allergy clinics underwent baseline and compression (10 pounds pressure) ultrasound of the anterolateral thigh to assess skin to bone (STBD) and skin to muscle distance (STMD) in short axis (transverse) approach.

RESULTS: In 53 infants (mean age 19.5 months, 54.7% male, 81.1% Caucasian, mean weight 11.0 kg, mean height 79.3 cm, mean BMI 19.0 kg/m^2) the mean baseline STBD was 22.8 mm (+/- 4.2) and the STMD was 8.2 mm (+/- 2.1). With 10 pounds compression, the mean STBD was 13.3 mm (+/- 2.1) and the STMD was 6.3 mm (+/- 1.2). A needle length of 12.7 mm would strike the bone in 43.1% of subjects during injection with 10 pounds compression in this population.

CONCLUSIONS: Our data suggest that the optimal needle length for an EAI for infants weighing 7.5 to 15kg should be shorter than the needle length in current, commercially available pediatric EAI, in order to avoid striking the bone and possible intramuscular injections.

919 Constitutive KIT Activity and IL-6 Production in Mast Cells Alters Levels of Reactive Oxygen Species (ROS) and the Scavenger Protein DJ-1 in Mastocytosis

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RATIONALE: Mastocytosis is characterized by hyperproliferation of mast cells (MCs) which is mostly associated with activating mutations in KIT, the stem cell factor (SCF) receptor. DJ-1, a scavenger protein of ROS in MCs and other tissue cells, has been linked to oxidative damage in atopic dermatitis, cancer and neurodegenerative diseases. We examined whether DJ-1 is dysregulated in indolent systemic mastocytosis (ISM) and the impact of KIT mutations on DJ-1 and ROS levels.

METHODS: Sera was collected from patients with ISM with tryptase ranging from 1-1000 ng/ml. P815 cells were injected i.v. into DBA/2 mice to induce SM. DJ-1 levels were measured by ELISA and ROS by a fluorescent assay.

RESULTS: Patients with ISM showed increased ROS and diminished DJ-1 levels in serum. DJ-1 but not ROS levels reverted towards normal values in patients with advanced ISM. Long-term exposure to SCF or expression of constitutively active mutant KIT in human MC cultures enhanced DJ-1 degradation. In contrast, IL-6, a cytokine which increases in serum with disease severity, induced DJ-1 transcription and promoted ROS release. Injection of mastocytoma cells harboring mutant KIT into mice reproduced the effects of human disease with biphasic changes in serum DJ-1 and increasing elevations in ROS and IL-6 as disease progressed. These effects and disease severity were reversed with anti-IL-6 receptor blocking antibody.

CONCLUSIONS: The link between IL-6 production in the context of aberrant KIT signaling to dysregulation of DJ-1 and ROS homeostasis suggests that IL-6 contributes to redox imbalance and worsening of ISM and provides potential targets for therapeutic intervention.
920 IgE-Mediated Atopic Dermatitis-like Skin Inflammation Is Downregulated By the Application of Allergen-Specific Monoclonal Antibody IgG1 Fab Fragments to the Skin

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RATIONALE: Antibody Fab fragments (Fabs) prepared by digestion with papain lack effector functions including mast cell degranulation due to the absence of the Fc portion. In the present study, we tested the hypothesis that the application of allergen-specific monoclonal antibody (mAb) IgG1 Fabs downregulated atopic dermatitis-like skin inflammation in mice.

METHODS: Balb/c mice sensitized by intraperitoneal injections of anti-ovalbumin (OVA) IgE mAbs on days 0, 1, 2, 7, 8, and 9 were challenged with OVA by its application to the skin on days 1, 2, 3, 8, 9, and 10. Anti-OVA IgG1 mAb (O1-10) Fabs were applied to the skin 30 min before the fourth to sixth challenges followed by measurement of clinical symptoms including erythema/hemorrhage, edema, scarring/dryness, and excoriation/erosion of the skin. Histological changes in the skin were also investigated.

RESULTS: Significantly increased clinical symptoms were observed during the third to sixth OVA challenges. The application of O1-10 Fabs to the skin resulted in marked suppression of all of the clinical symptoms. Intact O1-10 failed to affect the clinical symptoms. Histologically, epidermal thickness and neutrophil accumulation in the skin were decreased following the treatment with O1-10 Fabs. Furthermore, the suppression of the clinical symptoms by the O1-10 Fabs was associated with decreases in mast cells as well as IL-17A and IL-13 in the skin.

CONCLUSIONS: The present study demonstrates for the first time that the application of pathogenic allergen-specific IgG1 mAb Fabs to the skin appears to be effective in downregulating IgE-mediated atopic dermatitis-like skin inflammation.

921 Ibuprofen and Other Arylpropionic Acid Derivatives Can Be Responsible for Immediate Selective Responses to Sensitizers

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RATIONALE: Ibuprofen and other arylpropionic acid derivatives are the most commonly prescribed and consumed NSAIDs worldwide and very often it is available over the counter. Several studies indicate that they are progressively involved in hypersensitivity drug reactions that include those mediated by specific immunological mechanisms and those classically classified as cross-intolerance reactions. We present a series of cases with a selective response to ibuprofen and other arylpropionic derivatives confirmed by drug provocation tests (DPT).

METHODS: Subjects with hypersensitivity reactions to any arylpropionic acid derivatives were included in the study. A DPT was carried out to rule out cross-intolerance (non allergic hypersensitivity). Drug imputability was confirmed by DPT when after drug intake repetitive well defined episodes were reported. Serum tryptase was quantized by immunoassay and in the affected skin by immunohistochemistry and urine N-methyl histamine by immunoassay.

RESULTS: A total of 42 cases were classified as selective immediate responders. Ibuprofen was the drug most frequently involved, followed by naproxen and deskoprofen. Quantitation of trypstase levels in peripheral blood and skin biopsies and N-methyl histamine in urine were indicative of an IgE immediate selective response.

CONCLUSIONS: Arylpropionic acid derivatives are responsible for immediate allergic selective responses. Further studies are in progress for identifying the possible adducts (hapten-carrier complexes) implicated and the existence of cross-reactivity.

922 Anaphylaxis Preparedness Initiative for Allergen Immunotherapy – Implementation of a Policy for Carrying Autoinjectable Epinephrine

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RATIONALE: Subcutaneous immunotherapy (SCIT) is efficacious for allergic rhinitis and asthma. Due to the potential for severe and delayed systemic reactions (SR), we implemented a mandatory policy for all patients to carry autoinjectable epinephrine in association with receiving SCIT.

METHODS: A voluntary and anonymous survey was given to patients receiving SCIT. The survey included demographics and patient satisfaction questions, and used a 5-point Likert scale.

RESULTS: Over a 2-week period, 121 surveys were collected at three sites, accounting for 39% of inhalant immunotherapy patients; 61.9% were female, 38.1% were male, 45.3% were on build-up, 54.7% on maintenance. Median age was 39 years. Most patients (85%) agreed or strongly agreed that immunotherapy has been helpful, there was a difference in patients on build up (77.4%) compared to maintenance (92.2%), p=0.034. Most (72.4%) respondents agreed that the financial cost of an epinephrine autoinjector is worth the benefit of having it available in case of SR; there was a difference between patients on build-up (84.9%) vs. maintenance (61.9%), p=0.002. Only 19.6% of respondents agreed or strongly agreed that having epinephrine is not necessary for receiving SCIT, this differed in patients on build-up (13.2%) vs. maintenance (25%), p=0.19.

CONCLUSIONS: This study demonstrates the feasibility of implementing a universal policy for autoinjectable epinephrine in a large academic center. The majority of our patients receiving SCIT agree and have complied with the recommendation for having an epinephrine autoinjector, while continuing to receive SCIT.
923 Underutilization of Penicillin Skin Testing: A Call for Verifying Penicillin Allergy and Antibiotic Stewardship

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RATIONALE: Penicillin (PCN) allergy is the most commonly reported medication allergy, self-reported by approximately 10% of the United States (US) population. Historically, 80-90% of patients with PCN allergy history were not allergic using penicillin skin testing (PST). Over the last 20 years, incidence of negative PST has increased to 95-98%.

METHODS: A retrospective chart review at a 652-bed tertiary-care hospital from July 2011 to July 2014 was performed. Pre-Pen® orders in the electronic medical record were the trigger for inclusion. PST results were recorded for each patient.

RESULTS: 102 patients were referred, 88 were tested. 87 (98.9%) of patients had negative prick/puncture (PP) and intradermal testing (IDT). One had negative PP, but positive IDT. Fourteen were excluded; 6 refused testing, 1 was on antihistamines, 5 had no PST documentation, and 2 had no documented PCN allergy by history.

CONCLUSIONS: Almost all patients with PCN allergy history are not PCN allergic and tolerate beta-lactams well. Consequently, using broad-spectrum antibiotics that increase Vancomycin-Resistant Enterococci and Clostridium difficile infections, hospital length of stay and medical costs, in non-PST verified PCN allergy, is problematic.

Less than 0.1% of 25 million individuals with PCN allergy history undergo PST in the US annually. The public health implications are compelling and PST should be performed before instituting alternative antibiotic therapy for PCN-sensitive infections.

PST remains a sensitive and reliable test for true PCN allergy. Educating specialties outside of our field on PST will identify more individuals with inaccurate PCN allergy diagnoses, increase referrals, and play a critical role in antibiotic stewardship.

924 Health-Related Quality of Life Is Impaired in Families with Wheat Allergy Versus Grass Allergy

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RATIONALE: Allergic diseases generally impair the health related quality of life (HRQOL). No study has compared food allergy with respiratory allergy using the same generic instrument. The aim of this study was to compare the HRQOL between families with wheat allergic children and grass allergic children.

METHODS: Sixty-three children with wheat allergy (median age 5) and 72 children with grass allergy (median age 12) were included together with their parents. The Child Health Questionnaire (CHQ) was answered by the families during study visits.

RESULTS: Parents in the wheat group scored significantly lower for five items compared to parents in the grass group. These items were General behaviour (p<0.0001), General health perceptions (p=0.001), Parental Impact; Emotions (p=0.001), Parental Impact; Time (p<0.0001) and Family activities (p=0.001). The parents of the wheat group scored lower than the parents of the grass group for every item investigated except for Change in Health that scored significantly lower (p=0.020) by the grass group’s parents. Fifty-one grass allergic children answered the CHQ but only twenty-seven wheat allergic children, primarily due to low age. In the grass allergy group, children and parents reported similar scores on the different items. Poor parental-child correlation was observed in the wheat group.

CONCLUSIONS: Wheat allergy affected HRQOL more severely in families with wheat allergic children compared to grass allergy. Parent perception of the child’s HRQOL and child perceptions of HRQOL appeared to be comparatively consistent in families with grass allergy but less so in families with wheat allergy.

925 Socioeconomic Disparities in the Economic Impact of Childhood Food Allergy

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RATIONALE: The purpose of this study is to identify disparities in the economic burden of childhood food allergy. We test the hypothesis that direct medical and out-of-pocket costs of children with food allergy vary by socioeconomic characteristics of families.

METHODS: We analyzed cross-sectional survey data from 1,621 US caregivers with a food-allergic child collected between November 2011 and January 2012. We used a 2-part regression model to estimate mean costs and identified differences by levels of household income and race and ethnicity.

RESULTS: Children in the lowest income stratum spend two and one half times the amount on emergency department and hospitalization costs as a result of their food allergy than either of the other two income strata ($1,021, SE $228, SE $22) compared with the highest income stratum ($311, SE $94, p<0.05). Spending on specialists visits were lower in the lowest income stratum ($228, SE $22) compared with the highest income stratum ($311, SE $18, p<0.01). In terms of adjusted mean out-of-pocket costs, we found that increasing family income was significantly associated with increasing out-of-pocket medication costs ($171 lowest income stratum, SE $44, $366 highest income stratum, SE $94, p<0.001). African-American caregivers reported spending the lowest amount on direct medical and out-of-pocket costs, with average adjusted costs of $493 (SE $111) and $395 (SE $429), respectively.

CONCLUSIONS: Socioeconomic disparities exist in the economic impact of food allergy. Opportunities exist to mandate that life-saving medications are available more widely and to strengthen policy related to the management of food allergy in public spaces such as schools, parks, and restaurants.
926 Allergy Misconceptions Among Attending Physicians, Resident Physicians and Mid-Level Providers

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RATIONALITY: Although, allergic conditions are prevalent, misconceptions are common among physicians. This was recently confirmed in Ohio and Pennsylvania. All providers should have basic allergy knowledge in order to provide quality care. The objective of this study was to identify allergy knowledge gaps that exist at an academic medical center in Virginia.

METHODS: A survey was distributed via email and paper to attending physicians, resident physicians and mid-level providers from the pediatric, internal medicine, family practice, otolaryngology, general surgery and radiology departments. Response data was then entered into a database and analyzed.

RESULTS: Of the 464 surveys distributed, 359 were completed (77.4% response rate). The mean percentage correct was 32.12% or 3.13/9 questions (3.13 ± 1.72, 177). The means for pediatric and internal medicine providers were 3.26 and 2.84 respectively. 44.6% correctly identified epinephrine as the first line treatment for anaphylaxis. 8.9% of providers were aware that shellfish, iodine, and artificial dye allergies have no impact on imaging studies performed with radiocontrast. 32.40% and 35.19% of primary care providers incorrectly identified egg allergy as a contraindication to administration of MMR and Influenza vaccines respectively. 36.22% of providers answered at least 4 out of 9 questions correctly. Only 1 of the questions was answered correctly at a rate of above 45%. The correct response rate was lower than 40% for 4 out of 9 of the questions.

CONCLUSIONS: This study identified potentially harmful allergy knowledge deficits at our academic medical center similar to that found in Ohio and Pennsylvania.

927 Unified Airway Theory: Association of Bronchiectasis and Chronic Rhinosinusitis

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RATIONALE: Lower airway abnormalities other than asthma coexist with chronic rhinosinusitis (CRS); however, this association is not well studied. We investigated the association of bronchiectasis and asthma with CRS without nasal polyps (sNP) and CRS with nasal polyps (wNP), using asthmatics without CRS as a comparator.

METHODS: Patients with history of CRS with positive sinus CT and asthmatics without CRS were randomly identified via ICD-9 codes from Northwestern University’s data warehouse from 2002-2013. Chest CT scans were available in 187/516 (36%) patients with CRSsNP, 119/749 (16%) patients with CRSwNP and 288/316 (91%) asthmatics without CRS.

RESULTS: Bronchiectasis was present in 16% (16/101) of patients with CRSsNP without asthma, 5% (1/20) of patients with CRSwNP without asthma, 24% (21/86) of patients with CRSsNP and asthma, 14% (14/99) of patients with CRSwNP and asthma and 11% (31/288) of asthmatics alone (p<0.005, CRSsNP with asthma vs. asthmatics alone). There was a trend towards higher prevalence of bronchiectasis in CRSwNP with asthma compared to patients with CRSsNP and asthma (p=0.08). Radiographic sinus severity and prior sinus surgery did not correlate with the presence of bronchiectasis.

CONCLUSIONS: We observed a significantly higher prevalence of bronchiectasis in CRSsNP (16-24%) than in the general population (estimated at ~1%). Coexistence of asthma in both CRSsNP and CRSwNP increased the prevalence of bronchiectasis. Patients with CRSsNP and asthma together had considerably higher prevalence of bronchiectasis than asthmatics alone, which suggests that asthma and CRSsNP have an additive effect. This association of CRS with bronchiectasis supports the unified airway concept and has clinical implications.

928 A Novel Method of Measuring Nasal Specific IgE in Systemic and Local Allergic Rhinitis Patients

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RATIONALE: Several methods of measuring nasal specific IgE (sIgE) have been used with variable sensitivity/specificity and diagnostic value. We evaluated a novel method of detection of nasal sIgE in patients with allergic rhinitis (AR) and local allergic rhinitis (LAR) to D. pteronyssinus (DP).

METHODS: 12 AR (+ nasal allergen provocation test (NAPT), + skin testing/sIgE to DP), 12 LAR (+ NAPT, - skin testing/sIgE to DP) and 6 healthy controls (+NAPT, - skin testing/sIgE to DP) were recruited. DP-IgE ImmunoCAP solid phase was applied directly in the lower turbinate of each nostril for 10 minutes 24 hours after NAPT with DP and analyzed following the manufacturer’s instructions. ROC curve was performed to obtain the optimal cut-off point of nasal sIgE value to calculate sensitivity (S), specificity (SP), positive predictive value (PPV) and negative predictive value (NPV). Outcomes were compared with NAPT result (gold standard test). Study was approved by local ethics committee.

RESULTS: At 24 hours, all AR subjects had a positive sIgE determination (>0.35 kU/L) and were negative in all controls (mean sIgE control 0.04 kU/L, AR 6.2 kU/L, LAR 0.16 kU/L). ROC curves showed that 0.085 was the optimal cut-off point to discriminate LAR subjects from controls, with S 66.7% SP 83.3%, PPV 88.8% and NPV 55.5%, area under the curve (AUC) = 0.854. When this cut-off point is applied to AR, the S is 100% SP 83.3% with AUC 0.99.

CONCLUSIONS: Direct determination of nasal sIgE demonstrated good values of S and SP in both AR and LAR patients.
Nasal Polyps

929 Chronic Rhinosinusitis Patients with Gastroesophageal Reflux Disease Have Significantly Higher Prevalence of Atopic Conditions

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RATIONALE: Chronic rhinosinusitis (CRS) is characterized by chronic inflammation in the nasal and paranasal sinus mucosal membranes and is associated with increased risk of gastroesophageal reflux disease (GERD). However the mechanism underlying the link between CRS and GERD and the risk factors for GERD in patients with CRS are unknown.

METHODS: We investigated the diagnosis of GERD in a large cohort of patients with CRS between 2005-2015. The diagnosis of GERD was based on positive symptoms of heartburn/regurgitation plus response to empirical therapy with PPI. Cases with possible diagnosis without evidence for treatment or positive GI diagnostic results were excluded. Charts were then evaluated for presence or absence of asthma, allergic rhinitis, eczema and food allergy. Comparisons between groups were assessed by using logistic regression; all analyses were adjusted for age, gender and BMI.

RESULTS: Our cohort included 1005 patients with documented diagnosis of CRS; 211 (20.9%) had GERD. Patients with CRS and GERD were predominantly female, and had higher BMI and age compared to CRS without GERD. CRS and GERD patients had higher prevalence of asthma (47.4% vs 26.6%, p<0.05), food allergy (21.8% vs 10%, p<0.05), allergic rhinitis (36% vs 28.8%, p<0.05) and eczema (11.4% vs 6.4%,p<0.05) as compared to CRS patients without GERD. GERD in CRS patients was not associated with nasal polyps, loss of smell, need for increased surgical treatment or Lund-MackKay-score.

CONCLUSIONS: CRS patients with GERD are more likely to have atopic conditions. This may indicate that comorbid GERD and atopic disease are risk factors for development of CRS.

930 Proton Pump Inhibitors (PPIs) May Modulate More Than Just Reflux in Chronic Rhinosinusitis with Nasal Polyps

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RATIONALE: Chronic rhinosinusitis with nasal polyps (CRSwNP) is frequently characterized by tissue eosinophilia but the relationship of eosinophilia to other type 2 biomarkers has not been explored. Furthermore, recent data suggesting PPIs modulate eosinax-3 production in eosinophilic esophagitis may have therapeutic implications for CRSwNP. We sought to characterize levels of type 2 mediators and their relationship to tissue eosinophilia and radiographic severity in CRS. We further aimed to evaluate whether PPIs have therapeutic potential in CRS and identify possible mechanisms of action in airway epithelium.

METHODS: Type 2 mediators in nasal tissue and lavage fluid from control and CRS patients were measured by Lumixen assay. Human sinonasal epithelial cells and BEAS-2B cells were stimulated with IL-13 in the presence and absence of PPIs. The effects of PPIs on IL-13-induced effects were measured by ELISA, qRT-PCR, and pH imaging.

RESULTS: IL-13, eotaxin-2 and eotaxin-3 were highly elevated in CRSwNP compared to control and were correlated with tissue ECP and radiographic severity. CRS patients taking PPIs had significantly lower tissue eotaxin-2 and eotaxin-3 levels than those not taking PPIs. In vitro, 5 different PPIs and the competitive H+/K+-ATPase inhibitor SCH-28080 all significantly inhibited IL-13-induced eotaxin-3 release by airway epithelial cells. In addition, IL-13-induced eotaxin-3 expression was dependent on the presence of extracellular K+ and associated with a PPI sensitive efflux of H+ ions.

CONCLUSIONS: IL-13, eotaxin-2, and eotaxin-3 in tissue are potential biomarkers of eosinophilia and severity in CRSwNP. Inhibition of IL-13-induced eotaxin-3 by PPIs may provide therapeutic benefit in CRSwNP via a novel H+/K+-dependent mechanism.