Integrative Analysis of the Intestinal Metabolome of Childhood Asthma

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RATIONALE: The intestinal metabolome reflects biological consequences of diverse exposures and may provide insight into asthma pathophysiology. We performed an untargeted integrative analysis of the intestinal metabolome of childhood asthma in this ancillary study of the Vitamin D Antenatal Asthma Reduction Trial (VDAART).

METHODS: Metabolomic profiling was performed by mass spectrometry on fecal samples collected from 361 3 year-old subjects. Adjusted logistic regression analyses identified individual metabolites and modules of highly correlated metabolites associated with asthma diagnosis by age 3 years. Sparse canonical correlation analysis identified associations relevant to asthma between the intestinal metabolome and other “omics”: intestinal microbiome as measured by 16S rRNA DNA sequencing, plasma metabolome as measured by mass spectrometry, and diet as measured by food frequency questionnaire responses.

RESULTS: Several intestinal metabolites were associated with asthma at age 3 years, including inverse associations between asthma and polyunsaturated fatty acids (adjusted logistic regression beta = -6.3, 95% CI -11.3, -1.4, p = 0.01) and other lipids. Asthma-associated intestinal metabolites were significant mediators of the inverse relationship between exclusive breastfeeding for the first 4 months of life and asthma (p for indirect association = 0.04), and the positive association between a diet rich in fried and processed meats and asthma (p = 0.03). Specific intestinal bacterial taxa, including species of the family Christensenellaceae, and plasma metabolites, including gamma-tocopherol/beta-tocopherol, were positively associated with asthma and with asthma-associated intestinal metabolites.

CONCLUSIONS: Integrative analyses revealed significant interrelationships between the intestinal metabolome and the intestinal microbiome, plasma metabolome, and diet in association with childhood asthma.

Characterization of Gut Microbiome in Infants with Severe Respiratory Syncytial Virus Bronchiolitis

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RATIONALE: The effects of early life exposures, including respiratory syncytial virus (RSV) infection, on the infant gut microbiome may contribute to immune dysregulation and the development of asthma. Here, we describe the gut microbiome in infants during severe RSV bronchiolitis.

METHODS: This is a prospective cohort of infants with severe RSV bronchiolitis. Gut microbiome composition was analyzed by 16S rRNA gene sequencing of stool samples obtained during acute severe RSV bronchiolitis to identify microbial community composition.

RESULTS: Of 31 infants (15 males [48%], median age 2.6 months (range 1-10 months)), 18 infants were Caucasian (58%), 10 infants were Black (32%) and 3 were other/mixed (10%). A total of 109 genera of bacteria were identified in stool samples. Bacteroides, Parabacteroides, and Faecalibacterium were the most abundance genera. The abundance of five genera (Faecalibacterium, Ruminococcaceae, Roseburia, Fusobacterium, and Butyricoccus) each demonstrated linear relationships with age (r > 0.3). Breast feeding, dog exposure, and geography were significantly associated with the gut bacterial abundance. Parabacteroides abundance was lower in breast-fed subjects. Faecalibacterium, Veillonella, and Escherichia were more abundant in infants with dog exposure. Infants living in rural areas had a relative increase of Bacteroides and Enterobacter whereas infants from urban homes had a lower abundance of Bacteroides and greater abundance of Megaplasthpa.

CONCLUSIONS: During RSV bronchiolitis, gut microbiome composi- tion varied according to exposures such as breast feeding, dog, and geography. Further study on the implications of these findings on subsequent microbiome structure and risk for subsequent asthma is needed.

Acute Exacerbation of Asthma Phenotypes and Prognosis Identified by Cluster Analysis

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RATIONALE: Hospitalized patients for acute asthma exacerbation have more severe asthma, poorer quality of life and an elevated risk of death from asthma. To identify acute exacerbation of asthma phenotypes using cluster analysis and improve our understanding of heterogeneity in patients hospitalized for acute asthma exacerbation.

METHODS: Patients hospitalized for acute exacerbation of asthma between January 2009 to April 2014 have been prospectively and continuously included. Hierarchical cluster analysis was performed by using variables from baseline and follow-up during hospitalization on 825 patients to identify phenotypes.

RESULTS: Three clusters were identified. The three most influential variables for cluster assignment were asthma onset time, prehospital OCS use and CRP level within the first 24 hours of hospitalization. Patients in cluster 1 (n =97) were predominantly young, atopic, eosinophilic and with family history of asthma. Cluster 2 (n =526) was characterized by patients with mild, non-early onset and eosinophilic asthma. Cluster 3 (n =202) consisted mostly of severe and OCS required patients with high inflammatory indices (CRP and IL-6), higher risk of lung infection and higher burden of comorbidities. These were treated with the highest amount of systemic steroid and most likely to have been admitted to ICU, mechanical ventilation and death during hospitalization. They experienced the longest hospital length of stay and paid most direct cost for hospitalization.

CONCLUSIONS: This study identified three distinct phenotypes contributing to hospitalized patients with acute asthma exacerbation. Results can be used to predict outcomes of patients hospitalized for acute asthma exacerbation and to aid in development of personalized and precise treatment.
Sputum periostin in relation to different asthma phenotypes

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RATIONALE: Asthma is a heterogeneous disease, and appropriate classification of asthma phenotypes can improve our understanding of asthma pathogenesis, therapies and targeted management. Although Serum Periostin has been investigated as a novel biomarker in asthma, few studies have been concerned with the sputum periostin levels in correlation with asthma phenotypes. So, we aimed to evaluate the sputum periostin levels in different clinical and cellular asthma phenotypes.

METHODS: 96 patients with asthma (48 with mild to moderate asthma and 48 with severe asthma) and ten healthy controls were examined. sputum periostin, inflammatory cell counts in induced sputum and pulmonary function tests were performed.

RESULTS: Sputum periostin concentrations were significantly higher in patients with asthma than in controls. Sputum periostin is strongly correlated with age and sputum TLC and inversely correlated with FEV1. It is correlated with sputum neutrophil count and sputum eosinophil percentage. Best cut off value for sputum periostin is >252.85 ng/ml to differentiate between mild to moderate and severe asthma, with Area under the curve 0.921 (95% CI 0.86 - 0.97) sensitivity 95.8%, specificity is 77.1%, positive predictive value (PPV) is 80.7% and negative predictive value (NPV) is 94.9%.

CONCLUSIONS: sputum periostin levels provide a satisfying diagnostic accuracy in severe asthma with persistent airflow limitation than mild to moderate asthmatic adults.

The IL-17F Polymorphism rs763780 is Not Associated with Susceptibility to Neurophtilic Asthma in Ukrainian Adults

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RATIONALE: IL17F is a proinflammatory cytokine with multiple biological effects including neutrophil recruitment and airway remodelling in asthma. Polymorphisms of the IL-17F gene (rs763780) may be associated with susceptibility to neutrophilic asthma. This was explored in an adult Ukrainian population with a defined neutrophilic asthma phenotype.

METHODS: 61 patients with neutrophilic asthma were recruited who had: FEV1 < 65% of predicted and a neutrophil count in induced sputum > 75%. Asthma was diagnosed according to GINA 2012 guidelines. The control group included 83 healthy people without asthma or allergies. Single nucleotide polymorphisms of the IL-17F (rs763780) were analysed by PCR. Logistic regression was used to calculate odds ratios (OR). Written informed consent was provided by all study participants.

RESULTS: In neutrophilic asthma patients, the genotype distribution was as follows: AA – in 54 patients, AG – in 7 patients, and GG – in 0, while in the control group AA – in 71 subjects, AG – in 11 subjects, and GG – in 1 subject. The allele frequencies were as follows: A = 94.3% (n = 115) and G = 5.7% (n = 7) in asthmatics, and A = 92.2% (n = 153) and G = 7.8% (n = 13) in controls. There was no statistically significant increase in the odds of neutrophilic asthma in carriers of the G allele (OR = 0.716, CI = [0.277–1.853], p = 0.48, p > 0.05).

CONCLUSIONS: The IL-17F (rs763780) polymorphism was not associated with susceptibility to neutrophilic asthma in this Ukrainian adult population.

Comparison Of Bronchial Response To Mite And Cat Allergen In Asthma Subjects In ALYATEC Environmental Exposure Chamber (EEC)

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RATIONALE: It has been demonstrated during individual bronchial challenge that late asthmatic response (LAR) occurred more frequently with mite allergen as compared to cat allergen. Our objective was to compare the bronchial response to these 2 allergens in Alyatec EEC.

METHODS: 24 asthmatic subjects sensitized to mite were compared to 21 asthmatic subjects sensitized to cat (GINA 1 or 2), with or without rhinoconjunctivitis. The subjects had prick tests ≥ 5 mm and specific IgE ≥ 0.70 kU/l and a positive methacholine challenge test. Doses selected for mite and cat allergen were airborne allergen concentrations inducing the most frequently early asthmatic response (EAR), and/or LAR.

RESULTS: The frequency of LAR with mite allergens was 74% and 22.7% with cat allergen. With mite, the frequency of EAR was 87%; for EAR or LAR: 100%, and for EAR and LAR: 58%. In contrast, with cat allergen, 50% of patients had an EAR, 59.1% had EAR or LAR and 13.6% had an EAR and LAR. No significant differences were observed between cat and mite allergen regarding the severity and the time necessary to obtain an EAR and LAR.

CONCLUSIONS: The frequency of LAR in asthmatic subjects allergic to dust mite exposed in ALYATEC® EEC was higher than in asthmatics sensitized to cat. Our results confirmed previous results with individual bronchial challenge. Therefore, the mite allergic asthma is good model to study asthma pathophysiology and treatment.

Descriptive study of the function of the small airway in healthy and asthmatic children

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RATIONALE: Asthma is characterized by edema, inflammation and increased mucus throughout the bronchial tree, also affecting distal airway less than 2 mm (the “small airway”). Its affection is related to increase in the number of exacerbations and worse prognosis so its evaluation must be taken into account by a relevant therapeutic target.

METHODS: A retrospective observational study comparing the values of the small airway function (FEF 75-25, FEF75, FEF50, FEF25) of 84 patients with symptoms of suspicion of asthma: 20 healthy and 64 asthmatic children diagnosed by methacholine challenge test, using Student’s t-test. Other variables are studied: sex, age, BMI, data of spirometric, bronchodilator test and fractional exhaled nitric oxide (FeNO).

RESULTS: The sample consists of 40 boys and 44 girls, aged between 5 and 17 years (average age of 11.7 years). Average BMI is 19.5 Kg/m2. The values of FEF75/FVC, FEV1, and FVC are normal and the bronchodilator test negative in all patients. FeNO is over 25 ppb in 22 patients. The mean value of FEF75/25, FEF75, FEF50 and FEF25 is 3.6L (88.1%), 4.3L (90.9%), 4.2L (89.8%) and 1.5L (84.2%), respectively, in the asthmatic group, and 3.6L (101.2%), 5.7L (101.1%), 4.1L (103.5%) and 1.9L (96.1%) in the healthy group. We found significant difference in the values measured in percentage (adjusted to patient weight and size) of FEF75/25, FEF75 and FEF50 between the healthy and the asthmatic group (p = 0.0165, p = 0.0364 and p = 0.0085, respectively).

CONCLUSIONS: In our series, significant difference exists between FEF75/25, FEF75 and FEF50 between healthy and asthmatic children.
13 Indoor Allergen Sensitization Correlates with Asthma in Chicago Public Hospital Patients

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RATIONALE: Studies show sensitization and exposure to indoor allergens contributes to asthma morbidity in urban populations, but few focus on Chicago or include patients with and without asthma. We sought to confirm that sensitization to mouse urine, cockroach, or dust mite (DM) is associated with increased odds of having asthma and increased asthma severity in adult and pediatric patients in Chicago.

METHODS: We performed a retrospective chart review of 718 patients ages 1-90 seen at a Chicago public hospital from June 2015 through December 2016 who had in-vitro aerosol allergen testing. Data collected included patient demographics, aeroallergen sensitivities, physician-diagnosed asthma, and asthma severity. The data were analyzed using chi-square tests.

RESULTS: A total of 341/718 (47.5%) patients were sensitized to at least one of the three allergens studied, and 440/718 (61%) patients had a diagnosis of asthma. Sensitization to one or more allergens was associated with having asthma [OR 1.69 (1.24-2.29) p<0.001], as was sensitization to the individual allergens: mouse OR 3.52 (2.04-6.07), cockroach OR 1.49 (1.07-2.07), and DM OR 1.56 (1.14-2.13) p<0.01. 

CONCLUSIONS: Sensitization to mouse urine, cockroach, and DM was associated with increased odds of having asthma. Mouse sensitization had the strongest association. Consistent with previous studies, sensitization to cockroach was associated with having more severe asthma.

14 High Peripheral Blood Eosinophil (EOS) Levels Are Associated With Low FEV1, Reversibility (REV) In Patients With Severe Eosinophilic Asthma

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RATIONALE: Reslizumab, a humanized anti-interleukin-5 monoclonal antibody, improves asthma exacerbation rates, lung function, and patient-reported outcomes in patients with inadequately controlled eosinophilic asthma. This post-hoc analysis explored EOS levels and lung function among patients with low FEV1, REV to SABA.

METHODS: Data were pooled from two 52-week placebo-controlled trials of IV reslizumab 3mg/kg (Q4wks) in patients with screening EOS ≥400μL and REV ≥12% to SABA. REV by baseline (day of first dose) EOS category and lung function treatment effect in the lowest-REV/highest-EOS group were analyzed.

RESULTS: Patients (N=953) were categorized by baseline EOS <150 (n=65), 150–<400 (n=179), 400–<700 (n=365), and ≥700μL (n=344) and by baseline REV <14% (n=149), 14–<20% (n=276), and ≥20% (n=528). Patients with higher EOS levels showed trends towards lower mean REV and a higher proportion with REV <14% versus patients with lower EOS levels [EOS ≥700: mean ± SE %REV 24.7±1.4, 17% with REV <14%, 52% with REV ≥20%; EOS <150: 28.5±2.5, 12% with REV <14%, 60% with REV ≥20%]. Treatment effects at 52 weeks (reslizumab vs placebo) in the low REV (<14%) group, pooled two highest EOS categories (≥700, 400–<700): FEV1 168mL (95% CI: 4–322), %predicted FEV1 6.2% (1.1–11.2%), FVC 144mL (-6–350), and FEV25–75% 131mL (-96–357).

CONCLUSIONS: Higher blood EOS is associated with lower FEV1, REV in inadequately controlled eosinophilic asthma. Reslizumab treatment results in clinically significant improvements in lung function outcomes in patients with high EOS and low REV. Reslizumab may reverse relatively “fixed” airway obstruction in these patients.

15 Eosinophil progenitor cell blood levels inversely correlate with disease control in pediatric patients with asthma

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RATIONALE: Eosinophil progenitors (EoPs) are eosinophil lineage-committed, CD34+ progenitor cells that primarily reside in the bone marrow. Growing evidence demonstrates these cells are mobilized into the peripheral blood during allergic responses. We investigated whether EoP levels were increased in patients with asthma and whether they correlated with disease severity and asthma control.

METHODS: Pediatric patients (6-18 years) with severe eosinophilic asthma (n=8), mild allergic asthma (n=10) and non-atopic controls (n=9) were recruited. Asthma Control Test (ACT) scores, absolute eosinophil counts (AEC) and immunoglobulin E (IgE) levels were obtained at enrollment. Total CD34+ cells and EoPs were quantified in the blood by flow cytometry. Data are expressed as the mean ratio of CD34+ or EoP count per 1x106 lymphocyte gate events ±SD. Statistical analyses were completed with one-way ANOVA with post hoc comparisons using Tukey’s multiple comparison’s test and Spearman correlations.

RESULTS: Whereas the CD34+ population did not differ among groups, EoP levels were significantly increased (P=0.01) in the peripheral blood of patients with mild asthma (36.7±14.3) compared to controls (19.5±10.5). EoP levels were also elevated in patients with severe eosinophilic asthma (27±14.3), although the difference compared to controls was not significant. Notably, EoP levels inversely correlated with asthma control as assessed by ACT scores (r=-0.58, P=0.015), but did not correlate with AEC or IgE levels.

CONCLUSIONS: These data suggest that EoP cells are specifically mobilized into the peripheral blood of pediatric patients with asthma. Lower EoP levels may be associated with loss of asthma control, potentially via recruitment of these cells into the tissue.
16 Characterizing the prenatal inflammatory milieu associated with maternal asthma: A proteomics approach

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RATIONALE: Maternal asthma is associated with a pro-inflammatory state in pregnancy that contributes to asthma risk in children. The prenatal inflammatory milieu is a consequence of shifts in a host of molecular, cellular, and physiological states reflecting interacting systems including neuroendocrine and immune function. High-throughput technologies enable a more system-wide profiling of the prenatal inflammatory response related to maternal asthma.

METHODS: Analyses included n=438 mothers in the PRogramming of Intergenerational Stress Mechanisms pregnancy cohort. Women reported an asthma diagnosis. We characterized 92 inflammatory markers in maternal sera obtained at 30.0±5.8 weeks gestation using the Olink multiplex inflammation panel. We used multivariable logistic regression to estimate associations between each inflammatory marker and maternal asthma status (ever vs. never), adjusted for education, body mass index, race/ethnicity and age.

RESULTS: The sample was 31.5% Black and 33.6% Hispanic, and 24.8% had asthma status (ever vs. never), adjusted for education, body mass index, race/ethnicity and age.

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CONCLUSIONS: Approaches that comprehensively assess biomarkers across inflammatory response systems may better inform links between maternal asthma and fetal programming of asthma. Future work in this longitudinal study will employ network modeling to examine associations between the prenatal inflammatory milieu to assess whether these factors mediate associations between maternal asthma and children’s asthma risk.

17 Detection of Adrenal Insufficiency (AI) in severe and moderate asthma employing standard ACTH response curve of non-asthmatic healthy controls and with comparison with non-asthmatics with past history of high dose systemic steroid use

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RATIONALE: Patients with asthma have high risk of adrenal insufficiency(AI), which can become a risk for repeated exacerbation, though it has been under-estimated due to their unfamiliar manifestations. We compared 23 severe asthma(SA) (Group A) with 10 mild–moderate asthma(MA) (Group B), and 13 non-asthma patients but with history of high dose systemic steroid use(NA)(Group C).All 3 groups were compared to see the number of those with normal ACTH response.

METHODS: Normal response curve for rapid ACTH test reported in July,2000 in Jpn J Clin Pharmacol Ther 31(4) was employed to define normal cortisol response. Peak/Initial ratio for normal control was designated Z1/Z0 and Y1/Y0 for the patients. We compared Y1 and Z1, supposing the value to be Y1/Z1 = 1 if the reactivity was normal. Y1/Z1 was designated low if under 2SD.

RESULTS: Normal reactivity found in group A,B,C,were,17.4%(N=4/ 23),80%(N=8/10),53.8%(N=7/13),respectively. $X^2$ analysis was significant(P=0.001354). In Group A,39.1%(N=9/23)had Y1/ Z1 ratio below 0.5,while Group B had none and group C had 7.6%(N=1/13), suggesting serious adrenal insufficiency with low ACTH response in group A.

CONCLUSIONS: We have shown that it is possible to replicate features of the human “asthma puberty switch” using a murine asthma model. This will enable further mechanistic studies of asthma during puberty transition.

18 A Murine Model Of Asthma That Replicates The Human Asthma Puberty Switch

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RATIONALE: Before puberty, boys have an increased prevalence of asthma compared to girls, and boys are twice as likely to have an asthma exacerbation requiring hospitalization. After puberty, women have increased asthma prevalence compared to men, and women are three times more likely to be hospitalized for an asthma-related event. These sex-specific changes in asthma prevalence and severity are known as the “asthma puberty switch”. Here, we sought to develop a murine asthma model that replicates this “switch” to enable mechanistic studies of this phenomenon.

METHODS: We sensitized pre- and post-pubertal BalbC/J mice of both sexes using two intraperitoneal injections of ovalbumin (50 µg in alun) on days 0 and 7. On days 14, 16, and 18, mice were challenged intranasally with antigen (50 µg of ovalbumin in saline). We quantified eosinophils in bronchoalveolar lavage fluid (BALF) and lung tissue, classified leukocytes using flow cytometry, and measured lung type 2 cytokine expression and tissue remodeling markers by qPCR.

RESULTS: Post-puberty, antigen-challenged female mice had higher lung and BALF eosinophil counts when compared to their male littermates. Additionally, post-pubertal females had significantly higher lung tissue expression of IL-4, IL-5 and IL-13 as well as higher expression of epithelial remodeling markers tenascin, Wnt5a, and thrombospondin when compared to males. Of special significance, these sex differences were absent or reversed in pre-pubertal mice.

CONCLUSIONS: We have shown that it is possible to replicate features of the human “asthma puberty switch” using a murine asthma model. This will enable further mechanistic studies of asthma during puberty transition.
19 The Effect of Asthma on Activation of Brain Neurocircuits

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RATIONALE: Depression and anxiety are frequent co-morbidities in asthma, though neither the underlying mechanisms nor pathways between the lung and brain are established. We have previously shown an inhaled allergen provocation of asthma activates brain neurocircuits associated with emotion. As a consequence, we hypothesized that emotion neurocircuitry activation occurs in asthma in relationship to underlying disease severity and may have effects on cognitive function.

METHODS: Functional magnetic resonance imaging was used to measure brain responses to emotional stimuli in 107 participants with mild-to-severe asthma. Principal component analysis (PCA) was used to create composite scores that represent disease severity (e.g. lung functions, medication use and disease control) and T2-inflammation. Finally, to evaluate the cognitive consequences of long-term asthma, cognitive testing was performed on a subset with severe asthma.

RESULTS: Significant relationships were found between measures of disease severity and activation of the insula – a key component of a brain network that acts to determine the importance of internal sensory information from the body. Other areas of brain activation were found in relationship to FeNO values and lifetime burden of disease (severity X asthma duration). We also found that a greater lifetime burden of asthma was inversely related to measures of cognitive function; with greater severity for a longer time, cognitive function was lower.

CONCLUSIONS: Brain networks associated with emotion are activated in relationship to measures of asthma severity. Furthermore, our data suggest that a consequence of greater asthma severity for a longer duration may be a reduction in cognitive function.

20 Role of Periostin in Brazilian Patients with Aspirin Exacerbated Respiratory Disease

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RATIONALE: Aspirin exacerbated respiratory disease (AERD) is characterized by chronic rhinosinusitis with nasal polyps, asthma and hypersensitivity to Aspirin/NSAIDs. Increased levels of periostin have been described in patients with AERD. We evaluated serum periostin in Brazilian patients with AERD, and compared to patients with Perennial Allergic Rhinitis (PAR) and healthy individuals.

METHODS: Twenty-nine patients (20F/9M) with AERD underwent polyp biopsy through nasobrroscopy. Control groups of 12 patients with PAR (9F/3M) and 19 healthy subjects (11F/8M) had samples collected during rhinoplasty. Eosinophils were quantitated in blood, and in polyp tissue or nasal mucosa. Total IgE was determined by ImmunoCAP, and serum periostin by ELISA. Eosinophils and serum periostin were measured in patients with AERD were compared with those with PAR and healthy subjects.

RESULTS: Patients with AERD were older than patients with PAR patients and healthy controls (median 54, 30 and 29 years, respectively, p=0.0001). Peripheral blood eosinophils were higher in AERD as compared to PAR and healthy individuals (median 640/mm3, 200/mm3 and 100/mm3). Median tissue eosinophils were 113.3, 2.5 and 0.7cells/mmL in AERD, RAP and healthy individuals, respectively (p<0.05). Mean serum periostin levels were 109.9ng/ml(range 59.4-236.6); 102.4ng/ml(range 57.9-147.8); and 83.6ng/ml(range 40.1-139.5), in AERD, RAP and healthy individuals, respectively (AERD vs. healthy subjects, p=0.01).

CONCLUSIONS: In a subset of Brazilian patients with AERD, we observed higher blood and tissue eosinophils, as compared to patients with PAR and healthy individuals, and elevated serum periostin, indicating a strong type 2 response in AERD patients in our area.

21 The effect of gastroesophageal reflux and proton pump inhibitors on respiratory tract infections in patients with asthma

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RATIONALE: Co-morbid gastroesophageal reflux disease (GERD) is a significant factor associated with poor asthma control. Treatment with proton pump inhibitors (PPIs) have not consistently improved asthma control and there is evidence that PPIs may increase the risk of respiratory tract infections (RTIs). We aimed to study how GERD diagnosis and PPI treatment affect the risk of RTIs and related sequelae among children and adults with asthma.

METHODS: RTIs and RTI-related morbidity from four large asthma trials were analyzed for associations with self-reported GERD and PPI use. The primary outcome was rate of visits with an RTI, documented using standardized clinic visit interviews. Secondary outcomes included asthma exacerbations requiring systemic steroids. Multivariable negative binomial regression was used. Models controlled for age, gender, ethnicity, race, BMI classification, atopy, use of H2 antagonists or antacids, GERD symptom frequency, and study.

RESULTS: There were 1181 total subjects: 643 children (58 with GERD, 162 on a PPI) and 538 adults (138 with GERD, 78 with a PPI). In children, GERD did not increase the rate of RTI or RTI-related asthma exacerbations. PPI use was associated with increased rates of RTIs (rate ratio 1.2, 95% CI 1.0-1.4, p=0.04) and RTI-related asthma exacerbations (rate ratio=1.8, 95% CI 1.1-3.0, p=0.02). In adults, GERD and PPI use did not affect the rates of RTIs or RTI-related asthma exacerbations.

CONCLUSIONS: Independent of GERD, PPI use is associated with increased rates of RTI and associated asthma exacerbations in children but not adults with asthma.
All abstracts are strictly embargoed until the date of presentation at the 2019 Annual Meeting.

**22 Allergen-induced Innate Inflammation in Mice is Strain-dependent**

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**RATIONALE:** Activated group 2 innate lymphoid cells (ILC2) produce large amounts of IL-5 and IL-13, and are activated by epithelial derived cytokines including thymic stromal lymphopoietin (TSLP) in response to protease containing antigens. We hypothesized that the airway/lung expression of TSLP and the number of lung IL-5/IL-13 producing ILC2 is dependent upon the host genetic background in mice.

**METHODS:** We challenged A/J, C57BL/6J, and 129S1/SvImJ mice intranasally with 5 mg of an extract of *Alternaria alternata*, a common aeroallergen, and measured TSLP via ELISA in the BAL fluid and lung 6 hours later, during the peak of TSLP expression. We also challenged the same strains of mice for 4 consecutive days with 5 mg *Alternaria* extract and 24 hours after the last challenge we isolated and quantified IL-5/IL-13 producing ILC2 from the lungs via flow cytometry.

**RESULTS:** 129S1/SvImJ mice had a statistically significant 2-fold greater airway and lung TSLP expression compared to mice from A/J and C57BL/6J, and 129S1/SvImJ mice have significantly higher numbers of IL-5/IL-13 cytokine producing ILC2 compared to C57BL/6J mice. Further, the number of ILC2 number was approximately 5 times higher for 129S1/SvImJ than C57BL/6J mice.

**CONCLUSIONS:** These mouse strain differences in airway and lung TSLP expression and IL-5/IL-13 producing ILC2 suggest that QTL (quantitative trait loci) analysis will map genomic loci relevant to important features of the allergen-induced innate immune response.

**23 Serum concentration of TNFSF14/LIGHT receptors DcR3 and HVEM in asthma patients.**

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**RATIONALE:** Tumor necrosis factor family member 14 (TNFSF14/LIGHT) plays a role in the process of airway remodeling and its effects are regulated by decoy receptors DcR3 and HVEM. Our previous study demonstrated that TNFSF14/LIGHT concentration is elevated in asthmatic patients. The aim of this study was to evaluate serum concentration of DcR3 and HVEM in asthmatic patients.

**METHODS:** Serum samples were obtained from 42 asthmatic patients (A), including 28 controlled on inhaled corticosteroids (AICS) and 14 during asthma exacerbation before systemic corticosteroids therapy (AEX). In the latter group serum samples were also obtained during remission while still on oral corticosteroids (AOCS). In addition, 12 allergic rhinitis patients (AR) and 24 healthy controls were included (HC). Concentration of DcR3 and HVEM was evaluated using ELISA method.

**RESULTS:** The mean concentration of DcR3 and HVEM did not differ significantly between A and AR (p>0.05 for both), both being significantly greater than in HC (p<0.01 for each comparison). Among asthmatic patients serum concentration of DcR3 was significantly greater in AEX than in AICS (p<0.001) both being significantly greater than in HC (p<0.001). No significant difference of serum HVEM concentration could be demonstrated between individual subgroups of asthmatic patients. Significant decrease of serum DcR3 concentration could be demonstrated in AICS (p<0.01) in comparison to AEX. No significant difference of serum HVEM concentration between AEX and AOCS could be demonstrated (p>0.05).

**CONCLUSIONS:** In asthmatic patients altered expression of DcR3 and HVEM expression may participate in regulation of TNFSF14/LIGHT-dependent airway remodeling and progression of asthma.

**24 Decreased Airway Tone Measured by Impulse Oscillometry Identifies Concurrent Tracheobronchomalacia in Children with Asthma**

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**RATIONALE:** Children with asthma who have concurrent tracheobronchomalacia (TBM) often require additional treatments to assist with airway clearance during an exacerbation. Current diagnostic methods for TBM are invasive and effort-dependent, i.e. bronchoscopy and dynamic CT scan with forced expiration. We hypothesized that impulse oscillometry (IOS), a noninvasive and effort-independent modality to measure airway resistance and tone may be useful in diagnosing tracheobronchomalacia in children with asthma.

**METHODS:** A retrospective chart review of 44 pediatric patients with asthma, ages 0-21 who underwent IOS from January 2012-July 2017 was performed. Patients with TBM (N=6/44) were diagnosed by bronchoscopy, the gold standard. Exclusion criteria included patients whose TBM was suspected by pulmonary function testing alone, patients with congenital malformations and patients unable to complete IOS. A logistic regression analysis was performed to determine the predictive value of different IOS-derived parameters in the diagnosis of TBM.

**RESULTS:** The combination of reactance (i.e. airway tone) in small and large airways at 5Hz (X5) > -1.16 and in large airways at 25Hz (X25) > 0.52 provided an area under the curve of 0.92 (p = 0.01) for distinguishing children with asthma with bronchoscopy-diagnosed TBM. This cut-off level provided 67% sensitivity and 95% specificity and a positive predictive value of 67% with a negative predictive value of 95%.

**CONCLUSIONS:** Measurement of airway tone by IOS may provide a diagnostic alternative for diagnosing TBM in pediatric patients with asthma.
25 Exhaled Breath Temperature Measurement in Allergic Respiratory Disease

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RATIONALE: Asthma is characterized by airflow inflammation and remodeling of the airway walls, both of which contribute to the pathology of the disease. In recent years, it has been hypothesized that level of exhaled breath temperature (EBT) is related to the degree of airflow inflammation/remodeling. The purpose of this study was to evaluate the EBT in patients with allergic respiratory disease (asthma and/or allergic rhinitis) and healthy controls.

METHODS: Observational retrospective study on 245 patients aged 6-75 years (32.1 years) with asthma, allergic rhinitis and healthy volunteers which performed the measurement of EBT, attending an Allergy and Immunology Center in northeast of Mexico. We also evaluate the ambient conditions (laboratory humidity, atmospheric pressure), and physiological characteristics of the tested subjects (heart rate, respiratory rate, blood pressure, otic and axillary temperature).

RESULTS: Patients with allergic respiratory disease (ARD) 188, of whom 75 (39.6%) had asthma (53% controlled, 47% uncontrolled), 113 (46.1%) allergic rhinitis, and 57 (23.3%) healthy volunteers. Patients with ARD had significantly increased EBT compared with healthy controls (29.49 vs. 28.94 °C; p = 0.004), particularly those with uncontrolled asthma (29.11 vs. 28.26 °C; p = 0.026) compared with controlled asthma. In general population 167 (65.5%) was female, with EBT measurement 28.83 vs. 29.65 in male (p = 0.002). There were no significant differences between environmental and personal conditions.

CONCLUSIONS: We observed a higher temperature on exhaled breath in subjects with ARD, uncontrolled asthma and male gender. Exhaled breath temperature (EBT) is proposed as a noninvasive marker of bronchial inflammation in patients with allergic respiratory disease.

26 Levels of Chlamydia pneumoniae Immunoglobin E antibody in patients with asthma compared with non-asthma.

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RATIONALE: Chlamydia pneumoniae is an obligate intracellular bacterium that causes respiratory infection in adults and children. There is evidence for an association between atypical bacterial pathogens (C. pneumoniae, M. pneumoniae) and asthma pathogenesis, as well as production of immunoglobulin (Ig) E responses in vitro. Previous studies in our laboratory demonstrated the presence of anti-C. pneumoniae IgE antibodies (Abs) by immunoblotting in children with culture confirmed C. pneumoniae infection (pneumonia and asthma) who were wheezing. We sought to determine whether past C. pneumoniae infection triggers production of C. pneumoniae-specific IgE Abs in adult subjects with and without asthma, who had positive C. pneumoniae-IgG titters.

METHODS: Total serum IgE levels and C. pneumoniae IgE Ab responses were studied in adult asthmatic (N = 22) and non-asthmatic (N = 22) subjects by ELISA. Blood was obtained from subjects in a primary care setting. Data are reported as IU/mL, and mean antibody index values, respectively. Inclusion criteria included positive C. pneumoniae IgG titters.

RESULTS: Total serum IgE levels were similar in asthmatics compared with non-asthmatic subjects (186 ± 159 vs. 170 ± 142; P = 0.720). However, C. pneumoniae IgE Ab levels were significantly higher in asthmatic patients compared with non-asthmatic subjects (1.015 ± 0.305 vs. 0.39 ± 0.340; P < 0.001). No significant association was found between total serum IgE levels and C. pneumoniae IgE Ab levels (R² = 0.004, P = 0.981).

CONCLUSIONS: These findings indicate that C. pneumoniae infection may trigger IgE-specific responses in asthmatics. C. pneumoniae IgE Abs produced by chronic infection may also contribute to asthma pathogenesis.

27 Changes in forced oscillation technique (FOT) parameters during 4-year-follow-up in children and adolescents with asthma: possible indices for lung function decline.

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RATIONALE: Forced oscillation technique (FOT) has a potential to evaluate respiratory pathophysiology in asthma that spirometry does not detect. Since lung function decline in children with asthma has been reported to have significant impact on development of COPD in later life, we investigated changes in FOT parameters in children/adolescents with asthma in relation with changes in maximal expiratory flow at 50% of the forced vital capacity (MEF50), an index for the small airways.

METHODS: Subjects were children/adolescents with asthma who were followed for 4 years at our institution. Clinical data, spirometry and FOT (MostGraph®) measurements were retrospectively reviewed. The subjects were divided into 3 groups based on changes in MEF50 over the 4-year period; PLUS group were those in whom average data of MEF50 in the 4th year were larger than the 1st year, NC group had no changes and MINUS group had decline in MEF50 from the 1st to 4th year.

RESULTS: 542 paired data sets (PLUS: 134, NC: 154, MINUS: 254) were analyzed. In accordance with changes in MEF50, R5 and R20 significantly decreased (improved) in PLUS group and those in MINUS group significantly increased (deteriorated). However, R5 and R20 increased (deteriorated) in NC group. The tendency was more evident in subjects in whom initial MEF50 <60% of predicted values.

CONCLUSIONS: The results suggest that ‘no change’ in the small airway index of spirometry in childhood may not mean ‘stable’ but indicate loss of lung function development, which may lead to further decline in later life.
28 Stability of eosinophil classifications using common cut-points over time

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RATIONALE: Blood eosinophil levels are advocated to aid decisions regarding biologic asthma therapies. Historical measurements have been suggested to suffice for treatment decisions, making the variation over time of practical interest. This analysis examined the stability of eosinophil levels based on common cut-points over periods up to 1 year.

METHODS: Post-hoc analyses of placebo arm data from LUTE/VERSE (Phase IIb) and LA VOLTA I/II (Phase III) studies of lebrikizumab using patient data assessed monthly at ≥5 timepoints. The proportion of time a patient was classified in the same eosinophil category (<150, 150-299, ≥300 cells/μL) over a year was calculated.

RESULTS: Of 813 included patients, 751 (92.4%) patients had ≥5 eosinophil measures. Eosinophil classification stability (eg, ≥80% of time at same level classification) was lower among patients with baseline eosinophil levels 150-299 cells/μL (20.5%) compared with levels <150 cells/μL (44.7%) or ≥300 cells/μL (46.4%). Stability decreased as the minimum proportion of time a patient maintained in the same category increased (<150 cells/μL: 75%, 30%; 150-299 cells/μL: 71%, 7%; ≥300 cells/μL: 80%, 35%) for maintaining in the same category ≥60% or ≥90% of the time, respectively). Efficacy and safety aspects were not evaluated in this analysis.

CONCLUSIONS: Stability of eosinophil classification over time using common thresholds shows that the proportion of patients maintaining consistent levels decreases as the minimum proportion of time being stable increases. These findings indicate that eosinophil levels are variable over the studies’ 1-year timeframe, which should be considered when assessment of eosinophil levels is used for patient care.

29 Clinical Implication of Exhaled Breath Temperature in the Hospitalized Children with Asthma Attack

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RATIONALE: We aimed to investigate change of the level of Exhaled breath temperature (EBT) with time from the hospitalized children with asthma attack to well controlled status after discharge.

METHODS: This study included hospitalized children aged 5–18 years with asthma attack. Children diagnosed of asthma attack performed spirometry, bronchodilator response, fractional exhaled nitric oxide (FeNO). During the hospital stay, EBT, peak expiratory flow (PEFR), and asthma score were measured daily. These tests were performed during the 1 week and 1 month follow-up. The overall change in PEFR and EBT with time and their time-dynamic association were evaluated with linear mixed models.

RESULTS: We evaluated 38 children who admitted with asthma attack. Mean age was 9.9 ± 2.6 years and the ratio of male to female was 2.5. Forced expiratory volume in one second (FEV1) at admission (63.3 ± 24 % predicted) as lower than that at discharge (99.5 ± 14 % predicted, P < 0.001). Levels of EBT were higher at admission [34.1 (33.9–34.8)] compared to those at one week after discharge [33.6 (33.0–34.2), P = 0.007] and it decreased overall during the study period (P = 0.007). Within individuals, EBT was decreased while PEFR increased with time. Furthermore, EBT had a time-dependent dynamic association with PEFR during hospital period (P = 0.005) and from asthma attack to stable asthma status (P = 0.032).

CONCLUSIONS: EBT was elevated in asthma attack, and gradually decreased with the change of PEFR until well-controlled asthma after asthma attack. EBT might be a non-invasive and easy-to-use tool to monitor asthma control in children.

30 Does Exhaled Nitric oxide predict non-specific bronchial responsiveness in childhood asthma?

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RATIONALE: fractional concentration of exhaled nitric oxide (FeNO) values have been elevated only in subjects with atopic asthma which is common in childhood. Non-specific bronchial responsiveness induced by methacholine is used to diagnose asthma, but in children, some children occasionally cannot co-operate spirometry for methacholine challenge test. This study is to be determined if methacholine challenge test could be replaced by FeNO.

METHODS: Subjects were 255 children who performed methacholine provocation and FeNO on the same day had visited for evaluating asthmatic symptoms (cough, wheezes). BHR was defined as positive when Methacholine PC20 FEV1 (MChPC20) ≤ 16mg/mL.

RESULTS: Children with BHR had higher FeNO than children without BHR (39.5 vs 30.8, P = 0.016). Besides, there was correlation between MChPC20 and FeNO (r = -0.132, P = 0.0340) but very weak. ROC curve analysis was performed if the diagnostic value of FeNO was equal to Methacholine PC20, FEV1. Area under the ROC curve (AUC) was 0.595 (P = 0.0075). When FeNO > 37, sensitivity and specificity was 44.93 and 72.65, respectively.

CONCLUSIONS: Since FeNO has a different meaning from methacholine induced bronchoconstriction, methacholine provocation test cannot be replaced by FeNO. In pediatric asthma, the two tests are mutually complementary.
31 Obstruction phenotype as a predictor of asthma control and airway hyperresponsiveness to methacholine and exercise in children with asthma

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RATIONALE: It is suggested that an air-trapping obstruction and airflow limitation pattern of obstruction could be used to identify obstruction phenotypes that are indicators of risk for asthma severity and instability. We explored airway hyperresponsiveness (AHR) to methacholine and exercise relative to obstruction phenotype.

METHODS: The study included 147 asthmatic children aged 6–18 years. Exercise and methacholine bronchial provocation tests were performed, as was the Asthma Control Test (ACT). An air-trapping obstruction phenotype was defined as a forced vital capacity (FVC) z-score of less than -1.64 or an increase in FVC of -10% of the predicted value or greater with bronchodilation. The airflow limitation phenotype had a forced expiratory volume in 1 second (FEV1)/FVC z-score of less than -1.64 but not an air-trapping obstruction phenotype. The no airflow limitation or air-trapping (none) phenotype had neither an air-trapping obstruction phenotype nor an airflow limitation phenotype.

RESULTS: The 147 asthmatic children were divided into three phenotypes: asthmatics with the air-trapping obstruction phenotype (n=41), asthmatics with the airflow limitation phenotype (n=40), and asthmatics with the none phenotype (n=66). The air-trapping obstruction phenotype had significantly greater levels of the maximum decrease in FEV1 after exercise and significantly lower ACT scores compared to those with the airflow limitation phenotype and none phenotype. No significant differences were found in methacholine PC20 between the three phenotypes.

CONCLUSIONS: Obstruction phenotypes as defined by routine spirometric measurements could be predictors of AHR and asthma control. Air-trapping was more significantly related with AHR to exercise than with AHR to methacholine.

32 Validating the Composite Asthma Severity Index in adult asthmatics

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RATIONALE: To comprehensively assess asthma control in asthma patients, a Composite Asthma Severity Index (CASI) has been developed. It accounts for symptom severity, controller medication usage, lung function, and exacerbation frequency. CASI has been validated in children.

METHODS: We attempt to validate CASI for adults. METHODS: CASI and Asthma Control Test (ACT) scores were obtained for 78 adults with asthma of two phenotypes: Aspirin Exacerbated Respiratory Disease (AERD) (N=47) and aspirin-tolerant allergic (ATA) asthma (N=31). CASI and its domains were compared to ACT and then to the pediatric CASI validation data.

RESULTS: Increased CASI scores were associated with decreased ACT total scores in adult asthmatics: the correlation was r=-0.54, p=0.002 in ATA patients and it was r=-0.65, p<0.001 in AERD patients. Individual CASI domains corresponding to day and night symptoms were associated with ACT score in both adult populations as well as children. The FEV1 CASI component score was not associated with ACT score in either adult population or children ≥12 years of age. The CASI asthma exacerbation domain was significantly correlated with ACT in the ATA group (r=-0.39, p=0.032) and in children <12 years of age (r=-0.15, p=0.001), but not the AERD group or children ≥12 years of age. Interestingly, CASI treatment domain significantly correlated in children and AERD patients (r=-0.29, p=0.045), but not in ATA patients (r=0.19, p=0.30).

CONCLUSIONS: CASI could determine asthma severity level in adult patients with allergic asthma and with AERD. CASI could be used for clinical characterization of asthma control in adults.

33 Comparison of bronchodilator response in asthmatic children using spirometry and oscillometry

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RATIONALE: Bronchial asthma is a chronic inflammatory lung disease characterized by variable airflow limitation and underlying inflammation. Impulse oscillometry (IOS) has been to measure small airways function, but limited data are available that correlate the bronchodilator response using spirometry and IOS in asthmatic children.

METHODS: Bronchial response test was performed using spirometry and IOS in 91 children with asthma, aged 6 to 18 years, who visited to our hospital as a regular check-up. Lung function tests were carried out before and after inhalation of bronchodilator. FeNO was performed before lung function testing.

RESULTS: Based on the degree of prebronchodilator airflow obstruction and bronchodilator response (BR) as assessed by FEV1, the subjects were divided into three groups as follows: Group1, 41 children with pre%FEV1 >80% and BR <12%; Group2, 30 children with BR ≥12% regardless of pre%FEV1 values; Group3, 20 children with pre%FEV1 <80% and BR <12%. The patterns of BR in FEV1<75%, which is considered as a marker of the small airways, were similar to those in FEV1. On the contrary, significant BRs in R5-R20, X5, and AX, which are considered as markers of the small airway obstruction, were found even in Group3 as well as in Group2. FeNO levels were not significantly different among three groups.

CONCLUSIONS: IOS was able to detect BR even in asthmatic children who appeared to have fixed airway obstruction as assessed by spirometry. IOS can better assess lung function, especially small airway function.

34 Comparative respiratory impedance in Thai children with obesity and asthma by using oscillometry

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RATIONALE: The decline in lung function is observed among asthma and obesity. Measurement of obstructive airway by spirometry is suggested to confirm the diagnosis and monitor treatment outcomes in asthma. Nevertheless, spirometry is hard to complete in preschooler. Impulse oscillometry (IOS) is a new and easier technique to measure airway resistance. We aim to evaluate IOS parameter in Thai asthmatic patients and Thai obese children.

METHODS: Forty-two asthmatic children and thirteen obese children (without asthma), aged 5-15 years old, were enrolled in our study. They all consent/assent to performed IOS measurement (Jeaker, Germany) to determine airway obstruction.

RESULTS: Among fifty-five volunteers, male were predominant (25/42 in asthmatic group and 11/13 in obese group). Mean age of asthmatic patients was 9.25±3.02 and obese children was 10.08±3.15. ZBMI in asthmatic patients was 0.11±0.02 and obese children was 0.21±0.05. The airway resistance at 5 Hz(R5) were similar in both asthmatic and obese group (0.84±0.26 vs 0.84±0.31, p=0.971). The airway reactance to 5 Hz(X5) were increased in obese children (-0.12±0.1 vs -0.21±0.11, p=0.008). R20 and X20 measurement were not different in both groups [0.54±0.2 vs 0.385] and (-0.03±0.08 vs -0.03±0.18, p=0.889).

CONCLUSIONS: IOS in our study did not demonstrate airway resistance in Thai children with asthma. Though, this parameter may be advantage in obese children.
35 Evaluation of pulmonary function by impulse oscillometry in pre-school children with asthma

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RATIONALE: The diagnosis of asthma is based on clinical presentation, physical examination and evaluation of lung function. The impulse oscillometry (IOS) is simple to perform and effort-independent. We aimed to evaluate pulmonary function through IOS in pre-school children with asthma.

METHODS: Asthmatic patients and controls from 3 to 6 years participated. We used the EISL questionnaire to investigate the presence of wheezing, GINA to classify severity and TRACK questionnaire to assess the frequency of wheezing. Lung function was assessed by IOS with the MasterScreen TM (CareFusion, USA). Resistance values at 5Hz (R5) and 20Hz (R20), reactance at 5Hz (X5), resonance frequency (Fres), reactance area (AX) and bronchodilator response (BD) were registered.

RESULTS: We evaluated 224 children (150 asthmatics and 74 controls), 53% male. Among asthmatics, 70% had wheezing in the first year, 87% in the last year, 34% in the last month, 41% were mild, 15% moderate and 44% severe. There was a significant difference of R5% (105[91-124]% vs 97[88-109]%; p=0.02), R5-R20 (0.37 vs 0.31 KPa/L/s; p=0.07) and BD response (-21 vs -13%; p=0.01) among asthmatics. Wheezing in the last month was associated with an increase in R5 and Fres (p=0.01 and p=0.04) and maternal smoking during pregnancy had an AX increase (4.5 vs 3.8; p=0.02). There was no difference between the age of the first wheezing and values of lung function measured by IOS. No differences were found between asthma severity and IOS values.

CONCLUSIONS: IOS seems to be a useful and clinically relevant tool to evaluate lung function in pre-school children with asthma.

36 The Pediatric Asthma Risk Score (PARS) Predicts Atopic and Non-atopic Asthma Better than the Asthma Predictive Index

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RATIONALE: Despite the continued advancement of our understanding of asthma, identifying at-risk children continues to be difficult. We previously reported the results of a new scoring system called the Pediatric Asthma Risk Score (PARS). Here we compare the performance of the PARS vs the Asthma Predictive Index (API) to predict atopic vs non-atopic asthma and then replicate the results in a second population.

METHODS: The PARS was constructed using multivariate analysis of demographic and clinical data from participants in CCAAPS (Cincinnati Childhood Allergy and Air Pollution Study) with asthma diagnosis at age 7yrs (n=589). Atopic asthma and non-atopic asthma were defined as asthma ever with or without a positive skin-prick test (SPT) ever, respectively. The results were compared to the API and replicated in the Isle of Wight birth cohort (IOW, n=981; atopy and asthma defined at ages 4 and 10yrs, respectively). Area under the curve (AUC) was compared using DeLong’s test.

RESULTS: The PARS predicted atopic asthma significantly better than the API in both CCAAPS (AUC=0.82 vs 0.71, p=0.004) and the IOW (0.87 vs 0.74, p=0.004). PARS also predicted non-atopic asthma as well as the API in CCAAPS (0.71 vs 0.63, p=0.32) but significantly better in the IOW (0.74 vs 0.64, p=0.04).

CONCLUSIONS: The PARS outperformed the API in predicting the development of both atopic and non-atopic asthma in the CCAAPS. In addition, the robustness of the model is supported by replication in the IOW. In conclusion, the PARS was shown to be a robust model that better predicts atopic and non-atopic asthma.
38 Does small airway predict bronchial hyperresponsiveness? An observational retrospective study to evaluate small airways dysfunction

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RATIONALE: Small airway (bronchioles less than 2 mm in diameter) means less than 10% of total airway resistance. In despite of it is not commonly used at clinical practice because its variability, its dysfunction has been closely linked with severity of asthma (both with symptoms and with respiratory tests).

METHODS: We have done an observational retrospective study to evaluate the relationship between small airways dysfunction and bronchial hyperresponsiveness (BHR). We studied the small airway in 70 spirometries and the presence or not of BHR through methacholine provocations. We analyzed them with Student T-Test.

RESULTS: There was no difference in sex or age. The patients without BHR have a forced expiratory volume in one-second (FEV1) value statistically superior to patients with BHR (3.35 vs 2.93, p=0.02). In the same way, the values of forced expiratory flow at 75% (FEF75%) and at 50% (FEF50%) of the vital capacity, are statistically lower in patients with BHR: FEF 75% 6.93 vs 5.51, p=0.004; FEF 50% 4.18 vs 3.25, p=0.00. The smallest airway, FEF25% has not shown difference statistically significant between the groups: 1.890 vs 1.385, p=0.09.

No correlation was found between the patients who also have rhinitis symptoms, p=0.88. Neither it was a difference with other markers, such as fraction of exhaled nitric oxide, FENO (p=0.15).

CONCLUSIONS: Increasing evidence shows the relationship between the small airways and the clinical expression and severity of asthma. This study concludes the importance of small airway to predict bronchial hyperresponsiveness especially FEF75% and FEF50%. A better understanding of the role small airways is playing in asthma is needed.

39 Respiratory Comorbidities Associated with Bronchiectasis in Patients with Common Variable Immunodeficiency

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RATIONALE: Bronchiectasis are knowingly associated with lung infections; however, additional respiratory conditions may contribute to their development. Accordingly, we aimed to identify respiratory comorbidities associated with bronchiectasis in patients with CVID.

METHODS: We conducted a cross-sectional analysis of 869 CVID cases in the USIDNET registry. The main outcome was physician-reported bronchiectasis. Demographic and clinical characteristics were compared using chi-square or Wilcoxon-Mann-Whitney tests. Logistic regression models were built to evaluate associations between respiratory comorbidities and bronchiectasis.

RESULTS: There were 121 CVID patients with bronchiectasis. Affected individuals were significantly older (median age 52 yr. vs. 45 yr. in group without bronchiectasis, p=0.0001) and had lower serum IgA (median IgA 11 mg/dL vs. 29.5 mg/dL in unaffected patients, p=0.0179). Our analyses showed that sinusitis (OR = 2.29 95%CI 1.26, 4.16), pneumonia (OR = 3.66 95%CI 2.20, 6.08), lung abscesses (OR = 3.73 95%CI 1.11, 12.52) and bronchiolitis obliterans (BO) (OR = 6.49 95%CI 2.09, 20.14) were associated with increased odds of having bronchiectasis. In contrast, upper airway inflammatory conditions (allergic and non-allergic), inflammatory lower respiratory complications (e.g. granulomas, nodules, interstitial lung disease/pneumonia, GLILD, etc.) as well as lower airway disease (e.g. asthma, bronchitis, COPD) failed to demonstrate associations with bronchiectasis.

CONCLUSIONS: Our findings showed that not only lower but upper respiratory infections (sinusitis) and BO are independently associated with bronchiectasis in CVID. Our study has limitations (cross-sectional, risk of recall/selection/attrition bias) but nonetheless, examines a large patient population and motivates further investigation into a relevant topic. Early detection and treatment of respiratory coexisting conditions may contribute to prevent the development of bronchiectasis in CVID patients.

40 Evaluation of different treatments for Specific Antibody Deficiency with Normal Immunoglobulins

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RATIONALE: Specific Antibody Deficiency (SAD) is a primary immunodeficiency characterized by normal immunoglobulins with deficient response to polysaccharide antigen vaccination. Currently there is a lack of consensus regarding the management of this disease. The aim of this study was to determine whether there was a statistically significant difference in rate of infections in patients diagnosed with SAD who were managed with IVIG, prophylactic antibiotics, and clinical observation.

METHODS: We conducted a retrospective review of 26 patients recruited from the University of Kansas Medical Center with the diagnosis of SAD who were above the age 18. We determined the rate of antibiotic prescriptions per year for patients with SAD treated with immunoglobulin supplementation, prophylactic antibiotic, or clinical observation.

RESULTS: There was a significant rate of decreased antibiotic prescriptions in patients treated with IVIG (n=11, p=0.002) or prophylactic antibiotics (n=5, p=0.001) versus those clinically observed (n=11) using a paired t test. The mean difference in antibiotic prescriptions in those patients treated with IVIG versus prophylactic antibiotics was not statistically significant (p=0.254) using an analysis of covariance. The mean IgG level was 914 among all the patients. The mean number of years followed post intervention was 1.25.

CONCLUSIONS: In patients diagnosed with SAD, there was a notable difference in infection rate between treatment with either IVIG or prophylactic antibodies versus clinical observation. However, there was no notable difference in infection rate between IVIG and prophylactic antibiotics. Prophylactic antibiotic therapy for patients with SAD may serve to be more cost effective and practical approach to management.
41 Low IgG2 Level and Increased Risk of Infections in Lung Transplant Recipients

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RATIONALE: Our previous study has demonstrated that lung transplant (LT) recipients with severe hypogammaglobulinemia (HGG) are at increased risk for recurrent pneumonias and more antibiotic courses at 1-year post-transplant. The significance of IgG subclass deficiency has not yet been examined in the LT population.

METHODS: IgG subclass levels were measured before LT in a single-center prospective observational study and related to 1-year post-transplant infectious outcomes and survival. Analysis was performed using non-parametric tests.

RESULTS: 116 LT recipients were evaluated. The median age at transplant was 56.8 years, 62.2% of subjects were males, and 91.8% were Caucasian. 35% of subjects had idiopathic pulmonary fibrosis (IPF) and 32% had chronic obstructive pulmonary disease (COPD). Low IgG2 subclass level was associated with low pre-transplant pneumococcal titer (p = 0.005) as well as an increased incidence of pneumonias (p = 0.001) and decreased survival (p = 0.014). The total number of pneumonias, two or more pneumonias, and the number of days with pneumonia were also related to low IgG2 level (p = 0.0008 for all values). Low IgG2 subclass level was associated with a higher number of post-transplant hospital days (p = 0.01) and ICU days (p = 0.052). IgG subclass levels were not related to the type of induction agent, post-transplant immunosuppression regimen or lymphocyte levels.

CONCLUSIONS: Low pre-transplant IgG2 subclass level may represent an important novel immunologic biomarker in lung transplantation due to its association with increased pneumonias and decreased survival at 1-year post-transplant. The mechanism of these findings will need be studied further.

42 Serum Immunoglobulin Trough Levels Following Immunoglobulin Replacement Therapy in Obese and Non-obese Patients

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RATIONALE: Although immunoglobulin G (IgG) doses are calculated in g/kg body weight (bw) in patients with primary immunodeficiency (PID), dosing in obese patients is controversial. We compared doses and serum IgG levels in obese and non-obese PID patients to determine if different doses are required for similar efficacy.

METHODS: Data were collected from three studies, in which IgPro10 (Privigen®) or Carimune® (CSL Behring, Bern, Switzerland) were administered intravenously once every 3–4 weeks at 200–800 mg/kg bw, as previously individualized by their physicians. This analysis included only patients with a treatment duration of ≥170 days.

RESULTS: 134 non-obese (BMI<30 kg/m²) and 20 obese (BMI≥30 kg/m²) PID patients were eligible for analysis. The median (range) age of obese and non-obese patients was 53.5 (13–64.0) and 20.5 (3–81) years, respectively; the majority had CVID (100% and 69.4%). The IVIG infusion schedules were similar in both groups (4-week schedule: 70.0% vs 76.1%), as were median (range) 4-week IgG doses: obese, 456 (200–800) and non-obese, 489 (200–1066) mg/kg bw. Median (range) serum IgG trough concentrations were similar (obese, 9.29 [5.79–14.31]; non-obese, 9.32 [4.95–21.91] g/L), as were median (range) annualized rates of total infections (obese, 2.60 [0, 9.67]; non-obese, 1.97 [0, 16.65] events/patient year).

CONCLUSIONS: At similar IgG doses (g/kg bw), serum IgG trough levels in obese and non-obese PID patients are close, and we found no evidence of relevant difference in efficacy. Therefore, individualized dosing within the same ranges may be considered for both obese and non-obese patients.

43 A New 20% Concentration Immunoglobulin for Subcutaneous Administration (IGSC 20%)

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RATIONALE: Grifols has developed a new 20% immunoglobulin for subcutaneous administration (IGSC 20%). The purification process and formulation for IGSC 20% is the same as currently used for Gamunex® C, [Immune Globulin Injection (Human), 10% Caprylate/Chromatography Purified], also manufactured by Grifols, but it has twice the immune globulin concentration (20%) compared to Gamunex-C (10%). With over 15 years of clinical experience, Gamunex-C has an extensive record of safety and tolerability when administered intravenously and subcutaneously in diverse patient populations.

METHODS: A number of batches of IGSC 20% have been produced at full industrial scale in order to support clinical studies and process validation. A comprehensive panel of testing has been applied to characterize these batches, including tests for purity, composition and neutralizing activity. Results are presented as average ± standard deviation.

RESULTS: Test results show IGSC 20% consists of 100% gamma globulin by electrophoresis, and is present primarily as monomer plus dimer IgG (99±1%) with minimal aggregate or fragment. IgG distribution are at levels of 62±2% (IgG1), 30±1% (IgG2), 4.3±0.1% (IgG3) and 3.2±0.2% (IgG4). Results of specific antibody testing show the presence of neutralizing antibodies to Diphtheria toxin (14.0±4.9 AU/mL), Measles Virus (1.36±0.26 x US Reference) and Polio Virus Type 1 (0.93 ±0.18 x US Reference).

CONCLUSIONS: IGSC 20% shows characteristics comparable to Gamunex-C®, but with twice the IgG concentration to facilitate subcutaneous administration with reduced volumes. It has a subclass distribution similar to normal plasma, and demonstrated neutralizing activity for a number of specific antigens.
44  Progression Of Antibody Defects

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RATIONALE: While it is a commonly held idea that antibody deficiencies may worsen over time, there are very few published case examples. This report describes 7 pediatric patients with progression of an antibody deficiency over time. Such cases are important for building the knowledge needed to predict which children with recurrent infections might go on to develop a well-defined antibody deficiency.

METHODS: We identified patients in our immunology clinic with recurrent sinopulmonary infections who were known to have a normal IgG level at initial evaluation, and went on to demonstrate new onset of an antibody defect or progression of an initially subtle defect. We performed a retrospective chart review documenting immunoglobulin levels, vaccine response, and memory B cells. Patients with malignancy or serum protein loss were excluded.

RESULTS: Seven patients met criteria. At initial presentation, all had normal serum total IgG, two had absent IgA, and all had normal or elevated IgM. Over time, 6 of the 7 patients developed low IgG. 2 had a progressive loss of IgA, and 4 developed low IgM. Two patients failed to respond to both protein and polysaccharide vaccines. Five of these patients had abnormally low class-switched memory B cells.

CONCLUSIONS: This study demonstrates the need for continued monitoring and periodic lab evaluation in children with a persistent pattern of sinopulmonary infections despite initially normal results. Susceptibility to infections may present early, when the antibody compartment appears intact. While additional studies are needed, low class-switched memory B cells could correlate with progression of antibody deficiencies.

46  Withdrawn

47  Poor specific antibody response in patients with mucopolysaccharidosis

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RATIONALE: MPS are lysosomal disorders caused by the deficiency of different enzymes that degrade glycosaminoglycans (GAG). Lysosome represents a vital component of the immune system through autophagy and antigen processing/presentation. Organ dysfunction modifies the immune response of these patients which, associated with structural factors, could lead to recurrent sinopulmonary infections. The aim of this study is to carry out the initial immunological evaluation of MPS patients.

METHODS: Interviews were conducted across previous infections and laboratory tests for blood counts, serum immunoglobulins, and response to protein/polysaccharide vaccine of fourteen patients with MPS who were older than 4y/o and had complete vaccination schedule, including pneumococcal polysaccharide vaccine.

RESULTS: All patients underwent enzyme replacement therapy (ERT). They have reported previous pneumonia and had improvement in the frequency of infections after ERT. Eleven patients (80%) had background laboratory tests for blood counts, serum immunoglobulins, and response to protein/polysaccharide vaccine. Over 70% had no response to pneumococcal serotypes 1 and 9.

CONCLUSIONS: Infections are a major cause of death in MPS patients. Specific antibody response is a primary immunodeficiency and it may be evolved in the mechanisms leading to recurrent infections in these patients. Further studies are required to fully understand the reason why absence of specific antibody response is highly prevalent in this group.
Hypogammaglobulinemia is observed not only with B-cell depletion therapies, but also with alternative immunomodulatory agents for MS. Further efforts are needed to identify demographic, clinical, and medication dose-related predictors of hypogammaglobulinemia, significant infection, and need for IgG replacement, as baseline IgG levels alone do not appear to be predictive.

CONCLUSIONS: Hypogammaglobulinemia is associated with recurrent respiratory infections. We hypothesize that patients with frequent COPD exacerbations have an increased incidence of hypogammaglobulinemia. METHODS: Medical records at the Johns Hopkins Hospital were retrospectively searched (June 2016-June 2017) for all adults with frequent (2 or more) documented COPD exacerbations within any 12-month period. Hypogammaglobulinemia was defined as serum IgG below the lower limit of normal (<751 mg/dL). The incidence of hypogammaglobulinemia was compared in patients with frequent exacerbations, versus those with 1 or 0 yearly exacerbations.

RESULTS: 161 patients were found to have 2 or more COPD exacerbations within a 1-year period. 56/161 had IgG levels on record. 22/56 patients with frequent exacerbations, versus those with 1 or 0 yearly exacerbations.

CONCLUSIONS: This is the largest study of its kind illustrating the association between hypogammaglobulinemia and frequent COPD exacerbations. This data will serve as a cornerstone for future prospective studies evaluating antibody deficiency in COPD, and the potential role for immunomodulatory therapy in reducing COPD exacerbations.
51 Long Term Follow-Up of a Common Variable Immunodeficiency Patient with Infliximab Responsive Granulomatous Disease

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RATIONALE: The best treatment for common variable immunodeficiency (CVID) patients with granulomatous disease remains elusive.

METHODS: We describe the follow up of a CVID patient with infliximab responsive granulomatous disease.

RESULTS: We have previously described a now 72 year old white woman diagnosed as CVID at the age of 41. Serum IgG was 112 mg%, IgA 7 mg% and IgM 31 mg%. She was placed on monthly IVIG with good infectious control. From 1999 she developed necrotizing granulomatous nodular lesions affecting her vocal cords, conjunctiva and skin. Some of her skin lesions became ulcerated and painful. She initially improved on high dose prednisone but had severe steroid adverse effects including several vertebral fractures. Cutaneous lesions extended to all limbs, became ulcerated and severely painful. Ciclosporin up to 5 mg/Kg failed to control. In 2008, infliximab 5 mg/Kg was initiated and, after four courses, all but one ulcer were resolved. For the next 11 years, she had immediate skin flares as soon as infliximab was stopped. In 2017 she had an ITP, stopped infliximab and received high dose steroids. When steroids were tapered painful skin ulcers reappeared that were controlled again with infliximab. Laboratory studies showed an increase in IgM levels after placebo on infliximab that kept variable high until infliximab was stopped; high circulating CD4+ follicular helper T cells and CD20+ B cells diminishing over time to 1%.

CONCLUSIONS: Long term follow-up of this infliximab responsive CVID patient shows an unrelenting course of this complication and an unexplained relationship between serum IgM with infliximab.

52 Predicting Patient Response To Pneumococcal 23-vaccine (PPV23) Using Age, Baseline Immunoglobulins, and Pneumococcal Serotypes

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RATIONALE: The pneumococcal polysaccharide 23-serotype vaccine (PPV23) is an integral part of the evaluation and diagnosis of humoral antibody deficiencies. Although there are guidelines on how to interpret overall vaccine responses, there is a paucity of evidence on the significance of individual serotypes as possible predictors of immunodeficiency or future risk of immunodeficiency.

METHODS: We performed a statistical evaluation of age, serum immunoglobulins, and pre- and post-vaccination pneumococcal titers of individuals with recurrent infections to predict their response, non-response, or transient response. An ordinal method was used to determine statistical significance. Four hundred ninety-two patients were screened, and three hundred patients met the inclusion criteria.

RESULTS: If a pre-vaccine titer to serotype 8 is between 0.65 and 1.05 mg/mL and serotype 5 is less than 0.25 mg/mL, the patient will most likely respond to the vaccine (responder). If a pre-vaccine titer to serotype 8 is greater than 1.05 mg/mL and the serum IgG is less than 597.5 mg/dL, the patient will most likely not respond to the vaccine (non-responder). If the serotype 8 is less than 0.65 mg/mL, serotype 3 is less than 0.25 mg/mL, age is less than 34.5 years, and the IgA is between 64 and 124 mg/dL they will most likely be a transient responder (transient).

CONCLUSIONS: The predictability of initial immunological testing to determine progression has not been fully elucidated. We show that an evaluation of age, immunoglobulin levels, and pre-vaccination serotype titers can suggest a response to PPV-23 in a responder, non-responder, and transient responder.

53 Optimization and clinical application of lymphocyte proliferation test using 5-bromo-2′-deoxyuridine for the allergic patients

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RATIONALE: The lymphocyte proliferation test (LPT) has been used to diagnose allergic diseases such as food protein-induced enterocolitis syndrome (FPIES) or drug allergy. For most LPTs, the radioisotope- tritiated thymidine (3HTdR) is commonly used owing to its higher sensitivity and wider dynamic range. An alternative cell proliferation assay is LPT using 5-bromo-2′-deoxyuridine (BrDU), which is a non-radioactive analog of 3HTdR. We optimized the LPT protocol using BrdU and performed this test for patients with allergies.

METHODS: Peripheral blood mononuclear cells (PBMCs) were obtained from healthy individuals or patients with allergies after written informed consent, and an allergic response was stimulated with either an allergen or phytohemagglutinin (PHA) as a positive control. Stimulated samples were labeled with 10 μmol/L of BrdU in the final 2 hours or overnight and analyzed with a chemiluminescent-based BrdU ELISA kit. The stimulation index (SI) was calculated as the ratio of stimulated-to-unstimulated chemiluminescence intensity.

RESULTS: The overnight BrdU labeling showed higher signal intensity than the 2-hour BrdU labeling. The time course study for the incubation period of 3–6 days showed that days 5 and 6 were higher in allergen stimulation. Proliferation of PBMCs from patients with FPIES following antigen stimulation with milk, alpha casein, beta casein, kappa casein, and beta-lactoglobulin was observed using BrdU, which was consistent with that observed using 3HTdR.

CONCLUSIONS: LPT using BrdU may be applicable for the clinical diagnoses of allergic diseases. Additionally, the optimal stimulant dose and cutoff value need to be determined.
54 Expression of B7-Family Co-inhibitory Molecules by Dendritic Cells from Pancreatic Cancer Patients

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RATIONALE: Expression of both co-inhibitory and co-stimulatory molecules is a key feature of antigen-presenting cells which allow initiation or suppression of T-cell activation. Excessive expression of co-inhibitory molecules may be associated with tolerogenic properties of dendritic cells (DC). Expression of B7-family of co-inhibitory molecules by DC was assessed.

METHODS: Blood samples from 14 patients with stage II-III pancreatic cancer were studied. Monocyte-derived dendritic cells were obtained. Expression of CD273 (B7-H4), CD275 (B7-H2), CD276 (B7-H3), B7-H4, B7-H5 and B7-H6 molecules was assessed by FCM. CaCo-2 cell line served as a positive expression control.

RESULTS: Expression of CD276 molecule was approximately 100% (99.1; range 98.6 to 99.7) with high MFI (53.6; range 42.5 to 92.7), CD274 expression was 60.5% (range 53.6 to 66.9 %). Only 23.6% (range 20.6 to 38.3 %) of DC expressed CD273 and CD275* DC varied from 11.8% to 30.0% (median 14.8%). The expression of B7-H4, B7-H5 and B7-H6 were absent in the majority of DC. Only 2 DC samples expressed B7-H4 (2.6% and 3.1%), and 2 other samples of DC had noticeable B7-H5 expression (3.0% and 4.2%). B7-H6 was seen only in one DC sample at 9.6%.

CONCLUSIONS: CD274 and CD276 are constitutive for DC while expression of CD273 and CD275 is present in relatively low numbers of DC. Expression of B7-H4, B7-H5 and B7-H6 is also present in some of the DC samples in pancreatic cancer. The expression of these molecules by dendritic cells in pancreatic cancer patients may impact disease course.

55 Effect of azithromycin on Chlamydia pneumoniae – mediated Interleukin-4 responses

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RATIONALE: Chlamydia pneumoniae is an obligate intracellular bacterium that causes respiratory infection in adults and children. There may exist an association between atypical bacterial pathogens (C. pneumoniae) and asthma, as well as production of immunoglobulin (Ig) E responses in vitro. Interleukin (IL-4) is required for IgE production. Previous studies in our laboratory demonstrated that doxycycline suppresses C. pneumoniae-induced production of IgE and Interleukin (IL-4) responses in peripheral blood mononuclear cells from IgE- allergic asthmatic subjects. Whereas macrolides have anti-chlamydial activity, their effect on in vitro human IL-4 responses to C. pneumoniae has not been studied.

METHODS: Total serum IgE levels were assayed (ELISA). PBMC (1.5 x 10^5) from IgE negative adult atopic subjects (N=5) was infected +/- C. pneumoniae BAL69 (multiplicity of infection of 0.1), +/- azithromycin (0.1, 1.0 ug/mL) for 10 days. IL-4 levels were determined in supernatants by ELISA. A single unequivocally positive skin test, or history of atopic dermatitis or allergic rhinitis defined atopy.

RESULTS: Total serum IgE levels were low in all subjects (<100 IU/mL). IL-4 was detected in supernatants of PBMC on day 10. When azithromycin (0.1, 1.0 ug/ml) was added, IL-4 levels decreased (25%, 38%, respectively). When PBMC were infected with C. pneumoniae, IL-4 levels decreased (17%). Addition of azithromycin (0.1, 1.0 ug/mL) decreased IL-4 levels (20%, 10%, respectively).

CONCLUSIONS: These findings indicate that azithromycin decreased IL-4 responses in vitro. However, at low concentrations, azithromycin does modulate C. pneumoniae-induced production of IL-4.

56 Expression of T-bet, GATA-3 and FOXP3 in the Endometrium of Women with Endometriosis and Infertility

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RATIONALE: Endometriosis is the disease characterized by benign growth of the ectopic tissue similar to endometrium in morphological and functional characteristics but lying beyond the uterine cavity. Regulation of the immune response in endometriosis is in patiens with infertility was assessed.

METHODS: The expression of RNA for genes of the transcription factors of Th1, Th2 and T-reg differentiation – T-bet, GATA-3 and Foxp3 were assessed by PCR in endometrial tissue of 42 women with endometriosis associated with infertility and 12 healthy women as controls.

RESULTS: Endometriosis associated with infertility has an increase (p<0.001) in the expression of the RNA for genes of T-bet and GATA-3, respectively, with decrease in the T-bet/GATA-3 (p<0.05) ratio, which consistent with a Th2-dependent immune response. T-bet gene expression is increased (p<0.001) in the early stages of endometriosis, while an increase (p<0.05) in the expression of the GATA-3 gene occurs in later stages. Endometrial tissue in endometriosis patients with infertility has decreased expression of mRNA for Foxp3 (p<0.001) independent of the stage of disease.

CONCLUSIONS: Immunoregulatory factors have a role in the pathogenesis of endometriosis associated with infertility. Assessment of immune imbalance in this condition may provide new opportunities for therapeutic intervention.
57 Group 2 Innate Lymphoid Cells in Patients with Severe Atopic Dermatitis on Dupilumab

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RATIONALE: Dupilumab, a monoclonal antibody against IL-4 receptor alpha (IL-4Rα) that blocks signaling of IL-4 and IL-13 cytokines, is approved by FDA for treatment of severe atopic dermatitis. Th2 cytokines such as IL-4 and IL-13 are involved in the pathogenesis of atopic dermatitis and other allergic disorders. More recently, group 2 innate lymphoid cells (ILC2s) have been described to play a role in allergic disorders including atopic dermatitis. ILC2s produce Th2 cytokines including IL-4 and IL-13. We sought to identify the effect of dupilumab, which blocks IL-4 and IL-13 signaling, on ILC2s.

METHODS: Five patients with severe atopic dermatitis treated with dupilumab and three healthy controls were recruited from Albany Medical College Allergy Clinic. Peripheral blood mononuclear cells were separated from whole blood using Ficoll method. Flow cytometry was used to identify ILC2s.

RESULTS: In a subset of patients with severe atopic dermatitis on dupilumab, results showed there was reduced frequency of ILC2 compared to healthy controls.

CONCLUSIONS: Inhibition of IL-4 and IL-13 signaling through IL-4Rα may lead to decrease frequency of ILC2. More studies are needed to understand the exact mechanism by which IL-4 receptor signaling pathway affects ILC2s.

58 Recognition of synthetic antigenic determinants of clavulanic acid by dendritic cells in patients with immediate allergic reactions to this drug

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RATIONALE: Nowadays, selective reactions to clavulanic acid (CLV) account for 30% of all reactions to the combination of amoxicillin-CLV. However, the sensitivity of in vitro diagnostic tests is not optimal. The identification of the precise antigenic determinants (AD) that are recognized by the immune system could improve the diagnostic methods. Therefore, our aim was to evaluate the recognition of different synthetic determinants of CLV by dendritic cells (DCs).

METHODS: Based on different CLV degradation pathways, 2 AD were proposed and 3 structures were synthesized from each AD: AD-I (CLV1-3) and AD-II (CLV4-6). Peripheral blood mononuclear cells were collected from 10 patients with selective reactions to CLV and 10 controls. Monocyte-derived DCs were cultured with CLV and with the different synthetic structures, CCR7, CD40, CD80, CD83 and CD86 expression were analyzed by flow cytometry. Results were represented as maturation index (MI).

RESULTS: DCs from patients cultured with CLV did not show significant modification in the evaluated markers compared to controls. Higher MI of CCR7, CD40, CD80 and CD83 were found in DCs cultured with CLV2, CLV3 and CLV6 compared to controls. However, the inclusion of CLV1, CLV4 and CLV5 did not improve the analysis. No difference was shown in the expression of CD86 in any case.

CONCLUSIONS: Better recognition by DCs of CLV2, CLV3 and CLV6 is obtained compared with CLV itself. The inclusion of these analogs from both AD could improve the sensitivity of in vitro assays and become useful in the diagnosis of these reactions.

59 C/EBPδ of human coronary artery endothelial cells may play an important role in the IVIG-refractoriness of Kawasaki disease

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RATIONALE: Intravenous immunoglobulin (IVIG) treatment effectively suppresses coronary artery inflammation and reduces the incidence of coronary aneurysms in most patients with Kawasaki disease (KD). However, some patients develop coronary aneurysms, presumably due to IL-1β overexpression. We previously reported that IVIG effectively inhibited TNF-α-induced, but never IL-1β-induced, IL-6 expression by cultured human coronary artery endothelial cells (HCAECs). The aim of this study was to clarify the role of C/EBPδ, a transcription factor for IL-6, in HCAECs in IVIG-refractory KD.

METHODS: HCAECs were stimulated with TNF-α or IL-1β in the presence and absence of 10 mg/ml IVIG for 48 hours. IL-6 mRNA and protein were measured by qPCR and ELISA, respectively. Expression and DNA-binding activity of C/EBPδ were analyzed by immunoblotting and EMSA assay, respectively.

RESULTS: Consistent with our previous study, IVIG completely inhibited TNF-α-induced expression and activity of C/EBPδ in HCAECs. In sharp contrast, IVIG hardly affected IL-1β-induced activation of C/EBPδ in HCAECs.

CONCLUSIONS: C/EBPδ may play a crucial role in the anti-inflammatory mechanisms of IVIG and could be a novel therapeutic target, especially for IVIG-resistant KD.
Evaluation of progesterone-specific serum IgE assay for diagnosis of suspected progesterone hypersensitivity

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RATIONALE: Progesterone hypersensitivity (PH) manifests as dermatologic or other allergic symptoms during the luteal phase of the menstrual cycle. Confirming progesterone-specific IgE (sIgE) by skin testing can be unreliable. Therefore, development of a serum sIgE assay for confirming a diagnosis of PH would be useful for making appropriate treatment decisions.

METHODS: Serum was obtained from patients (N=81) with suspected PH. Commercially obtained progesterone-carrier protein conjugate was characterized by mass spectrometry and used to develop an IgE-specific ELISA. Sera (n=3) from women with classical PH symptoms and healthy non-atopic females (N=4) were used as positive and negative controls, respectively. Any value exceeding the OD cut-off (average negative control value + 3x the standard deviation) was considered positive. A subset of sera (N=16) was used for ELISA-inhibition and in a mediator release assay to evaluate the specificity and functional relevance of progesterone sIgE.

RESULTS: Mass-spectrometry demonstrated a shift of ~4400 Da for the progesterone-conjugate compared to the unconjugated carrier-protein indicating attachment of multiple progesterone molecules to the carrier protein. The results of the direct progesterone sIgE ELISA ranged from highly positive (>2x OD cut-off), mildly positive (>1x to < 2x OD cut-off) and negative (<1x OD cut-off) in 37%, 27% and 36% of sera, respectively. Using progesterone sIgE ELISA-positive sera compared to sIgE ELISA-negative or healthy control sera. ELISA inhibition and beta-hexosaminidase mediator release confirmed specificity and functional relevance of progesterone-sIgE, respectively.

CONCLUSIONS: This ELISA is reliable for detecting increased functionally relevant progesterone sIgE in patients with suspected PH.

High Frequency of S2377X mutation in Filaggrin 2 gene among Brazilian Patients with Atopic Dermatitis: no significant association with severity or persistence of disease

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RATIONALE: We have previously shown that Brazilian patients with moderate-to-severe Atopic Dermatitis (AD) who remained symptomatic despite anti-inflammatory and immunosuppressant therapy presented filaggrin (FLG) expression comparable to control individuals on skin biopsies (JACI 2016;137,AB144). FLG-2 S2377X mutation has been associated with more persistent AD in children of African ancestry. We have investigated FLG-2 mutations in AD patients and correlated results with clinical parameters.

METHODS: FLG-2 region of exon 3 encompassing the mutations S2377X and X2392S was amplified by PCR and sequenced by Sanger technique in 52 adult patients with AD. Total IgE and IgE to Der p1 and Der p2 were determined by ImmunoCAP and ImmunoCAP-ISAC. Vitamin D was measured by chemiluminescence.

RESULTS: S2377X mutation was identified in 24/52 (46%) patients (4 homozygous) and X2392S in one patient (heterozygous) who also presented S2377X mutation. There were no significant differences in: age at onset of symptoms (median 5 and 6.5 years); duration of disease (mean 22.5 and 19.1 years); SCORAD (mean 32.9 and 39.6); total IgE (median 1,439 and 3,635IU/mL); IgE to Der p1 (median 22.3 and 32.3ISU) and Der p2 (median 27.5 and 36.8ISU); vitamin D (mean 24.9 and 25.2ng/mL) and peripheral blood eosinophils (median 450 and 400/mm3), in patients bearing FLG-2 S2377X mutation, as compared to those without the mutation, respectively.

CONCLUSIONS: In Brazilian patients with moderate to severe AD, the presence of S2377X-FLG-2 mutation was not associated with persistence or severity of disease. Our results suggest that other factors including type-2 driven inflammation may play a more important role in pathogenesis.
Comparison of Th1 and Th2 Immune Responses in Chlamydia pneumoniae-infected Peripheral Blood Mononuclear Cells (PBMC) of Adult and Pediatric Asthmatics

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RATIONALE: C. pneumoniae is a common cause of upper and lower respiratory tract infections in both children and adults and can cause asthma exacerbations. Our laboratory has previously demonstrated that T-lymphocyte memory responses of PBMC infected with C. pneumoniae in vitro was increased in asthmatics compared to healthy subjects without asthma. However, there were both Th1 and Th2 responses present in the asthmatic population. In this investigation, we studied differences in the Th response (Th1 versus Th2) to C. pneumoniae infection of PBMC between pediatric and adult patients with asthma.

METHODS: PBMC (1x10^6/ml) from pediatric (<18y) (n=15) and adult (>18y) (n=9) asthmatics were infected or mock infected with C. pneumoniae CM-1 and cultured for 48h. Levels of IL-4 and IFN-gamma in supernatants were measured by ELISA. Cytokine levels of mock infected samples were subtracted from those of infected samples for each study subject. Differences between age groups were determined by Mann-Whitney Test.

RESULTS: PBMC from asthmatic adults produced more IL-4 in response to C. pneumoniae stimulation than those from asthmatic children (p<0.01). There was no significant difference in IFN-gamma production after C. pneumoniae infection between the two study groups (p=0.9).

CONCLUSIONS: We found that a C. pneumoniae-induced Th2 immune profile was prevalent in adult asthmatics, but not in pediatric asthmatics. Repeated or persistent infections with C. pneumoniae can occur and repeat exposure may lead to change in Th response with increasing age in predisposed individuals. Whether this age-specific response to C. pneumoniae contributes to the symptomatology of asthma remains to be further elucidated.

Diversity and complexity of mouse allergens in allergenic products assessed with an immunological approach

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RATIONALE: Mouse allergy is common among laboratory animal workers and infested homes. The predominant allergen, Mus m 1, is part of the Mouse Urinary Proteins (MUPs) complex. The full diversity and immunogenic potential of MUPs have not been fully established yet, and it is not clear that MUPs are the only relevant sensitizing agents. This work investigates the diversity and relative immunogenicity of various MUPs.

METHODS: Liquid chromatography/mass spectrometry (LC/MS) was used for deep proteomic analysis of mouse urine and epithelial extracts. Mouse proteins, resolved by two-dimensional polyacrylamide gel electrophoresis, were screened against IgG and IgE. Reactive spots were picked and examined using LC/MS. Finally, a multiple reaction monitoring (MRM) method was developed for total MUP as well as isoform-specific quantification. LC/MS and MRM results were compared to Mus m 1 quantification by ELISA.

RESULTS: We established a global proteomic signature and a detailed profile of MUPs including their post-translationally modified variants in commercial products and in collected mouse urine. MUP3 resolved into four different protein forms while MUP19 appears to have three protein variants. Using bioinformatics and sequence analyses, we identified unique tryptic peptides for 10 MUPs. Isotopically-labeled unique reference peptides were chemically synthesized and used to develop an MRM method for isoform-specific quantification of MUPS. The MRM assay is being evaluated for comparability with various ELISA assays of Mus m 1.

CONCLUSIONS: We established molecular and immunogenic fingerprints of mouse epithelial and urinary allergenic products. The results are key in guiding research, characterization, quality control, and standardization of existing and future products.
Annual Variation Among Tree Pollen In Las Vegas
From 2015-2018

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RATIONALE: Tree pollens are significant allergens that predominantly occur between February and May. Data are lacking in annual variations of tree pollen in Las Vegas. The objective of this study is to compare airborne tree pollen concentrations in Las Vegas from 2015-2018.

METHODS: Air samples were collected using a Burkard 7-day recording volumetric spore sampler located at a National Allergy Bureau certified sampling site in Las Vegas. Samples were analyzed with a compound light microscope at 400x magnification. Data were compared with a one-way ANOVA.

RESULTS: From 2015-2018, mulberry had the greatest annual mean (1,349 grains/m3 ± 143) when compared to all other tree pollen, peaking at 16,218 grains/m3 in March 2018. Cedar pollen was higher in 2015 when compared to 2016 and 2018 (P = 0.001). Olive concentrations reached a maximum of 855 grains/m3 in 2015. Ash concentrations reached a maximum of 610 grains/m3 in 2018. The mean concentrations of olive and ash were not significantly different between years (P = 1.00). An increasing trend in annual total tree pollen since 2016 was observed.

CONCLUSIONS: Mulberry was by far the predominant tree pollen from 2015-2018. Variations were observed in all airborne tree pollens monitored from year to year. The total tree pollen concentrations have shown a steady increase, possibly due to shorter winters and warmer springs. Further monitoring is needed to determine seasonal trends in tree pollen concentrations and provide timely forecasts for the community.

Exposure and Sensitization to Formaldehyde of Urban Children at Risk of Asthma and Rhinitis

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RATIONALE: Evidence supporting a link of indoor formaldehyde exposure to asthma and rhinitis is limited and controversial. Furthermore, few studies have examined the metabolite or sensitization to formaldehyde in subjects with asthma and/or rhinitis.

METHODS: We prospectively recruited 620 5th and 6th Grade elementary school students (10-12 years old). This general population-based cohort study was performed in 22 randomly selected classrooms of 11 elementary schools in Seongnam City, Korea between March 2017 and March 2018. We comprehensively investigated the association of indoor exposure in school classrooms, urinary excretion, and sensitization to formaldehyde with asthma and rhinitis, and upper and lower respiratory function. Thus, strategies for reducing inhaled formaldehyde are warranted in the school environment for vulnerable populations of children.

Fungal Exposure in New York City Low-Income Homes Enrolled in a Mold Intervention Study

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RATIONALE: Fungal (mold) contamination is a common problem in urban homes of lower-income families who have less control over housing conditions conducive to mold growth. The Environmental Related Moldiness Index (ERMI) is a standardized, quantitative polymerase chain (PCR) method for assessing fungal species related to water damage. The aim of the study is to characterize changes in fungal species following a cost-effective home intervention in a low-income, primarily Latino neighborhood with high asthma prevalence. We hypothesized that the baseline ERMI score from a child’s home would be associated with asthma symptoms.

METHODS: Settled dust was collected from 28 homes that participated in an intervention 2-5 years ago and 33 newly recruited homes (homes that have a child with asthma and a report of mold). The ERMI score was assessed in settled dust.

RESULTS: Forty-nine percent of homes had an ERMI score ≥5, which is a higher percentage than reported either for a nationally represented sample of homes (25% of homes) or homes we tested from middle-income NYC children with asthma and visible mold in their home (23%). ERMI scores did not differ among children in different recruitment groups (P=0.25). In a model adjusting for sex, age, maternal asthma, paternal asthma, study group and dust sieves method, the ERMI score was positively associated with reports of wheeze in the previous 12 months (odds ratio 1.3; P=0.027).

CONCLUSIONS: These preliminary findings suggest that fungal species in the homes of lower-income asthmatic children with asthma symptoms may differ from other communities and be associated with asthma symptoms.
69 Increase in Pediatric Respiratory Visits associated with Wildfires in San Diego County

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RATIONALE: There is significant data that demonstrates increased ER visits and hospitalizations for cardiopulmonary causes during wildfire outbreaks. This utilization correlates with increased PM 2.5 and other airborne pollutants and has been demonstrated to affect vulnerable populations such as those with asthma.

METHODS: All Emergency Room and Urgent Care visits from 2011 to 2017 were collected from Rady Children’s Hospital. Specific data fields collected included date of visit, date of birth, zip code of residence, insurance type, language, respiratory/non-respiratory visit, and diagnosis. Air pollution data was provided by San Diego Air Pollution Control Division from the Camp Pendleton monitor from 2014 to 2017. Specific dates of interest included May 12-23, 2014 and December 6-17, 2017.

RESULTS: A distinct and intense peak for PM 2.5 can be seen in May of 2014 consistent with the timing of the Bernardo fire. The majority of patients where younger, age 0-6 (70%) and had Medi-Cal insurance (74%). There was a significant deviation for respiratory visits for the May 2014 fires. By age group, there is a stronger signal for respiratory visits during the May 2014 fire for kids aged 0-6.

CONCLUSIONS: To our knowledge this is one of the first studies to link an increase in pediatric urgent care and emergency room visits associated with wildfire-linked PM 2.5. Natural disasters such as wildfires are expected to increase in frequency and intensity in the future. Climate change will disproportionately affect young children, magnifying existing disparities. As these conditions compound and wildfires become more frequent, it is important for those at risk to be prepared.

70 Comparative Evaluation Of Pulmonary Function Tests In Professional Cleaners While Exposed To The Occupational Workplace And After The Vacation Period

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RATIONALE: Cleaning workers are likely at high risk of developing asthma. The Forced Expiratory Volume in 1 second (FEV1) is an important marker of the severity of obstructive diseases and its prognosis. We aimed to comparatively evaluate the pulmonary function of these workers during the exposure to the workplace and after vacation. Additionally, we assessed the impact of smoking status and the presence of atopy. METHODS: The volunteers performed spirometry during the work period and after returning from vacation. Respiratory symptoms and smoking status were assessed through validated questionnaires. Atopy was measured with skin prick tests. Workers with respiratory infections and/or asthma were not included.

RESULTS: A total of 67 subjects were evaluated (83.6% were female). The mean age was 40.2 years. The FEV1 values obtained before and after the vacation were within the normal range. However, we found a significant increase in FEV1 values obtained after the holidays (p <0.05). There were no significant difference both between smokers (p = 0.84) and non-smokers (p = 0.60). Likewise, there were no significant differences between atopics (p = 0.69) and nonatopics (p = 0.72).

CONCLUSIONS: Spirometry values were within normal limits at both times of the study, but the significant increase in FEV1 after vacation suggests that exposure to the workplace might have a deleterious effect in lung function among these workers. We could not demonstrate whether atopy or smoking status would have an impact on lung function in this population.

71 Characterizing Airway Inflammatory Responses to Wood-Smoke Inhalation

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RATIONALE: U.S. wildfires have increased in frequency and duration in recent decades. Wildfires cause abrupt increases in ambient air particulate matter and can have negative effects on pulmonary health. Glutathione-S-transferase Mu1 (GSTM1) null genotype increases susceptibility to ozone, but its role in wood-smoke response is unknown.

METHODS: Healthy volunteers underwent exposure to 500 μg/m³ wood-smoke for 2 hours with alternating periods of exercise and rest. Induced sputum samples were obtained prior to exposure and 6 and 24 hours after exposure. GSTM1 genotype was determined. Participants were deemed wood-smoke “responders” if they experienced a ≥10% increase in sputum %PMN at 24 hours. A multiple variable regression analysis was performed to identify modifiers of response to wood-smoke.

RESULTS: Twenty-seven paired sputum samples were available for analysis. Eighteen of 27 (67%) participants were classified as wood-smoke responders. GSTM1 null status did not predict responder status, but null responders showed a more robust inflammatory response than sufficient responders. Among all subjects, GSTM1 null status was associated with an on average a 15% greater increase in sputum %PMN following exposure [β = 15.34 (6.04), 95% CI (3.51, 27.17), p = 0.01]. Higher baseline sputum TH1 cytokines (IL-1β, IL-6, IL-8 and TNF-α) was associated with greater inflammatory response to wood-smoke, while sex and body mass index were not significant response modifiers.

CONCLUSIONS: Our findings suggest that humans are not equally susceptible to the effects of wood-smoke and that GSTM1 genotype and other factors may impact response. This model will be used to study the efficacy of prophylactic anti-inflammatory treatments in susceptible individuals.
The page contains abstracts related to various topics including environmental health, allergy, and chemotherapy skin testing. Here are the summaries:

### AB24 Abstracts

**72 In vitro study of the adsorption of 2.5 \( \mu \)m particles (PM\(_{2.5}\)) by hydroxy-propyl-methyl-cellulose powder (HPMC)**

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- **Charité Universitätsmedizin Berlin, Berlin, Germany**
- **University Hospital Sv Ivan Rilski, Sofia, Bulgaria**

**Rationale:** Air pollution particles of 2.5 \( \mu \)m (PM\(_{2.5}\)), besides causing respiratory and cardiovascular disease, facilitate allergen absorption and exacerbate nasal allergy. Powdered hydroxyl-propyl-methyl-cellulose (pHPMC), insufflated nasally, swells and forms a gel barrier against offending allergens. This in vitro study examined the ability of pHPMC to adsorb PM\(_{2.5}\).

**Methods:** Squares of 1.5% agar (1 cm\(^2\)) were mounted on microscope slides. Gels of pHPMC and lactose (control) were prepared by mixing 0.25g of powder with 5ml saline to obtain the desired viscosity of gel. A thin—50\( \mu \)l layer of pHPMC, lactose or vehicle (no product control) was applied to each slide. Fluorescent particles (30\( \mu \)l, 1.7-2.2 \( \mu \)m) were applied adjacent to the test substance. Slides were incubated at 35°C and 90% relative humidity to stimulate nasal for conditions for 15, 30, 60, 180 and 360 minutes after which agar blocks were removed, the pHPMC removed by washing and PM\(_{2.5}\) adsorbed into the agar extracted and counted by flow cytometry.

**Results:** With lactose and no product, the number of particles adsorbed into the agar increased slowly with time to maxima of 12,989 \( \pm \) 1137 and 12,999 \( \pm \) 465 (mean \( \pm \) SEM) at 360 min. With pHPMC only 826 \( \pm \) 312 particles were recovered showing that pHPMC adsorbed PM\(_{2.5}\) not allowing uptake into the agar.

**Conclusions:** pHPMC adsorbed PM\(_{2.5}\), reducing their uptake into agar by 94% indicating it will have a potent ability, when insufflated into the nose, to protect the nasal mucosa from damage by PM\(_{2.5}\).

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**73 Comparison between PM2.5 levels on east coast and state of California in relationship to asthma**

- **Ariel J. Stateman, MS**, Hayat H. Sour, MS, Joshua K. Baguley, MS, Shandra V. Bellinger, MS, and Felix E. Rivera-Mariani, PhD
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**Rationale:** Asthma is a chronic disease that causes swelling of the airways making it difficult to breathe. Common triggers that cause inflammation in the airway include pollen, smoke, stress, chemicals, and extreme weather changes, which may contribute to asthma. There is limited research that explains why California, despite many wildfires, has a lower prevalence of asthma compared to the east coast.

**Methods:** Data on asthma prevalence, by state, for the year 2015 was obtained from Adults Asthma data collected via the Behavioral Risk Factor Surveillance System of the US Center for Disease Control and Prevention (CDC). PM\(_{2.5}\) concentrations for the year 2015 were retrieved from the publicly-available data from the Air Quality Index Report of the US Environmental Protection.

**Results:** For the year 2015, the highest prevalence of asthma was among the east coast (all states that have shorelines on the Atlantic Ocean) with 9.2% of adults. Despite California being in the top two states for wildfires, it has one of the lowest prevalence asthma (7.7%) nationwide. When looking at the number of days PM\(_{2.5}\) was the main pollutant across each state, California had a 19% less days (128.2 days) than the east coast states (153.4 days).

**Conclusions:** Different rates of asthma between different regions within the US may be due to different exposure risk to PM\(_{2.5}\) that originate from sources other than natural disasters, such as forest fires. Future studies should focus on other regions with regards to high PM\(_{2.5}\) levels in relationship to asthma.

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**74 Practice Patterns of Chemotherapy Skin Testing and Desensitization**

- **Amy Levin, MD**, and Aleena Banerji, MD
- **Massachusetts General Hospital, Boston, MA**

**Rationale:** Hypersensitivity reactions (HSRs) to chemotherapeutic agents are common and limit treatment options when skin testing and desensitization protocols are not utilized. We performed a survey to evaluate national practice patterns.

**Methods:** We sent an 8-question survey through the American Academy of Allergy, Asthma & Immunology (AAAAI) to allergy/immunology physician members actively in practice. Surveys were sent to a 20% representative sample. We obtained basic characteristics including gender, practice type, practice location, and year of fellowship graduation. Frequency of and barriers to chemotherapy skin testing and desensitization were assessed.

**Results:** Among 806 physicians who received the survey, 75 participated (response rate 9%). Seventy-two of the respondents met criteria for inclusion (three respondents not in active practice). Over half of respondents were male (41/72; 57%), completed training after 2000 (40/70; 57%), and practiced in a non-academic group setting (34/67; 51%). Few allergists performed chemotherapy skin testing (13/72; 18%) or desensitization (17/71; 24%). The most common barriers to chemotherapy desensitization included: lack of appropriate patient population (64%), lack of access to chemotherapy (43%), time (30%), cost (28%), personnel (28%), and lack of access to desensitization protocols (28%). Most respondents (50/71; 72%) were interested in learning about these protocols.

**Conclusions:** Allergists/immunologists infrequently skin test and desensitize to chemotherapeutic agents but are interested in learning more. They perform these two procedures at comparable rates, despite the greater ease and fewer resources required for skin testing. Expanded education efforts around chemotherapy skin testing and desensitization are important for expanding the scope of allergy practice and improving care.

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**75 Characteristics of Persistent Penicillin Allergy Labels in a Large Electronic Health Record Database**

- **Cosby A. Stone, Jr, MD, MPH**, Wei-Qi Wei, and Elizabeth J. Phillips, MD FAAAAI FIDSA; Vanderbilt University Medical Center, Nashville, TN.

**Rationale:** Penicillin allergy labels are prevalent, and associated with inferior individual and public health outcomes. Most penicillin allergy histories are either low risk or inaccurate: >96% of patients reporting penicillin allergy are negative on formal testing. To better target specific populations for penicillin allergy de-labeling we aimed to define characteristics of patients persistently labeled as penicillin allergic.

**Methods:** From the Vanderbilt Synthetic Derivative (n=2,993,336) we identified persons reporting penicillin-class allergies and stratified by age, sex, race, and linkage to Vanderbilt outpatient primary care. We examined risk factors for patients who were persistently labeled versus those who had their labels successfully removed.

**Results:** Of 2,993,336 patients studied, 237,144 (7.9%) had carried a penicillin-class allergy label at some point in their care. The proportion of penicillin allergy label carriage was significantly higher over the age of 50 (9.2%) versus under 50 (6.8%), in women (9.7%) versus men (6.8%), European- (10.3%) versus African- (6.5%) Americans, and those whose medical home was at Vanderbilt (14.3%) versus not (6.8%) (all p-values <0.0005, two-sided test of proportions). For patients ever labeled as penicillin allergic, 86,220 (36.4%) had received a penicillin-class drug, yet only 31,700 (36.7%) or 13.3% overall were effectively de-labeled. De-labeling was less common among age 18-50, men, European-Americans, and those whose medical home was not at Vanderbilt (all p-values <0.0005, chi-square test).

**Conclusions:** Despite prevalent penicillin exposure in patients labeled as penicillin allergic, penicillin allergy labels are frequently persistent and associated with age, sex and ethnicity. Both targeted and generalizable strategies for effective penicillin allergy label removal are needed.
Outcomes of beta-lactam antibiotic test dose procedures for patients with reported beta-lactam allergy performed in a large US healthcare system

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Rationale: A documented penicillin allergy is associated with increased alternative antibiotic exposures and related adverse events. We assessed beta-lactam test dose procedures prompted by an electronic guideline for inpatients with reported beta-lactam allergies in a large healthcare system.

Methods: We considered beta-lactam test dose procedures performed at two academic and three community Partners HealthCare System hospitals from September 2016 through December 2017. Patient history and test dose outcomes, including hypersensitivity reactions (HSRs) and allergy electronic health record (EHR) changes, were identified. HSR predictors were examined using a multivariable logistic regression model.

Results: 1,046 test dose procedures were included: 808 (77%) to cephalosporins, 149 (14%) to penicillins, and 89 (9%) to carbapenems. Test dose procedures were commonly performed at academic sites (83%), on internal medicine (45%), and ordered by housestaff providers (59%). Overall, 78 patients (7%) had signs or symptoms of an adverse reaction, with 40 (4%) consistent with HSRs. Most HSRs occurred at the full dose step (68%) and required no treatment beyond drug discontinuation (58%); 3 HSR patients were treated with epinephrine. Reported cephalosporin allergy history was associated with an increased HSR odds (aOR 2.96 [95% CI 1.34, 6.58]). Allergies were updated for 474 (45%) patients, with records specified (82%), deleted (16%), and added (8%).

Conclusions: 4% of hospitalized patients with beta-lactam allergy histories receiving guideline-driven beta-lactam test dose procedures had an HSR, and cephalosporin allergy histories conferred a 3-fold increased risk. Allergy records were updated less than half of the time after challenge procedures, suggesting additional education and/or EHR prompting is needed.

Nasal polyposis is a risk factor for having positive lysine-aspirin nasal challenges in aspirin-exacerbated respiratory disease

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Rationale: Aspirin-exacerbated respiratory disease (AERD) is a disorder of polyposis, rhinitis, asthma, and respiratory reactions to non-steroidal anti-inflammatory drugs (NSAIDs). The diagnosis is based on the clinical history and NSAIDs challenge, being nasal provocation test with lysine-aspirin (NPT-LASA) a safer and less time-consuming alternative than oral challenge. Our aim was to evaluate the potential factors related to positive results in NPT-LASA.

Methods: We performed NPT-LASA in 57 confirmed AERD subjects (≥3 episodes of respiratory manifestations with ≥3 different NSAIDs or positive oral challenge with ASA). We also included 30 tolerant individuals to NSAIDs. We analyzed age, gender, underlying diseases, number of episodes, NSAIDs-induced symptoms, time interval of drug intake-reaction onset and last reaction-study in both negative and positive NPT-LASA cases.

Results: From 57 confirmed AERD subjects with a mean of 42.5 (25.75-55.25) years 73.7% were female. The 70.4% had underlying rhinitis, 63% asthma and 30.2% polyposis. The 66% were atopic and 66.7% non-smoker. The 52.7% experienced asthma after NSAIDs intake, 30.9% rhinitis/asthma, 5.4% throat tightness/asthma and 3.64% rhinitis and/or throat tightness. NPT-LASA was positive in 45 patients and negative in all controls (sensitivity: 78.94%; specificity: 100%). The percentage of patients with nasal polyposis was higher in the group with NPT-LASA positive compared to those negative (50% vs 11.1% p=0.002, OR=8.1923-33.274), p=0.004).

Conclusions: NPT-LASA shows a high sensitivity and specificity for diagnosing AERD, being the risk of having a positive NPT-LASA 8 times higher in patient with nasal polyposis.
The Appropriate Cut-Off Value of Interferon-Gamma ELISPOT Assay for Drug Hypersensitivity Diagnosis in Clinical Practice

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RATIONALE: Interferon gamma (IFN-γ) enzyme-linked immunospot (ELISpot) assay has been introduced for drug hypersensitivity diagnosis, however, the cut-off value is not yet optimized. The aim is to determine the clinical cut-off value of IFN-γ ELISpot assay in patients with a history of drug hypersensitivity based on drug challenge test and/or skin test results.

METHODS: The frequencies of IFN-γ releasing cells after stimulating peripheral blood mononuclear cells (PBMC) with 72 suspected culprit drug(s) in 54 patients with a history of drug hypersensitivity were comparatively analyzed with the results of drug challenge test and/or skin test results. The optimal cut-off value was calculated based on the receiver operating characteristic (ROC) curve results.

RESULTS: About 40.7% (22/54) of patients in this study have a history of severe cutaneous adverse reactions (SCARs) including 8 drug reaction with eosinophilia and systemic symptoms, 5 Stevens-Johnson syndrome/ toxic epidermal necrolysis, and 9 acute generalized exanthematous pustulosis. The average frequencies of drug-induced IFN-γ releasing cells in confirmed drug hypersensitivity group were significantly higher than those in drug tolerant group (70.2 vs. 23.4 and 13.7 ± 10.8 cells/10^6 PBMC), respectively; p value=0.04. According to ROC curve analysis, the cut-off value of 22 cells/10^6 PBMC yielded 65.2% sensitivity, 95.9% specificity, and excellent positive likelihood ratio (15.9). The sensitivity and specificity increased to 77.8% and 100.0%, respectively, in drug-induced SCAR subjects.

CONCLUSIONS: Our study confirms that IFN-γ ELISpot assay has good clinical diagnostic values to identify the culprit drug, especially in SCARs. The suspected culprit drugs with positive ELISpot result should be avoided from further use due to high specificity of the test.

Hypersensitivity reactions to antituberculosis drugs confirmed by interferon gamma enzyme-linked immunospot assay

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RATIONALE: The identification of antituberculosis drugs (anti-TB) as a cause of hypersensitivity reactions is extremely difficult since all drugs were started simultaneously. This study was to explore clinical characteristics of anti-TB hypersensitivity in patients with positive interferon-gamma enzyme-linked immunospot (IFN-γ ELISpot) results.

METHODS: Thirty-four patients (18 males, 16 females) with a recent hypersensitivity reaction to anti-TB were recruited into this study. Drug-induced IFN-γ releasing cells were measured by using IFN-γ ELISpot assay upon stimulating peripheral blood mononuclear cells (PBMCs) with isoniazid, rifampicin, pyrazinamide, and ethambutol, separately. Positive ELISpot response was defined as ≥ 20 spot-forming units (SFU)/10^6 PBMCs.

RESULTS: Patients’ average age was 38.3±8.6 years and one-third of them (32.4%) were HIV-positive subjects. Nearly half of them (47.1%) yielded positive ELISpot response. Stevens-Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS) were diagnosed in 10 and 6 patients, respectively. Rifampicin was the culprit drug in 60.0% of ELISpot-confirmed SJS while isoniazid was the culprit drug in 44.4% of ELISpot-confirmed DRESS. Multiple drug reactors were observed in 80% of ELISpot-confirmed DRESS. Latency periods after drug exposure to first symptoms in ELISpot-confirmed SJS and DRESS were 17.3±5.5 and 48±5.9 days, respectively. Pyrazinamide and ethambutol were the responsible drugs in only 16% and 12% of all ELISpot-confirmed cases. The average frequencies of isoniazid, rifampicin, pyrazinamide, and ethambutol-induced IFN-γ releasing cells in confirmed cases were 65.3±19.7, 276.9±177.3, 144.3±110.8, and 44.7±11.6 SFU/10^6 PBMCs.

CONCLUSIONS: Rifampicin and isoniazid were the main culprits in anti-TB-induced SJS and DRESS, respectively. Multiple drug hypersensitivity was common in anti-TB induced DRESS.

Prevalence of physician-documented beta-lactam allergy in Canadian primary care practices

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RATIONALE: Research conducted in the U.S has determined the prevalence of reported beta-lactam allergy to be between 10-17%. Currently, there is a lack of available Canadian data on beta-lactam allergy prevalence. The purpose of this study is to describe the prevalence of physician documented beta-lactam allergy in a Canadian outpatient population and to comment on associated characteristics of patients and providers.

METHODS: We conducted a retrospective cohort study using Electronic Medical Record (EMR) data from the Manitoba Primary Care Research Network (MaPReN). An algorithm was generated to define and extract data on physician documented beta-lactam allergy from the EMR dataset (n = 221,132). Once established; prevalence, provider, and patient variables were analyzed using a multivariate regression to assess differences between patients with reported beta-lactam allergies and those without.

RESULTS: Of the 221,132 records in the MaPReN database, it was found that 2.89% (6397/221,132) of patients had a recorded beta-lactam allergy. Documented beta-lactam allergy was found to be associated with female sex (1.542 OR, 95% CI 1.463-1.623) and medical comorbidities including asthma and eczema (P<0.001 for both asthma and eczema).

CONCLUSIONS: Prevalence of physician reported beta-lactam allergy in Manitoba was lower than previously recorded American studies. The validated algorithm will be applied to the larger Canadian Primary Care Sentinel Surveillance Network repository to describe epidemiology at a national scale and to further aid efforts in reducing burden associated with erroneous labelling.
**Use of a Penicillin Allergy Screening Algorithm Incorporating Direct Challenges to Manage Penicillin Allergic Inpatients**

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**Rationale:** Penicillin skin testing (PST) may be unnecessary to de-label low-risk patients. We describe the utility and safety of a penicillin allergy history algorithm (PAHA) that incorporates graded challenges to penicillin (GCP) into the inpatient management of penicillin allergy.

**Methods:** Pharmacists identified adult inpatients with penicillin allergy receiving alternative antibiotics when a β-lactam antibiotic was indicated. The PAHA was administered to identify patients for PST versus GCP. Patients were evaluated by an allergist in person or via telemedicine. Patients with negative evaluations were transitioned to β-lactam therapy.

**Results:** Of 106 patients qualifying for inclusion, 50 consented. Per the PAHA, 23 and 27 patients underwent PST and GCP, respectively. PST group historical reactions included recent hives (12, 52.0%), angioedema (11, 44.4%), dyspnea (7, 26.9%), syncope (3, 11.5%), and/or other (2, 7.7%). GCP group historical reactions included hives (11, 44.4%), non-specific rash (15, 56.7%), and unknown (1, 3.7%). PST was negative in 23/23 patients. GCP was negative in 26/27 (96.3%) patients, with one patient experiencing flushing and eye swelling, treated with diphenhydramine. Patients transitioned from vancomycin (11/50, 22%), fluoroquinolones (7/50, 14%), aztreonam (3/50, 6%), and/or linezolid (2/50, 4%) to a β-lactam antibiotic. 11/50 (22%) patients were transitioned from an intravenous cephalosporin to amoxicillin. 628 days of second-line antibiotic therapy were avoided, with an estimated direct cost savings of $371/patient.

**Conclusions:** The use of the PAHA incorporating GCP is safe, effective, and facilitated inpatient transition to β-lactam antibiotics. Our approach adds to the growing evidence of the safety of GCP in appropriate patients.

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**Clinical Characterization of a Population of Patients With Positive Drug Provocation Test to Amoxicillin**

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**Rationale:** Betalactam (BL) are the principal cause of drug hypersensitivity, being amoxicillin the most involved in Spain. Sensitivity of skin tests is not 100%; therefore, drug provocation test (DPT) is necessary for diagnosis.

**Methods:** We included 50 patients with confirmed immediate reaction to a BL compound, negative skin tests and positive DPT to amoxicillin. Patients were classified in 2 groups according to symptoms reported in clinical history: Group 1, anaphylaxis and Group 2, urticaria. We analyzed data related to positive DPT: Symptoms, median cumulative dose and interval time between dose administration an onset of positive DPT.

**Results:** Patient median age was 41.14 (15-76) years-old and 64% female. BL implicated were amoxicillin 19 (38%), amoxicillin-clavulanate 23 (46%), Penicillin 5 (10%), Cefazoline, Cefuroxime and Cefalexine 1 (2%) respectively. In Group 1, 23 patients were included and 27 in Group 2. During DPT 16 patients (32%) developed anaphylaxis, (12 from Group 1 and 4 from Group 2), and 34 (68%) urticaria (11 from Group 1 and 23 from Group 2). Group 1 reacted to 170.4 mg of AX in DPT and group 2 to 233.7 mg (p<0.05). Patients of group 2 reacted after a longer period of time for positive DPT than group 1, median 15 minutes (15-30) vs 30 minutes (15-60) (p=0.01).

**Conclusions:** Patients with anaphylaxis need lower doses and less time for a positive DPT. The severity of the symptoms developed in the BL allergic reaction did not determine the response in the DPT.
84 Assessing Demographic Factors That Predict the Long-Term Effectiveness of Penicillin Allergy De-labeling

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RATIONALE: About 10% of patients report allergy to penicillin. Of those patients evaluated with a penicillin skin test (ST) and challenge, 90-99% are able to tolerate penicillin, resulting in penicillin allergy de-labeling. However, while patients are often de-labeled in the short term, factors that predict the persistence of penicillin allergy de-labeling remain unknown.

METHODS: A retrospective chart review was conducted on patients evaluated for penicillin allergy from 2012-2017 (inpatient and outpatient). Data was collected from the electronic medical record (EMR), pharmacy records, as well as a follow-up telephone survey with patients.

RESULTS: Thirty-three patients were successfully de-labeled of their penicillin allergy (negative ST and tolerated oral challenge). One-third of these patients had persistence of their penicillin allergy in the EMR (11/33), and 7 patients had persistence in their pharmacy records (21%). Persistence of the penicillin allergy label was not significantly associated with age (p=0.73), gender (p=0.35), or whether the evaluation was done inpatient or outpatient (p=0.88). Follow-up telephone survey was done with 24 patients (nine patients were unavailable for follow-up), and 96% (n=23) recalled the results of their allergy evaluation correctly. Despite accurate recall, 3 patients continued to avoid penicillin for fear of a possible reaction.

CONCLUSIONS: This study found that while penicillin allergy de-labeling is safe and effective, there is a discrepancy between the allergy evaluation and the appropriate removal of the penicillin allergy from the EMR and pharmacy records, which may include patient apprehension as a cause. Neither age, gender, nor place of evaluation predicted persistence of the penicillin allergy label.

85 A Retrospective Analysis of Esophageal Eosinophilia in Patients with Aspirin-exacerbated Respiratory Disease

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RATIONALE: Gastrointestinal symptoms are the most common side effect leading to discontinuation of aspirin therapy in patients with aspirin-exacerbated respiratory disease (AERD). Some patients with gastrointestinal symptoms on high-dose aspirin demonstrated biopsy-proven esophageal eosinophilia (EE). In a large cohort of patients with AERD we report on this novel clinical entity.

METHODS: Charts from 387 patients enrolled in the Brigham and Women’s Hospital AERD registry were reviewed for history of biopsy-proven EE. All subjects were diagnosed with AERD by a Partners Healthcare physician. Data was analyzed using student’s t-test and chi-square tests where appropriate.

RESULTS: 13 (3.4%) patients had a history of biopsy-proven EE documented in the medical chart. 10 of 13 were desensitized to aspirin with 9 of them first developing EE 3 months to 6 years after aspirin initiation. AERD subjects with EE demonstrated greater rates of gastric irritation at follow-up visits (p<0.001) and of aspirin discontinuation due to gastric irritation (p=0.013, Pearson’s Chi-Squared test) than the non-EE group. Those with EE reported a faster rate of nasal polyp regrowth compared to the non-EE group (4.75±3.35 versus 14.9±20.8 months, p<0.001).

CONCLUSIONS: Our study is the first to explore the relationship between aspirin therapy in AERD and the development of EE. We observed that EE develops in subjects with AERD both before and after initiation of daily aspirin therapy with more cases reported after starting aspirin. We found that the presence of EE is associated with faster regrowth of nasal polyps suggesting more severe sino-nasal mucosal pathology in this population.

86 Characteristics of nonsteroidal anti-inflammatory drugs hypersensitivity at Songklanagarind Hospital

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RATIONALE: Evaluate the characteristics of self-reported NSAID hypersensitivity and identify patients at high risk of NSAID hypersensitivity.

METHODS: Patients who presented at Songklanagarind Hospital between January-December 2017 with reported NSAID-hypersensitivity were evaluated. Clinical information obtained from a review of medical records was further supplemented with data gained from a telephone-administered questionnaire.

RESULTS: From a total of 535 patients with reported NSAID hypersensitivity, 301 were included in the study. The mean age of onset of NSAID hypersensitivity reaction was 30.3 ± 14.9 years old, and 65.1% were female. A total of 84 patients (27.9%) were hypersensitive to 2 or more chemically-unrelated NSAIDs. NSAID hypersensitivity was to propionic acid derivatives (73%) followed by acetic acid derivatives (28.9%). Immediate reaction (≤1 hour) was identified in 171 patients (57.8%) and angioedema was the most frequently reported symptom (179 patients, 59.5%), followed by urticaria and anaphylaxis in 85 (28.2%) and 62 (20.6%) patients, respectively. DPT test was performed on 53 patients, and NSAID hypersensitivity was confirmed in 38 patients (71.6%). Independent factors identified which could predict NSAID hypersensitivity were personal history of allergic rhinitis/chronic rhinosinusitis, onset of NSAID hypersensitivity over 15 years old, and immediate reaction.

CONCLUSIONS: Angioedema was the most typical symptom and propionic acid derivatives were the most frequently reported culprit drugs. The significant risk factors predicting NSAIDs hypersensitivity were personal history of AR/CRS, onset of NSAID hypersensitivity reaction over 15 years old, and immediate reaction.
87 Characterization of subjects experiencing selective hypersensitivity reactions to non-steroidal anti-inflammatory drugs (NSAIDs)

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RATIONALE: Selective hypersensitivity reactions (SHR) are the second most frequent NSAID-induced hypersensitivity. Our aim was to characterize a group of patients with SHR to NSAIDs, analyzing symptoms, culprit drugs and diagnostic methods.

METHODS: We verified acetylsalicylic acid (ASA)-tolerance and classified as single NSAID-induced urticaria/angiocardema/anaphylaxis (SNIIUA) or single-NSAID-induced delayed hypersensitivity reactions (SNIIIDHR) whether the symptoms appeared less or more than 24 hours after NSAIDs administration. In metamizole-induced SNIIUA, we performed skin tests (STs), and if negative basophil activation test (BAT) was performed. When these tests were or other drugs were involved with <2 episodes reported, drug provocation test (DPT) with the culprit was performed.

RESULTS: We included 518 patients with a mean age of 43 (31.25-54) years, 459 SNIIUA and 59 SNIIIDHR, and 66.2% were female. In SNIIUA, anaphylaxis (32.4%) was the most frequent entity, and in SNIIIDHR was maculopapular exanthema (44.1%). Metamizole was the most frequent culprit in SNIIUA (39.7%, p=0.003) and propionic acids in SNIIIDHR (46.8%, p>0.05). In 11.2% patients, DPT with the culprit was performed. In 60.4% patients, diagnosis was established by a history of repeated episodes (76.3% SNIIIDHR vs 63.6% SNIIUA, p>0.05). STs with metamizole was positive for 72% SNIIUA and for 57.1% SNIIIDHR (p>0.05). BAT was positive in 25.8% metamizole-induced SNIIUA patients with negative STs.

CONCLUSIONS: SNIIUA to metamizole is the most frequent type of NSAID-induced SHR. Although STs and BAT may aid in the diagnosis of these reactions, their sensitivity is low. Further research is needed to develop better diagnostic tools.

88 Different maturation pattern between myeloid dendritic cells and monocyte-derived dendritic cells in patients with immediate alleracy reactions to betalactams

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RATIONALE: The analysis of maturation of dendritic cells (DCs) is a useful in vitro assay to analyze their specific response to betalactams. Nevertheless, most studies use monocyte-derived dendritic cells (moDCs) instead of myeloid DCs (mDCs) because of the low number of the later in blood. Although this approximation is well-validated, moDCs could be more similar to monocyte than from DCs. Therefore, the main objective of this study was to analyze the maturation and activation differences between moDCs and mDCs during the recognition of two betalactams, amoxicillin (AX) and clavulanic acid (CLV).

METHODS: mDCs and monocytes were isolated from peripheral blood mononuclear cells from allergic patients with selective immediate reaction to AX (N=10) or CLV (N=10) and controls (N=10). To obtain moDCs, monocytes were cultured with GM-CSF and IL-4. mDCs and mDCs were cultured with the culprit drug. Expression of CCR7, CD40, CD80, CD83 and CD86 markers were analyzed by flow cytometry and represented as maturation index (MI).

RESULTS: Higher expression of maturation and activation markers were found in allergic patients compared to controls. Higher MI of CCR7, CD40, and CD86 were found in mDCs compared with moDCs in AX allergic patients (p=0.006, p=0.02, p=0.02, respectively). Likewise, higher MI of CCR7 (p=0.04) and CD80 (p=0.01) were found in mDCs from CLV allergic patients. No differences were found for CD80 and CD83 expression.

CONCLUSIONS: The analysis of maturation and activation in mDCs showed higher MI levels suggesting that the use of these cells could represent a more realistic and accurate approximation to the biological process.

89 Perioperative Use and Safety of Cephalosporin Antibiotics in Patients with Documented Penicillin Allergy

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RATIONALE: Questions remain regarding safest strategies for cephalosporin administration in patients with listed penicillin allergy (PA). This is highly relevant in the peri-operative setting, where unnecessary avoidance of first-line cephalosporins is associated with increased surgical site infections.

METHODS: Between 6/23/2015–5/31/2018, anesthesia records of adult surgical encounters for patients with listed PA at a tertiary care center were reviewed for age, gender, drug allergies, and peri-operative medications administered. Allergic hypersensitivity reactions (HSR) were graded per NIAID/FEEN criteria. Statistical analyses were conducted in Stata15.

RESULTS: Of 8,770 patients with listed PA, 37.9% [3324/8770] received full doses of peri-operative beta-lactam antibiotics (cefaclor 77.3% [2570/3324], 3rd-5th generation cephalosporins 10.0% [334/3324]), 18.2% [1597/8770] received clindamycin, and 37.4% [3279/8770] received no antibiotic.

Nine HSR occurred (0.10% [9/8770]) in those with a PA. Two HSR occurred after beta-lactam administration (both to cefazolin; anaphylaxis in 0.4% [1/2570]; mild reaction in 0.4% [1/2570]) in patients with mild documented penicillin reactions (non-urticarial rash, itching). Patients with documented penicillin anaphylaxis had no observed HSR to any betalactams. The relative risk of HSR in patients with a PA who received clindamycin, cefazolin, or no antibiotics were 8.98 [95%CI 2.25-35.88], 0.69 [0.14-3.32], and 0.48 [0.10-2.30] respectively.

CONCLUSIONS: This study provides further evidence that patients with listed PA can receive most cephalosporin antibiotics safely. HSR rates were comparable between cefazolin and clindamycin, highlighting the lack of cross-reactivity between penicillin and cefazolin. Data indicate that cefazolin and 3rd-5th generation cephalosporins can be administered as full doses without penicillin skin testing, even in patients with documented penicillin anaphylaxis.
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90 Characterization of Amoxicillin-Associated Reactions Presenting to the Emergency Department

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RATIONALE: Recent studies published by allergists demonstrate most children with amoxicillin-associated reactions (AAR) are non-allergic when rechallenged, irrespective of initial presentation of urticaria, maculopapular exanthem (MPE), or serum sickness-like reaction (SSLR). If generalizable to all children with AAR, these studies have significant impact. Surprisingly, no studies have been published which carefully phenotype children presenting with AAR in primary care settings, such as the emergency department (ED).

METHODS: Retrospective chart review was conducted on Cincinnati Children’s ED encounters July 1, 2015-June 30, 2017 using 11 relevant ICD-10 billing codes. Patients with AAR, age <19 years, were extracted and 3 clinical phenotypes (urticaria, MPE, and SSLR) identified based upon detailed provider description.

RESULTS: Of the 668 children with AAR, 290 (43%) presented with urticaria, 242 (36%) with MPE, and 71 (11%) with SSLR. Median (25th, 75th percentiles) age at presentation was earliest for MPE (1.6, 5.0) (p=0.01). Day of onset post-antibiotic initiation was bimodal for MPE; whereas urticaria and SSLR had unimodal peaks at days 7 and 8 respectively (p<0.0001). Patients with SSLR had higher rates of associated angioedema and fever and more frequently received oral steroids and returned to the ED (p<0.0001).

CONCLUSIONS: We characterized for the first time a pediatric cohort of ED patients with AAR notable for their young age and at least 3 distinct clinical phenotypes. Prospective studies are needed to determine the rate of tolerance with amoxicillin re-exposure following ED AAR, particularly in clinical phenotypes. Prospective studies are needed to determine the rate of tolerance with amoxicillin re-exposure following ED AAR, particularly in clinical phenotypes. Prospective studies are needed to determine the rate of tolerance with amoxicillin re-exposure following ED AAR, particularly in clinical phenotypes.

91 Skin Test Boosting Effect In Amoxicillin Allergic Children

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RATIONALE: Non-immediate drug hypersensitivity (NIDH) to amoxicillin is prevalent in the pediatric population. Even though skin tests (ST) are usually performed to assess beta-lactam hypersensitivity, their predictive value are of limited help in this particular population. Since a boosting effect following a recent NIDH reaction is physiologically plausible in T cell-mediated immunity, we assessed the predictive value of a repeated ST in this population.

METHODS: The sample consisted of consecutive children evaluated for a history suggestive of hypersensitivity to amoxicillin between February 2015 and May 2017. Investigation was first performed by prick and intradermal ST with penicilloyl-polysine (PPL) and benzylpenicillin (BP). Patients then underwent drug provocation test (DPT) to amoxicillin (45 mg/kg) in the allergy outpatient clinic followed, if necessary, by a four-day ambulatory course. Patients presenting a positive amoxicillin DPT were scheduled for a cephalosporin DPT, and ST were repeated then.

RESULTS: We evaluated 156 children and amoxicillin NIDH was confirmed by DPT in 49 (4.2%; 95% CI 3.2-5.6). All patients presented a mild to moderate NIDH. Skin tests were first performed in 26 of them and then repeated in 9 patients. Results of ST were negative (immediate and delayed) in both assessments, yielding a positive predictive value for repeated ST of 0.0% (95% CI 0.0-34.5).

CONCLUSIONS: We did not observe any boosting effect by repeating ST in pediatric patients presenting mild to moderate amoxicillin NIDH. Moreover, our cohort strengthens the idea that ST are of limited contribution in this population.

92 Elevated tryptase during aspirin desensitization in aspirin-exacerbated respiratory disease

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RATIONALE: Reactions to nonsteroidal anti-inflammatory drugs (NSAIDs) in aspirin–exacerbated respiratory disease (AERD) are classified as pseudoallergic and thought to be caused by non IgE-mediated, non-immunologic mast cell activation. Aspirin desensitization, followed by long-term daily aspirin therapy in AERD has been shown to reduce regrowth of nasal polyps and decrease requirement of oral steroids.

METHODS: Retrospective chart review of patients who underwent aspirin desensitization for AERD was performed and patients with severe manifestations were selected.

RESULTS: Total of 21 patients with AERD underwent outpatient aspirin desensitization as per published recommendations. All patients were pretreated with leukotriene receptor antagonists and H1-antihistamines. During desensitization three of these patients developed significant adverse effects, involving multiple systems and had tryptase measured. Clinical manifestations included severe, intractable gastrointestinal (abdominal cramping/pain, vomiting, diarrhea), respiratory (cough, dyspnea, nasal congestion) and cutaneous symptoms (pruritic rash). Gastrointestinal symptoms were predominant and protracted. None of the patients developed hypotension. All three patients had significantly elevated tryptase (13.7-17.2 ng/ml), compared to basal level (4.1-7.2 ng/ml). Two of these patients successfully completed aspirin desensitization and continued daily treatment with high-dose aspirin. One patient declined to complete aspirin desensitization.

CONCLUSIONS: It is important to remember that mast cell activation/degranulation can be a feature of pseudoallergic reactions as well as in IgE-mediated allergic reactions. Patients with AERD can develop mast cell activation/degranulation with release of tryptase during aspirin challenge/desensitization. It appears that the presence of gastrointestinal symptoms during aspirin desensitization in AERD may be indicative of significant mast cell degranulation.
93 **Beta-lactam Administration Patterns at a Safety-net Hospital with Limited Access to Inpatient Penicillin Skin Testing**

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**RATIONALE:** Inaccurate beta-lactam allergy (BLA) labeling is associated with worse clinical outcomes due to over-avoidance of beta-lactam antibiotics. Although BLA de-labeling with penicillin skin testing (PST) can increase beta-lactam use, it is not readily available at many hospitals. There is a need to assess beta-lactam administration patterns at hospitals without readily available PST to identify potential areas for improvement.

**METHODS:** Admission records of 282 patients with listed BLA who required antibiotics during hospitalization between June 2017 and July 2018 at a safety-net hospital with limited access to inpatient PST were reviewed retrospectively.

**RESULTS:** Full doses of beta-lactams were administered without reaction in 73.0% [157/215] of patients with documented penicillin allergy (PA). Penicillin antibiotics were administered in 15.8% [34/215], 1st-generation cephalosporins in 11.6% [25/215], 2nd-generation cephalosporins in 0% [0/215], 3rd-generation cephalosporins in 26.5% [57/215], and 4th-generation cephalosporins in 20.0% [43/215]. The 34 patients who received penicillin antibiotics had the following documented reactions: other 50.0% [17/34], hives 17.6% [6/34], rash 17.6% [6/34], anaphylaxis 5.9% [2/34], shortness of breath and swelling 2.9% [1/34], not documented 2.9% [1/34], and fatigue 2.9% [1/34]. Conversely, of the 13 patients with documented allergy to 3rd/4th/5th-generation cephalosporins, 38.5% [5/13] received full doses of a penicillin antibiotic without reaction.

**CONCLUSIONS:** Beta-lactam administration was higher than expected, with full doses of penicillin and cephalosporin antibiotics administered without reaction in many patients with documented PA, including patients with documented penicillin anaphylaxis. Further investigation is needed into provider beliefs surrounding BLA cross-reactivity and the role of PST in patients undergoing PST.

94 **Study of sensitization to quinolone drugs**

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**RATIONALE:** Quinolone antibiotics represent the second most used group of antibiotics. Ciprofloxacin is the second most prescribed antibiotic in USA. We present a group of 39 patients with a complete study of 3 quinolones in order to assess hypersensitivity to these drugs.

**METHODS:** We performed skin prick tests (SPT) and intradermal tests (IDT) with different concentrations of 3 quinolones. Ciprofloxacin: SPT 2mg/ml, IDT 0.02mg/ml; levofloxacin: SPT 5mg/ml, IDT 0.05mg/ml; moxifloxacin: SPT 4mg/ml. The patients underwent placebo controlled drug provocation tests (PCDPT) when needed.

**RESULTS:** The 39 patients (34 female/5 male), with a median age of 55.3 (17-93) years, referred an adverse reaction with the following quinolones: ciprofloxacin (22 patients), levofloxacin (11 patients) and moxifloxacin (6 patients). The symptoms were pruritus along with urticaria (15 patients), angioedema (4 patients), urticaria/angioedema (4 patients), exanthema (7 patients), erythema (3 patients), anaphylaxis (6). We diagnosed the 6 cases of anaphylaxis after convincing history, 3 were due to moxifloxacin (1 with positive SPT) and 3 due to ciprofloxacin (2 with positive tests).

**Diagnosis obtained:**
- Levofloxacin: SPT:2, IDT:6, PCDPT:3.

**Allergy to ciprofloxacin (22 patients): 14 tolerated levofloxacin, 3 moxifloxacin, both.**

95 **Preliminary Results Comparing Outpatient Oral Graded Challenges to Penicillin Skin Testing**

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**RATIONALE:** Graded challenges (GC) may be as safe as penicillin skin testing (PST) in low risk patients. We designed a longitudinal, non-inferiority trial to evaluate PST followed by an amoxicillin challenge compared to a 2-step GC to amoxicillin without PST.

**METHODS:** Penicillin allergy histories were reviewed in all patients presenting to an allergy/immunology practice from 4/2018 onward. Patients >5 years old (y/o) with a cutaneous-only or unknown reaction (> 1 year ago for ages 5-17, > 10 years ago for 18+) were randomized 1:1 to PST or GC. All children <5y/o underwent graded challenge and patients with extra-cutaneous reaction histories underwent PST. All groups were monitored 30 minutes after amoxicillin administration for reactions. Preliminary descriptive results are reported using means (SD) and percentages.

**RESULTS:** Penicillin allergy was reported in 256/1622 (15.8%) patients, 139 consented to further evaluation. 13/256 (5.1%) patients <5y/o underwent direct challenge; all were negative. 10/256 (3.9%) patients with angioedema and/or extra-cutaneous symptoms underwent PST; 1/10 patients had positive PST. A total of 116 patients were randomized to GC (49.1%) or PST (50.9%). SPT was negative in 53/59 (89.8%) patients. All 53 patients had a negative amoxicillin challenge. GC was negative in 56/57 (98.2%) patients. Average time for patients undergoing PST was 72.7 (±5.2) minutes, and 68.4 (%98.2) patients. Average time for patients undergoing GC was 72.7 (±13.6) minutes for patients undergoing GC.

**CONCLUSIONS:** Preliminary results demonstrate a low reaction rate among GC patients. Future non-inferiority analysis upon completion of this trial may provide foundational evidence for use of GC instead of PST in low risk patients.
96 Enhancing Antibiotic Selection through Inpatient Penicillin Allergy Evaluation

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RATIONALE: Penicillin allergy testing has historically been underutilized in the inpatient setting where it may directly impact treatment. We expanded penicillin allergy testing to hospitalized patients to determine the rate of penicillin hypersensitivity, the barriers of inpatient testing, and the subsequent use of beta-lactams or cephaplsorins.

METHODS: We evaluated 55 hospitalized patients from 9/2017-8/2018 with reported penicillin allergy that were referred by primary teams or specialists if beta-lactams or cephaplsorins were desired for prophylaxis or to treat underlying infection. Qualifying patients then underwent skin testing followed by oral Amoxicillin challenge.

RESULTS: 37 patients (67%) underwent testing with 35 (94%) proving to be tolerant of beta-lactams or cephaplsorins. Of the patients that were tested, direct drug challenges were administered to 19 (51%) patients based on clinical history, with no reported adverse outcomes. Of the 35 tolerant patients, 25 (71%) had a beta-lactam added to their treatment, 9 (26%) received a cephaplsorin, whereas 4 (11%) received other antibiotics. Barriers to testing included patients with incompatible medication use (4), clinical instability (5), or delayed symptoms (4); 4 patients declined testing.

CONCLUSIONS: Our results suggest that 6% of patients with reported penicillin allergy exhibit true sensitivity, consistent with previous reports. A majority of patients were able to tolerate direct drug challenge, indicating that improved utilization of clinical history can simplify testing protocols and may prove sufficient for many patients. Additionally, most subsequent treatment plans for tested patients included a beta-lactam or cephaplsorin. Despite barriers, inpatient penicillin allergy testing may decrease reported allergies and broaden antibiotic options.

97 Drug-Induced Severe Cutaneous Adverse Reactions (SCARs): Determine the Cause and Prevention

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RATIONALE: Approximately 45% of all the adverse drug reactions are manifested in the skin, but most are mild; however, Severe Cutaneous Adverse Reactions (SCARs) are potentially lethal. Our objective was to investigate SCARs reactions at our institution.

METHODS: A 10-year retrospective analysis of drug-induced skin adverse reactions at Penn State was queried. Search included Stevens-Johnson Syndrome [SJS] (L51.1), Drug Rash with Eosinophilia and Systemic Symptoms [DRESS] (L270.0 and T88.7), Acute Generalized Exanthematous Pustulosis [AGEP] (L270), Toxic Epidermal Necrolysis [TEN] (L51.2) and TEN/SJS overlap (OL).

RESULTS: A total of 1379 cases with adverse drug reactions were screened, and 596 cases of drug rash were identified (43%). Out of these 596 cases of drug-induced rash, a total of 35 (5.9%) cases of SCARs were encountered (M: F ratio; 1:06:1; mean age of 48.5 year). Of those 35 cases, 32 were Caucasian (91.4%). The most common manifestations were DRESS (19/ 54.3%), SJS (8/22.8%), AGEP (6/17.1%), TEN (1/2.9%), and OL (1/2.9%). The most common drugs implicated were antibiotics (93.5%). Among the 10 cases of SJS/TEN/Overlap syndrome, trimethoprim/sulfamethoxazole (40%) was the most common causative agents. In DRESS, amoxicillin (26.3%) and ciprofloxacin (26.3%) together accounted for 52.6% of the cases. Twenty-five of the 35 patients with SCARs were hospitalized. Most of the patients with SCARs were given triamcinolone cream and prednisone alone (18/51.4%), methylprednisolone alone (1/2.9%), methylprednisolone/prednisone combined (4/11.4%), methylprednisolone/prednisone (1/2.9%) or prednisone/prednisolone (1/2.9%).

CONCLUSIONS: The most common SCARs at Penn State Hershey were DRESS>SJS>AGEP>TEN>OL. The most common causative drugs were trimethoprim/sulfamethoxazole > amoxicillin > ciprofloxacin.

98 Delayed hypersensitivity reaction caused by iodine contrast: efficacy of pretreatment

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RATIONALE: The frequency of delayed reactions to radiocontrast media (RCM) occurred in approximately 0.5-23.0% of patients and the majority of these reactions are thought to be due to T cell mediated mechanisms. However, optimal pretreatment regimen is not established and there are not enough data to support the efficacy of premedication in patients with delayed reactions to RCM.

METHODS: A retrospective chart review was conducted on 29 patients with previous delayed hypersensitivity reactions to iodine RCM who visited the allergy clinic for the prevention of reaction in the rechallenge of RCM in Seoul National University Bundang Hospital in 2016-2017.

RESULTS: The mean age was 52.2 years and 72.4% were female. The onset of reactions was 1hr to 3 days after exposure to RCM. Reaction duration was 24 hours to 3 months and 89.66% resolved in 2 weeks. All patients exhibited skin symptoms. After the delayed reactions to RCM, pretreatment was performed to patients at the next exam using RCM. As pretreatment, 21 patients received steroid and antihistamine 1 hr before RCM injection and 4 received steroid additionally 12 hrs before RCM injection. As post RCM treatment, 12 patients were given oral steroids for 2-3 days, and 18 patients were given antihistamines for 3-7 days after RCM injection. With these pretreatments, there was a symptom improvement in all patients and symptom disappeared completely in 19(65.52%) patients.

CONCLUSIONS: Premedications showed beneficial effect when it is necessary and not contraindicated. Further investigations are needed to establish practical pretreatment protocol for prevention of delayed reactions to RCM.
99 Survey of Beliefs and Clinical Outcomes in Patients with Reported Penicillin Allergy

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RATIONALE: Allergy to penicillin, and related cephalosporins, is one of the most common drug allergies reported, affecting approximately 10% of patients. Despite the frequency of reported reactions, most patients are either not truly allergic or lose sensitivity over years. Unnecessary avoidance of penicillins affects quality of care and increases health care costs. Here we examine patients’ history of penicillin reactions and attitudes regarding testing and outcomes of testing.

METHODS: We identified adult patients presenting to our allergy/immunology practice who reported penicillin allergy during the visit. Patients completed a survey inquiring about reaction history, subsequent antibiotic use, knowledge/beliefs about testing, and demographics. The medical record was reviewed to collect testing results, if performed.

RESULTS: Twenty-two patients (18% male, mean age 47 years) participated. Nineteen (86%) reported receiving an alternative antibiotic due to penicillin allergy, including 7 patients (32%) treated for Group B Strept or syphilis. Half of patients reported awareness of testing prior to visit; 17 (77%) reported interest in testing afterward. Fourteen patients (64%) reported they would have sought evaluation sooner had they known the favorable outcomes of testing. Four patients (18%) underwent testing; three had negative skin testing and oral challenge with removal of the penicillin allergy label; one had indeterminate skin testing and declined challenge.

CONCLUSIONS: Despite available testing, reports of penicillin allergy continue to be common, though most patients are likely tolerant. Mislabeling leads to unnecessary utilization of alternative antibiotics and growing resistance. Further patient education regarding the natural history of penicillin allergy and safety and importance of testing is required.

100 Six-step Trimethoprim-Sulfamethoxazole Desensitization Protocol in non-HIV patients with Self-reported Sulfadiazine Allergy: A Single Center Experience

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RATIONALE: Patients allergic to sulfa-drugs are sometimes prescribed alternative medications over trimethoprim-sulfamethoxazole (TMP-SMX) despite it being first-choice in several scenarios such as Pneumocystis jirovecii pneumonia (PCP) prophylaxis, urinary tract infections, and soft tissue infections. The purpose of the study was to evaluate our experience with a six-step desensitization protocol for TMP-SMX in non-HIV patients with sulfa allergy.

METHODS: We conducted a retrospective chart review of all TMP-SMX desensitizations performed between December 2014 and May 2018 in our Allergy Clinic. The demographic and prior allergy reaction data were collected for each subject. All subjects underwent a previously published 1-day 6-step TMP-SMX protocol (Pyle et al. J Allergy Clin Immunol Pract 2014). A descriptive analysis was then performed.

RESULTS: Fifty-two patients were included in the study; most were women (86.5%), and white was the prevailing ethnicity (84.6%). The most common self-reported reaction was rash (55.8%) followed by hives (15.4%), and itching (13.5%). The most common indication for TMP-SMX was PCP prophylaxis (67.3%). Ninety-eight percent of subjects tolerated this protocol without adverse reactions. Only one protocol was stopped before completion after the subject developed urticaria and requested the procedure to be suspended. No severe IgE-mediated reactions were reported during desensitization.

CONCLUSIONS: According to the data we have extracted from our Allergy Clinic, this is a safe desensitization protocol with a very low tendency to produce symptoms during the procedure and with a high success rate. This is in agreement to what was published by Pyle et al. and may prove to be a protocol worth of standardization.

101 Developing in vitro and in vivo Models to Predict Drug-Induced Acute Allergic Adverse Reactions

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RATIONALE: All medications have the potential to produce adverse events (AEs) and such adverse events lead to significant morbidity and mortality. Lower frequency serious AEs, particularly acute allergic reactions can have life-threatening consequences and occur minutes after drug administration. These AEs have been considered significant enough to take drugs off the market.

METHODS: Methods are based upon current understanding to the mechanisms of a clinical anaphylaxis, including: 1) Drug-specific IgE screening and in vitro Type 1 sensitization (drug-binding antibodies and mast cell degranulation); 2) Drug-specific IgG/IgM screening followed by complement-activation through classical and non-classical pathway-generated anaphylatoxins assay (C3a, C4a and C5a); 3) Direct mast cell degranulation; 4) Cytokine storm assays (activated T cells and macrophages using PBMC or whole blood culture); and 5) Contact system (kinin/kallikrein) activation assay. In addition, we developed a C1 inhibitor deficient mouse model to enhance the prediction of contact system-associated acute allergy in vivo.

RESULTS: From the study of 2008 heparin AEs which caused hundreds of Omontys (peginesatide) which caused serious hypersensitivity reactions including anaphylaxis, our research group has established several in vitro and in vivo models to quickly pinpoint the potential cause of an acute allergic reaction.

CONCLUSIONS: These in vitro and in vivo models will not only help the agency to quickly identify and respond to potential causes of drug-induced acute allergic AEs, but also better determine the likelihood and potentially mitigate the risk of acute reactions for regulated products.

102 Skin and In Vitro Tests are Positive in Every 10th Patient with a Plausible History of Betalactam Allergy

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RATIONALE: Many patients claim “allergy” to betalactam antibiotics, a history which is often wrong and confirmatory tests are required to rule out or confirm this. Provocation tests put patients at risk during testing, while in vitro and skin tests can be performed on a rather safe base.

METHODS: We performed a retrospective review of a cohort of patient charts, who had visited the “Floridsdorfer Allergie Zentrum” (Floridsdorf allergy center (FAZ), Vienna) for a suspected penicillin or cephalosporin allergy from January 1st, 2016 to December 31st, 2017. A drug-specific history was obtained from all patients. Specific IgE was determined (ImmunoCAP, Thermofisher, Penicillin G + V, Amoxycillin, Ampicillin, MDMD, Cefaclor) and skin prick tests, intradermal tests and patch test (Penicillin G + V, Amoxycillin, Ampicillin, Cefazolin, Cefuroxim, Ceftriaxon) were performed and read after 20 min and after 24 hours. This study was approved by the Ethics’ comittee of the Medical University of Vienna, Austria.

RESULTS: Of 792 patients (562 female and 232 males, average age 42.3 years +/- 21-9 years SD), who were eligible for inclusion into the study, 100 had positive skin- or in vitro tests (12.62%). In detail, there were more positive immediate (42 = 5.03% skin test, 44 = 5.56% specific IgE) than delayed (19 = 2.40%) reactions. Specific IgE to Penicilllin V was the most frequent positive single test result (27 = 3.68%).

CONCLUSIONS: Skin and in vitro testing are sensitive, easy and safe tools in the confirmation of betalactam-allergy in about every 10th patient.
Adverse Reactions during Desensitization to Chemotherapy Agents

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Rationale: Drug desensitization is very useful to continue treatment with first-line chemotherapy agents in allergic patients. The introduction of new phenotypes of hypersensitivity reactions has influenced the handling of these reactions.

The objective of this research was to report the type of the hypersensitivity reactions observed during desensitization to these agents in the General University Hospital of Alicante from April to August 2018.

Methods: The phenotype of the hypersensitivity reactions was established according to the clinical characteristics, the result of the skin tests and the biomarkers (tryptase and IL-6) at the time of the reaction, and they were also classified according to their severity.

Results: We observed 44/2 (9.5%) hypersensitivity reactions in 3 patients. The first patient, with prior grade II reaction to Oxaliplatin, phenotype I, during the desensitization presented a similar grade II reaction, which required only intravenous chlorpheniramine. Three patients presented reactions of the Cytokine Release Phenotype: a patient with a previous grade II reaction to Paclitaxel, who during the desensitization presented a similar grade I reaction, which was treated with acetylsalicylic acid (ASA) orally. Another patient with a previous grade III reaction to Docetaxel, reacted during two desensitizations, both grade II, Cytokine Release Phenotype, resolved with fluids, ASA, montelukast, and intravenous opioids.

Conclusions: The reactions to chemotherapy during desensitization are usually of the same phenotype as those of the initial reaction, their proper identification allows to anticipate the treatment to be used in case of reactions.

Current Practice Of The Diagnosis Of Drug Allergy In Korea

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Rationale: Different languages of the researchers from all over the world prevent rare cases of drug allergy to be shared with other researchers. We conducted a literature review on the diagnosis of drug allergy from Korean journals to evaluate the current practice on the diagnosis of drug allergy in Korea. We especially focused on finding literature in the Korean language in order to share our data with researchers from other countries.

Methods: We searched KoreaMed.org which was a search engine for Korean journals. After reviews, the articles which described drug allergy diagnosis procedure well were selected. For drug skin tests, papers which described the concentration of the drugs and the results from the healthy controls were considered to have adequate quality. For drug provocation tests, papers which contained information on the starting dose and interval between doses were selected.

Results: There were only 15 and 24 articles from 632 searched with adequate quality on drug skin test and drug provocation test procedure, respectively. Clinical diagnosis of most cases was drug-induced anaphylaxis. The numbers of healthy control used in drug skin tests were from 3 to 27 people. The starting dose of drug provocation tests was between one-eighth of usual dose and one usual dose. When there was positive drug provocation reaction, the reaction usually occurred within twice the time that the initial reaction taken.

Conclusions: There was quite a lot of valuable information on the drug allergy diagnosis in Korean journals.
106 Novel foods: Enzymatic and thermal food processing make edible insects non-allergenic

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RATIONALE: Insects are increasingly used as nutrient source for people and animals. As they are considered as “novel food”, several safety aspects need to be evaluated initially, including the risk of allergenicity.

METHODS: IgE from patients allergic to crustaceans, house dust mite (HDM) and/or stable flies was evaluated for cross-recognition of proteins in house cricket Acheta domesticus (AD), desert locust Schistocerca gregaria (SG) and Yellow mealworm Tenebrio molitor (TM). For food processing, different extraction methods, enzymatic hydrolysis, and thermal treatment were applied to migratory locust Locusta migratoria (LM) extract. Then we proceeded with in vivo testing of crustacean allergic subjects. Crude, enzymatically processed and heat-treated extracts of LM were tested in skin prick test (SPT) in patients with clinical crustacean allergy, first as diluted extracts (1:10 v/v in glycerin 50%) followed by SPT with concentrates. Ditto SPT were performed with centrifuged TM (no enzymes).

RESULTS: IgE from patients with crustacean-allergy shows cross-recognition of extracts from AD, SG and stable flies; house dust mite allergics’ IgE binds to AD and SG proteins; and the flies-allergic patient recognized AD, SG and LM. Food processing such as enzymatic hydrolysis or heat treatment of LM extract not only completely abolished in vitro-binding of cross-reactive IgE, but also its IgE crosslinking capacity in in vivoskin prick tests. However, centrifugation of TM did not reduce SPT reactivity.

CONCLUSIONS: This study provides evidence that enzymatic and thermal processing of insects can reduce the risk of these novel foods to elicit cross-reactivity and allergenicity in crustacean- and HDM-allergic patients.

107 Sensitization to Api m 1, Api m 2, and Api m 4 in Japanese beekeepers who had experienced systemic reactions to honeybee stings

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RATIONALE: The major allergen components of honeybee (HB) venom are phospholipase A2 (Api m 1), hyaluronidase (Api m 2), and melittin (Api m 4). IgE antibodies specific(s) to phospholipase A2, hyaluronidase, and melittin bind to recombinant (r)Api m 1, rApi m 2, and rApi m 4, respectively, and show increased test specificity due to the lack of carbohydrate determinants in the recombinant protein. The differences in sensitization due to race or stinging environment and the significance of measuring sIgE to these allergen components are not known. In this study, we analyzed sensitization to Api m 1, Api m 2, and Api m 4 in Japanese beekeepers who had experienced systemic reactions (SRs) to HB stings.

METHODS: The participants comprised 121 beekeepers Japan. Of the beekeepers, 34 who had experienced an SR to a HB sting were analyzed in this study. All participants underwent a medical examination including an interview with an allergist and peripheral blood tests were performed on the day of the examination.

RESULTS: sIgE positivity to HB venom, rApi m 1, rApi m 2, and rApi m 4 was identified in 32 (94.1%), 31 (91.2%), 33 (97.1%), and 18 (52.9%) beekeepers, respectively. Double positivity to rApi m 1 and rApi m 2 was found in 30 individuals (88.3%). The combination of rApi m 1 and rApi m 2 improved the sensitivity from 94.1% (32/34) to 100% (34/34).

CONCLUSIONS: Combination measurement of sIgE to rApi m 1 and rApi m 2 improves the sensitivity for HB venom allergy detection.

108 Hymenoptera-venom allergy, outcomes of immunotherapy and peripheral blood mast cell biomarkers in a non-European Mediterranean cohort

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RATIONALE: Most of the data on Hymenoptera venom allergy (HVA) is derived from European studies. We hypothesize that investigation of patients from a different geographic or ethnic origin may provide additional insights into HVA and its management.

METHODS: We included all patients who were referred for HVA immunotherapy in a single referral center (Meir Hospital, Israel). Patients were evaluated for baseline serum tryptase and peripheral-blood c-KIt D816V mutation. Clinical data were obtained from patient medical charts.

RESULTS: A total of 153 subjects were enrolled, showing a low median age of 21 yrs, compared to 40-50 yrs in other studies. The most prevalent allergen was bee venom (89%, vs. 20-30% in European reports). Elevated tryptase levels were detected in only 5 subjects (3.3% vs. 10-16% as previously published) and c-KIt D816V mutation was found in 4 individuals (4.4%). Factors associated with severe sting anaphylaxis were advanced age, multiple venom sensitization and tryptase levels. Unlike other studies, the peak incidence of near-fatal reactions to stings was at tryptase values of 5.5-7.0 ng/mL rather than at higher levels. Similar to previous reports, bee venom sensitization was linked to VIT adverse reactions, however, with no correlation to tryptase levels.

CONCLUSIONS: This Mediterranean cohort exhibits variations from previously published European studies on HVA patients. Our work underscores population differences suggesting that interpretation of risk factors should be adjusted to specific cohorts.
109 Sensitization To Messor barbarus Ant In A Sample Of Patients With Hymenoptera Venom Hypersensitivity

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RATIONALE: In Europe, hypersensitivity reactions to ants are exceptional. In 2013 we described the first case of anaphylaxis due to Messor barbarus (MB) ant in a patient with hymenoptera venom allergy and systemic mastocytosis (SM). SDS-PAGE Immunoblotting identified an IgE binding band of 45-55 kDa in the extract of MB’s body which showed partial cross-reactivity with venom protein from Apis, Polistes and especially Vespuila. Thus, we decided to investigate the possible sensitization to MB proteins in a sample of patients with Hymenoptera venom hypersensitivity.

METHODS: Twenty-two patients were studied. Exhaustive anamnestic of exposition and reaction to ant bites, prick test with MB’s body extract (10 mg/ml), tryptase serum determination, and REMA score (Spanish Network on Mastocytosis) to predict systemic mastocytosis were carried out. RESULTS: Three women and 19 men, average age of 50 years, were studied. Sixteen presented with systemic reactions and 6 local ones. Four of 22 patients referred ant bites but only one experienced symptoms (anaphylaxis). Prick tests with MB’s body extract were positive in 10 patients. Only in 3 patients, subsequently diagnosed of systemic mastocytosis, tryptase serum was positive and REMA score was more than 2 points.

CONCLUSIONS: We detected sensitizations to MB ant body in almost half of patients with Hymenoptera venom hypersensitivity. Nevertheless, we do not know its clinical relevance because most of them had not suffered ant bites. But taking into account our previously reported case, we consider that the investigation of sensitization to other kinds of Hymenoptera may be of interest, especially in patients with systemic mastocytosis.

110 Oral Plasma Kallikrein Inhibitor BCX7353 Is Safe and Effective as an On-Demand Treatment of Angioedema Attacks in Hereditary Angioedema (HAE) Patients: Results of the ZENITH-1 Trial

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RATIONALE: In a phase 2 trial, BCX7353 was superior to placebo in reducing the angioedema attack rate (N Engl J Med 379: 352-362, 2018). We hypothesized that BCX7353 would also be superior to placebo in treating angioedema attacks.

METHODS: ZENITH-1 is a double-blind, placebo-controlled, randomized, cross-over, dose-ranging trial. Adults with HAE Type I or II self-administered a dose of blinded study drug for 3 attacks: 2 treated with active drug and 1 with placebo, in a randomized sequence. Subjects were free to use approved on-demand medications if needed, but were asked to wait 4h post-study drug if possible. Symptom diaries were completed prior to dosing and at 1, 2, 3, 4, 8 and 24h after study drug. Outcomes were compared using generalized logistic regression models. The completed first dose cohort (750mg) is reported; lower dose cohorts (500mg or 250mg) are in progress.

RESULTS: 33 patients treated a total of 95 attacks; 30 treated all 3 attacks. At 4h postdose, 67.7% of BCX7353-treated angioedema attacks versus 46.7% for placebo were stable or improved by composite VAS (OR=2.771, p=0.0387). At 24h, subjects reported no or mild symptoms by patient global assessment in 64.1% of BCX7353-treated attacks versus 32.3% for placebo (OR=4.614, p=0.0038). Rescue medication was used in 29.7% of attacks treated with BCX7353 compared with 61.3% of placebo attacks (OR=0.196, p=0.0029). There were no Grade 3/4 AEs or laboratory abnormalities.

CONCLUSIONS: BCX7353 750mg was superior to placebo and was well-tolerated. These results support further development of BCX7353 as an oral on-demand treatment for HAE attacks.
**111 Recombinant Human C1 Esterase Inhibitor as Short-Term Prophylaxis for Dental Procedures in Patients With Angioedema: A Case Series**

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**RATIONALE:** Patients with hereditary angioedema due to C1 esterase inhibitor deficiency (C1-INH-HAE) are at risk for an attack during and after medical procedures; short-term prophylaxis may minimize this risk. This analysis evaluated recombinant C1-INH (rhC1-INH) as short-term prophylaxis prior to dental procedures.

**METHODS:** Patients with angioedema received rhC1-INH prior to dental procedures; angioedema attacks were recorded through 2 days and >2-7 days postprocedure.

**RESULTS:** 29 patients (median age, 44 years [range, 17.5-73.1 years]; 72.4% female; 89.7% HAE type I; median of 17 attacks/year [range, 0-90]) were treated for 37 procedures. More than half (56.8%) of the 37 dental procedures were extractions. A median rhC1-INH prophylactic dose of 3505 IU (range, 2100-4200 IU) was administered on the median of 60 minutes prior to the dental procedure. Twenty-five (67.6%) cases had rhC1-INH administered 30-60 minutes preprocedure. Nine (24.3%) cases were also receiving long-term prophylaxis (danazol [n=1], tranexamic acid [n=1]). Overall, 97.3% (36/37) of cases did not have an attack within 2 days postprocedure; 91.9% (34/37) during >2-7 days postprocedure. For the 1 attack occurring within 2 days, rhC1-INH (4200 IU; 37.5 IU/kg) was administered 230 minutes preprocedure; the patient experienced mild knee edema and required no treatment. No adverse events were reported. In a retrospective self-control subgroup, 15 (93.8%) of 16 dental procedures (no long-term/short-term prophylaxis preprocedure) were followed by an attack within 2 days after the procedure.

**CONCLUSIONS:** Short-term prophylaxis with rhC1-INH, administered within ~60 minutes before a dental procedure, was efficacious and safe in patients with angioedema/C1-INH-HAE and reduced the risk of an attack postprocedures.

**112 Efficacy of Lanadelumab in Hereditary Angioedema Patients Switching From C1 Inhibitor Long-Term Prophylaxis: Interim Results From the HELP Open-Label Extension Study**

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**RATIONALE:** Lanadelumab demonstrated sustained prevention of hereditary angioedema (HAE) attacks in the double-blind, phase 3 HELP Study (N=125; NCT02586805). The HELP open-label extension (OLE; NCT02741596) enrolled lanadelumab-treated patients (HELP Study rollover; n=109/113 [96.5%] completers) and lanadelumab-untreated patients (nonrollover; n=103). Here we report interim results (26May2016–1September2017) for rollover and nonrollover patients switching from C1 inhibitor (C1-INH) long-term prophylaxis (LTP) to lanadelumab treatment.

**METHODS:** All patients ≥12 years old with HAE type I/II received lanadelumab 300 mg every 2 weeks (q2wks); nonrollover switching patients could receive both C1-INH and lanadelumab to Day 15 (LTP tapering period). The number of investigator-confirmed HAE attacks was reported as monthly attack rates (attacks/4 weeks) and compared with historical rates per 4 weeks for the 3 months preceding HELP (rollover)/ OLE (nonrollover) treatment.

**RESULTS:** Overall, 106/212 patients (50.0%) received prior C1-INH only LTP (53 rollover and 53 nonrollover). Historical median (range) attack rate for all patients using C1-INH was 2.0 (0.0–15.4)/4 weeks. After lanadelumab treatment median (range) attack rate was 0.1 (0.0–4.1)/4 weeks, representing 97.4% median reduction (74.8% mean reduction). Patients without prior LTP use (n=87) had median (range) attack rates/4 weeks of 1.8 (0.0–27.6) historically and 0.0 (0.0–4.9) with lanadelumab (100% median reduction; 90.2% mean reduction). Patients switching from other LTP (n=19) also experienced attack rate reductions with lanadelumab.

**CONCLUSIONS:** Open-label treatment with lanadelumab 300 mg q2wks led to significant reductions in HAE attack rate compared with 3-month historical experience in patients with and without prior C1-INH LTP use, consistent with findings from the HELP Study.
113 Long-term Health-related Quality of Life in Patients Treated With Subcutaneous C1-Inhibitor Replacement Therapy for the Prevention of Hereditary Angioedema Attacks

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RATIONALE: Hereditary angioedema (HAE) due to C1-esterase inhibitor (C1-INH) deficiency is known to have a significant negative impact on patients’ health-related quality of life (HRQoL). We evaluated the impact of long-term prophylaxis with subcutaneous C1-INH (C1-INH (SC)) in the HELP Study.

METHODS: In the HELP Study, patients >4 HAE attacks within a consecutive 2-month period (N=126) self-administered C1-INH (SC) 40 or 60 IU/kg twice weekly for up to 52 or 140 weeks (US only), HRQoL was self-assessed by patients at various points during the OLE using several instruments, including the European Quality of Life-5 Dimensions (EQ-5D) questionnaire, Hospital Anxiety and Depression Scale (HADS), and Work Productivity and Activity Impairment (WPAI) assessment.

RESULTS: With C1-INH (SC) 60 IU/kg, significant improvements from baseline to the end-of-study visit were observed on the EQ-5D, HADS, and 3 of 4 WPAI domains. Clinically meaningful improvements versus baseline (mean [95% CI]) were observed on the Health State Value (0.07 [0.01, 0.12]) and Visual Analogue Scale (7.45 [3.29, 11.62]) of the EQ-5D. Improvements were also noted on the HADS Depression (-0.95 [-1.57, -0.34]) and Anxiety (-1.23 [-2.08, -0.38]) scales and WPAI domains of Presenteeism (-23.33 [-34.86, -11.81]), Work Productivity Loss (-26.68 [-39.92, -13.44]), and Activity Impairment (-16.14 [-26.36, -5.91]).

CONCLUSIONS: Long-term prophylaxis with C1-INH (SC) leads to significant and clinically meaningful improvements in various HRQoL measures in patients with HAE.

114 Increased Response to Higher Dose Lanadelumab in Hereditary Angioedema Patients: Exploratory Findings From the HELP and HELP OLE Studies

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RATIONALE: The plasma kallikrein inhibitor lanadelumab effectively prevents hereditary angioedema (HAE) attacks compared with placebo in the HELP Study (NCT02586805); 96.4% of lanadelumab-treated patients achieved ≥50% attack rate reduction versus run-in period. We report exploratory findings for HELP Study “nonresponder” patients who had <50% reduction and continued lanadelumab treatment in the HELP Open-Label Extension (OLE: NCT02741596).

METHODS: In the HELP Study, patients ≥12 years old with HAE type I/II and ≥1 attack/month during run-in were randomized to lanadelumab 150mg q4wks, 300mg q4wks, 300mg q2wks, or placebo. Patients continuing to the OLE received a single lanadelumab 300mg dose until first attack, then 300mg q2wks. Individual patient level data are described.

RESULTS: Of 84 lanadelumab-treated patients in the HELP Study, 3 were identified as nonresponders; all had received lanadelumab 150mg q4wks, and continued in the OLE with 300mg q2wks. Monthly attack rates (attacks/4 weeks) for patient 1 during the HELP Study run-in (baseline) and treatment period, OLE treatment period, and OLE steady-state period were 1.93, 1.53 (21% reduction), 0.75, and 0.74, respectively. Attack rates for patient 2 were 1.00, 0.92 (8% reduction), 0.63, and 0.82, and for patient 3 were 1.00, 1.82 (82% increase), 0.92, and 0.19. Moderate/severe attack rates were reduced for all 3 patients when receiving 300mg q2wks. Patient 2 experienced 3 laryngeal attacks on 150mg q4wks but none on 300mg q2wks.

CONCLUSIONS: Patients who did not respond to lanadelumab 150mg q4wks in the HELP Study experienced improvements with 300mg q2wks in the HELP OLE Study.
116 KVD900 as a Single Dose, Rapid, Oral Plasma Kallikrein Inhibitor for the On-Demand Treatment of Hereditary Angioedema Attacks: Pharmacokinetic and Pharmacodynamic results from a Phase 1 Single Ascending Dose Study

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RATIONALE: The pharmacodynamic (PD) effects of orally administered KVD900 were evaluated using ex vivo whole plasma assays for plasma kallikrein catalytic activity and high molecular weight kininogen (HK) cleavage.

METHODS: KVD900, a potent and selective small molecule plasma kallikrein inhibitor, was administered orally to 8 single ascending dose cohorts of healthy adult males (n=6 active, 2 placebo per cohort). Samples for pharmacokinetic and PD assessment were taken at repeated intervals over 48hrs. PD measurements were determined in dextran sulfate (DXS)-stimulated whole plasma using a fluorogenic enzyme assay and capillary-based HK cleavage immunoassay.

RESULTS: Orally administered KVD900 achieved rapid and dose-dependent plasma exposure over the range of doses tested from 5mg to 600mg. The mean plasma exposure following the 600mg dose of KVD900 was 3162 +/- 1031 ng/ml at 30mins and 3680 +/- 846 ng/ml at 1hr. Enzyme assays demonstrated that this dose provided >90% inhibition of plasma kallikrein catalytic activity between 30mins and 6hrs post-dose and >50% inhibition for 10hrs. The 600mg dose of KVD900 protected HK from DXS-stimulated cleavage for at least 10hrs post-dose. Whilst all doses from 80mg and above were able to completely inhibit plasma kallikrein catalytic activity and consequently provide effective protection of HK cleavage, the duration of these PD effects was dose proportional.

CONCLUSIONS: Orally administered KVD900 achieves rapid plasma exposure sufficient for highly effective plasma kallikrein inhibition and protection of HK cleavage. A single 600mg dose provided these effects for at least 10hrs. These properties of KVD900 are well suited as a rapidly-acting oral treatment of HAE attacks.

117 Long-term Safety of Subcutaneous C1-Inhibitor in the Prophylactic Treatment of Hereditary Angioedema

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RATIONALE: Subcutaneous C1-inhibitor ([C1-INH(SC)], HAEGARDA®, CSL Behring) is indicated as routine prophylaxis for prevention of hereditary angioedema (HAE) attacks. We evaluated the long-term safety of C1-INH(SC) in an open-label extension of the phase III COMPACT trial.

METHODS: Patients aged ≥6 years with ≥4 attacks within 2 consecutive months pre-enrollment self-administered C1-INH(SC) 40 or 60 IU/kg twice weekly for 52 weeks (dose increases to 80 IU/kg were allowed for treatment optimization) or up to 140 weeks (US only). Safety endpoints included treatment-related serious adverse events (SAEs), AEs leading to premature discontinuation, AEs of special interest (thromboembolism, anaphylaxis), solicited AEs (injection-site reactions [ISRs]), hospitalizations for HAE, and clinically significant laboratory abnormalities.

RESULTS: Of 126 patients randomized, 110 completed the study (discontinuations: 4, pregnancy; 4, AEs; 8, patient decision). The AE rate (1811 events/18,699 injections) was not dose-related (40 vs 60 IU/kg: 11.3 vs 8.5 AEs/patient-year of exposure). None of the 12 SAEs were assessed as treatment-related. One unrelated serious HAE attack resulted in hospitalization but did not lead to discontinuation. No related thromboembolic events were recorded. No cases of anaphylaxis were reported. ISRs accounted for 99% of treatment-related AEs (1251/1257 events) and were reported more frequently with the 40 IU/kg dose; 99% were mild and 92% occurred within 24h of injection. No patients had neutralizing anti-C1-INH antibodies at baseline or post-baseline visits.

CONCLUSIONS: C1-INH(SC) has a favorable long-term safety profile in the prophylactic treatment of HAE, with no dose-dependent safety concerns. No cases of anaphylaxis and no related thromboembolic events were reported during C1-INH(SC) treatment.
118 Treatment of Patients with Hereditary Angioedema with Normal C1 Inhibitor: Evaluation of 295 Patients

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RATIONALE: Hereditary angioedema (HAE) with normal C1 inhibitor (HAE nC1-INH) is a rare condition, with clinical features similar to those of HAE with C1-INH deficit. Hormones have a special role as triggering factor. There is no biomarker for diagnosis, requiring a compatible clinical and familial history and/or identification of associated mutation (Factor 12, Angiopeptin 1 and Plasminogen).

METHODS: We evaluated 295 patients (242 F: 53 M) out of 101 families with confirmed diagnosis of HAE nC1-INH from 16 reference centers in Brazil.

RESULTS: 72.9% (215/295) were symptomatic (194F:21M) and 27.1% (80/295) asymptomatic with age range 3 - 91 years (median: 36). Genetic evaluation showed: F12 mutation 178/245 (72.6%); angiotensin I in 4/245 and 63/245 had unknown mutation. Symptoms initiated between 2 - 68 years old (median = 18). Main triggering factors: hormones 68.3%; stress 59.6%; trauma 47.6%; dental therapy 13.9%; unknown 13% and others 27%. Edema occurred in: face 84.6%; abdomen 75.5%; extremities 61.1%; laryngeal 36.1%; tongue 23.1% and others. Three patients died due to HAE. One third of the patients improved after contraceptive withdrawal only; 21.3% (36) treated on demand; continuous prophylaxis was used in 68.6% and 18.3% for surgical procedures; 22.5% increased doses of prophylactic medications during the attacks. Main prophylactic drug was tranexamic acid (n=45).

CONCLUSIONS: F12 mutation was present in a high number of our patients in comparison with other reports. Symptoms persisted in the majority of patients although estrogen therapy was interrupted. Plasmin inhibitor was effective in HAE nC1-INH.

119 Prodromal Symptoms In Bradykinin Vs. Histamine-Mediated Angioedema

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RATIONALE: Prodromal symptoms (PS) in bradykinin-mediated angioedema (B) have been well described however data regarding prodromes in histamine-mediated angioedema (H) is lacking. We assessed the prevalence, types and reliability of prodromes in spontaneous histamine-mediated angioedema.

METHODS: 73 patients (men and non-pregnant women between the ages of 18-70) receiving care at the US HAEA Angioedema Center were recruited for an anonymous 11 question survey. 30 patients had spontaneous histamine-mediated angioedema and 43 patients had either of the following bradykinin-mediated forms of angioedema: hereditary angioedema (HAE) with C1 inhibitor deficiency/dysfunction or HAE with normal C1 inhibitor. Frequencies were summarized and statistical analyses were calculated using Fisher’s exact, Mann-Whitney U or Independent t-tests.

RESULTS: 95.3% of B and 66.7% of H patients reported PS prior to their last angioedema (AE) attack (p=0.002) and 97.6% of B and 80% of H patients reported PS associated with any previous AE attacks. The average number of PS before the last AE attack was 6.17 in B and 2.35 in H (p<0.005). The most frequent PS in B was upset stomach/nausea (63.4%) and in H was cutaneous numbness/tingling (40%). 71% of B and 63% of H patients reported being able to predict AE attacks based on PS at least 75% of the time. PS were followed by AE attacks at least 75% of the time in 80.5% of B and 45% of H patients.

CONCLUSIONS: Prodromal symptoms occur in a majority of patients with histamine-mediated angioedema though appear more prevalent and predictive in bradykinin-mediated conditions.

120 Exposure-Response Analyses of Lanadelumab in Patients with Hereditary Angioedema

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RATIONALE: Lanadelumab is a plasma kallikrein (pKal) inhibitor (monoclonal antibody) indicated for prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients ≥12 years of age. 2-chain high-molecular weight kininogen (cHMWK), a product of active pKal, has been evaluated as a potential biomarker for the effect of lanadelumab. Exposure-response (ER) analyses were performed to support dosing of lanadelumab in patients with HAE.

METHODS: Data from 125 patients in the HELP Study treated with placebo, lanadelumab 150 mg Q4W, 300 mg Q4W, or 300 mg Q2W for 6 months were analyzed. The longitudinal ER model included a logarithm of the Poisson distribution to assess the impact of treatment duration and drug exposure on the number of HAE attacks/month. Time to first attack was assessed using Kaplan-Meier analyses and Cox proportional hazard modeling with steady state exposure and cHMWK suppression as continuous parameters.

RESULTS: The relationship between lanadelumab and the number of attacks/month was described using a placebo model (linear time-response model) and an Emax-type model for drug effect (ER model). The ER was very steep, with plateauing of effect observed at Month 5-6. An Emax of −3.74 HAE attacks/month was estimated. Higher exposure to lanadelumab and suppression of cHMWK following administration of lanadelumab 300 mg Q2W were associated with a significant prolongation in the time to first attack.

CONCLUSIONS: Exposure-response analyses suggest that longer chronic treatments with the 300 mg Q2W regimen were associated with further improvement in HAE control (number of HAE attacks/month) and a significant delay in time to first attack.
121 Effect of Lanadelumab on Coagulation Parameters in Patients With Hereditary Angioedema: Findings From The Phase 3 HELP Study

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RATIONALE: Hereditary angioedema (HAE) results from a deficiency of C1 esterase inhibitor, allowing for excessive conversion of prekallikrein (PK) into plasma kallikrein. Lanadelumab specifically inhibits plasma kallikrein, and prevented HAE attacks in the HELP Study (NCT02586805). Plasma kallikrein contributes to the aPTT coagulation test; therefore, a prolonged aPTT is an expected effect of lanadelumab. No effect on prothrombin time (PT) is expected. We evaluated the effects of lanadelumab on coagulation parameters in HAE patients.

METHODS: Patients ≥12 years old with type I/II HAE and ≥2 attack during a 4-week run-in received subcutaneous lanadelumab 150mg q4wks, 300mg q4wks, 300mg q2wks, or placebo over 26 weeks. Coagulation testing was performed at screening and throughout the study using standard laboratory tests.

RESULTS: Lanadelumab reduced plasma kallikrein activity (indicated by cleaved high molecular weight kininogen; cHK) by mean±SD 31.9%±36.6–48.2%±19.3% from baseline to Day 182. At baseline, mean±SD (range) aPTT was 28.21±3.013s (22.2-34.1), 28.46±4.066s (19.6-37.2), and 28.61±5.465s (20.0-42.3) in the lanadelumab 150mgq4wks, 300mgq4wks, 300mgq2wks groups with 28.38±3.835s (24.3-40.5) for placebo. At Day 182, mean±SD (range) aPTT was 30.60±3.013s (25.5-35.3), 34.06±4.979s (27.0-46.8), and 35.26±4.764s (26.9-44.3) with increasing lanadelumab doses vs 27.15±2.875s (21.4-33.9) with placebo. These data show the prolongation in aPTT assay with lanadelumab as expected. PT was not altered.

CONCLUSIONS: These data indicate that lanadelumab prolonged aPTT in treated groups, but not outside the normal range and with no association with abnormal bleeding events. Based on these data, lanadelumab inhibition of plasma kallikrein activity is sufficient for effective HAE prophylaxis without alteration of hemostasis or thrombosis in vivo.

122 Population Pharmacokinetic/Pharmacodynamic Modelling Reveals A Positive Relationship Between Complement 4 Serum Antigen Concentrations And C1 Inhibitor Functional Activity Levels

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RATIONALE: While the relationship between hereditary angioedema (HAE) attack risk and C1-INH functional activity (C1-INH(f)) is well established, its relation to complement 4 (C4) serum antigen concentrations—which are low in HAE and thus a potential disease activity biomarker—is unknown. This analysis aimed to quantify this relationship using a population pharmacokinetic/pharmacodynamic (PK/PD) model in HAE patients.

METHODS: C1-INH(f) and C4 antigen concentrations were measured in three trials (NCT01912456, NCT01576523, NCT02316353 [COMPACT Phase 2], and open-label extension studies), their correlation visually evaluated, and a population PK/PD model developed (NONMEM v7.3). The previously developed model was used to describe the PK of C1-INH(f) after subcutaneous administration of C1-INH to HAE patients. Several PD models were tested to describe the relationship between C1-INH(f) and C4 antigen concentrations.

RESULTS: A positive linear relationship was observed between C4 antigen concentrations and C1-INH(f) in type I and II HAE patients based on the Loess fit until C1-INH(f) of ~50%, at which point signs of saturation were apparent. A mechanistic quantification of this relationship was established with the indirect response model with C1-INH causing inhibition of the loss of C4 (rate of loss= k_log) showing best performance in data characterization. Baseline C4 antigen concentration was estimated at 7.52 mg/dL (29.4% inter-individual variability). The IC50 was estimated at 56.3% C1-INH. No covariates were found to be significant to describe the parameter variability.

CONCLUSIONS: The relationship between C1-INH(f) and C4 antigen concentrations in HAE patients was adequately described by a mechanistically accurate indirect response model with inhibition of removal process.

123 Safety, efficacy, and pharmacokinetics of intravenous C1 esterase inhibitor (human) prophylaxis in children with hereditary angioedema (HAE)

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RATIONALE: Intravenous (IV) C1-INH concentrate (Shire, USA) is approved for long-term prophylaxis against HAE attacks in patients with C1 esterase inhibitor (C1-INH) deficiency aged ≥6 years in the European Union (for severe and recurrent attacks) and the United States. Safety, efficacy, and pharmacokinetic (PK) data from three clinical trials of C1-INH for HAE attack prevention in children are presented.

METHODS: Safety and efficacy data from two phase 3 efficacy and safety trials of IV C1-INH, one in patients aged ≥6 years (NCT01003588), another specifically targeting patients aged 6-11 years (NCT02052141), and an open-label trial in patients aged ≥21 years (NCT00462709) were analyzed. Eligible patients in these studies had an attack frequency of ≥1 to ≥2 attacks/month or any laryngeal edema. Fixed doses ranged from 500 to 1000 U administered every 3-4 or 3-7 days. Study NCT02052141 also collected PK data.

RESULTS: Of 296 treatment-emergent adverse events (TEAEs) in 22 children aged 6-11 years who received 1493 infusions, 41 were possibly related to C1-INH (fatigue, irritability, HAE attack, diarrhea, erythema, pruritus, pyrexia, dizziness, mouth ulceration, headache, and nausea), all mild or moderate in severity. No serious adverse events were related to C1-INH and no TEAEs led to drug discontinuation. Compared with baseline, children aged 6-11 years had a 78.9-84.5% reduction in their number of HAE attacks with 1000 U C1-INH. There was no observed accumulation of C1-INH with multiple doses.

CONCLUSIONS: When used for long-term prophylaxis of HAE attacks in children, IV C1-INH concentrate was safe, well tolerated, and effective.
124 Subgroup Analyses From the Phase 3 HELP Study of Lanadelumab for the Prevention of Hereditary Angioedema Attacks

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RATIONALE: Treatment with the plasma kallikrein inhibitor lanadelumab significantly reduced hereditary angioedema (HAE) attack rate versus placebo over 26 weeks in the HELP Study (NCT02586805). Here we report findings from subgroup analyses for the primary endpoint.

METHODS: Patients ≥12 years old with HAE type I/II and ≥1 attack/month at baseline were randomized 2:2:2:3 to lanadelumab 150 mg every 4 weeks (q4wks), 300 mg q4wks, 300 mg q2wks, or placebo. Exploratory analyses were planned for subgroups with adequate numbers of patients for Poisson regression.

RESULTS: Overall, 125 patients were treated. Mean monthly attack rates were consistently reduced with lanadelumab versus placebo across all subgroups analyzed. Percentage reductions from placebo (n=41) were observed for the following demographic and disease characteristic subgroups with lanadelumab 300 mg q4wks (n=29) and 300 mg q2wks (n=27) respectively: age <18 years (20.5% and 62.3%), 18~<40 years (80.3% and 84.5%), ≥40~<65 years (71.5% and 89.8%); male (82.4% and 90.3%); female (69.6% and 85.8%); weight 50~<75 kg (78.4% and 93.1%), ≥75~<100 kg (74.0% and 84.0%), ≥100 kg (61.3% and 82.7%); HAE type I (73.4% and 87.8%), type II (60.1% and 69.5%); prior laryngeal attacks (64.2% and 85.7%), no prior laryngeal attacks (85.8% and 88.0%). Subgroups treated with 150 mg q4wks (n=28) also experienced attack rate reductions versus placebo (data not shown).

CONCLUSIONS: Patients with HAE type I/II treated with lanadelumab 300 mg q2wks or q4wks experienced clinically meaningful and persistent reductions in HAE attack rate compared with placebo regardless of age, sex, weight, and baseline HAE clinical characteristics.

125 Cleaved High Molecular Weight Kininogen Correlates With Hereditary Angioedema Due To C1-Inhibitor Deficiency

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RATIONALE: Hereditary angioedema with C1 inhibitor deficiency (HAE-C1-INH) is characterized by recurrent episodes of angioedema of cutaneous and submucosal tissue, and gastrointestinal and respiratory tracts. Our group has described the mutation c.351delC in SERPING1 gene, causing HAE type I in a large Brazilian family. Prospective follow-up revealed that there are currently 33 members diagnosed by genetic analysis. We aimed to compare the cleavage of high-molecular-weight kinogenin (HMWK) both during HAE attacks and in remission among HAE patients in this family.

METHODS: Whole blood was collected from 24 HAE-C1-INH patients, 13F/11M, aged 6-80 years-old, during remission; 6 HAE-C1-INH patients up to 12 hours after the onset of an acute attack (10 attacks), and 5 normal controls. Cleavage of HMWK was assessed by SDS-PAGE and immuno blot analysis. HMWK was identified using goat polyclonal anti-HMWK light chain antibody and biotinylated rabbit anti-goat antibody. Native HMWK appears as a single band with M, 130,000, and upon cleavage, it is replaced by bands of M, 107,000 and 98,000. The density of the bands was measured using Image Lab. Kaolin-incubated plasma was used as control sample. The amount of cleaved HMWK was expressed as a percentage of total HMWK.

RESULTS: Cleaved HMWK was increased in HAE-C1-INH patients during remission, as compared to normal controls (mean 0.44 ±0.05 and 0.38 ±0.03 respectively, p=0.01). Cleaved HMWK was higher in 3/6 patients during 5/10 attacks, as compared to remission period.

CONCLUSIONS: Our results support the evidence that evaluating plasma levels of cleaved HMWK may contribute to identify laboratory markers of disease in HAE-C1-INH patients.

126 Angioedema Due To Acquired C1-Inhibitor Deficiency: Spectrum And Treatment With C1-Inhibitor Concentrate

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RATIONALE: The purpose was to describe characteristics and associated disorders of patients with acquired angioedema due to C1-inhibitor deficiency (AAE-C1-INH) and assess the efficacy of plasma derived C1-INH concentrate (pdC1-INH).

METHODS: Forty-four patients with AAE-C1-INH were assessed for associated disorders. In 32 of the patients, the duration of swelling attacks was measured before and after treatment with pdC1-INH. The time between injection and disappearance of symptoms was recorded and treatment evaluations were provided by the patients.

RESULTS: The following associated disorders were present: monoclonal gammapathy of undetermined significance (47.7%), non-Hodgkin lymphoma (27.3%), anti-C1-INH autoantibodies alone (11.4 %), and other conditions (4.5%). In 9.1% patients, no associated disorder could be found. AAE-C1-INH led to the detection of lymphoma in 75% of patients with the malignancy. Treatment with pdC1-INH shortened attacks by an average 54.4 (±32.8) hours (P<0.0001). The earlier the attack was treated, the shorter the time between injection and disappearance of symptoms (P=0.0149). A total of 3553 (97.7%) of 3636 treated attacks were effectively treated with pdC1-INH as assessed by the patients. pdC1-INH was effective in 1246 (93.8%) of 1329 attacks in 8 patients with anti-C1-INH autoantibodies and in 344 (99.4%) of 346 attacks in 6 patients without autoantibodies. The average dose per effectively treated attack was 1238.4 U in patients with anti-C1-INH autoantibodies and 510.2 U in patients without autoantibodies.

CONCLUSIONS: pdC1-INH is highly effective in treating AAE-C1-INH patients. It reduces attack duration and is fast-acting. It is also effective in the vast majority of attacks in patients with anti-C1-INH autoantibodies.
**127 Icatibant Treatment of Acute Attacks in Pediatric Patients With Hereditary Angioedema: Findings from the Icatibant Outcome Survey**

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**RATIONALE:** Icatibant is a subcutaneous bradykinin B2 receptor antagonist used to treat acute attacks in patients with hereditary angioedema type I/II (C1-INH-HAE). In some countries, icatibant is approved in pediatric patients aged 2 years and older. This analysis examines real-world findings for pediatric patients treated with icatibant.

**METHODS:** The Icatibant Outcome Survey (IOS; NCT01034969) is an ongoing, international, prospective, observational study monitoring long-term safety and effectiveness of icatibant in a real-world setting. IOS data for pediatric patients in 6 countries were analyzed (follow-up period: July 2009–February 2018).

**RESULTS:** Twenty-three patients <18 years old (at IOS enrollment) were enrolled at data cutoff; 8 received icatibant during follow-up. In the treated cohort, median age at enrollment was 17.0 years (range 8.7–17.9), 62.5% were female, all had C1-INH-HAE type I. Median time between symptom onset and first icatibant injection (n=6, 32 attacks) was 2.0 hours (range 0.5–21.0). Median time to resolution for treated patients (n=6, 7 attacks) was 10.0 hours (range 4.5–21.8). Median duration of attack (n=6, 6 attacks) was 16.0 hours (range 5.0–38.0). Nine adverse events (AEs) in 3 patients were recorded, including 5 serious AEs in 2 patients (abdominal pain and 3 pregnancies in 1 patient aged 17.1 years at IOS entry; pregnancies occurred at ages 17.5, 18.1 and 18.6 years), tooth impacted/extraction [1 patient]. Recorded AEs were mild/moderate in severity; none were treatment-related.

**CONCLUSIONS:** Icatibant was effective with no new safety signals identified in this registry analysis of pediatric patients, further supporting its addition to the pediatric treatment armamentarium.

**128 Co-Occurrence of C1 Esterase Inhibitor Deficiency and Autoimmune Disease: A Systematic Literature Review**

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**RATIONALE:** Hereditary angioedema (HAE) is caused by a congenital deficiency or dysfunctional C1 esterase inhibitor (C1-INH), resulting in chronically low/undetectable C4 levels. The prevalence of autoimmune diseases (ADs) in patients with HAE appears to be higher than in the general population. A systematic literature review was conducted to examine the co-occurrence between HAE and ADs.

**METHODS:** PubMed was searched for English-language reviews, case reports, observational studies, retrospective studies, and randomized controlled trials up to April 15, 2018 that mentioned patients with HAE or genetic C1-INH deficiency and comorbid ADs. Non-human or in vitro studies and publications of acquired C1-INH deficiency (ie, secondary to lymphoproliferative disorders or ACE inhibitors) were excluded. A similar EMBASE search was conducted for abstracts published from April 15, 2015–April 15, 2018. Data on ADs was abstracted from the records and classified by MedDRA V21.0 High Level Terms (HLT).

**RESULTS:** In all, 2880 citations were screened for inclusion; 245 were selected for full-text review. Data were subsequently extracted from 77 citations. The ADs by MedDRA HLT with mentions of diagnosis in >5 citations were: Lupus Erythematosus and Associated Conditions, n=52; Endocrine Autoimmune Disorders, n=22; Gastrointestinal Inflammatory Conditions, n=16; Glomerulonephritis and Nephrotic Syndrome, n=16; Rheumatoid Arthritis and Associated Conditions, n=11; Eye, Salivary Gland and Connective Tissue Disorders, n=10; and Immune and Associated Conditions Not Elsewhere Classified, n=5.

**CONCLUSIONS:** Based on reports in the literature, lupus is the most common AD co-occurring with HAE and/or C1 INH deficiency. Detailed studies are warranted to further examine the AD/C1-INH relationship.

**129 Efficacy and safety of lanadelumab for prophylactic treatment in adolescents with hereditary angioedema (HAE)**

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**RATIONALE:** The efficacy and safety of lanadelumab, a monoclonal antibody targeting plasma kallikrein, in adolescents with HAE with C1-inhibitor deficiency (HAE-C1-INH) were investigated in a phase 3 trial and its open-label extension.

**METHODS:** In a multicenter, double-blind trial (NCT02586805), patients aged ≥12 years with ≥1 investigator-confirmed attack/4 weeks were randomized to placebo, or 150 mg every 4 weeks (150 mg q4w), 300 mg q4w, or 300 mg q2w lanadelumab. In the open-label extension study (NCT02741596, May 2016-September 2017), rollover patients from the phase 3 study and non-rollover patients received 300 mg q2w. Monthly attack rate (MAR) and other treatment-emergent events (TEAEs) were recorded.

**RESULTS:** In the phase 3 trial, 10/125 patients (8%) were adolescents (aged ≥12 to <18 years). In the placebo, 150 mg q4w, 300 mg q4w, and 300 mg q2w arms, respectively, 4, 1, 3, and 2 patients had a mean (SD) MAR of 1.825 (1.460), 1.000, 0.989 (0.020), and 1.948 (1.341) during the run-in period and 0.917 (0.992), 0.000, 0.304 (0.263), and 0.306 (0.433) during the treatment period. Three patients had 13 non-serious lanadelumab-related TEAEs. In the extension study, 21/212 patients (9.9%) were adolescents. Rollover patients (n=8) and non-rollover patients (n=13), respectively, had a mean (SD) MAR of 1.65 (1.158) and 1.54 (0.971) at baseline and 0.35 (0.635) and 0.07 (0.166) during the treatment period, ie, a mean (SD) percent change of -84.37 (18.94) and -94.89 (10.52). Nine patients had 65 non-serious lanadelumab-related TEAEs.

**CONCLUSIONS:** Lanadelumab safely reduced the MAR in adolescents with HAE-C1-INH.
RATIONAL: Angioedema (AE) is a benign and transient condition, but can also be life-threatening when the upper airway, or tongue are involved. The aim was to describe clinical characteristics facial angioedema (FAE).

METHODS: A retrospective-descriptive study including patients older than 15 years old diagnosed with FAE at the ED of a third level Hospital, January-2013 to December-2016 was conducted.

RESULTS: In 4 years, 839 AE patients were attended, 595 (70.9%) of them had FAE. Mean age: 48.5 ± 18.1, 66.1% women. AE compromised eyelid in 52.9% (26.7% as an isolated location), lips in 53.6% (21.7% isolated), forehead/cheeks in 89.5% (7.1% as a unique area). Erythema was present in 8.07% and pruritus in 9.41%. Other peripheral area was also involved in 3%: 2.7% extremities, 0.17% genitals and 0.17% trunk. In 23.9% an area of the oropharyngeal tract was also implicated (uvula: 11.26%, tongue: 7.06%, faringo-larynges: 2.18%. Breathing and/or swallowing difficulty was present in 7.9%. The ED doctor suspected an etiology of angioedema in 26.5%, NSAID intolerance in 5.5%, and ACEIs-induced AE in 2.2%. Other: 9.4%. It was not specified in 19.7%. Patient received: antihistamines (48.40%), corticosteroids (33.61%), adrenaline (2.02%) or Icatibant (1.01%). Mean length of stay at the ED was 6h 45min. None required hospital admission nor OTI.

CONCLUSIONS: Facial angioedema is present in most of the patients with angioedema at the emergency department, most as an isolated location. Although some ENT area is present in some patients, respiratory difficulty is uncommon, and oral intubation or hospital admission because facial angioedema may be exceptional.

A Comparison of Traditional and Novel Hereditary Angioedema Therapies

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RATIONAL: Traditional intravenous (IV) prophylactic therapies for Hereditary Angioedema (HAE) have been shown to reduce the frequency of attacks. The disadvantages to these are side effects, expense, and inconvenient route of administration. With newer subcutaneous (SC) C1 esterase inhibitor (C1-INH) replacement, easier administration and superior efficacy are anticipated. We assessed historical attack frequency in our cohort of patients before and after starting SC C1-INH.

METHODS: This study was IRB exempt. We retrospectively assessed attack frequency per history while patients were on prophylaxis with IV C1-INH or without prophylaxis. This was compared to attack frequency after these patients were switched to SC C1-INH. Dosing was 1000-2000 U twice weekly and 5000-9000 U twice weekly for IV and SC therapy, respectively.

RESULTS: Of 19 patients on SC C1-INH, we had sufficient data on 9 females and 3 males to make an adequate comparison. The average age of our subjects was 47.5 years. Attack frequency before starting the SC therapy was 38.7 attacks/year on average (range: 12 to 120 attacks/year). Attack frequency after starting SC therapy was reduced to 3.8 attacks/year on average (range: 0 to 12 attacks/year). Overall, the patients tolerated the SC injections well without any significant side effects and were satisfied with the route of administration.

CONCLUSIONS: Subcutaneous prophylactic therapies are likely to lead to great improvement in the care of HAE patients who are anticipated to have an improved quality of life with fewer attacks and ease of medication administration.
Response to H1 Antihistamine Therapy in Idiopathic Angioedema

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RATIONALE: Up to 40% of patients with angioedema without urticaria have no identifiable trigger. Previous studies have found that 80% of these patients can be classified as histaminergic based on clinical response to H1 antihistamines. Therefore, we sought to analyze changes in frequency of episodes after starting daily antihistamine therapy in patients previously identified with recurrent idiopathic angioedema.

METHODS: We examined a cohort of patients previously diagnosed with idiopathic angioedema and seen at a University of Wisconsin Allergy clinic. Patients who had recurrent episodes of angioedema at baseline and were subsequently started on daily H1 antihistamine therapy were identified. Data collected included demographics and frequency of symptoms both at baseline and at last contact with a healthcare provider.

RESULTS: Of 157 patients with idiopathic angioedema, 82 were started on daily long-acting H1 antihistamines. 68 of these patients had recurrent episodes prior to starting therapy. Frequency of episodes at baseline was daily (16%), weekly (15%), monthly (49%), greater than once yearly (16%) and once yearly (4%). For patients not lost to follow-up, frequency decreased to 0% daily, 2% weekly, 4% monthly, 6% greater than once yearly, and 12% once yearly. 44% of patients had no episodes at this time. Overall 48 patients (63%) had an absolute decrease in frequency of episodes (p < 0.001).

CONCLUSIONS: A significant portion of patients with idiopathic angioedema can be classified as histaminergic based on response to antihistamine therapy. Daily long-acting antihistamines can be effective in reducing the frequency of angioedema episodes.

Mutational spectrum of the SERPING1 gene in a pediatric population from Southern Spain with Hereditary Angioedema due to C1 inhibitor deficiency

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RATIONALE: Hereditary angioedema due to C1 inhibitor deficiency (C1-INH-HAE) is a rare disorder with a great genetic complexity. More than 400 mutations related to its pathogenesis have been published. We analyzed the mutational spectrum of the SERPING1 gene in our pediatric population with C1-INH-HAE.

METHODS: We prospectively studied 13 children from 12 unrelated families with laboratory and/or clinical diagnosis of C1-INH-HAE. At the time of the study, children were age 1 to 18 years (53.85% males). DNA samples were collected from peripheral blood and all eight exons and adjacent intronic regions of SERPING1 gene were sequenced following standard protocols.

RESULTS: A total of 12 different mutations were identified (two of the children were siblings). We observed a great variability, the mutations comprised 4 frameshift mutations, 3 nonsense mutations, 3 missense mutations and 1 mutation affecting the splicing sites. Only one large insertion of SERPING1 gene was detected. Few of the detected mutations were novel and not published previously, including a novel mutation affecting the second intronic region. No correlation between genotype and clinical expression was observed.

CONCLUSIONS: In our pediatric C1-INH-HAE population we corroborated the great allelic heterogeneity with each individual carrying their own mutation.

Effect of estrogen containing birth control pills on the constituents of bradykinin expression in plasma

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RATIONALE: Hereditary angioedema with C1-INH deficiency (HAE-C1-INH) is a rare autosomal disorder presenting with recurrent angioedema. Estrogen-containing medications trigger angioedema in many patients. Conversely, progesterone may decrease attack frequency. The mechanism by which estrogen exacerbates HAE-C1-INH is not well characterized.

METHODS: To evaluate whether oral contraceptives (OCPs) containing >20μg estrogen alter plasma protein levels of bradykinin (BK), and its precursor, high-molecular-weight kininogen (HMWK), plasma was collected prior to, and 3-months after initiation of OCPs. Protein HMWK and BK were measured by ELISA. As estrogen use is contra-indicated for patients with HAE-C1-INH, females without a history consistent with HAE and with a normal C4 were recruited.

RESULTS: Nine adult females (<40 years of age) had median baseline HMWK of 33,411,500 pg/ml [IQR: 23,690,750-40,076,250] and BK of 6,756 pg/ml [IQR: 2,268,9-12,652]. After 3 months of OCP therapy, the median HMWK increased to 36,386,500 pg/ml [IQR: 34,587,750-45,506,500] and BK to 7,980 pg/ml [IQR: 3,956-2,9-206,2]. These values corresponded to a mean fold increase of 0.94 (HMWK) and 0.83 (BK).

CONCLUSIONS: This preliminary study, performed in females without HAE, suggests that estrogen may exacerbate angioedema by increasing the production of HMWK and BK, an important mediator of HAE-C1-INH. Additional work is needed to address the effects of estrogen on BK degradation and expression of the bradykinin B2-receptor.

Lanadelumab And Cardiovascular Risk: Findings From The Phase 3 HELP Study

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RATIONALE: Hereditary angioedema (HAE) results from a deficiency of C1 esterase inhibitor, causing uncontrolled plasma kallikrein activity and excess production of bradykinin, a regulator of blood pressure. Lanadelumab specifically targets active plasma kallikrein, and was efficacious in the prevention of HAE attacks in the phase 3 HELP Study (NCT02586805). We examined the effect of lanadelumab-associated reductions in kallikrein activity on blood pressure.

METHODS: Patients ≥12 years with type I/II HAE and ≥1 attack during a 4-week run-in received SC lanadelumab 300mg q2wks, 300mg q4wks, 150mg q4wks, or placebo over 26 weeks. Angiotensin-converting enzyme (ACE) inhibitor use was not permitted during the study period.

RESULTS: 125 patients received ≥1 dose of study medication (lanadelumab, n=84; placebo, n=41) and were included in the safety analyses. Of these, 78 [92.8%] and 35 [85.4%] patients in lanadelumab and placebo arms completed the study. At baseline, 18 (14.4%) patients had a history of hypertension, 6 (14.6%) in the placebo arm and 12 (14.3%) in lanadelumab arms. Blood pressure remained stable over time with lanadelumab, while diastolic blood pressure slightly decreased over time with placebo (change from baseline to day 182: -3.17 mmHg vs 1.34 mmHg with lanadelumab, p=0.002). There was no increased use of anti-hypertensive medication with lanadelumab vs placebo. One patient receiving lanadelumab 150mg q4wks reported a treatment-emergent adverse event (TEAE) of increased blood pressure to 124/91 mmHg. No clinically significant ECG abnormalities were observed.

CONCLUSIONS: These data suggest there is no increased risk of hypertension or ECG abnormalities with lanadelumab vs placebo in patients with HAE.
137 Measurement of Functional C1 Inhibitor Levels to Inform Clinical Decision Making in Patients with Hereditary Angioedema: A Case Series

Melanie C. Wayne, MSN, FNP-BC and Kraig W. Jacobson, MD; Oregon Allergy Associates, Allergy and Asthma Research Group, Eugene, OR. RATIONALE: Low functional C1 inhibitor (C1-INH) levels are associated with a high risk of an angioedema attack in patients with hereditary angioedema with C1-INH deficiency (C1-INH-HAE). We measured functional C1-INH levels to inform treatment decisions for long-term prophylaxis with plasma-derived C1-INH in patients with C1-INH-HAE, including dose escalation of intravenous C1-INH and switching to subcutaneous C1-INH. METHODS: Three female patients (aged 50, 45, and 15 years) are described in this case series. Functional C1-INH was measured using the commercially available ELISA method (Quidel, San Diego, CA). Measurements were taken at the nadir immediately before the next scheduled dose. RESULTS: Despite receiving intravenous C1-INH (Cinryze®) 1000 U twice weekly for long-term prophylaxis, patients continued to have breakthrough attacks. Functional C1-INH levels were 33%, 40%, and 29%, respectively. Intravenous doses were administered in the clinic because patients had venous access problems. Doses were escalated to 2500 U in two patients and 1500 U in one patient. After dose escalation to 2500 U, functional C1-INH levels were 76% and 72%, respectively. Patients switched to subcutaneous C1-INH (Haegarda®) for multiple reasons, including the ability to administer treatment at home. After receiving subcutaneous C1-INH for 2 weeks, functional C1-INH levels were 72%, 91%, and 73%, respectively. Patients have received subcutaneous C1-INH for 10 months with no physician-confirmed attacks. CONCLUSIONS: Measurement of functional C1-INH levels was useful in identifying when patients required higher doses of C1-INH long-term prophylaxis. Patients had normal and sustained functional C1-INH levels and better control of symptoms after switching to subcutaneous C1-INH 60 IU/kg twice weekly.

138 Short term prophylaxis in patients with hereditary angioedema undergoing dental procedures

Andrea Zanichelli, Mario Ghezzi, Ivan Santichia, Maddalena A. Wu, Francesca Perego, PhD, Antonio Gidaro, MD, Chiara Suffritti, PhD, and Marco Cicardi; Department of Biomedical and Clinical Sciences Luigi Sacco, University of Milan, ASST Fatebenefratelli Sacco, Milan, Italy, University of Milan, Italy. RATIONALE: Hereditary angioedema with C1 inhibitor deficiency (C1-INH-HAE) is a rare disease. Clinical manifestations include recurrent episodes of swelling in subcutaneous-submucosal tissues. Laryngeal edema can be fatal if not treated. Dental procedures are known triggers of attacks involving the oropharyngeal-laryngeal mucosa. Short term prophylaxis (SPT) is indicated to prevent post-procedural attacks. Dentists are generally not familiar with C1-INH-HAE and patients report difficulty in receiving proper dental care. Aim of the study was to evaluate severity of oral disease, efficacy of SPT with plasma-derived-C1-INH in preventing post-procedural attacks and the impact of dental care on disease activity in C1-INH-HAE patients. METHODS: From 2010 to 2017 C1-INH-HAE patients requiring dental care visited by dentists collaborating with our center were enrolled. Data on need for dental care, use of SPT, disease activity were collected. RESULTS: 31 patients included in the study, 16 females, mean age 43 years. 90.3% had C1-INH-HAE, 6.5% acquired C1-INH deficiency (AAE) and 3.2% histaminergic angioedema. 22 patients underwent dental procedures, 13 females, mean age 43.2 years. 58% had moderate-severe oral disease. Only 2 patients experienced post-procedural attacks: 1 AAE-patient positive for C1-INH-antibodies with SPT and 1 C1-INH-HAE-patient without SPT. The latter had no attacks following a second procedure with SPT. Frequency of attacks decreased in 4 C1-INH-HAE patients and in 1 histaminergic angioedema patient. CONCLUSIONS: Most of the patients showed moderate-severe oral disease confirming difficulty in receiving dental care. SPT was effective in preventing angioedema attacks. Improvement of dental care had a positive impact on disease activity.

139 A Questionnaire Survey Study To Determine Association of Dental Hygiene Practices in Hereditary Angioedema Subjects With The Incidence of Post-Procedural Angioedema Attacks

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140 Impact of C1-INH(SC) on Type I/II Hereditary Angioedema: Findings from a US Patient Survey

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RATIONALE: Hereditary angioedema (HAE) is a genetic disorder characterized by recurrent peripheral, abdominal and laryngeal edema. Patient-reported outcomes on a newly-approved treatment, C1-INH(SC), outside clinical trial are limited.

METHODS: A convenience sample of 41 US patients, 33 with self-reported type I/II HAE completed a web-based survey. Patients were aged ≥18 (Mean=48) with 82% females. All have been receiving C1-INH(SC) for ≥3 months, 73% ≥5 months. 70% received both prophylactic and on-demand therapy prior to C1-INH(SC); of which 74% received Cinryze, 17% Berinert, 9% Danazol as prior prophylaxis.

RESULTS: Patients reported a median 3 attacks (of these 2 attacks required rescue medications) in a typical month prior to C1-INH(SC) compared to a median 0 attacks and rescue medications used in the last month whilst receiving C1-INH(SC). Around half (52%) experienced no attacks in the last month whilst receiving C1-INH(SC). 25% experienced a severe attack in a typical month prior to C1-INH(SC) compared to 9% during the last month on C1-INH(SC). Compared with prior treatment, 68% felt very much better and 26% a fair amount better since receiving C1-INH(SC).

Almost all were very satisfied or fairly satisfied with C1-INH(SC) for; ability to fit treatment into schedule (100%), ease to prepare (97%), time to prepare (97%), effectiveness in reducing the number of HAE attacks (97%) and overall as a prophylactic medication for HAE (97%).

CONCLUSIONS: Type I/II HAE patients in this study reported a reduction in attacks whilst receiving C1-INH(SC) with a high degree of treatment satisfaction.

141 Clinical Features of Patients With Primary Angioedema With Normal Levels of C1-Inhibitor

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RATIONALE: Angioedema patients classified according to Hawk 2014 criteria, were considered. C1 inhibitor deficient patients, hereditary angioedema with normal C1 inhibitor and angioedema related to ACE inhibitor were excluded. Specific analysis was restricted to idiopathic histaminergic and non histaminergic acquired angioedema (IH-AAE and InH-AAE).

METHODS: Angioedema patients classified according to Hawk 2014 criteria, were considered. C1 inhibitor deficient patients, hereditary angioedema with normal C1 inhibitor and angioedema related to ACE inhibitor were excluded. Specific analysis was restricted to idiopathic histaminergic and non histaminergic acquired angioedema (IH-AAE and InH-AAE).

RESULTS: Of a total of 788 patients evaluated at our outpatient angioedema clinic, 76 (10%) fulfilled the inclusion criteria: 65 (86%) were classified as IH-AAE (46% CR, 38% PR, 11% on demand treatment, 5% unknown) and 11 (14%) as InH-AAE. Females were 54%, median age 50 years. Overall 87% had recurrent attacks without differences between IH-AAE and InH-AAE. In 62% IH-AAE-patients attacks were recurrent and treated with anti-histamines. The localization of attacks in the IH-AAE was 86% neck-face, 37% cutaneous peripheral, 38% oral cavity/larynx, 5% abdominal. The PRs vs CRs reported a trend toward a higher frequency (96% vs 76%, p=0.06) of localization to neck/face and a lower frequency (50% vs 24%, p=0.06) of peripheral.

CONCLUSIONS: Among acquired angioedema, idiopathic histaminergic forms are highly more frequent. Management of primary angioedema constitutes 10% of ambulatory activity, mainly addressed to IH-AAE. A marked proportion of IH-AAE response to anti-histamine is partial suggesting that histamine is just one of the mediator.

142 The French Side of the Global Angioedema Registry

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RATIONALE: Angioedema is a recurrent localized swelling of cutaneous and mucosal tissues. Potentially life-threatening, creates temporary disability which deteriorates quality of life. Seven inherited or acquired forms of angioedema without wheals are yet classified, included hereditary or acquired C1 inhibitor deficiency (C1-INH-HAE and C1-INH-AAE). This year, the French angioedema network (CREAK) joined the registry of angioedema without wheals (Cloud-R HAE). Here we present the contribution of the Grenoble Alpes University Hospital (CHUGA) to this disease registry.

METHODS: Study population is composed of C1-INH-HAE/AAE patients with a proved diagnosis. The following items are collected: patients’ personal-demographic data, clinical/laboratory/genetic characteristics, major comorbidities, treatments (prophylaxis/acute attacks). As from Cloud-R HAE structure, patients can directly provide information on angioedema attacks and their treatment through a dedicated electronic app, web connection or paper support, which is then transferred into the registry at CHUGA.

RESULTS: Since February 2018, 21 C1-INH-HAE patients have been included (informed consent signed). Fifteen per cent of them provide prospective data on angioedema attacks. Within C1-INH-HAE, median age is 43 years (range 24-71), sex-ratio: 6/15 (M/F). Due to the frequency of symptoms, 28% of them are on long-term prophylaxis (LTP) with tranexamic acid (4%), Danazol (19%), and C1-INH concentrate (5%).

CONCLUSIONS: Angioedema registry gives the possibility to gather information to define natural history of angioedema and to evaluate treatment efficacy in real life. The possibility that data from single countries merge into a global structure facilitates improvement and dissemination of the knowledge on this rare disease and its treatment.
143 Hereditary Angioedema Precipitated by Heroin Use

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RATIONALE: Hereditary angioedema (HAE) is an autosomal dominant disease caused by the lack of or a dysfunctional C1-inhibitor protein, affecting the skin, mucosal tissues of the upper respiratory tract and gastrointestinal (GI) tract. Trauma, infections, stress, and drugs such as estrogen-containing medications, and angiotensin-converting enzyme inhibitors are known triggers. Heroin use precipitating attacks has never been reported. Herein, we report the cases of identical twins with angioedema leading to respiratory failure after heroin use.

METHODS: Single-center retrospective observational case series

RESULTS: 55-year-old female twins with confirmed HAE since childhood presented one week apart with severe angioedema attack both precipitated immediately following abuse of heroin. Urine toxicology screen was positive for heroin. The first sister presented to the emergency department (ED) with angioedema flare of her upper airway. Her course was uncomplicated as she already had tracheostomy placement from previous attack and her flare rapidly resolved after C1 esterase replacement therapy. One week later, her twin sister presented to the ED with similar symptoms immediately after heroin use and she required mechanical ventilatory support. Her flare also resolved post administration of C1 esterase. Both were released from the hospital improved.

CONCLUSIONS: These 2 patients are the first reported cases of angioedema attacks resulting from heroin abuse and illustrate management challenges. HAE is known for painful flares involving the GI tract, which can often predispose patients to narcotic dependence for pain relief. In addition to medications, long-term management of HAE is avoiding the triggers. More research needs to be done regarding illicit drug abuse HAE attacks.

144 The Process of Joining to the Global Hereditary Angioedema Registry - Experience of the Hungarian Angioedema Reference Center

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RATIONALE: Hereditary angioedema (HAE) is a rare disease; its characterization requires safe and long-term storage of clinical and laboratory data accumulated from the patients. This is the purpose and function of the Global HAE Registry (GHR) established in the GHR-Conference. The GHR operates along corporate bylaws and protocols defined by HAE experts and IT professionals (Cloud-R).

METHODS: Joining the GHR is a multi-step process. Candidates file a membership application with the Global HAE Registry Board, and attend a kick-off web seminar. Then, the protocol is submitted to and approved by the Ethics Committee. The Letter of Appointment of the Data Processor is countersigned by the Data Controller of the collaborating center. A collection of signed, original copies of informed consent should also be submitted. A training delivered by Cloud-R and the GHR Project manager should be completed. Finally, 10 valid clinical report forms (complete with laboratory findings confirming the diagnosis), and an outpatient record of a follow-up visit should be presented.

RESULTS: Having fulfilled all the requirements, the Hungarian Angioedema Reference Center joined among the first to the GHR.

CONCLUSIONS: By joining the GHR, our center contributes to the database. The analysis of data from a large number of patients will lead to more accurate understanding of the disease. Further, it will allow for improving the treatment protocols in consideration of interindividual differences in therapeutic response. Finally, the GHR is a reliable source of high-quality information for research.

145 Delays in Seeking Health Care Among Patients with Hereditary Angioedema

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RATIONALE: The negative impact of hereditary angioedema (HAE) on patients’ quality of life is well documented. The unpredictability of attacks and fear of asphyxiation contribute to anxiety even among diagnosed patients who have access to HAE-specific on-demand medications. In this exploratory survey-based study, we sought to determine whether anxiety surrounding HAE attacks leads to delays in seeking routine, preventive, or necessary health care.

METHODS: We developed a brief questionnaire to assess whether patients with HAE delay recommended health procedures (eg, mammograms, dental work, cardiac tests) due to fear of an HAE attack. Questionnaires were sent via email to all patients on a patient advisory board. Responses were discussed in detail during follow-up group telephone interviews.

RESULTS: Seven of 9 patients responded to the questionnaire; all respondents were female (mean age: 45 years) with an average of 4.4 attacks per month (range: 1 to 10) in the absence of prophylaxis. Four respondents (57%) reported delaying or avoiding routine health care procedures due to fear of an attack. Dental work (including dental surgery) was the most common type of health procedure delayed/avoided—respondents noted that fear of a laryngeal attack leading to asphyxiation was the primary reason for delaying health procedures. Three of these 4 patients reported experiencing attacks of varying severity during routine health procedures.

CONCLUSIONS: Although preliminary and observational, the results suggest that a substantial proportion of HAE patients may delay dental work or other procedures that might trigger a laryngeal attack due to fear of asphyxiation. These findings warrant further study.
146 Kinetic Profiling of Clinical Symptoms and Basophil Parameters During Treatment of Chronic Spontaneous Urticaria with Omalizumab

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RATIONALE: Omalizumab is a humanized IgG1κ anti-IgE monoclonal antibody approved for treatment of chronic spontaneous urticaria (CSU). Details are lacking regarding the timing of omalizumab’s clinical effect relative to high affinity IgE receptor (FceRI) downregulation and its function on various cell types. The purpose of this study is to examine the kinetics of clinical symptom improvement relative to basophil phenotype shifts during treatment of CSU with omalizumab.

METHODS: Adults with antihistamine-refractory CSU were recruited and treated with omalizumab 300 mg monthly for 90 days, following a 2 week run-in period to establish baseline symptoms. Subjects recorded Urticaria Activity Scores (UAS) twice daily, and weekly UAS-7 scores were calculated. Clinical assessments and blood sampling occurred at baseline and days 1, 3, 6, 10, 20, 30, 60 and 90 following initial omalizumab administration. Basophil measures included manual counts, blood histamine content, histamine release response, BAT and flow cytometric analysis of surface markers (IgE, FceRI, CRTh2).

RESULTS: A 50% reduction in UAS-7 scores was achieved on average by day 13 ± 6 (n=6) after the first dose of omalizumab. At that time, basophil counts following enrichment on Percoll increased by an average of 50%. Basophil surface IgE and FceRI were reduced by 50% by day 6. Additionally, at the time of 50% symptom reduction, CRTh2 expression increased by approximately 30%.

CONCLUSIONS: At the time of 50% symptom reduction in baseline UAS-7 scores with omalizumab therapy, basophil surface IgE and FceRI were reduced. Increased CRTh2 expression and blood basophils were noted at the time of CSU symptom reduction.

147 Inverse Association of Chronic Idiopathic/Spontaneous Urticaria with Osteoporosis and Fractures

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RATIONALE: Patients with chronic idiopathic/spontaneous urticaria (CIU/CSU) have risk factors for decreased bone mineral density, including systemic inflammation and systemic immunosuppressant use (including corticosteroids). However, few studies examined the association of CIU/CSU with osteoporosis and fractures.

METHODS: We analyzed data from 198,102,435 children and adults, including 570,733 with CIU/CSU, in the 2006-2012 National Emergency Department Sample, a 20% cross-sectional cohort of all emergency care visits throughout the United States. CIU/CSU was defined by previously validated ICD-9-CM codes.

RESULTS: Patients with CIU/CSU were significantly younger (mean±SD, 26.2±0.5 vs. 38.4±0.2), more likely to be female (59.0% vs. 55.0%), have Medicaid (31.6% vs. 24.6%) or private insurance (39.7% vs. 32.2%), and have a history of long-term corticosteroid use (0.3% vs. 0.2%). Pooled analysis across all 7 years showed that patients with CIU/CSU had significantly lower odds (multivariable logistic regression including age, sex, primary payer, income quartile, and history of long-term steroids; adjusted odds ratio [95% confidence interval]) of diagnosis with osteopenia (0.391 [0.333-0.460]), osteoporosis (0.515 [0.479-0.554]), all fracture (0.036 [0.033-0.040]), pathologic fracture (0.228 [0.175-0.297]), and stress fracture (0.107 [0.015-0.744]). Similar results were found in sensitivity analyses in age ≥50 years. Patients with CIU/CSU had significantly lower odds of osteopenia, osteoporosis, and/or pathologic fractures compared to patients with atopic dermatitis or asthma.

CONCLUSIONS: Patients with CIU/CSU have lower odds of osteopenia, osteoporosis, and fracture than those with atopic dermatitis, asthma or other disorders. Future studies are needed to confirm these findings and determine why CIU/CSU is associated with decreased likelihood of osteopenia, osteoporosis and fractures.

148 Autoimmune Laboratory Testing Practices for Evaluation of Chronic Urticaria

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RATIONALE: Current guidelines recommend against autoimmune testing for chronic urticaria (CU) without findings suggestive of autoimmunity. Despite the majority of cases being idiopathic, patients and referring physicians often consult A/I specialists to identify the etiology of disease. Here we describe current autoimmune laboratory testing practices and utility.

METHODS: Retrospective chart review of patients evaluated at an allergy/immunology practice for CU. Autoimmune lab tests, biopsies, and resultant referrals were reviewed.

RESULTS: Among 149 patients, autoimmune testing was performed in 81.2% (121) with 43.8% (53) being indicated based upon current autoimmune diagnosis (50.9%), family history of autoimmune disease (41.5%), concerning review of systems (37.7%), or abnormal rash quality (11.3%). The most common tests ordered included TSH (86.0%), C4 (47.9%), TPO (36.4%), and ANA (31.4%). The most frequently abnormal tests were ANA (31.5% 13/38), ESR (20.8% 5/24), SSA (16.7% 1/6), and thyroglobulin (14.0% 6/43). There was no difference between indication for testing versus whether testing was sent overall (OR 0.90, 95% CI 0.39-2.1) or for each individual test. Of the thirty-seven patients with abnormal results- 45.9% resulted in no action, 54.1% were referred for further evaluation. Though those with testing indications, when compared to those without indication, did not have more abnormal results, they had 5 times greater odds of undergoing further intervention (OR 5.38,95% CI 1.2-12.2).

CONCLUSIONS: There was no association between testing indication and the ordering of tests or abnormal results. Routine extensive testing may lead to higher health care related costs without increased clinical benefit.
149 Predictors Of BAT Positivity In Chronic Spontaneous Urticaria And Clinical Characteristics Of Patients

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RATIONALE: Diagnosing autoreactivity in chronic spontaneous urticaria (CSU) can predict a more prolonged disease course, higher disease activity, need for higher doses of anti-histamines and the responsiveness to cyclosporin A and omalizumab. The BAT can identify these patients but is not widely available. Finding a combination of clinical data that helps identify these patients is clinically relevant. We aimed to analyse the clinical and laboratory characteristics of BAT positive CSU patients and identify predictors of BAT positivity.

METHODS: Cross-sectional study of 64 patients with CSU, with a 1-year follow-up. Data were analysed using SPSS: Student’s t test, Chi-square test, Kappa coefficient, Odds Ratio, multivariable logistic regression model and ROC curve.

RESULTS: Twenty-five patients were BAT negative and 39 were BAT positive. Six characteristics were significantly more frequent in the BAT positive group (p<0.05): a positive ASST, a UAS7>36, presence of angioedema, presence of nocturnal symptoms, symptoms for >5 days/week, and presence of anti-TG/TPO autoantibodies. This group also had a tendency for worse DLQI and UCT scores, a higher number of patients requiring therapy with omalizumab and had a lower total serum IgE. The combination of these characteristics showed good sensitivity and specificity at identifying BAT positive patients and statistical analysis demonstrated that they had a good discriminant power (area under the ROC curve 0.836).

CONCLUSIONS: CSU patients can be divided into two distinct subsets using the BAT. BAT positive patients have a more severe disease and are strongly associated with 6 clinical characteristics that may be used in the future as surrogate markers.

150 Omalizumab for Chronic Idiopathic Urticaria: Potential to Taper Dose and Frequency?

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RATIONALE: Omalizumab is FDA-approved for treatment of chronic idiopathic urticaria (CIU). There is limited data on the long-term use of omalizumab for CIU, particularly with regards to frequency, dosing, and potential for tapering its use.

METHODS: With an IRB-approved protocol, 48 adult patients diagnosed with chronic urticaria and treated with omalizumab were identified in the electronic medical record (EMR). 21 patients were excluded for having diagnosis of mastocytosis and/or less than 1 year of omalizumab use. Of the remaining 27 patients, clinic notes from the Allergy clinic were accessed to collect the following data: age, sex, BMI, omalizumab starting and current dose, frequency and use of additional medications before and after starting omalizumab.

RESULTS: The 27 patients with CIU on omalizumab for at least 1 year (average duration 38 months) included 5 males and 22 females with an average age of 48 years. 70% of the patients in this study were obese (BMI ≥30). The average starting cumulative dose of omalizumab usage was 320 mg/4 weeks and the average current cumulative dose of omalizumab usage was 299 mg/4 weeks. 21 patients (81%) decreased or remained on the same dose of omalizumab. Overall, all patients had complete (85%) or almost complete (15%) urticaria symptom control.

CONCLUSIONS: The majority of patients in this study remained on the same or decreased cumulative dosage of omalizumab for multiple years. All patients achieved complete or almost complete control of symptoms, suggesting an opportunity for tapering omalizumab dose and frequency.
152 Elevated Serum Fortilin Levels In Subjects With Chronic Idiopathic Urticaria

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RATIONALE: Fortilin, a molecule also known as histamine-releasing factor (HRF), has demonstrated histamine-release activity and been implicated in various allergic diseases. While mast cell release of histamine is thought to play a role in chronic idiopathic urticaria (CIU), the pathogenesis remains unclear, as does reliable serologic testing. A potential role of fortilin in CIU has not yet been reported.

METHODS: Twenty adult subjects with CIU, defined as the presence of hives with itching for more than 6 consecutive weeks without clear etiology, were recruited for this study. The CIU group consisted of 5 males and 15 females with a mean age of 43.3 years. Thirty-five control patients without CIU were also recruited, consisting of 8 males and 27 females with a mean age of 41.4 years. Serum samples were obtained from all enrolled subjects and fortilin levels examined using ELISA. Unpaired two-tailed t-tests using GraphPad Prism software were performed for analysis.

RESULTS: Compared to non-CIU patients (mean 6.74ng/mL ± SEM 1.3), subjects with CIU demonstrated elevated serum levels of fortilin (12.33ng/mL ± 2.7; p<0.05).

CONCLUSIONS: The newly-developed fortilin assay enabled accurate quantification of serum fortilin levels. CIU subjects demonstrated almost double the serum fortilin levels present in non-CIU subjects. Elevated fortilin levels have been reported in BAL fluid of asthmatics and in nasal lavage fluid from subjects with allergic rhinitis, with fortilin inhibition able to alleviate mast cell-mediated airway inflammation. Fortilin may contribute to the pathophysiology of CIU by stimulating mast cell degranulation, and provide a potential therapeutic target for the treatment of CIU.

153 Inflammation markers are associated with disease activity in patients with chronic urticaria

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RATIONALE: The evaluation of disease activity and severity of chronic idiopathic urticaria (CIU) is essential for the treatment of patients. However, there is no reliable biomarker for such evaluations. Recently, several markers of inflammation have been revealed to be elevated in severe cases of CIU. In this article, we studied the inflammation markers and coagulation markers and their relationship to disease activity in patients with CIU.

METHODS: Data on 132 patients with CIU reported in a single tertiary allergy center in Korea during January 2017 to December 2017 were obtained. We collected information regarding various laboratory tests including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), complete blood count (CBC) with differential count, fibrin degradation products (FDP), D-dimer, C5, C4, anti-nuclear antibodies (ANA), anti-neutrophil cytoplasmic antibody (ANCA) and thyroid function test. We also collected data on age, gender, autologous serum skin test (ASST) and medication score.

RESULTS: Eighteen percentages of CIU patients revealed abnormal thyroid-stimulating hormone (TSH) and about one-third of CIU patients had elevated levels of ESR and D-dimer. The levels of CRP in patients with abnormal TSH result were significantly higher than those in patients with normal TSH result (P = .001). But no other differences in FDP, D-dimer and ESR were observed among patients with abnormal TSH result. C-reactive protein showed correlation with numbers of medication ($R^2=0.303, P < .001$) but FDP, D-dimer and ESR showed no correlation with numbers of medication.

CONCLUSIONS: The measurement of serum CRP may be useful for the assessment of disease activity of CIU.

154 Treatment Refractory Chronic Spontaneous Urticaria Patients Achieves Remission with Low Molecular Weight Heparin

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RATIONALE: Chronic spontaneous urticaria (CSU) is an autoimmune disorder thought to be caused by mast cell activating auto-antibodies to IgE or FcεRI. Standard treatments include second generation antihistamines, omalizumab, and cyclosporine. We present two treatment-refractory CSU patients with elevated D-Dimer, who achieved remission with a low molecular weight heparin (LMWH).

METHODS: We reviewed the charts of 2 patients with elevated D-Dimer.

RESULTS: Patient A, 67 year old male, presented with urticaria in 2013. Labs were unremarkable excluding elevated D-Dimer (1303ng/mL) and C-Reactive Protein. Patient was prescribed omalizumab 300mg monthly and updosed to 600 mg. The patient was prescribed 30mg of enoxaparin, an LMWH, daily for 3 weeks following a planned hip replacement. The patient’s Urticaria Activity Score (UAS-7) went from 42 to 0 post-enoxaparin. However, returned to 42 following the 3 weeks. The patient has resumed enoxaparin 30mg daily for 9 months and still reports a UAS-7 of 0.

Patient B, 55 year old male, presented with urticaria in 2016. Labs were unremarkable excluding elevated D-Dimer (1657 ng/mL) and C-Reactive Protein. The patients’ UAS-7 was 30. Patient was prescribed omalizumab 300mg, then updosed to 600 mg. Was then prescribed enoxaparin 30mg daily, and their UAS-7 immediately went from 30 to 0, and has remained there for 4 months.

CONCLUSIONS: It has been reported that D-Dimer could be a marker of urticaria activity and treatment response. However few patients have ever been treated with LMWH. The coagulation pathway is involved in mast cell degranulation and LMWH may be useful for CSU patients with elevated D-Dimer.
AB52 Abstracts

**155 Asthma Control Test Score is Associated with Economic Outcomes among U.S. Asthma Patients**

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**RATIONALE:** The Asthma Control Test (ACT) is a standard validated questionnaire for assessment of asthma control. The relationship between asthma control and economic outcomes warrants further clarification.

**METHODS:** Patients aged ≥18 years with a self-reported physician diagnosis of asthma were identified from the 2015–2016 U.S. National Health and Wellness Survey, a patient-administered, internet-based questionnaire. Patients were grouped into different levels of asthma control using the ACT score (≥15: poorly-controlled; 16–19: partly-controlled; 20–25: well-controlled asthma). The Work Productivity and Activity Impairment-General Health Scale (WPAI-GH v2.0) and patient-reported health resource utilization (HRU; including healthcare provider visits, emergency room visits, and hospitalizations in the previous 6 months) were used to derive indirect and direct healthcare costs, respectively. Generalized linear models examined differences in economic outcomes by ACT scores, controlling for covariates.

**RESULTS:** Overall, 1,360 (17.4%), 1,572 (20.1%), and 4,888 (62.5%) patients had ACT<15, 16–19, and 20–25, respectively. Mean work impairment was higher (p<0.001) in patients with ACT<15 (44.6%) or 16–19 (31.96%) versus patients with ACT=20–25 (19.12%). All HRU outcomes were also higher for patients with ACT<15 and 16–19 compared with patients with ACT=20–25 (p<0.02 for all outcomes). Mean indirect and direct costs were significantly higher for patients with ACT<15 ($14,764, p<0.001 and $15,262, p<0.001) and ACT=16–19 ($10,448, p<0.001 and $8,554; p=0.001) versus patients with ACT=20–25 ($6,353 and $6,012.)

**CONCLUSIONS:** Lower ACT scores were associated with greater HRU and work productivity loss. Interventions to address asthma control may result in direct and indirect cost savings.

**156 Defining Minimal Clinically Important Differences (MCID) on the Leicester Cough Questionnaire (LCQ): Analyses of a Phase 2 Randomized Controlled Trial in Chronic Cough**

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**RATIONALE:** Chronic cough (CC) is a condition resulting in negative impacts on QoL. The LCQ is a cough-specific QoL measure which has a Total, Physical, Psychological, and Social domain scores. The objective was to define minimal clinically important differences (MCID) for the LCQ.

**METHODS:** Pooled data from a Phase 2 RCT of an investigational treatment for CC were analyzed. Participants were non-smokers, had refractory/unexplained CC for ≥1yr, and baseline cough severity VAS ≥40mm. LCQ (Baseline, Week4) and Patient Global Impression of Change (PGIC; Week4) data were analyzed. MCIDs were defined using distribution-based (MCID-D; ½ standard deviation and standard error of measurement) and anchor-based (MCID-A; receiver operating characteristic curves [ROC] and PGIC) analyses.

**RESULTS:** Analyses (n=253; mean age 60.2; 76% female) resulted in MCID-D estimates of 1.5-point increases for LCQ Total and 0.42-0.85-point increases for domain scores. MCID-A/ROC analyses indicated that mean increases ≥1.7 points for LCQ Total and ≥0.8, 0.9, and 0.8 points for Physical, Psychological, and Social domain scores, respectively, had the best sensitivity/specificity for predicting Week4 PGIC responses of “somewhat improved,” “improved,” or “very much improved.” Among participants with Week4 LCQ Total score increases ≥2 points, 93.7% responded as at least “somewhat improved” (58.3% “improved” or “very much improved”; 35.4% “somewhat improved”).

**CONCLUSIONS:** These results provide guidance on the degree of change in LCQ scores that can be considered clinically meaningful to help guide treatment decisions and drug development. Specifically, clinicians may consider a 1.5- to 2-point increase in the LCQ Total score as a clinically meaningful improvement for individual patients.


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**RATIONALE:** The economic burden of asthma is considerable. This study provides updated health care costs of asthma patients receiving medium-to-high-dosage ICS/LABA (moderate to severe asthma [MSA]), with and without exacerbations and/or high rescue medication use (Ex/R).

**METHODS:** US administrative claims from the IBM MarketScan® Research Databases were evaluated for patients with asthma aged ≥12 years with records between 1/1/2012–12/31/2015. Patients were indexed on their earliest medical claims for asthma and were required to have had evidence of ≥2 years of continuous eligibility. MSA classification required ≥1 medium-or high-dosage ICS/LABA claim, ≥1 omalizumab claim, or systemic corticosteroid supply covering ≥50% of the 12-month baseline period. MSA with Ex/R classification followed ERS/ATS criteria for severe uncontrolled asthma, modified for claims data. Health care costs were measured during the 12-month post-index period and are reported in 2017 USD.

**RESULTS:** The study identified 605,614 total asthma patients; 92,027 (15.2%) with MSA, and 37,220 (6.1%) with MSA and Ex/R. Compared with non-MSA patients, MSA patients incurred greater total ($15,244 vs $10,860) and asthma-related ($3,853 vs $1,670) health care costs during the 12-month follow-up period. MSA patients with Ex/R incurred greater total health care costs than MSA patients without Ex/R ($18,233 vs $13,215), and greater asthma-related pharmacy expenditures ($2,160 vs $327).

**CONCLUSIONS:** Cost differences between MSA and non-MSA patients were primarily driven by the sub-group of MSA patients with Ex/R, partly because of asthma-related pharmacy expenditures. Future research exploring approaches to minimize and better control exacerbations, which may reduce the economic burden of asthma, is warranted.
Clinical Outcomes in Patients with Persistent Asthma (PA) by Attainment of Healthcare Effectiveness and Data Information Set (HEDIS) Measures: Stratification by Medication Management (MM) and/or Asthma Medication Ratio (AMR) Attainment

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RATIONALE: Attainment of asthma-specific HEDIS quality measures may be associated with improved clinical outcomes. This study assessed asthma exacerbation outcomes for PA patients stratified by attainment of MM and/or AMR.

METHODS: This retrospective analysis of claims linked to ambulatory electronic medical records included patients aged ≥2 years with evidence of PA and continuous enrollment from May 2015 to April 2017. Patients attaining MM (proportion of days covered with asthma controller medication [ACM] ≥75%) and/or AMR (ratio of ACM to total asthma medications ≥6.0) were identified during a 1-year baseline period. Asthma exacerbations (AE; asthma-related hospitalizations [AHR], emergency department visits [EDV], or oral corticosteroid bursts [OCS]) were identified during a 1-year follow-up period. Exacerbation outcomes were compared between those who attained/not attained MM (+MM/-MM) and attained/not attained AMR (+AMR/-AMR).

RESULTS: The study included 12,042/20,706 attained/not attained MM (+MM/MM), and 24,388/8,360 attained/not attained AMR (+AMR/-AMR) patients. Demographics were similar for all patients (mean age 39–44, 60% female). During baseline, a higher proportion of patients with +MM/+AMR versus -MM/-AMR visited asthma specialists and primary care versus primary care alone. Patients with +MM/+AMR were less likely to have exacerbation outcomes versus -MM/MM: AE: 12.8%/14.3% versus 18.7%/23.3%; ≥1 AHR: 5.1%/4.9% versus 5.8%/7.4%; ≥1 EDV: 8.4%/9.5% versus 13.6%/18.1%; OCS use: 41.8%/43.8% versus 48.1%/51.4%. Adjusted analyses also showed lower risk of AE for +MM/+AMR versus -MM/MM. All results were significant (p<0.001).

CONCLUSIONS: MM and AMR attainment were associated with significantly improved clinical outcomes; the magnitude of the differences between +MM and -MM were larger than those between +MM and -MM.

Application of Guideline-Based Definition of Severe Asthma Exacerbation with Objective and Subjective Methods to Evaluate Sensitivity on Treatment Response in a Randomized Controlled Trial

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RATIONALE: Current clinical trials have generally harmonized on ATS/ERS guideline definitions of severe asthma exacerbation (SAEX) [i.e., 3 consecutive days of systemic corticosteroid (SCS), emergency department visit requiring SCS, or hospitalization for asthma]. However, because there is no consensus for defining event start/stop dates, the impact of applying different event detection methods on treatment response is unclear. Using data from a recently completed randomized, controlled asthma trial (comparing montelukast furoate-formoterol [MF/F] to montelukast furoate alone [MF]), we examined SAEX results using two different event detection methods.

METHODS: In the primary analysis, objective SAEX event start/stop dates were based on when an individual SAEX criterion was initially met and fulfilled, respectively. In another prespecified analysis, subjective start/stop dates were based on investigator-assessment of when SAEX symptoms first occurred and resolved, respectively. Time-to-first SAEX was analyzed using a Cox proportional hazards model.

RESULTS: Among 11,729 subjects who received at least one dose of MF/F (n=5868) or MF (n=5861), a total of 1,487 SAEXs were identified with the objective method and 1,432 SAEXs were identified by investigator-assessment. The hazard ratio for the time-to-first SAEX in MF/F vs MF was 0.89 (95% CI: 0.80 to 0.98, p=0.021) using the objective method and 0.87 (95% CI: 0.78 to 0.96, p=0.007) by investigator-assessment.

CONCLUSIONS: Although the data suggest a symptom-based detection method may underestimate the number of SAEX events, the guideline-based SAEX definition appears to be robust as both objective and subjective methods resulted in a similar time-to-first SAEX result.
**161 The Feasibility Of Integrating The Asthma Control Test In An Urban Primary Care Resident Clinic**

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**Rationale:** Asthma control reflects the overall management of underlying airway inflammation. The purpose of this quality improvement project was to assess the feasibility of integrating the Asthma Control Test (ACT) into an urban residency based internal medicine clinic to reliably and consistently assess asthma control at all visit types.

**Methods:** Patients 18 years of age or older were prompted to self-identify as having asthma by signs located in exam rooms. The ACT questionnaires were placed adjacent to those signs. Providers gave completed questionnaires to a designated medical assistant who uploaded them into the electronic medical record. A Plan-Do-Study-Act (PDSA) cycle was developed to guide the integration process. An electronic survey asked residents about their utilization of the ACT in clinic at the end of the seventh month. A goal was set for a 20% completion rate of the ACT.

**Results:** Seven months after the introduction of the questionnaires, 40 ACT were collected out of the 432 patients with asthma that attended clinic appointments, resulting in a 9.3% completion rate. The electronic survey reported that 68.97% of residents did not use the ACT, with lack of familiarity with the questionnaire (33.3%), time constraints (33.3%) and forgetting to use it (33.3%) as prevailing rationales.

**Conclusion:** We demonstrated that the integration of the ACT into a resident clinic is feasible, but requires a multifaceted approach. Next steps are to develop additional PDSA cycles to address the challenges that arose, such as provider education and efficiency in clinic workflow, to reach the completion goal.

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**162 The Effect of a Five-Day Educational Program for Children with Asthma on Airway Inflammation**

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**Rationale:** The aim of this study was to investigate the effectiveness of a 5 day educational program in children with asthma on airway inflammation as measured by FeNO.

**Methods:** Fifty-one children with asthma were enrolled in Camp Wheez. Written consent was obtained for each participant. Children were educated on the early signs of asthma, identifying triggers and the use of controller medication. The curriculum was provided by the asthma camp consortium by AAAAI. The NIOX VERO was used as a 6 to 10 second, single breath, quantitative measurement. We measured FeNO on day one (baseline) and day 5 (end of camp.)

**Results:** Fifty-one children were enrolled in the study with an average age 6-17 years. (range 6-17) Baseline determinations were done on day one and end of camp determinations were done on day 5. The baseline FeNO was 36.3 ppb, compared to 33.1 ppb at the end of camp. The average FeNo levels were the same at day 1 and 5 in campers with a low (<20 ppb) and intermediate FeNO (20-35ppb). However, in 21 campers with high baseline at >35 ppb (average 75 ppb), there was a 10% improvement at the end of camp at 67.5 (p=.001). None of the campers were informed on their baseline levels or received individual coaching.

**Conclusion:** This study demonstrated the effectiveness of a 5-day asthma education program on 50 children with asthma. Our results showed a significant improvement in FeNO with a 10% improvement (significance at P<.001) at the conclusion of asthma education.

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**163 AEPEAL (Allergy to Peanuts Impacting Emotions and Life): Pan-European Results on Peanut Allergy Impact on Allergic Individuals, Parents and Caregivers**

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**Rationale:** Peanut allergy (PA) is usually lifelong and known to affect quality of life (QoL). The AEPEAL study evaluated the psycho-social impact of PA on patients and their parents/caregivers.

**Methods:** AEPEAL was a quantitative European online 30-minute survey, conducted in 8 European countries (Denmark, France, Germany, Ireland, Italy, Netherlands, Spain, UK). Adults with PA and parents/caregivers of individuals with PA were eligible to participate in the study (self-report). Parents/caregivers could also fill out a questionnaire on behalf of PA individuals for whom they cared.

**Results:** A total of 1846 responses were analyzed. 1300 participants completed the survey: adults with PA (n=419, self-reporting), and parents/caregivers of a person with PA (n=881, self-reporting). Sixty-two percent of parents/caregivers also completed a questionnaire, on behalf of a PA individual (n=546, proxy-reporting).

39.8% (n=735) felt frequently or very frequently frustrated by the limitations and restrictions of living with PA, and 28.2% (n=521) reported being somewhat frequently frustrated. Furthermore, 39.9% (n=736) reported high or extremely high level of uncertainty of living with PA. Regarding the stress due to living with PA, 39.9% (n=737) experienced an extremely high or high level of stress. These findings are consistent through the different European countries.

**Conclusions:** AEPEAL, the first multidimensional pan-European online survey, specifically designed to study the psycho-social burden of PA on individuals’ lives and on their families, revealed that across the European countries studied, participants are experiencing a high level of frustration, stress, and uncertainty in everyday life when managing their PA using avoidance.
A Randomized Control Trial to Reduce Food Allergy Anxiety about Casual Exposure by Holding the Allergen: TOUCH Study

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RATIONALE: Patients with nut allergies often fear casual exposure to allergens, which is unlikely to cause a severe reaction. The study assessed if a behavioral exposure intervention, whereby patients were guided to touch their allergen, along with education, results in a reduction of patient and parent worry about casual exposure compared with education alone.

METHODS: Enrollment criteria included patients aged 9 to 17.5 years with peanut or tree nut allergy who endorsed worry about casual exposure to their allergen. Participants were randomized to the touch condition plus education about the risks of casual exposure (n=30, intervention) or to receive education only (n=30, controls). The primary outcome was the difference in patient-reported worry from pre- to immediately post-intervention between the conditions. Secondary outcomes included improvement in patient- and parent-reported worry within groups and improvement in quality of life (QoL) one month after study participation.

RESULTS: There was no greater improvement in patient worry in the intervention group compared to the control group from pre- to immediately post-intervention (P=0.12). Rather, both groups experienced a statistically significant decrease in patient- and parent-reported worry (P<0.001). Both study arms had improvement in QoL one month after the visit (P-value 0.03 and 0.01, respectively), but the intervention was not superior to control (P=0.76).

CONCLUSIONS: Supervised contact with the nut is not superior to education alone. Education about the risks of casual exposure can decrease worry and improve QoL, an effect that was sustained even one month after the visit.

Racial/ethnic differences in food sensitization and food allergy in a diverse multi-center cohort of U.S. infants

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RATIONALE: The relation of race/ethnicity to food allergy remains unclear. We examined associations between race/ethnicity and food-specific IgE or food allergy during infancy.

METHODS: We analyzed data from a multi-center infant cohort enrolled during hospitalization for bronchiolitis (MARCI-35). Race/ethnicity was assigned by parent report. IgE to milk, egg, peanut, cashew, and walnut were measured at enrollment (median age, 3 months). Food allergy was defined by affirmative parent response to the question: “Has your child ever had any doctor-diagnosed food allergy?” or by food-specific IgE ≥3.5 kU/L with an affirmative parent response to the following question about the same food: “Has your child ever experienced skin or breathing problems (hives, swelling, itching, cough or wheezing) within 2 hours after eating?” We performed logistic regression with adjustment for age, sex, maternal atopy, poverty, and insurance using propensity scores.

RESULTS: Among 921 infants, 44% were Non-Hispanic White (NHW; n=401), 23% Non-Hispanic Black (NHB; n=210), and 30% Hispanic (n=275). Food-specific IgE was elevated in 161 infants (17%). At age 12 months, 32 infants (3%) met food allergy criteria: 28 by doctor-diagnosed report, 2 by food-specific IgE with reported symptoms, and 2 by both. After adjustment, NHB (OR 2.1, 95%CI 1.2-3.8) and Hispanic infants (OR 2.0, 95%CI 1.2-3.6) were more likely than NHW infants to have elevated food-specific IgE at enrollment. Race/ethnicity was not significantly associated with food allergy during infancy (e.g., NHB 0.6, 95%CI 0.2-1.9).

CONCLUSIONS: Among infants, food-specific IgE differed by race/ethnicity but doctor-diagnosed food allergy did not. We will continue to track this issue into childhood.

Factors Associated With College Students’ Willingness And Readiness to Act in a Food Allergic Emergency (WilRAFAE)

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RATIONALE: Most campuses do not have stock epinephrine auto-injectors (EAIs) available for use by unlicensed individuals, and only a handful of states have policies permitting unlicensed individuals to administer EAIs. The aim is to identify factors associated with willingness and readiness to act in a food allergic emergency (FAE) on a college campus.

METHODS: An electronic survey was distributed by e-mail to students on one college campus in Spring, 2017.

RESULTS: A total of 474 individuals responded. The participants’ ages ranged from 18 to 64 (22.9), female (83.8%), male (15.6%), undergraduate students (88%) and health professions students (55%). All readiness components (knowledge, familiarity, experience, training and confidence) were highly correlated with each other and with readiness to act. Willingness components (fear and bystander’s likelihood to respond) correlated with each other and with willingness to act. Age, having children, college major had statistically significant correlations with readiness and willingness to act. Readiness to act was highly predictive of willingness to act in an FAE. Based on five predictor variables (R² = .35) 35% of variability in willingness to act was explained by age, being a health professions student, desire to be trained, social desirability, and readiness. Students in non-health related majors expressed low readiness, but high willingness to act.

CONCLUSIONS: A pool of trained individuals willing to act in an FAE would be highly desirable on college campuses. Two key policy areas to insure safety on a college campus should be the availability of stock epinephrine and training of unlicensed, willing to act individuals.
All abstracts are strictly embargoed until the date of presentation at the 2019 Annual Meeting.

167 Distinguishing Parental Anxiety And Quality Of Life In Parents Of Food-allergic Children: Evidence From Factor Analyses

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Rationale: While parental anxiety is commonly observed clinically in the food-allergic (FA) population, studies of FA patients and their parents have mainly focused on using broader measures (e.g., quality of life (QoL)) to capture this phenomenon. Moreover, measures of QoL have often been equated to measures of health anxiety. The current study sought to use factor analyses to determine whether parental anxiety and quality of life are distinct constructs.

Methods: Canadian parents of children with FA were invited to participate in an online survey through Food Allergy Canada about their generalized (state) anxiety using the State Trait Anxiety Inventory (STAI-S) and their QoL using the Food Allergy Quality of Life Parental Burden (FAQoL-PB) questionnaire. Factor analyses were used to evaluate the psychometric properties of STAI-S and its relation to FAQoL-PB.

Results: Factor analysis was first conducted separately for each measure: STAI-S yielded two factors (presence versus absence of anxiety) and the FAQoL-PB also yielded two factors (physical limitations on life versus emotional distress). Subsequently, factor analysis of all items (20 items from STAI-S and 17 items from FAQoL-PB) combined resulted in four factors that were orthogonal. These findings suggest that, although significantly correlated (r =0.54, p<0.001), parental anxiety and QoL are two distinct constructs.

Conclusions: While it is very useful to understand the quality of life and parental burden as it relates to parenting children with FA, our findings demonstrate the importance of developing a separate measure for understanding food allergy-associated parental anxiety.

168 Quality of Life is Lower in Adults with Childhood-Persistent Food Allergy Compared to Adult-Onset Food Allergy

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Rationale: Differences in food allergy (FA) phenotype and quality of life (QOL) between childhood-onset and adult-onset FA are not known.

Methods: We administered a FA history survey and validated FA-QOL questionnaire to consented adult patients with FA at Northwestern selected by ICD-9/ICD-10 codes via REDCAPTM. Participants with adult-onset FA (AOFA, symptom onset > 18 years old) vs childhood-persistent FA (CPFA, symptom onset < 18 years old) were compared using SPSS, version 25.0.

Results: 225/316 consented participants had a history suggestive of FA. Respondents were categorized by age of onset for first FA into CPFA (n =81, median age 5 years old, 74% female) and AOFA (n =144, median age 28 years old, 76% female). QOL composite scores were reduced in CPFA compared to AOFA in four domains: allergen avoidance/dietary restriction (p =0.001), emotional impact (p =0.001), risk of accidental exposure (p =0.0001), perceived risk (p =0.002) with no difference in FA related health (p =0.999). AOFA were more likely to have mixed foods (51%; fruits/vegetables/legumes/grains) and shellfish (26%) as triggers, while CPFA had tree nut (54%) and peanut (42%) as FA triggers. Cutaneous (OR 5.29, p =0.022), respiratory (OR 2.47, p =0.004), and gastrointestinal symptoms (OR 2.58, p =0.001) were more common in CPFA. Increased epinephrine use (p =0.0001) and FA ER visits (p =0.003) were observed in CPFA.

Conclusions: Trigger foods and symptoms in CPFA are consistent with previous pediatric FA studies, and these patients have reduced QOL compared to AOFA. This data suggests phenotypic differences between adults with FA, dependent on age of presentation; tailored care based on phenotype may be appropriate.

169 Screening for Food Allergy-Related Anxiety in an Outpatient Allergy Clinic Setting: A Quality Improvement Project

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Rationale: Several studies show that children with food allergy have increased anxiety. Food allergy-related anxiety is not routinely screened for, even in allergy practices. The aim of this quality improvement project was to develop an effective anxiety screening process for food allergic patients in two large academic outpatient allergy clinics.

Methods: This project focused on patients with confirmed or suspected food allergy. Following a two-week audit period, a food allergy-related anxiety questionnaire was developed. Multiple strategies were employed to develop clinic-specific processes over 8 plan-do-study-act (PDSA) cycles (1week/cycle).

Results: The audit period yielded 0% patients screened for anxiety. Cycle 1-an email asked nurses to screen during general intake resulting in 6% screened. Cycle 2-a pictorial clarification was added resulting in 0% screened. Cycle 3-an electronic medical record phrase introduced to providers resulted in 3% screened. Cycle 4-paper reminders placed on all computers resulted in 17% screened. Cycle 5-a daily provider email yielded 33% screened. Cycle 6-additional nurse-distributed questionnaires resulted in 38% screened. Cycle 7-a daily nurse and provider email resulted in 47% screened. Cycle 8-front desk clerks distributed questionnaires directly to patients upon check-in with significant increase of 67% screened for anxiety.

Conclusions: It is important to treat the whole food allergic patient including psychological distress, but implementation of additional clinical tasks in provider and nursing routine proved difficult. Employing anxiety screening early in the workflow to bypass provider variables was the most effective intervention. Moving forward, automated implementation of this process during check-in may increase screening percentage.

J ALLERGY CLIN IMMUNOL FEBRUARY 2019

AB56 Abstracts
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170 An examination of Quality of Life and General Anxiety Disorder in Parents, Children and Teens in Russia

Daniel Munblit, and Audrey DunnGalvin, PhD

Rationale: Research into Food Allergy. Quality of Life (FAQLQ) has raised awareness of patient issues and has impacted provision of resources and policy. No auto-injectors are registered in Russia, which may result in anxiety. We examined 1) the performance of the FAQLQ measures and 2) associations between FAQLQ in children/teens and anxiety in parents.

Methods: FAQLQ (parent proxy-report, child/teen self-report) and Food Allergy Independent measures (FAIM) were translated and completed by patients (8-18 years) and/or their parents (0-12 years). Parents completed the General Anxiety Disorder (GAD) measure. The data were collected in The Research and Clinical Institute for Pediatrics Moscow. Analysis included Cronbach’s alpha, analysis of co-variance (ANCOVA), and linear regression (LR).

Results: N=142 completed FAQLQ and FAIM and N=89 parents (93% mothers) completed GAD. All FAQLQ had alpha > 0.94, and discriminated between number of allergies, number of foods avoided, FAIM and GAD scores (p<0.06). Relationship strength between GAD and FAQLQ increased according to age (p<0.004); with < 2 years (r=0.4), 6 to 12 years (r=0.5) and > 13 years (r=0.7). Eighteen percent had GAD score >10 indicating moderate to severe anxiety. In LR, GAD score predicted FAQLQ PF score (t2=0.75, p<0.01), controlling for age, sex, number of allergies, reaction severity and recency.

Conclusions: The FAQLQ questionnaires are valid and reliable for use in Russia. The findings will contribute to the development of online manual of normed scores for FAQLQ. The significant association found between general anxiety in parents and quality of life in children and teens has practice, screening and resource implications.

171 Increasing Discussions On Early Peanut Introduction- A Quality Improvement Project

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Rationale: Results of the 2015 LEAP Study suggest early peanut introduction to prevent the development of peanut allergy. A quality improvement project educating pediatric residents at Nicklaus Children’s Hospital (NCH) on the NIAID guidelines was conducted to increase discussion of early peanut introduction in infants, and further evaluation of peanut allergy in high risk infants.

Methods: During a 6 month period, a retrospective chart review of 100 health maintenance visits of infants and toddlers under 15 months old was performed at the resident continuity clinic at NCH. Documentation of discussion regarding peanut introduction, evaluation/ specific IgE testing and/or referral to allergy was reviewed. Educational intervention through didactic lectures and handouts were provided to residents, and chart review was repeated for a 3 month period on a total of 33 charts.

Results: Baseline data was collected from 100 charts. Prior to the educational intervention, 0% documented a discussion on peanut introduction, specific IgE testing, or referral to allergy. Fifteen patients were diagnosed with eczema. Post-educational intervention demonstrated discussion on peanut introduction increased to 21.2% as documented in the charts. However, none of the patients had specific IgE testing or referral to allergy. Almost a quarter of patients had documented eczema. Neither egg allergy nor classification of eczema severity were recorded in pre- or post-intervention data collection.

Conclusions: Educational interventions for providers are effective in increasing peanut introduction discussion at the health maintenance visits of infants. Future studies could address the importance of risk categorization of infants to optimize their plan of care.

172 Quality of Life in Spanish Children with Allergy to Multiple Foods Using a Spanish Version of the Food Allergy Quality of Life Questionnaire-Parent Form (S-FAQLQ-PF)

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Rationale: The impact of food allergy on patient’s quality of life has been demonstrated by different studies. Our aim was to investigate the impact of food allergy on the quality of life of children with “multiple food allergy” (at least 2 different not related group of foods).

Methods: Patients aged of 0-12years attended in our “multiple food allergy outpatient clinic” from November 2017 to June 2018 were included. S-FAQLQ-PF were completed by parents. We analyzed if sex, age, eliciting food (number and type), symptoms (type and severity) and adrenaline as a treatment were related to the global impact on quality of life and to each domain of the questionnaire.

Results: 17 patients (12 males), with a median age of 8 years (IQR:6.5-11) were included. Four (23.4%) had allergy to 4 or more not related groups of foods. The most frequent impeded food were nuts (91.4%). The most frequent symptom was urticaria (76.5%). Five patients had anaphylaxis. Adrenaline was used in 4 patients. S-FAQLQ-PF results were: Median global impact 2.8 (IQR:1.48-3.88), emotional impact 2.5 (IQR:1.30-3.25), food anxiety 4.00 (IQR:2.12-5.00), social/dietary restrictions 2.77 (IQR:1.21-4.05).

Conclusions: Multiple food allergy had an impact in the quality of life in our patients. Food anxiety was the most affected domain. Being allergic to more foods is related to poorer quality of life.

173 Disguised Dairy: Anaphylaxis to “Hidden” Allergens in Routine Vaccinations in Child with Severe Cow’s Milk Allergy

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Rationale: IgE-mediated cow’s milk allergy (CMA) affects 2.3% of children under the age of 3. Allergic reactions to vaccines have been documented in egg allergic patients, however sparsely reported in the CMA population.

Methods: A 5-year-old male with severe IgE-mediated CMA was evaluated for anaphylaxis following two routine vaccinations. The patient received Adacel-Polio (TDaP-IPV) and Priorix-Tetra (MMR-V) as per immunization schedule. Within minutes of being immunized, the patient developed itchy eyes, sneezing, and facial swelling. The patient was treated and recovered. Allergen investigation in vaccines identified casamino acids and lactose in the Adacel-Polio and Priorix-Tetra, respectively. Skin prick testing (SPT) to common allergens followed by SPT to full strength and intradermal testing (IDT) to 1/100 concentrations of Adacel-Polio and Priorix-Tetra vaccination were carried out.

Results: Milk protein was positive (15 mm). Very high levels of sIgE to total cow’s milk (>100 kU/L) and casein (79.80 kU/L) were found. Positive SPTs were identified to Adacel-Polio (7 mm) and Priorix-Tetra (5 mm). IDT were positive to Adacel-Polio (10 mm flare) and Priorix-Tetra (15 mm flare). Immunological assays (ELISA) for presence of cow’s milk protein in both vaccinations are pending.

Conclusions: TDaP-IPV and MMR-V vaccinations are generally well tolerated in children with food allergies. However, both vaccines have derivatives of cow’s milk protein that may pose as an allergenic source in certain children with severe CMA. It is important to educate physicians of potential reactions as neither vaccine’s product monograph identifies any risk of allergic reaction in this population.
174 Mining Social Media Data to Assess the Risk of Skin and Soft Tissue Infections from Allergen Immunotherapy

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RATIONALE: Allergen immunotherapy (AIT) treatment for allergic rhinitis and asthma is used by 2.6 million Americans annually. Clinical and sterility testing studies identify no risk of contamination or infection from extracts prepared using recommended aseptic techniques. Regulatory changes to extract preparation are under consideration. Social media can be used to investigate rare adverse events not captured by traditional studies. We investigated large social media databases for suggestion of AIT related SSTI.

METHODS: We analyzed USA-restricted data from over 10 common text-based social media platforms including Facebook, Twitter and Reddit between 2012-2016. We employed natural language processing (NLP) to identify posts related to AIT, or influenza vaccination, a comparator procedure with a sterile pharmaceutical. NLP was followed by manual review to identify posts suggesting skin and soft tissue infections (SSTI) associated with either AIT or influenza vaccination. SSTI frequencies with 95% confidence intervals (CI) were compared.

RESULTS: We identified 25,126 AIT related posts, which were matched by social media platform to 25,126 influenza vaccination related posts. NLP identified 4,088 AIT posts that required manual review, with 6 posts (0.02%, 95% CI 0.018, 0.022) indicative of possible AIT related SSTI. NLP identified 2,689 influenza posts that required manual review, with 7 posts (0.03%, 95% CI 0.028, 0.032) indicative possible influenza vaccination related SSTI.

CONCLUSIONS: Social media data suggest that SSTI from AIT and influenza vaccination are equally rare events. Given that AIT’s SSTI risk appears comparable to the risk using a sterile pharmaceutical based on social media data, current aseptic technique procedures seem safe.

175 Blomia tropicalis And Component Resolved Diagnosis: Performance Outcomes In Moderate-Severe Allergic Rhinitis

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RATIONALE: The group 5 allergen of Blomia tropicalis, Blo t 5, is considered the dominant major allergen. Blo t 5 is recognized by IgE up to 98% of mite-allergic and/or asthmatic patients in tropical regions. The aim of this study is to evaluate the performance of Component Resolved Diagnosis (CRD) in patients with moderate-severe allergic rhinitis.

METHODS: We selected 20 non-consecutive patients highly sensitized to B. tropicalis with persistent moderate to severe allergic rhinitis according to the ARIA Guidelines. Skin prick test (SPT) with standardized crude extracts of B. tropicalis were performed following by immediate reading. Serum blood samples were obtained from all participating subjects. Total IgE, specific IgE to B. tropicalis, and semi-quantitative ImmunoCAP ISAC was performed in all 20 serum samples.

RESULTS: All 20 subjects (11 females, 11 to 45 y.o.) showed a positive SPT to B. tropicalis. Total IgE (UI/mL) ranged from 20.02 to 2581, specific IgE to B. tropicalis (crude extract) was present in all 20 sera, ranging from 0.35 to >100 kU/L (mean value: 19.36 kU/L). Measurements of specific IgE to Blo t5 detected values ranged from 0.1 to 96 ISU-E (mean value: 10.5 ISU-E). Interestingly, specific IgE to Blo t5 (≥0.3 ISU-E) was not detected in the majority (55%) of the serum samples.

CONCLUSIONS: Current CRD could not identify the majority of patients with moderate to severe allergic rhinitis confirmed sensitization to the crude extract of Blomia tropicalis. Additional allergen components are promptly warranted to achieve a precise diagnosis in specific populations.

176 SAFETY OF HYMENOPTERA VENOM IMMUNOTHERAPY ADMINISTERED IN RUSH REGIMEN

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RATIONALE: The frequency of systemic reactions to hymenoptera venom immunotherapy (VIT) varies depending on the studies, ranging from 8 to 20%. They have been associated to several risk factors, mainly: the extract administered, an accelerated build-up phase and mastocytosis. ACE-inhibitors and betablockers are no longer considered as independent risk factors of adverse reactions. Our aim was to assess the safety and efficacy of the rush build-up phase regimen used in our Center (day 1, with the vial at its highest concentration: 5-10-20-20mcg; day 2: 50-50 mcg; day 5: 50-50mcg; day 12: 50-50mcg; followed by a 100 mcg dose each month).

METHODS: We completed a registry of all the patients who were receiving VIT in our Center at the moment of submission, using the aforementioned regimen, comprising a total of 58 patients. We took into account the following data: age, gender, concomitant beta-blocker or ACEi therapy, other comorbidities, REMA score (for prediction of mast cell clonality), baseline level of tryptase, mastocytosis, the extract administered, total IgE, specific IgE to the culprit venom, profession, previous stings and the delay until VIT was initiated.

RESULTS: None of the patients experienced a reaction during the build-up phase. We only observed autolimited local erythema in 27 out of 58 patients. One systemic reaction (IV grade Mueller’s Scale) was detected during the maintenance phase, in a patient diagnosed with mastocytosis.

CONCLUSIONS: The regimen used in our Center is safe and it does not increase the risk of reactions during the build-up phase, considering traditional risk factors associated to systemic reactions.
177 Use of Buccal Allergen Provocation to Identify Early and Late Responses to Allergen

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RATIONALE: Mechanisms of allergy may include IgE-dependent and IgE-independent; allergen-specific granulocyte-mediated and lymphocytic reactions; and nonspecific hypersensitivity. Buccal allergen challenge imitates natural exposure providing a non-invasive readily available biosample using saliva for diagnosis instead of blood.

METHODS: 13 patients with food allergy and allergic asthma with positive skin prick tests and serum specific IgE were studied in addition to 11 healthy volunteers. Saliva was collected. Both groups were subjected to buccal (mucosal) allergen challenge using a saline solution of dust mite allergen. Saliva was re-collected in 30 minutes and 24 hours after the provocation. The level of myeloperoxidase, elastase, and tryptase in saliva were determined by ELISA.

RESULTS: In patients with allergy, levels of tryptase and myeloperoxidase increased at 30 min after the provocation. Tryptase in saliva increased to 0.07 (range 0.04 to 0.19) pg/ml (p = 0.0006). Elevated levels of myeloperoxidase, elastase, and tryptase in saliva were seen which correlated with the levels of tryptase at 30 min (R = 0.46; P<0.05). Levels of elastase increased only at 24 hour after the buccal provocation. In healthy volunteers this increase was not observed.

CONCLUSIONS: The identification of tryptase, myeloperoxidase, and elastase in saliva may be used for diagnosis of allergy with tryptase and myeloperoxidase as mediators of early (immediate) responses to allergen and elevated levels of myeloperoxidase and elastase in saliva possibly providing evidence the neutrophil involvement in late phase responses.


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RATIONALE: Allergic rhinitis is a common disorder that is associated with adverse health outcomes and socio-economic impact. We estimated workdays missed and industry- and occupation-specific prevalence of doctor-diagnosed allergic rhinitis among working adults.

METHODS: The 2013–2017 National Health Interview Survey (NHIS) data for adults aged ≥18 years who were working during the 12 months prior to the interview were analyzed. Respondents with allergic rhinitis were those who reported being told by a doctor or other health professional that they had hay fever in the year prior to the interview. The mean number of workdays missed at a job or business because of illness or injury in the prior year was estimated. Data were adjusted for nonresponse and weighted to produce nationally representative estimates.

RESULTS: During 2013–2017, an estimated (annual average) 164 million adults were working at any time during the past 12 months, 7.2% of whom had allergic rhinitis. Allergic rhinitis prevalence was highest among workers in the education services industry (9.9%) and in education, training, and library occupations (10.5%). More workers with allergic rhinitis missed at least one workday due to illness or injury than those with no allergic rhinitis (52.7% vs 41.2%; mean 4.6 days vs. 3.5, p<0.001). Workers with allergic rhinitis in the information, agriculture, forestry, fishing, and hunting, and accommodation and food services industries and sales and related occupations had significantly greater mean workdays lost than those without rhinitis.

CONCLUSIONS: Following rhinitis guidelines-directed management is important to alleviate the disease impact on workers well-being and productivity.

179 Hymenoptera Immunotherapy. Safety analysis of a cluster protocol in our population

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RATIONALE: Venom immunotherapy (VIT) is an effective treatment for subjects with hymenoptera allergy, but systemic reactions may occur in 5% to 15% of patients, especially in the build-up phase. The standard protocol for the build-up phase lasts 8-15 weeks to reach the maintenance dose. During this time, the patient does not have protection and remains at risk for a reaction. Cluster schedules reduced number of visits. We present the safety of a cluster schedule comprising 5 doses of VIT over 2 weeks/2 visits.

METHODS: Twenty eight patients with new diagnosis of bee venom allergy and 1 with vespula allergy were included. All of them have indication for VIT, (26 males and 3 females, mean age 49.4 years, range 8-76 years).

We used Apis mellifera (28) and Vespula (1) venom extracts (Hal Allergy; Venomenhal) in 2-day, 5 doses induction cluster schedule: Day 0: 10µg + 20µg + 20µg, and day 7: 50µg + 50µg were administrated subcutaneously at 30-minutes intervals. This was followed by a monthly administration of 100µg. Pretreatment with antihistamines were given, and local cold were applied on arms immediately after the injections.

RESULTS: Three patients (10.3%) experienced 4 systemic reactions (2.7% build-up doses). All were mild (skin symptoms). Delayed local reactions were seen in 7 patients in the build-up phase and disappeared in 1-4 days. Eight patients tolerated 11 spontaneous bee stings at countryside.

CONCLUSIONS: Two day cluster program with VIT is safe and appropriate for patients at high risk of spontaneous stings, in our population.
180 Utility of Skin Tests for Diagnosis of Hypersensitivity Reactions to Iodinated Contrast Media

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RATIONALE: Hypersensitivity reactions to iodinated contrast media (ICM) are a common problem and can cause anaphylaxis. The clinical utility of skin testing for ICM reactions is uncertain.

METHODS: Retrospective analysis was done of data from 47 patients (18 males, 29 females, average age 55 years) with a history of hypersensitivity reactions to ICM referred to Vilnius University Hospital from 2014 to 2017. Skin prick (SPT) and intradermal tests (IDT) with ICM were performed according to the EAACI guidelines including assessment of ICM iohexol, iopromide, diatrizoate, iodixanol, and iopamidol.

RESULTS: Cutaneous symptoms were most common (55.6%) followed by cardiovascular symptoms (17.5%), respiratory symptoms (9.5%) and gastrointestinal symptoms (7.9%) with some (9.5%) nonspecific symptoms. SPT were negative in all patients. Seven out of 47 (14.9%) patients had positive IDT. 3 patients had positive reactions to 2 or more ICM. Reactions to ICM were not more severe in patients with positive skin test results. Clinical patterns of IDT positive patients did not differ from patients with negative skin tests. Five of 23 patients tested less than one year after the reaction had a positive IDT, while 2 of 24 patients having a reaction more than 1 year after the reaction had a positive IDT. Patients with negative skin tests. Five of 23 patients were positive to 2 or more ICM. SPT were negative in all patients.

CONCLUSIONS: Allergy to ICM was seldom produced positive IDT in skin test results. with positive and negative skin tests.

181 Being “SCIT” Careful in the Spring: Analyzing Patterns of Immunotherapy-Induced Anaphylaxis Over the Years

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RATIONALE: Subcutaneous immunotherapy (SCIT) is an effective treatment for allergic individuals. Despite SCIT success, anaphylaxis remains a risk, albeit less than 1% of injections. We aimed to characterize patterns of anaphylaxis in a community clinic administering SCIT, to help identify patterns of increased risk.

METHODS: A retrospective chart review was carried out over a 15-year period (January 1, 2004 to August 15, 2018). Data was collected on patients who had sustained a SCIT-induced anaphylaxis. Demographic profiles, timing and reaction details were analyzed. A 5-year subset (2012-2017) was used to calculate total average injection rates in May and November.

RESULTS: Sixty patients were identified with 64 total reactions. Thirty-four of 64 (53%) were female. One female patient sustained 3 anaphylactic reactions and 2 males sustained 2 reactions. Forty-one (68%) patients were polysensitized (2, 3, 4, or 5 IT allergens) and 19 were monosensitized. April (10/64) and May (15/64) were the most active months for anaphylaxis, totaling 39% of yearly reactions. Fifty-six of 64 (88%) reactions occurred in the afternoon. The mean afternoon injections in May were 317/378 (84%). The mean afternoon injections in November were 35/150 (77%). Twenty-five (42%) patients discontinued SCIT following anaphylaxis; 35 (58%) remained on immunotherapy.

CONCLUSIONS: SCIT induced anaphylactic reactions were most common in the Spring season (April-May). More anaphylactic reactions occurred in the PM, although consistent with the ratio of PM/total daily injections. Anaphylaxis induced a high drop-out rate, yet the majority continued on SCIT. Polysensitized patients receiving SCIT in Spring afternoons may benefit closer monitoring for anaphylaxis.
Preoperative Sinonasal Symptom Scores Predict Post-Surgery, Post-Aspirin Desensitization Disease Status in Aspirin Exacerbated Respiratory Disease

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RATIONALE: Aspirin exacerbated respiratory disease (AERD) is a challenging upper and lower respiratory disease which requires joint management between allergists and otolaryngologists. Complete sinus surgery followed by aspirin desensitization (AD) appears to improve outcomes long-term. Recent studies have demonstrated a relationship between high preoperative, pre-AD sinonasal symptoms scores and severity of reactions during AD. In this study, we provide the first evidence for using stratified preoperative, pre-AD sinonasal symptom scores to predict postoperative, post-AD outcomes.

METHODS: Retrospective chart review of all patients with aspirin challenge-proven AERD who underwent complete endoscopic sinus surgery followed by AD. Preoperative, postoperative/pre-AD, and short-term (<2 months) and long-term (>6 months) postoperative/post-AD sinonasal symptom scores were collected (22-item Sino-Nasal Outcomes Test, SNOT-22). A longitudinal linear mixed-effects model was used for data analysis.

RESULTS: Preoperative SNOT-22 scores (n = 47) were divided into tertiles (cutoffs of 36 and 54 indicating mild [22.5 ± 13.7], moderate [44.3 ± 12.2], and severe [72.9 ± 19.7] disease). Postoperative, pre-AD SNOT-22 in all disease groups decreased and were not significantly different (12.3 ± 13.7, 11.1 ± 12.2, and 22.7 ± 19.7; p = 0.074). Following AD, only the severe group scores worsened (35.0 ± 20.3, p < 0.001), whereas the other groups demonstrated negligible change (9.3 ± 14.3 and 14.4 ± 12.2). At 6 months post-AD, all groups redemonstrated convergence in symptom scores (23.7 ± 20.9, 19.4 ± 15.4, and 31.0 ± 27.6, p = 0.304).

CONCLUSIONS: Preoperative SNOT-22 scores may be used as a predictor of postoperative, post-AD patient-reported outcomes in AERD. Patients with mild and moderate disease may derive benefit from AD alone, whereas those with severe disease may require additional interventions (e.g., biologics).

Evaluation Of Clinical Changes In Pediatric Patients With Atopic Dermatitis And Respiratory Allergy Receiving Allergen-Specific Immunotherapy

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RATIONALE: Atopic dermatitis (AD) is a chronic illness with recurrent relapses. Allergen-specific immunotherapy (ASIT) directed towards IgE has proven effective in respiratory allergy. In Mexico however, there is currently no report of the clinical response in patients with ASIT and AD.

METHODS: Observational, ambispective study including patients 3-16 years of age with atopic dermatitis and respiratory allergy who attended the outpatient clinic from January 2016 to June 2017. Group 1: patients that started ASIT 6 months prior to inclusion and observed for 9 months total; Group 2: patients with ASIT started upon study initiation. In both groups SCORAD, use of medicines, quality of life and flares were evaluated.

RESULTS: A total of 17 patients were included. 9 in group 1 which had 6 patients (66.6%) with mild AD, 3 (33.3%) with moderate and none with severe AD. Group 2 had a total of 8 patients: 4 patients (50%) with mild AD, 2 patients (25%) moderate and 2 (25%) with severe AD. Dermatophagoides farinae and pteronyssinus, Atriplex canescens, Fraxinus americana, Junglans regia and Canis familiaris were allergens included in the ASIT. The mean SCORAD was compared in the initial and last visit finding a statistical significance with p = 0.002 in group 1. p = 0.005 in group 2 and in both groups combined p = 0.001. Days of treatment required and flares were reduced and improvement fo quality of life was seen in both groups.

CONCLUSIONS: ASIT is effective in patients with AD, resulting in significant clinical changes regarding SCORAD, quality of life, need of medication and flares.

A Systematic Review on the Association between Rhinovirus and Sinusitis

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RATIONALE: Rhinovirus (RV) infections are the most common cause of viral URIs, and in the majority of persons self-resolve. However, in others, viral URIs can progress to bacterial sinusitis and induce chronic rhinosinusitis (CRS) exacerbations.

METHODS: We conducted a comprehensive PRISMA review through April 2018 based on MEDLINE, Embase, Web of Science-SCI and CPCI-S using keywords: RV, respiratory virus, sinusitis, and airway epithelial cells. The goal of this systematic review was to (1) determine the prevalence between RV and CRS, (2) investigate the pathophysiologic mechanisms by which RV induces sinonasal inflammation, (3) study the changes that occur after experimental RV inoculation, and (4) explore the treatment options available for RV-associated sinusitis. Data regarding study design, research question, intervention, subjects, outcomes, and biases was extracted.

RESULTS: The initial search yielded 2395 unique abstracts, of which 600 were selected for full-text review, and 147 included in the final review. We determined that (1) the prevalence of RV infections is increased in those with CRS, (2) RV-A and RV-C challenges in vitro to sinonasal epithelia produce robust cytokine responses and differential gene changes, (3) humans challenged in vivo with RV secrete local and systemic inflammatory mediators with radiographic mucosal thickening and (4) no current therapies have produced consistent and significant resolution of disease.

CONCLUSIONS: RV infections are common in persons with CRS, and incite inflammatory reactions that may result in CRS exacerbations and progression of disease. Further studies assessing RV-species, and the host-virome response are required to develop new strategies targeting RV-induced CRS.
Quality of Life Improvements Following Treatment with Olopatadine/Mometasone Combination Nasal Spray in Patients with Seasonal Allergic Rhinitis: A Pooled Analysis

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RATIONALE: Seasonal allergic rhinitis (SAR) symptoms are troublesome and often impair quality of life (QoL). Demonstrated efficacy, safety and QoL of GSP301, a fixed-dose combination nasal spray containing olopatadine hydrochloride (antihistamine) and mometasone furoate (corticosteroid), have been reported previously. Pooled QoL analysis from 3 SAR studies conducted across different pollen seasons are presented here.

METHODS: Twice-daily (BID) treatment results from double-blind, randomized, placebo-controlled 14-day studies (NCT02318303, NCT02631551, NCT02870205; N=2,971) were pooled. SAR patients (12–65 years) were equally randomized to GSP301 (lopatadine 665 g/mometasone 25 g BID), olopatadine (665 g BID), mometasone (25 g BID), or placebo (BID). Results from once-daily treatments, evaluated only in NCT02318303, are not shown here. Mean change from baseline to day 15 in overall Rhinoconjunctivitis Quality of Life Questionnaire–Standardized Activities [RQLQ(S)] score was analyzed using ANCOVA (P<0.05=statistically significant). Individual QoL domains were also assessed.

RESULTS: GSP301 BID demonstrated statistically significant improvements in overall RQLQ(S) scores vs placebo (least squares mean difference [95% CI]: -0.48 [-0.67, -0.30], P<0.001). GSP301 also provided statistically significant improvements vs placebo in each individual domain: activities (-0.55 [-0.75, -0.35], P<0.001); emotional (-0.49 [-0.69, -0.29], P<0.001); eye symptoms (-0.48 [-0.68, -0.27], P<0.001); nasal symptoms (-0.69 [-0.89, -0.49], P<0.001); non-nose/eye symptoms (-0.33 [-0.51, -0.14], P<0.001); practical problems (-0.62 [-0.83, -0.41], P<0.001); and sleep (-0.40 [-0.60, -0.19], P<0.001). Treatment-emergent adverse events were low and comparable across treatments (reported elsewhere).

CONCLUSIONS: In a pooled analysis of SAR studies conducted across different pollen seasons, GSP301 BID treatment provided statistically significant improvements in QoL vs placebo and was well tolerated.

Rapid Nasal Symptom Onset of Action and Ocular Symptom Relief With Olopatadine/Mometasone Combination Nasal Spray in Patients with Seasonal Allergic Rhinitis: A Pooled Analysis

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RATIONALE: GSP301, a fixed-dose combination nasal spray containing olopatadine hydrochloride (antihistamine) and mometasone furoate (corticosteroid), was efficacious for treating seasonal allergic rhinitis (SAR) nasal and ocular symptoms, with a rapid onset of action (OOA), and was well tolerated (previously reported). Pooled analysis of OOA and ocular symptoms from 3 SAR studies are reported here.

METHODS: Twice-daily (BID) treatment results were pooled from double-blind, randomized, placebo-controlled, 14-day studies (NCT02318303, NCT02631551, NCT02870205; N=2,971). SAR patients (12–65 years) were equally randomized to GSP301 (olopatadine 665 g/mometasone 25 g BID), olopatadine (665 g BID), mometasone (25 g BID), or placebo (BID). Results from once-daily treatments, evaluated only in NCT02318303, are not shown here. OOA (mean change from baseline in instantaneous Total Nasal Symptoms Scores from 15 minutes to 4 hours post-dose vs placebo) was analyzed using mixed-effect model repeated measures (MMERM; P<0.05=statistically significant). Average of AM and PM 12-hour reflective Total Ocular Symptom Scores (tTOSS) was also assessed.

RESULTS: GSP301 BID OOA was observed at 15 minutes post-dose (least squares mean difference [95% CI]: -0.23 [-0.41, -0.05], P=0.011); at all 9 subsequent timepoints, OOA was maintained and differences were clinically meaningful and significant (P<0.001, all). GSP301 significantly improved tTOSS vs placebo from baseline to day 14 (-0.47 [-0.66, -0.28], P<0.001) and on each day (1-14; P<0.001, all). Treatment-emergent adverse events were low and comparable across treatments (reported elsewhere).

CONCLUSIONS: GSP301 BID provided rapid OOA of 15 minutes, statistically significant ocular symptom improvements, and was well tolerated in a pooled analysis of SAR studies conducted across different pollen seasons.

Nasal Eosinophil Count and Percentage in Children with Allergic Rhinitis

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RATIONALE: The total count and percentage of eosinophils in a nasal smear sample are useful for diagnosing allergic rhinitis. Although some studies have evaluated the presence of nasal eosinophilia for diagnosing allergic rhinitis, the use of this criterion is not sufficiently investigated. In addition, no study has determined the correlation between eosinophil count and percentage in sample nasal smears. Therefore, this study aimed to investigate the correlation between nasal eosinophil count and percent in patients with rhinitis.

METHODS: This was a retrospective cohort study of patients with a clinical history of rhinitis, under 19 years of age, examined at an outpatient clinic of a tertiary referral hospital in Korea, between January and August 2017. Nasal smears of patients were obtained by swabbing the nasal inferior turbinate 3–4 times with a cotton swab. The sample was then placed on a glass slide and stained with Giemsa stain. All specimens were examined by the same pathologist, who was blinded to the clinical history of each patient.

RESULTS: A total of 106 pediatric patients underwent nasal smear examinations. There was a positive correlation between the nasal eosinophil count and percentage in patients with rhinitis. Y = 0.768 X + 0.280 (Y = eosinophil count; X = eosinophil percent). The cut-off value was based on the nasal eosinophil count (10 cells/high-powered field) or a nasal eosinophil percent >10% in the patients with allergic rhinitis.

CONCLUSIONS: The nasal eosinophil count and percent can be useful tools for the diagnosis of allergic rhinitis in pediatric patients.
**189** Olopatadine/Mometasone Combination Nasal Spray for the Treatment of Seasonal Allergic Rhinitis: A Pooled Analysis of Efficacy and Safety

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**RATIONALE:** Efficacy and safety of GSP301, a fixed-dose combination nasal spray containing olopatadine hydrochloride (antihistamine) and mometasone furoate (corticosteroid), were demonstrated in 3 seasonal allergic rhinitis (SAR) natural-allergen exposure studies and an Environmental Exposure Chamber (EEC) study (previously reported). Pooled analysis of nasal symptom scores and treatment-emergent adverse events (TEAEs) from these studies are presented here.

**METHODS:** Total Nasal Symptom Scores (TNSS) from twice-daily (BID) treatments were pooled from three 14-day randomized, double-blind, placebo-controlled (RDBPC) studies (NCT02318303, NCT02631551, NCT02870205; N=2,971). SAR patients (12-65 years) were equally randomized to GSP301 (olo patadine 665µg/mometasone 25µg BID), olopatadine (665µg BID), mometasone (25µg BID), or placebo (BID). Mean change from baseline in average AM and PM 12-hour reflective and instantaneous TNSS (rTNSS, primary; iTNSS, secondary) were analyzed using mixed-effect model repeated measures (P<0.05=statistically significant). TEAEs were pooled from the 3 RDBPC studies plus a 14-day EEC study (NCT03444506). Results from once-daily treatments evaluated only in NCT02318303 and efficacy results from the EEC studies are not shown.

**RESULTS:** GSP301 demonstrated significant and clinically meaningful improvements in average AM and PM rTNSS (least squares mean difference [95% CI]; -0.94 [-1.17, -0.70], P<0.001) and iTNSS (-0.91 [-1.14, -0.69], P<0.001) vs placebo. rTNSS and iTNSS results were similar for GSP301 vs olopatadine (P<0.01) and mometasone (P<0.001). TEAE rates were 13.9% (GSP301), 13.2% (olo patadine), 7.9% (mometasone) and 9.5% (placebo).

**CONCLUSIONS:** GSP301 BID provided statistically significant and clinically meaningful SAR nasal symptom improvements vs placebo and monotherapies and was well tolerated in a pooled analysis of studies conducted across different pollen seasons.

**190** Exhalation Delivery System (EDS) Intranasal Steroid vs Conventional Inhaled Nasal Steroids (INS): Patient Preference, Comfort and Ease of Use

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**RATIONALE:** Intranasal steroids, usually by inhalation (INS), are first-line therapy for chronic rhinosinusitis, but most patients are frustrated with treatment efficacy. We compare patient satisfaction and ease-of-use with INS vs an exhalation delivery system (EDS-FLU; XHANCE™), that can help achieve better superior/posterior drug deposition.

**METHODS:** Analysis of ease-of-use and comfort in two 24-week (16 double-blind+8 open-label; N=322/321) RCTs with EDS-FLU in patients with CRS with nasal polyps. Patients reported current (or most recent) prescription intranasal steroid at screening and compared to EDS-FLU at weeks 4, 16, and 24. Self-reported “real world” survey results from patients prescribed EDS-FLU outside clinical trials were also evaluated.

**RESULTS:** In the RCTs, at screening, 77-84% and 71-74% of patients reported their current/most recent inhaled INS was easy-to-use and comfortable-to-use, respectively. At weeks 4, 16, and 24, 86-88%, 87-91%, and 90% reported EDS-FLU was easy-to-use and 80-85%, 82-85%, and 83-85%, reported it was comfortable to use, respectively. Compared to their current/most recent inhaled nasal steroid, at 4 weeks, EDS-FLU patients reported less loss of drug to drip down the back of the throat (61-67.0%) or out the front of the nose (55-64%). In a “real world” patient survey (N=2733), 89% of patients electing to complete the survey reported treatment satisfaction and 77% preferred EDS-FLU to prior inhaled steroids or steroid rinses.

**CONCLUSIONS:** Large RCTs and a large survey of ‘real-world’ patients suggest that patients find EDS-FLU easy-to-use, comfortable, and associated with improved symptoms and high patient satisfaction.

**191** Capsaicin Nasal Spray Showed Significant And Rapid Relief In All Nasal Symptoms In Subjects With Non-Allergic Rhinitis

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**RATIONALE:** Non-Allergic Rhinitis (NAR) has been estimated to affect 17 million Americans annually. Few therapeutic studies have been conducted on well-characterized patients with NAR. Alternative therapies have been proposed but have ineffective for the treatment of NAR conditions. Studies have demonstrated topical capsaicin is effective at reducing nasal congestion and discharge in allergic and NAR. The aim of this work was to further assess the onset of action and benefits of capsaicin in NAR.

**METHODS:** A total of 46 subjects with NAR and negative skin prick test were enrolled in this study. Subjects received capsaicin or placebo (23 per arm) 1-2 sprays/nostril twice daily to maximum of 8 total sprays/day for 14 days. Subjects recorded their instantaneous and reflective nasal symptoms (TNSS) using an electronic diary (ePDAT™). Time of first relief of symptoms were measured by patients using a stopwatch.

**RESULTS:** TNSS significantly improved from as early as 10 minutes post dosing in the capsaicin treatment group versus placebo. This improvement was sustainable until 60 minute time-point. It was observed that the majority of subjects treated with capsaicin (12/23) 52.2%, showed relief under one minute and (17/23) 74.0% of patients showed relief for all the symptoms under 2 minutes from time of first-dosing.

**CONCLUSIONS:** Capsaicin Nasal Spray showed significant rapid and sustainable relief in overall composite symptom scores of TNSS. The Nasal Spray was generally well-tolerated and there were no safety concerns raised during the study. This finding corroborates and confirms the nasal symptom results from a previous study with the same product.
SATURDAY

192 Evidence for a role of endoplasmic reticulum stress in local IgE secretion from plasma cells in allergic rhinitis

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RATIONALE: IgE plays a central role in the development of allergic rhinitis (AR). Although endoplasmic reticulum (ER) stress has been implicated in the pathogenesis of allergic airway diseases, such as asthma, its role in AR is poorly studied.

METHODS: Real-time PCR, immunohistochemistry and western blot analysis were applied to detect the expression of ER stress markers GRP78, CHOP, ATF6α, XBP-1, its splice variant (sXBP-1), and p-eIF2α in nasal tissue samples from control subjects and AR patients. Immunostaining of serial tissue sections were performed to detect the cellular sources of GRP78 and CHOP. Nasal explant tissues from AR patients were cultured ex vivo and secretion of IgE to culture supernatants were measured.

RESULTS: Compared to control tissues, the mRNA and protein expression of ER stress markers GRP78, CHOP, ATF6α, XBP-1, sXBP-1, and p-eIF2α were all significantly up-regulated in nasal tissues from AR patients compared to control tissues as detected by RT-PCR, immunohistochemistry and western blot analysis. The immunoreactivity of GRP78 and CHOP were mainly located in CD138+ plasma cells in lamina propria in nasal tissues. The numbers of GRP78 and CHOP positive cells correlated with the numbers of plasma cells and IgE+ plasma cells. In addition, after treated with 4-Phenylbutyric acid (4-PBA), an ER stress inhibitor, the mRNA and protein levels of GRP78, CHOP, ATF6α, XBP-1, sXBP-1, and p-eIF2α were all significantly down-regulated in nasal explant tissues and IgE levels were all significantly reduced in culture supernatants.

CONCLUSIONS: The ER stress may be involved in the regulation of local IgE secretion from plasma cells in AR patients.

193 Biofilm Propensity of *Staphylococcus aureus* Skin Isolates is Associated with Increased Severity and Barrier Dysfunction in the Mechanisms of the Progression of Atopic Dermatitis to Asthma in Children (MPAACH) Cohort

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RATIONALE: Atopic dermatitis (AD) patients are often colonized with *Staphylococcus aureus*, with staphylococcal biofilms reported on adult AD skin lesions. However, these biofilms are understudied on pediatric AD skin. We sought to characterize *S. aureus* and *S. epidermidis* colonization and biofilm propensity (BP) in pediatric AD, and determine their associations with AD severity, barrier function, and gene expression of the skin barrier protein, Filaggrin, and S100A8 and S100A9, which form an antibacterial biological chelator.

METHODS: Using the MPAACH cohort (n=300), the first large-scale analysis of staphylococcal colonization and BP was performed. BP of staphylococcal isolates was assessed by crystal violet assays, and gene expression was measured using keratinocyte RNA extracted from tape strips. AD severity and expression of FLG and S100A8 were compared between weak and strong BP using goodness-of-fit tests and Wilcoxon rank sum.

RESULTS: *S. aureus* and/or *S. epidermidis* were cultured from 81% of MPAACH children, and 20% were co-colonized. A total of 424 clinical isolates were collected. Sixty-two percent of the isolates formed moderate to strong mono-species biofilms. Of the 59 co-colonized MPAACH children, 66% formed cooperative mixed-species biofilms. Children colonized with *S. aureus* with stronger BP had increased AD severity (p=0.02, 0.0001) and decreased FLG (p=0.003) and S100A8 expression (p=0.02).

CONCLUSIONS: *S. aureus* strains colonizing the skin of children with severe AD are stronger biofilm producers than the strains colonizing mild AD skin. Biofilm propensity of *S. aureus* isolates was strongly associated with skin barrier dysfunction and expression of skin barrier genes, suggesting a pathogenic role for *S. aureus* biofilms.

194 DOCK8 Deficiency Exacerbates Skin Contact Hypersensitivity

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RATIONALE: DOCK8 deficiency is characterized by a combined immunodeficiency with impaired T regulatory (Treg) cell function. Almost all DOCK8 deficient patients develop atopic dermatitis. However, the mechanisms underlying this cutaneous inflammation are not fully understood. We investigated the effect of DOCK8 deficiency on contact hypersensitivity, as a model of skin inflammation.

METHODS: Dock8−/− (KO), Cd4-CreTg/0Dock8flox/flox (cKO) mice and WT controls were subjected to Oxazolone (OXA)-induced contact hypersensitivity (CHS). Ear thickness was measured. Ears were examined histologically, cell infiltrates were evaluated by flow cytometry and cytokine mRNA expression was assessed by RT-qPCR. KO and WT mice were administered OXA orally prior to OXA challenge.

RESULTS: KO and cKO mice exhibited increased and prolonged ear swelling following OXA challenge, compared to WT controls. This was accompanied by increased infiltration of CD45 cells, CD4+ T cells, CD8+ T cells, eosinophils and neutrophils. Ears from KO and cKO mice exhibited increased Ifng, Cxcl1, Cxcl9 and Ccl12 mRNA expression compared with WT controls. Induction of tolerance by oral OXA administration, which is mediated by Tregs, reduced cell infiltration and ifng mRNA expression in response to OXA challenge in WT mice. In contrast, KO mice could not be orally tolerated to OXA.

CONCLUSIONS: Our results indicate that DOCK8 deficiency in T cells aggravates CHS by enhancing cellular infiltration and type 1 responses in the skin, and demonstrate that Treg-mediated induction of oral tolerance is impaired in DOCK8 deficient mice. Defective Treg function may contribute to the increased skin inflammation and the eczema in DOCK8 deficient patients.
**195 Mast cell expression of IL-33, ST2 and TSLPR in the skin of atopic dermatitis post-allergen exposure**

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**RATIONALE:** Epithelial cell-derived cytokines are critical regulators in the pathogenesis of atopic dermatitis (AD). We examined mast cell expression of IL-33, ST2, and TSLPR in skin biopsies from patients with AD after intradermal allergen challenge.

**METHODS:** Intradermal challenges with allergen and saline control were conducted in patients with moderate-to-severe AD. Punch biopsies were collected from the site of challenge 24 hours later, and stained with immunofluorescent antibodies to tryptase, IL-33, ST2, and TSLPR. Images were obtained and analyzed by selecting regions of interest, and cells positive for the selected markers were expressed as cells per mm² of the area examined.

**RESULTS:** Compared to saline challenge, there was a significant increase in the number of tryptase-positive cells in the dermis (2-fold) and in the epidermis (3-fold) at 24 hours post-allergen (p<0.05). There was also an increase in the number of IL-33-positive cells in the dermis (2-fold) and epidermis (8-fold) after allergen compared to saline (p<0.05). Post-allergen, most cells expressing IL-33 were tryptase-positive. Furthermore, there was a significant increase in the number of cells in the dermis and epidermis co-localizing tryptase and IL-33 after allergen compared to saline (p<0.05). In contrast, few tryptase-positive cells expressed ST2 and TSLPR, and expression of these receptors on tryptase-positive cells was not different between allergen and saline.

**CONCLUSIONS:** Most cells expressing IL-33 post-allergen are tryptase-positive, and these cells that co-localize tryptase and IL-33 significantly after allergen challenge. These data suggest that mast cells are a major source of IL-33 in the skin following exposure to allergen.

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**196 Proliferation control of specific-effector T cells and T-Regulatory cells by Tim-3 and Galectin-9 in Drug-Induced Maculopapular Exanthema**

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**RATIONALE:** Galectin-9 is a molecule with a wide range of biological activities, including the control of some immunological processes. The inability to produce enough amount of Galectin-9 and/or an incorrect interaction with its receptor Tim-3, could be responsible for the uncontrolled increase of Th1 cells as happen in Drug-Induced Maculopapular Exanthema (DIMPE). Our aim was to examine the role of Galectin-9 and Tim-3 in the proliferation of specific-effector T cells and Tregs in patients with DIMPE.

**METHODS:** Peripheral blood mononuclear cells (PBMCs) were isolated from 18 patients with DIMPE and 10 controls. PBMCs were cultured with the culprit drug in presence of carboxyfluoresceinseuccinimidyl 1 ester (CFSE) to analyze the proliferation of Th1 (CD4×CD8×), Tim3-Th1 (CD4×CD8×Tim-3), and Tregs (CD4×CD25×Foxp3×) by flow cytometry. Exogenous Galectin-9 was added, as well as antibodies αTim-3 to enhance or block the interaction respectively. Results were represented as proliferation index (PI).

**RESULTS:** Higher PI was found when Th1, Tim-3-Th1 and Tregs cells from allergic patients with DIMPE were cultured with the culprit drug compared to controls (p=0.008, p=0.012, p=0.002 respectively). The addition of antibodies αTim-3 did not reduce the proliferation of any population. On the contrary, the addition of Galectin-9 reduced the proliferation of Th1 (p=0.025) and Tim-3-Th1 cells (p=0.026), whereas increased the PI of Tregs (p<0.001).

**CONCLUSIONS:** Galectin-9 has an important dual effect: its addition reduces the proliferation of specific-effector cells, whereas promotes the proliferation of Tregs in DIMPE patients. These data suggest that Galectin-9 could represent a therapeutic candidate able to control the disease.

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**197 NFκB transcription factor binding is altered at many Atopic Dermatitis disease loci**

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**RATIONALE:** Atopic Dermatitis (AD) has a strong genetic component. GWAS have identified 80 independent genetic AD risk loci (p<5×10^-8). Greater than 95% of these associations are in non-coding regions of the genome; we thus hypothesize that specific transcription factors (TFs) are enriched at AD risk loci.

**METHODS:** We applied our computational tools RELI and CIS-BP to identify enriched binding of transcription factors to disease risk loci and predict genetic variants that will alter transcription factor binding sites, respectively.

**RESULTS:** After linkage disequilibrium expansion (5,102 variants at 80 loci), 24 independent NFκB (RELA, NFKB1, REL, NFKB2) chromatin immunoprecipitation datasets demonstrated enriched binding at AD risk loci (p=5.73×10^-9 – 3.43×10^-30), collectively overlapping 280 AD risk variants. Pathway analysis of genes near variants overlapped by NFκB revealed enrichment for numerous immunological gene sets including MHC class II receptor activity, positive regulation of immune system, and cytokine signaling (IL13, TNFSF4, IL6R) (adjusted p<0.005). 178 genes near AD risk variants overlapped by NFκB are eQTLs including IL13, IL5, IL18R1, IL18 RA, and IL6R, and 12 different MHC class II genes across numerous cell types (e.g. HLA-DQB1 p=10^-25 in skin, 1.1-fold effect size). Based on the DNA sequence of the alleles and NFκB binding motif models, we expect allele-dependent NFκB binding at eight of the overlapped SNPs.

**CONCLUSIONS:** These data are consistent with common genotype-dependent transcriptional control mechanisms operating across multiple AD risk loci in a shared intracellular environment downstream of canonical NFκB signaling. Ongoing studies using samples from patients will confirm genotype-dependent activity of NFκB at AD risk variants.
198 Correlation of Clinical Atopic Dermatitis Scores with Levels of Eosinophil Progenitors in Skin after Intradermal Allergen Challenge

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RATIONAL: Systemic and local eosinophilia is thought to contribute to disease progression in acute and chronic lesions of patients with atopic dermatitis. We have previously shown an increase in eosinophil lineage-committed progenitors (EoP) in skin during the late cutaneous response after intradermal allergen challenge, and in chronic skin lesions from patients with atopic dermatitis. This study examined the relationship between levels of EoP in the skin, and atopic dermatitis clinical scores, EASI and SCORAD.

METHODS: Sixteen patients with moderate-to-severe atopic dermatitis underwent full skin assessments using EASI and SCORAD scores. After 8 days of systemic steroid washout, intradermal challenge was performed with allergen and saline control. 24 hours later, biopsies were obtained from the site of the late cutaneous response and from a chronic lesion. Immunofluorescence staining was performed on skin biopsies. EoP defined as CD34+/IL-5Ra+/Von Willebrand factor-ve were measured in the papillary dermis using Nikon Imaging Software. Levels of EoP were compared to EASI and SCORAD using non-parametric Spearman correlation.

RESULTS: The level of EoP in chronic lesions positively correlated with disease severity measured by EASI (r=0.71, p<0.05) and SCORAD (r=0.65, p<0.05). In allergen-challenged skin there were trends for a positive relationship between EoP and disease severity measured by EASI (r=0.48, p=0.07) and SCORAD (r=0.46, p=0.09).

CONCLUSIONS: These results highlight the potential involvement of EoP in the pathogenesis and clinical presentation in patients with atopic dermatitis.

199 IL-4 and IL-13 Produced During Allergic Skin Inflammation Exacerbate Mouse Model of Cutaneous Staphylococcus aureus Infection

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RATIONAL: Staphylococcus aureus (S. aureus) commonly colonizes the skin of patients with atopic dermatitis (AD) and its presence correlates with disease severity. The factors that promote colonization of AD skin with S. aureus are not fully understood. We investigated the potential reciprocal relationship between S. aureus skin infection and allergic skin inflammation.

METHODS: Il4−/−, Il13−/−, Il4−/−Il13−/− mice and WT controls were epicutaneously (EC) sensitized with ovalbumin (OVA) or saline as control, and superficially infected with S. aureus. Cytokine mRNA expression was assessed by quantitative PCR, cell infiltrates were evaluated by flow cytometry, and bacterial burden was evaluated by counting colony-forming units in skin homogenates.

RESULTS: OVA sensitized mouse skin exhibited increased S. aureus loads compared to saline sensitized skin. Superficial S. aureus application on OVA sensitized skin sites exaggerated infiltration by CD45+ cells, CD4+ T cells, eosinophils, basophils, ILCs and neutrophils. In addition, it enhanced Il4 and Il13 expression and decreased Il17a expression, but had no detectable effect on Ifng mRNA expression. Bacterial loads following S. aureus application to OVA sensitized skin were lower in Il4−/−Il13−/− and Il4−/−Il13−/− mice compared to WT controls.

CONCLUSIONS: Our results suggest a feed forward loop in which cutaneous S. aureus infection aggravates allergic skin inflammation and enhances the local type 2 responses, which in turn promote S. aureus growth and/or persistence.

200 Evaluation of Genetic Variants of ALOX5 and LTC4S in Aspirin-Induced Acute Urticaria/Angioedema

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RATIONAL: NSAIDs are among the most used drugs worldwide and also induce a number of hypersensitivity reactions, mainly without the participation of specific immunological recognition mechanisms. It is believed that the inhibition cyclooxygenase-1 directs the arachidonic acid pathway towards the release of cysteinyl-leukotrienes (CysLTs), triggering a reaction in some individuals. The most common clinical phenotype is aspirin (or NSAID)-induced acute urticaria/angioedema (IAUA). Two key enzymes are involved in CysLTs biosynthesis: arachidionate 5-lipoxygenase (ALOX5) and leukotriene C4 synthase (LTC4S). Considering that individual susceptibility to develop IAUA may be under the influence of genetic factors, we analyzed the potential involvement of genetic variants in these enzymes in this pathology.

METHODS: A total of 569 individual were included: 269 IAUA patients and 300 healthy controls, without significant sex or age differences between them. We selected 19 tag single nucleotide polymorphisms (tSNPs) in ALOX5 and 2 in LTC4S according to the 1000 Genomes Project data for Europeans, which were genotyped using the iPLEX Sequenom Mass Array technology.

RESULTS: The ALOX5 rs28395868 intronic variant was linked to an increased risk of IAUA (OR=2.61, IC=1.37-4.98), remaining this association statistically significant after Bonferroni multiple testing correction (corrected p-value=0.015). A marginal association for the ALOX5 tSNP rs3780901 was also found.

CONCLUSIONS: Our results suggest a role for ALOX5 genetic variants in IAUA, potentially by affecting splicing mechanisms. However, additional studies are necessary to replicate our findings and to disentangle these associations at molecular level.
Association of Single Nucleotide Polymorphisms in *PTGS1* and *PTGS2* with Aspirin-Induced Urticaria/Angioedema

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RATIONAL: Nonsteroidal anti-inflammatory drugs (NSAIDs), one of the most highly consumed medicines, are among the main triggers of drug hypersensitivity reactions. Clinical phenotypes induced by NSAIDs-hypersensitivity include aspirin (or NSAIDs)-exacerbated respiratory disease (AERD), in patients with underlying rhinitis and/or asthma with/without nasal polyps, and aspirin-induced acute urticaria/angioedema (AUAJ) in otherwise healthy individuals. It is thought that cyclooxygenase-1 (COX-1) inhibition shunts the arachidonic acid metabolism towards the synthesis of cysteinyl-leukotrienes, which in turn elicit a reaction in susceptible individuals. Such susceptibility may be influenced by genetic variants, which have mainly been studied in AERD although AUAJ is most frequent. We evaluated the overall genetic variability in the COX-1 encoding gene *PTGS1* (prostaglandin-endoperoxide synthase 1) and its inducible isoenzyme, the COX-2 encoding gene, *PTGS2*, in AUAJ patients.

METHODS: We included 269 AUAJ patients and 300 aspirin-tolerant controls with no significant age and sex differences. Twelve tagging single nucleotide polymorphisms (tSNPs) in *PTGS1* and 9 in *PTGS2* were selected, using European population’s data available from the 1000 Genomes Project. Genotyping was performed using the iPLEX Sequenom MassArray technology.

RESULTS: Two tSNPs in *PTGS1* (rs10306194 and rs1330344) were statistically associated with AUAJ (corrected p-values of 0.014 and 0.019, respectively). In addition, other 2 variants in *PTGS1* (rs3119773 and rs76942325) and one in *PTGS2* (rs8948467) were marginally associated.

CONCLUSIONS: Our results suggest a role for UTR *PTGS1* variants in AUAJ, possibly by affecting gene expression. However, further studies are required to replicate these associations and to shed light on the molecular basis underlying these associations.

Ehlers-Danlos Syndrome is associated with Idiopathic Urticaria – a Retrospective Study

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RATIONAL: Ehlers-Danlos syndrome (EDS) is a genetic disorder of the connective tissues of the body, with joint hypermobility (Type 3) being the most common. Mast cells reside in the connective tissues of the body. Multiple case reports and case series have reported an association between EDS and mast cell disorders. To investigate this connection more robustly, we reviewed the electronic medical record at a large institution. We hypothesized that symptoms and signs commonly associated with mast cell disorders (specifically urticaria) are more prevalent in patients with Ehlers-Danlos than in the general population.

METHODS: A retrospective chart review was conducted using the Informatics for Integrating Biology and the Bedside (i2b2) program through the University of Iowa Hospitals and Clinics. De-identified patient data was obtained using a database of over 2 million patients. Search criteria included key terms such as urticaria and Ehlers-Danlos. Fully identified data was requested on a subset of patients matching the search criteria, and the data was analyzed using odds ratios. Only patients with idiopathic urticaria (chronic or recurrent) that have been formally diagnosed with Ehlers-Danlos by the genetics department were included in the study.

RESULTS: There was a statistically significant increase in prevalence of idiopathic urticaria in patients with Ehlers-Danlos compared to random co-occurrence of the two disorders in the general population (OR 5.88, 95% CI 4.04-8.54, p < 0.0001).

CONCLUSIONS: Idiopathic urticaria has a significant association with Ehlers-Danlos syndrome.

IgE reactivity to Pacific cod (*Gadus macrocephalus*) fish allergens in dogs with canine atopic dermatitis

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RATIONAL: Canine atopic dermatitis (AD) is clinically similar to human AD, implicating it as a useful model of human allergic diseases. The allergic properties of fish in canine AD have not yet been analyzed. This study aimed to investigate IgE reactivity to crude as well as purified cod allergens in dogs with canine AD, and to identify the allergenic components of cod fish.

METHODS: Reactivity of specific IgE to crude cod antigen in the sera of 179 dogs with canine AD was evaluated using ELISA and immunoblot analysis. Parvalbumin, collagen (Sakaguchi et al. JACI 106:579-84, 2000) and tropomyosin (Miyazawa et al. JACI 98:948-53,1996), to which human patients with allergies have shown IgE reactivity, were isolated from Pacific cod (*Gadus macrocephalus*) fish.

RESULTS: Twenty (36/179) percent of the dogs with canine AD had specific IgE to crude cod antigen. Of the 36 dogs sensitive to crude cod allergen, 9 (25%) had specific IgE to parvalbumin, 14 (39%) had specific IgE to collagen, and 18 (50%) had specific IgE to tropomyosin. These results were validated by immunoblot analysis that detected IgE reactivity of sera of dogs with specific IgE to the aforementioned allergens.

CONCLUSIONS: The dogs in this study showed IgE reactivity to crude cod allergens, parvalbumin, collagen, and tropomyosin, similar to those in humans. Thus, this study suggests that the dog might be the best model to study IgE reactivity to fish allergens in human allergic diseases.
204 Impact of Triple Drug Therapy for Chronic Abacterial Prostatitis on Immune and Symptom Parameters

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RATIONALE: Chronic abacterial prostatitis (CAP) results from cytokine induced inflammation which impacts prostatic secretions. The efficacy of treatment for CAP using a combination of sodium diclofenac, tamsulosin, and the extract of Serenoa repens was assessed including impact on cytokine production.

METHODS: 32 patients with CAP aged 18–45 years were assessed using microscopy and culture evaluation of ejaculate. Patients received diclofenac sodium (100 mg/day, orally, 2 weeks), tamsulosin (0.4 mg/day, orally, 1 month), and Serenoa repens extract (320 mg/day, orally, 6 months). Levels of TNF-α and IL-10 in ejaculate were assessed pre- and post-treatment.

RESULTS: Treatment significantly decreased dysuria and pain (NIH-CPSI scale, uroflowmetry). Improvement in patients was observed in 47% after 2 weeks, in 63% after 1 month, and in 72% after 6 months. In patients with good results at 6 months, recurrence of symptoms of CAP occurred in 10%, but re-introduction of diclofenac and tamsulosin induced remission in all cases of relapse. Adverse effects included epigastritis pain in 10% due to diclofenac use of more than 7 days, and retrograde ejaculation in 78% due to tamsulosin. Drug withdrawal was not required. A significant decrease in concentration (p < 0.05) of TNF-α and increase IL-10 occurred, but in 34% cytokine levels were normal.

CONCLUSIONS: The assessed treatment regimen for CAP increased the immune-regulatory cytokine IL-10 and decreased the inflammatory cytokine TNF-α while improving symptoms and urine flow.

205 A Live Microbial Biotherapeutic Product for Induction of Allergy-Protective Immunity

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RATIONALE: The gut microbiome develops in early life and is essential to the establishment and maintenance of peripheral immune tolerance. Infants who develop allergy and asthma in childhood harbor a distinct gut microbiota depleted of a range of bacteria and functional gene pathways; perturbations that are evident from birth and throughout the first year of life.

METHODS: Using longitudinal gut microbiota data generated from stool samples collected over the first year of life and clinical data from a San Francisco-based birth cohort of healthy and high risk for asthma infants, we designed a mixed-species bacterial consortium that encodes a broad range of lactic acid bacteria. We aimed to design a consortium that provides a platform for inducing the establishment of allergy protective immunity in neonates.

RESULTS: The consortium was designed to: (1) encode the antigen-presenting properties of specific bacteria, (2) encode the ability to provide tolerogenic antigens, (3) induce an IL-10 response, and (4) induce regulatory T cell activity.

CONCLUSIONS: The designed bacterial consortium reduces allergic sensitization in a murine model. Supplementation of high-risk infants may influence gut microbiome development and promote immune tolerance in humans.

206 Epitope Mapping of 2S albumins and Comparison of Ara h 2, Ara h 6 and Ara h 7 from Peanut

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RATIONALE: Peanut allergy is increasing worldwide. Of all the peanut allergens identified, Ara h 2 has been shown to be most correlated with and diagnostic of peanut allergy. In this work, we probed peptide microarrays with peanut allergic sera to identify and compare the linear epitopes of the peanut conglutins, Ara h 2, Ara h 6 and Ara h 7 and other potentially cross-reactive tree nut 2S albumins.

METHODS: 15-mer peptides that were offset by 5 amino acids were printed on glass slides. Patient sera were incubated with the slides. IgE and IgG4 binding was detected with a combination of fluorescently-labelled antibodies. The linear epitopes were mapped to molecular models of the 3-dimensional structures of the allergens.

RESULTS: The majority of the epitopes mapped to the surface of the proteins. In addition, while Ara h 6 and Ara h 7 share 77% and 60% homology with Ara h 2, respectively, not all epitopes identified in these conglutins were shared among the three allergens. Common epitopes of cross-reactive 2S albumins in tree nuts were identified.

CONCLUSIONS: These results not only identify important epitopes for 2S albumins as well as Ara h 6 and 7, they demonstrate that while the peanut conglutins share some epitopes, they also have their own unique IgE and IgG4 epitopes and are not necessarily diagnostically or immunologically equivalent to Ara h 2.

207 Adjutant-free intragastric sensitization to peanut promotes anaphylaxis in CC027/GeniUnc mice

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RATIONALE: Recently we identified CC027/GeniUnc mice to be reactive upon oral challenge with peanut extract, following gastric sensitization with peanut plus cholera toxin (CT). Here, we aimed to determine if CT was critical for breaking oral tolerance.

METHODS: Female CC027/GeniUnc, C3H/HeJ and BALB/cJ mice, aged 4–6 weeks, were sensitized by the gastric route for four weeks with either (1) PBS, (2) peanut extract once/week, (3) peanut extract three times/week, or (4) peanut extract plus CT once/week. Mice were challenged with peanut extract via oral gavage one week after sensitization. Fecal pellets and serum were collected at baseline and one day before oral challenges. Mice were bled 60 minutes following the challenge to measure mediators and Ara h 2 in the serum.

RESULTS: Following oral challenge with peanut, CC027/GeniUnc mice sensitized with peanut alone, once or three times/week, experienced anaphylaxis (>3°C body temperature decrease), comparable to mice sensitized with peanut plus CT. Contrarily, all groups of C3H/HeJ and BALB/cJ did not experience anaphylaxis. CC027/GeniUnc mice sensitized with peanut once/week had higher levels of peanut-specific IgE, IgG1 and IgG2a post-sensitization compared to C3H/HeJ and BALB/cJ (p < 0.05). CC027/GeniUnc serum levels of Ara h 2 post-challenge were correlated with reaction severity (p = 0.0004). All groups of CC027/GeniUnc mice produced minimal total fecal IgA post-sensitization, while C3H/HeJ and BALB/cJ mice produced higher levels of fecal IgA.

CONCLUSIONS: These results demonstrate that CC027/GeniUnc can be intragastrically sensitized to peanut alone, indicating an innate failure of oral tolerance. Low fecal IgA may be an important factor that makes them susceptible to sensitization.
208 Identification of Almond (Prunus dulcis) Vicilin as a Food Allergen

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RATIONALE: Four almond allergens have been officially designated by WHO/IUIS. In addition, a protein that recognized by at least one patient serum was reported to be Pru du 2S albumin. However, a recent report suggested that it might be Pru du vicilin. Vicilins from many species, including several tree nuts are known food allergens. We hypothesize that almond vicilin is a food allergen.

METHODS: Genomic DNA of the Nonpareil almond was isolated. The vicilin gene sequence was PCR amplified. The coding sequence of vicilin was determined and synthesized with codon optimization. Recombinant almond vicilin was expressed in E. coli and purified by FPLC. The recognition of the recombinant almond vicilin by IgE in sera from 18 subjects with almond allergy was analyzed by Western blot.

RESULTS: Most of the sera contained IgE specific to almond proteins yet to be identified. Twenty-seven percent of sera recognized the recombinant almond vicilin. Among these, some recognized both the N- and C-terminal domains of vicilin, while others only recognized one of the domains.

CONCLUSIONS: almond vicilin is a food allergen.

209 Infant Egg Allergy Is Associated With Maternal Permeability Of The Mammary Epithelium

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RATIONALE: There remains limited mechanistic understanding of how maternal variability and breast milk composition may influence infant allergic disease development. In this study, we investigated associations between maternal permeability of the mammary epithelium and infant allergic disease outcomes.

METHODS: In mothers with a history of allergic disease, the permeability of the mammary epithelium was assessed by measuring the breast milk sodium/potassium ratio at two (n=88), four (n=87) and six (n=82) weeks of lactation. At one year of age, infant allergic disease outcomes were assessed, including medically diagnosed eczema, allergen sensitization measured by skin prick testing to common food and environmental allergens, and food challenge proven IgE-mediated egg allergy.

RESULTS: At two weeks of age, sodium/potassium ratios were lower (p=0.03) in the breast milk consumed by infants who developed egg allergy (n=10), median 0.51 (interquartile range [IQR] 0.42-0.67), compared to those without egg allergy, median 0.66 (IQR 0.54-0.82). The breast milk sodium/potassium ratios of the infants with allergen sensitization (n=15) were median 0.56 (IQR 0.45-0.67), compared to those without sensitization median 0.67 (IQR 0.53-0.82), p=0.06. There were no associations between breast milk sodium/potassium ratios at four or six weeks of lactation and infant egg allergy or sensitization. Infant eczema (n=19) was not associated with permeability of the mammary epithelium.

CONCLUSIONS: Maternal permeability of the mammary epithelium in the first two weeks of lactation is associated with infant IgE-mediated egg allergy development. These results highlight a potential important maternal characteristic that may influence early infant food allergy development.

210 House dust promotes sensitization to peanut through the airway

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RATIONALE: Recent evidence indicates sensitization to foods can occur through non-oral routes, including the skin and respiratory tract. Environmental adjuvants in house dust can promote allergic sensitization to inhaled antigens, but whether this contributes to food allergy development is unclear. Here, we investigated the ability of house dust extracts to promote sensitization to peanut through the airway.

METHODS: Female C57BL/6 mice, age 7-10 weeks, were exposed to peanut alone or together with house dust extract by oropharyngeal aspiration twice weekly for two weeks. One week later, mice were challenged with peanut by intraperitoneal injection, and body temperatures were measured to monitor anaphylaxis. To evaluate peanut sensitization, we measured serum levels of peanut-specific immunoglobulins and cytokine production by peanut-specific T cells in lung-draining lymph nodes and spleens.

RESULTS: Inhalational exposure to combined peanut and house dust extract, but neither alone, resulted in production of peanut-specific IgE, IgG1 and IgG2c. Accordingly, mice sensitized to inhaled peanut with house dust extract, but not peanut alone, experienced anaphylaxis upon intraperitoneal challenge with peanut, as evidenced by a >5°C decrease in body temperature at 30 minutes post-challenge. Airway sensitization to peanut and house dust extract resulted in increased IL-4 and IL-17A production by peanut-specific T cells compared to peanut alone.

CONCLUSIONS: Inhalational exposure to peanut and house dust extract induces peanut allergy in mice. These findings suggest that indoor environmental adjuvants may facilitate sensitization to foods through the airway.

211 B Cell Responsiveness to IL-10 in Peanut-Tolerant and Peanut-Allergic Children

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RATIONALE: Increased food-specific IgG4 has been associated with tolerance to foods. While IL-10 has been shown to enhance B cell production of IgG4, the role of IL-10-producing B cells and B cell responsiveness to IL-10 in the pathogenesis of food allergy has not been well explored.

METHODS: Blood samples were collected from peanut-tolerant and peanut-allergic children between 2 and 6 years of age seeking treatment at Children’s National Medical Center. Peripheral blood mononuclear cells (PBMCs) and highly purified total B cells were cultured with combinations of IL-4, IL-10, and anti-CD40. Immunoglobulin isotypes were quantified from culture supernatants using multiplexed immunoassays. Flow cytometry was performed to determine the frequency of IL-10 receptor (IL-10R)-expressing B cells and frequency of IL-10+ B cells.

RESULTS: With data collection and analysis ongoing, preliminary results suggest that frequencies of IL-10R+ cells are highest in transitional B cell and plasmablast subsets, and lowest in naïve and memory B cell subsets in peanut-tolerant children. Frequencies of IL-10+R+ transitional B cells and plasmablasts trended lower in peanut-allergic children compared to peanut-tolerant children. Frequencies of IL-10+ B cells were overall low in both peanut-tolerant and peanut-allergic children and varied widely among subjects within each of the two groups. IL-10 decreased IL-4-induced IgE production in peanut-tolerant children, with mixed effects on IL-4-induced IgG4 production.

CONCLUSIONS: Preliminary data suggest that IL-10R is most frequently expressed on transitional B cells and plasmablasts, with trends toward lower frequencies in peanut-allergic children than peanut-tolerant children. IL-10+ B cells are detectable at varying frequencies in both peanut-tolerant and peanut-allergic children.
Expression of iNOS by CD33+ monocytes in PBMC correlated with asthma severity and control scores in adults with allergy and asthma

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RATIONALE: Exhaled breath NO (FeNO) is a biomarker of asthma, but blood NO response has not been standardized. We previously reported that PBMC of IgE+ allergic adults produce significantly more NO at 5 days of culture compared with IgE- adults. This study used a new method to detect the response earlier.

METHODS: Blood from IgE+ (n=15) and IgE- (n=12) adults was collected in the morning. FeNO, serum IgE (Niox Vero; ImmunoCAP) and NIH asthma severity and asthma control (ACT) scores were determined. PBMC were incubated for 18 hrs at 37°C. IL-4 (1 ng/ml), IL-15 (10 ng/ml) and vitamin D3 (20 pmol/ml) (Cyt+D3 stimulation of PBMC from IgE+ subjects significantly increased the numbers of CD33+iNOS+ monocytes (% PBMC) compared with IgE- subjects (22.7±11.0 vs.11.4±8.0, p<0.01). There was no difference without stimulation (15.0±9.8, 9.2±6.3, respectively, p=0.07). The numbers of CD33+iNOS+ monocytes from stimulated and unstimulated PBMC correlated with both asthma severity (p=0.038, 0.046, respectively) and asthma control scores (p=0.02, 0.009, respectively), but not FeNO levels (p=n.s. for both).

CONCLUSIONS: iNOS expression in CD33+ monocytes (the iNOX assay) is a novel biomarker of innate immune responses and links blood inflammatory responses in allergy/asthma with asthma severity and control scores, but not airway NO responses.

Association of global trends of national tobacco smoking rates with prevalence of pediatric asthma and allergy

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RATIONALE: As there is a global decline in tobacco smoke prevalence, the rates of allergic diseases are increasing. Interestingly, tobacco exposure increases T-regulatory activity in murine models, which may suppress allergic responses. We determined whether there is an association between change in national tobacco smoking prevalence and change in childhood asthma and allergy throughout the world.

METHODS: We compared the prevalence of asthma, allergic rhinoconjunctivitis and eczema results from phase I and phase III of the ISAAC study in children ages 6-7 and 13-14 with concurrent WHO tobacco prevalence for each ISAAC nation (n=55), with an average of 7.2-year interval between ISAAC phase study. Change in raw prevalence’s were determined. Statistical analysis was done using the Spearman correlation coefficients.

RESULTS: Tobacco rates between year1 (Phase I) and year2 (Phase III) were 2% (SD=2.6) lower on average. There was a significant positive correlation between the change in tobacco rate and asthma prevalence in the 13-14-year group (p=0.02) but not the 6-7-year group (p=0.6).

Gut Microbiome Composition Prior to Sensitization Predicts Reaction Severity in Peanut Allergic Mice

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RATIONALE: Aberrant colonization of the gut by commensal microbes in early-life is associated with increased susceptibility to allergic diseases. Here we evaluated the influence of the gut microbiome on anaphylaxis in peanut in mice. Specifically, we retrospectively examined the relationship between the pre-sensitization composition of the gut microbiome and post-sensitization reactivity when challenged with peanut.

METHODS: CC027/GeniUnc X C57BL/6J F1 and F2 mice were sensitized with peanut and choler toxin for 4 weeks and challenged with peanut the following week. Fecal pellets were collected before and after sensitization and sequenced using 16S rRNA. Mice were characterized as strongly reactive (n=22) and non-reactive (n=23). Phylogenetic investigation of communities by reconstruction of unobserved states (PICRUSt) was used to predict each sample’s gut metagenome from its 16S data.

RESULTS: Using supervised learning, we identified 5 clusters of metagenomic ratios important for predicting non-reactive versus strongly reactive mice (AUC = 0.85). Cox regression identified a significant association between the log-ratio of glutamyl-tRNA reductases (K02492) to dipeptide transport system permease proteins (K12369) and reaction severity hazard. Strongly reactive mice with a log-ratio of K02492 to K12369 in the top 50th percentile had a mean predicted reaction time of 13.90(11.14–16.66) minutes compared to mice in the bottom 50th percentile with mean predicted reaction time of 8.67(6.47–10.87) minutes. Further, a log-ratio of K02492 to K12369 in the top 50th percentile versus bottom 50th percentile (HR=0.34, p=0.025) is associated with a reduction in reaction severity hazard.

CONCLUSIONS: Metagenomic log-ratios derived from gut microbiome data may be important for predicting anaphylaxis.
215 Impact of Allergist-Facilitated Education on Public Healthcare Provider Confidence in Counseling about Early Peanut Introduction

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RATIONALE: In 2017, NIAID guidelines recommending early peanut introduction to infants at high risk of peanut allergy were released. In Canada, some parents with concerns about severe allergic reactions to peanut seek the advice of nurse or dietitian public healthcare providers (PHPs). This pilot project sought to increase confidence of PHPs in counseling parents about peanut introduction through an education session. This is a novel knowledge translation collaboration of tertiary care providers and PHPs.

METHODS: With input from PHPs to identify relevant work-based educational needs, an education session was developed and led by a pediatric allergist. PHPs completed a pre- and post-survey at the education session to evaluate confidence (1=no confidence to 5=very confident) in supporting parents to introduce peanut, and a follow-up survey three months later.

RESULTS: 16 PHPs attended the education session and completed pre- and post-surveys, and 14 completed the follow-up. At baseline, confidence in counseling parents about peanut introduction was 3.50, and confidence in ability to educate parents to recognize an allergic reaction was 3.69. Confidence in both domains increased significantly from pre- to post-survey (mean score change: 0.81, p=0.01 and 0.69, p=0.03, respectively). This difference disappeared at the 3-month follow-up, after most PHPs had counseled parents.

CONCLUSIONS: An allergist-facilitated education session increased PHP confidence in counseling about peanut introduction and educating families to recognize allergic reactions. This increased confidence disappeared 3 months later, suggesting that periodic case-based learning modules/de-briefing about difficult encounters may help maintain confidence levels.

216 Minimizing Adverse Drug Reactions to IVIG in the Home Setting Through Application of an Evidence-Based Clinical Care Management Program

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RATIONALE: Intravenous immunoglobulin (IVIG) infusions are associated with predictable adverse drug reactions (ADRs), some of which are life threatening. The application of a clinical program at the specialty pharmacy (SP) level can decrease both the frequency and severity of reactions.

METHODS: A retrospective review of 4,155 patients receiving IVIG over a 10-month period was conducted using the specialty pharmacy electronic medical record. Patients were included if they placed at least one refill of IVIG, age fell between 18 and 89 years, and a refill assessment template was completed and reviewed by a pharmacist for every refill placed. Data included diagnosis, brand, dose and frequency of the IVIG, and history of patient reported problems since the previous infusion. For problems determined to be ADRs, nursing notes were reviewed for premedication regimens, concentration and rate of infusion of the IVIG, and patient tolerability.

RESULTS: 6.4% (4,588/32,537) of assessments revealed a patient reported problem since the previous infusion of IVIG. The majority of these problems were infections (2,897/4,588) or involved the mechanics during administration (1,318/4,588). The number of true ADRs was 373, revealing an adverse event rate associated with the infusion of IVIG in the home of 0.53% (373/32,537). Two of these reactions were considered life threatening (anaphylaxis and pulmonary embolism), while sixteen were classified as severe (potential aseptic meningitis or thromboembolic event).

CONCLUSIONS: Our data show that the application of an evidence-based clinical care management program can reduce the incidence of ADRs associated with IVIG below the literature benchmark.

217 Omalizumab: A Potential Therapy Option for Allergic Bronchopulmonary Aspergillosis (ABPA) in Asthma Patients

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RATIONALE: ABPA is associated with deteriorating lung function and is a common complication in asthma patients. Long-term therapy with oral corticosteroids is usually required for repeated exacerbations, resulting in drug toxicity. It has been reported that anti-IgE therapy with omalizumab can be an effective therapy option in ABPA patients.

METHODS: We report 3 asthma patients with ABPA taking prednisone at 20mg/day for patient 1 (M, 45y.o.), 40mg/day for patient 2 (M, 70y.o.), and 20mg/day for patient 3 (F, 31y.o.); also treated with omalizumab 375 mg every 2, 3, and 4 weeks for patient 1, 2, and 3 respectively. Patients were evaluated for steroid reduction, respiratory symptoms, and pulmonary function parameters.

RESULTS: All 3 patients had skin test positivity to A. fumigatus, bronchiectasis, and high IgE levels suggesting ABPA diagnosis. For Patient 1, prednisone was decreased to 10mg/day 3 months after starting omalizumab treatment (OT) and stopped 9 months after. Patient 2 and 3 stopped taking prednisone 12 and 3 months after OT, respectively. All patients reported about 3 ABPA exacerbation per year prior to OT and about 1 exacerbation while on omalizumab. Only patient 1 experienced FEV1 improvement from baseline (2.70l to 3.00l) 3 months after therapy. Patients reported significant clinical improvement of respiratory symptoms, decreased exacerbations, and overall improvement in health as early as 3 months after therapy.

CONCLUSIONS: Omalizumab has the potential to be an effective alternative or as an additional therapy option for ABPA in asthma patients who fail to respond to corticosteroids, providing a steroid sparing effect.
218 Initial results from a 24-hour recall interview to assess food allergy management behaviors among children

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**Rationale:** Assessment of adherence to food allergy management behaviors is limited by a lack of available measures. In other chronic illness populations 24-hour recall interviews are valid, reliable indicators of disease management behaviors. The current study details initial results from a 24-hour recall interview that assesses children’s food allergy management behaviors during meals.

**Methods:** Thirty-nine children diagnosed with food allergies, ages 10-14 years, and their parents, completed a 24-hour recall interview regarding a total of 340 meals/snacks For each meal/snack during the previous day, children reported who was present, if epinephrine was available, and how the child determined the meal/snack was safe to eat. Descriptive statistics and frequencies were computed for each domain.

**Results:** Most participants had multiple food allergies (86.8%) and were prescribed epinephrine (94.9%). Participants reported having epinephrine available at less than half of their ingestions (35%); most indicated epinephrine was stored in a nearby room (73.9%) rather than on the child (13.4%) or parent (19%). Adults observed less than one third of meals (28.8%). In general, children ate foods they had eaten previously (96.5%) and someone determined that the meal/snack was safe to eat (58.8% by child; 31.1% by parent) either by reading a label (35.8%), preparing food at home (19.3%), or assuming it was safe since it had been in the past (65.8%).

**Conclusions:** The use of a 24-hour recall measure yields valuable information about food allergy management behaviors and division of responsibilities, but additional refinement is needed to understand how these behaviors differ across settings.

219 Effectiveness Of Clinician Dose Blinding In An Oral Immunotherapy Protocol

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**Rationale:** Double blinding in oral immunotherapy (OIT) trails is of great importance to maintain scientific integrity, but there is limited literature on the subject. For a phase 2 clinical trial of OIT with randomized into a low (maximum combined dose 300mg) or high (maximum combined dose 1200mg) dose groups, we utilized oat flour to blind groups from clinical staff and participants.

**Methods:** Random allergen combinations of low (n=4, 60 vs 240mg) or high (n=4, 300 vs 1200mg) dosages were created. All low doses had an identical weight of 4g, high doses had an identical weight of 8g. Oat flour was used to normalize weights (2786-7524mg). Staff (n=13) were asked which OIT dose had more allergen. Staff were allowed to visually examine each pair mixed individually with a 30 second interval between inspections.

**Results:** There was significant difficulty identifying both high or low allergen dose. On average, clinical staff correctly selected high or low allergen 51% of the time. Of the 8 combinations, correct identification ranged from 3/13 to 9/13. Comparing low doses under 300mg had a rate of 44% (23/52). Comparing high doses 300mg had a rate of 59% (31/52).

**Conclusions:** The use of oat flour in OIT protocols is an effective way of keeping clinicians and participants blinded in varied dose amounts. Center staff were no better than random chance at deciphering doses, even in quick succession. In addition, doses in a trial environment are never in proximity to each other, further increasing effective dose blinding.

220 A Community Voice for Food Allergy Families: A Four-Year Successful Educational Experience

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**Rationale:** Food allergies (FA) are a serious and growing public health issue affecting every area of life for children with FA. Families with children with FA in the Houston region had no formal program or venue to address their needs.

**Methods:** At Texas Children’s Hospital, the Food Allergy Program implemented a Food Allergy Symposium (FAS) in 2014 for children with FA and their families. The FAS was held annually from 2014-2017. Speakers covered topics of general allergy information, research updates, psychosocial implications of FA, nutrition and advocacy. The program offered breakout sessions for questions within a smaller group setting. Youth (ages >6 years) met separately to discuss FA experiences. Interactive activities allowed open discussion (bullying, sleepovers, etc.) and expressive art projects. Program evaluations consisted of statements rating speakers on a Likert scale (1=Strongly Agree-5=Strongly Disagree) and qualitative statements. Descriptive statistics and qualitative statements were used for future planning.

**Results:** Over 4 years, 271 adult participants and 136 children attended from the Greater Houston region and Louisiana. A total of 224 (55%) completed evaluations were obtained. Over 95% found the program helpful and 100% would recommend the program to others. Qualitative statements were overwhelmingly positive. The Food Allergy Family Network, a support group for those with FA, developed in 2015 and has increased as more participants attend the FAS.

**Conclusions:** Positive feedback confirms the beneficial aspects provided families with FA through this FAS. The FAS format offers a model for similar events to promote education, support and community awareness for families with FA.

221 Emotional Quotient Improves in Autoimmune Disease Participants in 8 weeks

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**Rationale:** The effect of autoimmune diseases and emotional quotient (EQ) has not been well documented. We explore the effect than an educational program has on EQ among participants with autoimmune diseases. EQ has been linked to job quality, promotions and leadership ability.

**Methods:** An 8-week educational depression and anxiety program was organized by previously trained facilitators. Participants met for 2 hours each week. The weekly program included video presentations of health professional, small group discussions and hands on exercises emphasizing mental and physical habits such as positive thinking, exercise, diet, among others. Participants’ baseline and post-program EQ was measured using the Depression and Anxiety Assessment Test which measured depression, anxiety, demographics and autoimmune conditions.

**Results:** N=5861 participants that finished the program their mean age was 52.4, SD 15.1, n=4114 were females. N=431 had an autoimmune disease. Mean age was 54.9, SD 13.3, n=368 were females. At baseline, autoimmune participants had a mean EQ score of 95.9, SD 14.8. The post-program mean EQ score was 106.17, SD 15.2. EQ paired t-test of t(430)=−15.69, p<0.001. From the n=5430 without autoimmune condition. At baseline they had a mean EQ score of 100.4, SD 15.1 and an end EQ score of 109, SD 14.4. The change was significant with a paired t-test of t(5429)=.46.72 and p<0.001.

**Conclusions:** Autoimmune conditions seemed to have a negative effect on EQ. The educational program was effective in improving the scores of both groups. Further follow-up is needed to investigate whether the EQ improvement lasts long-term.
**222 House Dust Mite isn’t Selfish When it Comes to Shellfish**

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**RATIONALE:** Shellfish and house dust mite (HDM) allergies are common in North America. Often, both allergies are seen in the same patient. It is hypothesized that the homology of tropomyosin or other potentially shared proteins is the main factor for this co-existence. We discuss the findings of a patient population that presents with shellfish allergy and are assessed for HDM allergy.

**METHODS:** We undertook a retrospective chart review of 27 new consult patients, aged 9 to 50, who were referred for possible shellfish allergy. Our primary endpoint was to assess for presence of HDM sensitization in this population using skin prick test results.

**RESULTS:** Of the 27 patients, 18 skin tested positive for lobster, shrimp and crab; 4 for lobster and shrimp, but not crab; 3 for shrimp and crab, but not lobster; and 2 for lobster alone. 24 of 27 patients (89%) were found to be skin test sensitive for HDM. The 3 not allergic to HDM included a 16 year old female allergic to shrimp and crab, while the third was a 19 year old female allergic to shrimp and crab. We did not see any correlation between shellfish and HDM skin test size.

**CONCLUSIONS:** In our patient population, 24 of 27 shellfish allergic patients were sensitized to HDM. Patients being evaluated for shellfish allergy should be assessed for potential HDM allergy. HDM immunotherapy need be applied cautiously, limiting crustacean exposure, to reduce risk of inducing clinically significant allergic reactions while treating patients.

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**223 When Milk isn’t the Problem—Carrageenan as a Trigger for Allergic Reactions to Dairy Products**

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**RATIONALE:** Carrageenan is a thickening or emulsifying agent in food and medicinal products that is derived from red seaweed algae. Adverse reactions to carrageenan have been reported sparingly with barium enema solution, but may also be associated with adverse reactions to food.

**METHODS:** A 12 year old male patient presented to a community allergy clinic with an immediate, suspected allergic reaction to ice cream. The allergy evaluation included skin testing, and oral challenges to a sample of the ice cream, ASA, and carrageenan.

**RESULTS:** Skin testing to common foods was negative. An oral challenge in office to a sample of the ice cream resulted in chest tightness and throat discomfort. Salicylates were suspected as a potential trigger, ruled out on subsequent ASA oral challenge. The patient later had a reaction to whipped cream, which among other ingredients previously ruled out for allergy, contained carrageenan. Skin testing to carrageenan revealed a borderline response. A blinded oral challenge to powdered carrageenan in a food vehicle was carried out. The first oral challenge dose containing 0.1 g elicited symptoms of chest pain and a reduction of 10% in FEV1 from baseline, which reversed by 14% post-bronchodilator, confirming an immediate allergic response. Carrageenan avoidance was recommended. Information was given to the family on avoidance of carrageenan in food products and medications.

**CONCLUSIONS:** Carrageenan may account for allergic reactions to foods or medications in the absence of other allergic triggers. Potential carrageenan sources include dairy products, milk alternatives, protein supplements, meat products, and oral medications.

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**224 A Multi-Disciplinary Quality Improvement Project to Assess and Improve the Accuracy of Documentation of Food and Drug Allergies in the Electronic Medical Record**

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**RATIONALE:** Documentation of a patient’s allergies are kept in a central location (allergy tab) in the electronic medical record (EMR) to allow all providers to view this information. However, this information may be inaccurate, which can lead to patient harm. We sought to assess the accuracy of allergy tab documentation amongst patients seen in our outpatient allergy clinic and implement a quality improvement project to improve upon this.

**METHODS:** A retrospective chart review of outpatient clinic visits was performed within The Children’s Hospital of Colorado division of Allergy and Immunology over one month to assess for allergy tab accuracy, defined by whether allergies in the allergy tab matched the physician’s documentation from the clinical visit. We additionally distributed a survey to allergy clinical staff to determine who is currently completing the allergy tab and who is most appropriate to complete it. A chart review was similarly performed post intervention.

**RESULTS:** At baseline, 36% of charts reviewed had inaccurate documentation. Review of staff survey demonstrated that updating the allergy tab was not currently assigned to any one role, with 65% of individuals feeling the physician was the most appropriate person. Therefore, the intervention for our first PDSA cycle identified physicians as responsible for updating the allergy tab and provided education on this. Post education, chart inaccuracy declined to 30%, which was not statistically significant (p=0.27).

**CONCLUSIONS:** Defining standards for documenting allergies in the EMR helps prevent inaccurate documentation. Further work is needed to ensure allergy accuracy in patient charts to improve patient safety.

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**225 Pantoprazole-Induced Anaphylaxis**

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**RATIONALE:** Proton pump inhibitors are the most commonly used medications in the reduction of stomach acid. Of clinical importance is the recognition of rare adverse effects of PPIs.

**METHODS:** We report a case of anaphylactic reaction due to pantoprazole in a 39-year-old female.

**RESULTS:** A 39-year-old female with unknown drug allergies began to experience anaphylactic episodes with no known association. Symptoms reported include angioedema, pruritus, pyrexia, vomiting, and diarrhea. Episodes lasted for approximately 1.5 hours. She had 8 episodes over a period of 1 year. She did not report to the emergency ward as symptoms would resolve on their own. Eventually, in retrospect, she realized that the attacks correlated with the ingestion of pantoprazole, which she took in 40 mg tablets for the treatment of acid reflux. Symptoms would occur 20 minutes to 8 hours after ingestion of pantoprazole. She does report one episode which did occur immediately after ingestion. Epicutaneous testing to pantoprazole confirmed suspicions as it yielded a largely positive reaction with a wheal diameter of 10 millimeters. She was advised to avoid this drug.

**CONCLUSIONS:** This is one of the few cases of anaphylactic reaction to pantoprazole reported. Pathophysiology of this rare condition is still to be elucidated. Questions to determine are whether this is a class effect, solely due to this molecule, or due to other components of the medication.
**226** Serum leptin levels reflect the severity of eosinophilic rhinosinusitis according to Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis Study (JESREC Study)

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**RATIONALE:** Chronic rhinosinusitis (CRS) is a heterogeneous chronic inflammatory disease generally divided based on presence or absence of nasal polyps (NPs). One of the clinical features is the comorbidity of asthma. Recently, the relationship between metabolic disorder and asthma have been well documented, however, it had not been well understood about CRS and metabolic disorder. We hypothesized that CRS may be related to metabolic disorders.

**METHODS:** We measured the serum levels of leptin and adiponectin from patients with CRS with nasal polyp (CRSwNP), patients with allergic rhinitis (AR), and healthy control subjects. According to Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis Study (JESREC Study), we divided CRSwNP patients into four group; non-eosinophilic CRS (non-EIRS), mild EIRS, moderate EIRS, and severe EIRS group.

**RESULTS:** Although the levels of adiponectin showed no significant differences, the serum levels of leptin in EIRS group were significantly elevated compared to non-EIRS, AR, and control subjects. The levels of leptin had significant correlations between JESREC score, and the number of eosinophils in both NPs and in peripheral blood.

**CONCLUSIONS:** Our results indicated that serum leptin levels is related to the severity of EIRS, which results may also reflect that EIRS may be related to metabolic disorders.

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**227** Particle Pollution with PM 2.5, Reduction of Indoor Aeroallergen and Overall Particle Count Using AHPCO and Plasma Hybrid Technology for Air Purification

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**RATIONALE:** Worldwide allergy and asthma cases are on the rise. The primary concern of the present decade is air pollution as aerosols in the form of particulate matter (PM), also known as particulate pollution. We have analyzed the PM 2.5 and aerosol data of the Texas Panhandle including the aeroallergens from the Burkard Spore Trap for the past 18 years. A hybrid air purification system of AHPCO, or Advanced Hydrated Photocatalytic Oxidation, and Plasma Nanotechnology were used for efficient air purification.

**METHODS:** We assessed the effect of AHPCO and the Bi-Polar air purification units on the PM 2.5 count using two fiber glass chambers connected to two DUST-TRAK Spectrometers. We also used the double sticky tape coated slides to assess the periodic local PM 2.5 counts. We used Burkard Spore Trap, Digital and Fluorescence microscopy to analyze the local aeroallergen.

**RESULTS:** The AHPCO and Plasma nanotechnology reduced the particulate counts in both the chambers gradually with varied time intervals. The indoor aeroallergen data showed a gradual reduction on using this air purification system.

**CONCLUSIONS:** Strong wind current, local feedlots and a gradual shift in flowering season contributed to a high incidence of allergy and asthma. The hybrid AHPCO and Plasma Nanotechnology that reduced the indoor particulate counts including all forms of aeroallergen. The novel iAdaptAir® with hybrid full spectrum air purification, combining the best high-end HEPA and carbon filters, AHPCO®, Bi-Polar ionization, and germicidal ultraviolet technology were used for air purification to reduce aeroallergen, dander and bacteria in animal laboratory facilities.

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**228** A role of mast cells in ovalbumin-induced mouse allergic asthma responses suppressed by natural product mixture (Hwangchango)

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**RATIONALE:** Mast cells play important roles in the inflammation related to allergic asthma. We observed that natural product mixture (Hwangchango, HCG) that contains garlic, onion and Zizania reduced various responses caused in mast cells in preliminary experiments. This study aimed to examine a role of mast cells in ovalbumin (OVA)-induced mouse allergic responses suppressed with HCG.

**METHODS:** BALB/c mice were sensitized and challenged by OVA to induce asthma. The recruitment of inflammatory and mast cells recruited, or deposition of gablet cells and collagen II into BAL fluid or lung tissues was determined by Diff-Quik, H&E, May-Grünwald Giemsa, PAS, trichrome staining, respectively, expressions of c-kit, tryptase, FceRI, EMBP, Mac5ac, CCL2/CCR2, VCAM-1 in lung tissues by Western blot, COX1/2 expression by RT-PCR, and IgE, inflammatory mediators and cytokines in sera by ELISA.

**RESULTS:** HCG reduced the numbers of inflammatory cells, mast cells and goblet cells, collagen deposition, and the expression of EMBP, Mac5ac, markers of mast cell surface (c-kit, tryptase, FceRI), molecules related to mast cell migration (CCL2/CCR2, VCAM-1), or enzymes (COX1/2, 5-LOX) producing the mediators in BAL fluid or lung tissues of OVA-induced mouse allergic asthma. HCG reduced the amounts of IgE and inflammatory mediators (histamine, PGD2, LTC4, cytokines).

**CONCLUSIONS:** The data suggest that HCG may attenuate the development of allergic diseases via regulating various inflammatory mediators produced in mast cells recruited into BAL fluid and lung tissues. Now, we are under study to identify single component from Zizania because bioactive materials for garlic (allicin) and onion (quercetin) were already known.

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**229** Scombroid Poisoning versus Crab Food Allergy in an Adolescent Patient

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**RATIONALE:** Scombroidosis is a food poisoning that can sometimes be confused with food allergy. Here we describe a patient who presented with anaphylaxis that was thought to be seafood allergy.

**METHODS:** Typtase level at hospital 2 hours after event and 7 weeks post incident. Immediate Hypersensitivity Skin Testing (IHST) with extract to flat and shellfish and Specific IgE to multiple flat and shellfish.

**RESULTS:** 13 year old female presented with rash, flushing and feeling of throat closure following ingestion of “seafood sausage” produced from flatfish. She was treated at hospital with injection of epinephrine 0.3 mg and dexamethasone 20mg with resolution of throat closure. Mother reported that she had the same sausage with no symptoms, but did not finish due to untoward taste. Typtase in the ER was elevated at 16.5 ug/L. Seven weeks later typtase was WNL at 2.7 ug/L. Cod, crab and shrimp IgE and IHST extract were negative 1 week following the incident. The patient has eaten crabs and shrimp since that time, with no adverse reaction. She has been offered a challenge to flatfish.

**CONCLUSIONS:** Scombroidosis should always be considered in the differential diagnosis of a patient presenting with an allergic reaction believed to be triggered by fish ingestion. Typtase level at the time of presentation and repeated at least 24 hours later will assist in establishing the reaction as life threatening anaphylaxis. Specific IgE and or IHST will aid in the differentiation of a food allergy from scombroidosis.
**AB75**

**230**

**Rhinocconjunctivitis induced by exposure to Swiss chard**

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**RATIONALE:** Food allergy is common, although allergic symptoms can sometimes be produced by skin contact or inhalation of volatile food antigens. Exposure to these allergens is also relatively common in non-occupational settings, such as the home. We present a case of food allergy to Swiss chard.

**METHODS:** Total and specific IgE (sIgE) were determined by ImmunoCAP® and ImmunoCAP® ISAC 112. Skin prick tests, SDS-PAGE and Immunoblotting with extract of leaf and stem of Swiss chard were carried out. Protein sequencing was analysed by mass spectrometry.

**RESULTS:** Prick were positive to extracts from *D. pteronyssinus*, dog epithelium, pollens from *P. pratense*, *P. lanceolata* and *O. europaea*, spinach, carrot and chard. Prick by prick with cooked and raw chard and apple peel were also positive. Total IgE: 222 kU/L. sIgE to apple, Mal d 1 and chard were negative. ImmunoCAP ISAC 112 was positive for rPhl p 1 and 2 and nOle e 1.

By means of SDS-PAGE and Immunoblotting we detected IgE binding bands about 55 kDa, 27 kDa and 20 kDa in leaf Chard extract and about 37 kDa and 30 kDa in stem Chard extract. In the apple extract two IgE binding bands about 70 kDa and 30 kDa were observed.

**CONCLUSIONS:** We present a patient with allergy to Swiss chard and tomato. IgE binding bands are detected around 20 kDa. To our knowledge, this is the first report to identify a new allergen in raw Swiss-chard extract.

**231**

**The Impact of Allergic Disease in Adults with Chronic Idiopathic Urticaria**

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**RATIONALE:** Patients with chronic idiopathic urticaria are frequently concerned about an association with underlying allergic disease. There is limited data on allergy risk factors for chronic urticaria in adults. This study aimed to determine the prevalence of co-existing allergic and the role of atopic disease in health care utilization (HCU) in adult patients with chronic idiopathic urticaria (IU) and co-morbid urticaria/angioedema (CUA).

**METHODS:** We retrospectively identified patients with chronic idiopathic urticaria seen in a university allergy immunology clinic from September 2007-2017. We classified patients as comorbid urticaria and angioedema (CUA), isolated urticaria (IU), or isolated angioedema (IA) and collected data on patient-reported drug allergies. Patients with ACE-inhibitor induced angioedema were excluded from analysis.

**RESULTS:** 451 patients with urticaria and/or angioedema were identified. Drug allergies were reported in 62% (n=280). Patients who reported drug allergies were older (median 47 vs. 36 years, p<0.001) and had higher BMI (median 28.3 vs. 26.6, p=0.002). There was no difference by gender (p=0.57). Patients with IA had the highest frequency of reported drug allergy (76%), significantly higher than CUA (60%) and IU (57%) (overall p=0.007). Allergy to >1 drug was reported in 171 patients (38%). The frequency of multiple drug allergy did not differ by subgroup (p=0.26).

**CONCLUSIONS:** Our study suggests that patients with idiopathic urticaria and/or angioedema have a much higher reported frequency of drug allergy than the general population. Further studies are needed to explore these findings.

**232**

**High Prevalence of Drug Allergy in Patients with Urticaria and Angioedema**

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**RATIONALE:** While allergic reactions to drugs can be a cause of acute urticaria and angioedema, the frequency of patient-reported drug allergies in chronic urticaria and angioedema has not been explored. The prevalence of adverse drug reactions in the general population is 7%. We aim to determine the prevalence of patient-reported drug allergies in patients with chronic urticaria and/or angioedema. We hypothesize that prevalence of reported drug allergies in this population will be higher than the general population.

**METHODS:** We retrospectively identified patients with chronic idiopathic urticaria and angioedema seen in a university allergy immunology clinic from September 2007-2017. We classified patients as comorbid urticaria and angioedema (CUA), isolated urticaria (IU), or isolated angioedema (IA) and collected data on patient-reported drug allergies. Patients with ACE-inhibitor induced angioedema were excluded from analysis.

**RESULTS:** 451 patients with urticaria and/or angioedema were identified. Drug allergies were reported in 62% (n=280). Patients who reported drug allergies were older (median 47 vs. 36 years, p<0.001) and had higher BMI (median 28.3 vs. 26.6, p=0.002). There was no difference by gender (p=0.57). Patients with IA had the highest frequency of reported drug allergy (76%), significantly higher than CUA (60%) and IU (57%) (overall p=0.007). Allergy to >1 drug was reported in 171 patients (38%). The frequency of multiple drug allergy did not differ by subgroup (p=0.26).

**CONCLUSIONS:** Our study demonstrates a high prevalence of allergic disease in adults with chronic urticaria. However, the co-existence of allergic disease or family history of atopy does not increase HCU. Further studies are needed to determine the underlying mechanism of chronic urticaria in adults.
School Personnel Apprehension Related To Stock Epinephrine In Greater Houston Area

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RATIONALE: Texas law currently allows stock epinephrine in schools. We sought to determine the demographics, knowledge, beliefs, and attitudes of school personnel related to stock epinephrine implementation in the greater Houston area.

METHODS: We created a 35-item survey and administered it to school personnel. Kruskal-Wallis and Wilcoxon rank-sum tests were used to assess differences in knowledge, belief, and attitude. Attitude items were used to calculate apprehension score (0-100) with higher scores representing more apprehension. Independent linear regressions were used to test the association between potential risk factors and apprehension. Factors found to be significant were considered for multivariable linear regression.

RESULTS: Fifty-eight surveys from nurses (59%), teachers (26%), administrators (12%) and clinic assistants (3%) were assessed. Teachers had an average apprehension score 14 points higher (95% CI:7.6, 19.7, p<0.001) than those from schools without. The comparisons of knowledge scores among participants with different beliefs and attitudes were not found to be statistically significant.

CONCLUSIONS: There is more apprehension in teachers and clinic assistants than in nurses about stock epinephrine in schools. Increased apprehension was observed in public school personnel and those in schools with stock epinephrine. Additional responses will be collected to determine if lack in food allergy education is associated with apprehension.

Hypertensive Disorders of Pregnancy and Recurrent Wheezing: 12 Month Follow-up of a Birth Cohort Study

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RATIONALE: Hypertensive disorders of pregnancy, in particular preeclampsia, are associated with an increased risk of developing wheezing in childhood.

METHODS: A controlled birth cohort study was carried out involving 109 infants born in Santos, Brazil. Offspring exposed to chronic hypertension of pregnancy (blood pressure ≥140 mmHg systolic and/or 90 mmHg diastolic before 20 weeks of gestation)(n=17), maternal preeclampsia (blood pressure ≥140x90 and proteinuria with dipstick ≥+1 present in at least one urine sample after 20 weeks of gestation)(n=46), gestational hypertension (elevated blood pressure alone after 20 weeks of gestation) (n=6) and newborn after normotensive pregnancies (n=40) were enrolled and followed during 12 months. We collected information of child’s health, environmental exposures and presence of wheezing at 6 months and 1 year old. We considered recurrent wheezing as ≥3 episodes of wheezing. Unadjusted and adjusted logistic regression models evaluated odds ratios and 95% confidence intervals.

RESULTS: In a multiple regression analysis adjusting for potential confounders, chronic hypertension of pregnancy and gestational hypertension, but not preeclampsia, related to high risk of recurrent wheezing (odds ratio [OR]4.7; 95% confidence interval [CI95%], 1.29-17.56).

CONCLUSIONS: Chronic hypertension in pregnancy and gestational hypertension were associated with recurrent wheezing in the first year of life.

Wahoo Cool for School: Bridging the Clinic to the Classroom to Update Student-Specific Food Allergy Recommendations

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RATIONALE: Schools remain challenged by food allergy, especially due to limited communication between families, medical providers, and schools. Families are similarly challenged by time constraints, financial limitations, and unfamiliarity with allergy specialists. One goal of Wahoo Cool for School was to provide updated, student-specific allergy information to families, schools, and primary care providers (PCPs).

METHODS: School nurses provided parents/guardians with the program’s public website, where parents/guardians completed the enrollment questionnaire. The program team contacted the parent/guardian to schedule two appointments, free of charge: Visit 1 included targeted history, exam, and allergy testing; Visit 2 included comprehensive discussion of results and allergy and epinephrine education. Relevant allergy information, such as new anaphylaxis action plans, was shared via fax with the child’s school and PCP.

RESULTS: 37 parents/guardians completed the questionnaire; 32 children had appointments scheduled; 29 children attended appointments. Ages ranged from 1 to 17 years; races included Caucasian (67%), African American (25%) and Asian (14.3%). Peanuts and tree nuts were the most commonly reported food allergens. In 85% of children, food allergy was newly-diagnosed or confirmed; 71% were likely tolerant of at least one food they were avoiding, so were recommended for food challenge. 100% of families with food allergy were provided follow-up recommendations, epinephrine education, and anaphylaxis action plans, and the child’s school and PCP were faxed updated action plans.

CONCLUSIONS: This program successfully connected patients with food allergy providers, updated allergy status for 29 children at no cost to families, and created a model for communication for pediatric food allergy management.
236

Preferred Medication Changes in High Risk Asthma Patients Leads to Increased ED Visits and Hospitalizations

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RATIONALE: Insurance companies frequently change the preferred inhaled corticosteroid (ICS) for asthma. This causes gaps in medication utilization as pharmacies, physicians, and patients work to comply with the change. To determine if these changes impacted children with severe-persistent asthma, we performed a two year retrospective chart review (2016-2017) of hospitalization and emergency department (ED) visits.

METHODS: Hospitalization and ED visits of 98 children (median age 10 years) in our high-risk asthma clinic were reviewed between January 2016 to December 2017. Medication refill history, changes in insurance, and reasons for ED visits/hospitalizations were reviewed. Patients with <2 refills of ICS within 3 months and physician documentation of not taking medication despite continuous ICS access, were labeled “non-compliant.” Patients encountering changes in preferred ICS were labeled as “medication refill issue.” Data were analyzed using Wilcoxon non-parametric test.

RESULTS: In our high-risk asthma patients, a change in preferred ICS was associated with increased rates of ED visits (p=0.002) and hospitalizations (p=0.009). When examining the reason for the ED visit or hospitalization, we found that “non-compliant” patients had more ED visits than patients who were always compliant with medication (p=0.002), but they did not have higher hospitalization rates (p=0.37). Furthermore, “medication refill issues” led to increased ED visits (p<0.001) and hospitalizations (p=0.012).

CONCLUSIONS: High-risk asthma patients have a higher likelihood of ED visits and hospitalizations when their ICS changes. Working to keep their preferred ICS consistent is crucial in reducing health care costs. Further investigation is needed to determine if non-compliance may be linked with frequent ICS changes.

237

Elevated Testosterone is Associated with Decreased Likelihood of Current Asthma Regardless of Gender

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RATIONALE: Asthma prevalence decreases in males post-puberty, suggesting that testosterone may protect against asthma pathobiology. Indeed, animal studies have demonstrated that testosteron inhibits airway smooth muscle proliferation and bronchospasm. We therefore investigated whether serum testosterone inversely correlates with current asthma prevalence using cross-sectional data from the 2011-2012 National Health and Nutrition Examination Survey (NHANES) database.

METHODS: Serum testosterone and current asthma history were obtained from n=7,584 patients ages 1-80 years, n=601 with current asthma. Logistic regression was used to determine associations between serum testosterone and current asthma, adjusting for demographic variables and stratifying for gender and age.

RESULTS: Each 25ng/dl serum testosterone increase in the general study population resulted in a 3% decrease in the odds of current asthma (95%CI 1-4%, p=0.002). When the range of serum testosterone was divided into tertiles, the highest tertile was associated with a 58% decrease in the odds of current asthma relative to the lowest tertile (n=1,904, 95%CI 29-75%, p=0.003). In continuous data, this trend was present regardless of gender, and more prominent in females: males (3% decrease, 95%CI 1-7%, p=0.044), females (31% decrease, 95%CI 11-46%, p=0.006). For patients older than or equal to 12 years, the highest serum testosterone tertile was associated with a 47% decrease in the odds of current asthma relative to the lowest tertile (n=4,930, 95%CI 30-59%, p<0.001). No association was seen in patients younger than 12 years (n=782).

CONCLUSIONS: Data from NHANES demonstrate an inverse relationship between serum testosterone and current asthma prevalence suggesting a possible protective effect of testosterone on asthma development.

238

Prenatal exposure to acid suppressant medications and the risk of recurrent wheeze at 3 years of age in children with a history of severe bronchiolitis

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RATIONALE: Infants diagnosed with severe bronchiolitis are at higher risk for developing recurrent wheeze and asthma. Prior studies from outside the United States (U.S.) suggest that prenatal exposure to acid suppressant medications (ASM), such as proton pump inhibitors and histamine-2 receptor antagonists, may increase the risk of developing asthma. We tested the hypothesis that prenatal exposure to ASM increases the risk of recurrent wheeze among a high-risk population of children with a history of severe bronchiolitis.

METHODS: We enrolled 921 infants hospitalized for bronchiolitis from 2011-2014 in a multi-center, U.S.-based prospective cohort. ASM use during pregnancy was ascertained by parent report. Children were followed for the development of recurrent wheeze by age 3 years (defined by 2007 NIH guidelines). Time-to-event analysis was performed using multivariable Cox-proportional hazards models stratified by age and adjusted for sex, race/ethnicity, income, maternal history of atopy, maternal smoking during pregnancy, use of antibiotics during pregnancy, gestational age at birth, multiple gestation and mode of delivery.

RESULTS: Of the 921 infants enrolled in the longitudinal cohort, 900 children with complete data were included in this analysis. Prenatal exposure to ASM occurred in 16% (144/900) of children. Recurrent wheeze developed in 31% (233/756) of unexposed children as compared to 39% (56/144) of exposed children (unadjusted HR 1.38;95%CI, 1.03-1.85). The finding did not change after adjustment (adjusted HR 1.40;95% CI, 1.02 -1.91).

CONCLUSIONS: In this high-risk cohort of U.S. children with a history of severe bronchiolitis, prenatal exposure to ASM further increased the risk of developing recurrent wheeze by 3 years of age.
Identification of Two Early Life Eczema and Non-Eczema Phenotypes With High Risk For Asthma Development

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Rationale: The “atopic march” has been considered a progression starting with eczema and culminating with development of asthma. Not all asthma cases, however, are preceded by eczema, and not all children with early eczema develop asthma. The aim of this study was to explore the impact of allergic sensitization patterns on the association between early eczema (<=4 yr) and later childhood asthma. Given reported associations of KIF3A genotype with the atopic march, we also examined the impact of KIF3A risk allele rs12186803.

Methods: We studied 505 participants in the Cincinnati Childhood Allergy and Air Pollution Study (CCAAPS), a prospective birth cohort, with longitudinal eczema and asthma outcomes as well as data regarding sensitization to foods and aeroallergens. KIF3A genotypes were available on all children. Multiple logistic regression was used to evaluate main effects and interactions between early sensitization and KIF3A genotype.

Results: Two high-risk groups were identified. The high-risk group with early eczema was more likely to be sensitized to food allergens, while the group without early eczema was more likely to be poly-sensitized to aeroallergens. The KIF3A rs12186803 risk allele interacted with food sensitization to increase asthma risk in children with eczema (p=0.02). In children without eczema, asthma was associated with the interaction between rs12186803 and aeroallergen sensitization (p=0.007).

Conclusions: Two asthma phenotypes were identified: one in children with a history of eczema and one in children without. KIF3A interacted differentially with sensitization pattern to increase the risk of asthma in both groups.

Early Life Risk Factors for Asthma at Early Adulthood

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Rationale: We aimed to identify relationships among early life risk factors such as viral illnesses and aeroallergen sensitization and the persistence of asthma to early adulthood.

Methods: 180 newborns at high-risk based upon parental histories of asthma and/or allergy were enrolled at birth in the Childhood Origins of Asthma (COAST) study and followed prospectively to 17-18 years of age. Current asthma was diagnosed based on physician diagnosis of asthma, medication use and symptoms in the prior year. The associations between early life risk factors and asthma at age 17-18 years were assessed by logistic regression.

Results: Passive smoke exposure (OR = 2.7, 95% CI 1.4-5.5, p=0.005) and sensitization to aeroallergens (OR = 6.4, 95% CI 2.3-18, p=0.0003) or food (OR = 4.1, 95% CI 2.0-8.4, p<0.0001) at 1 year of age was associated with significantly increased risk for asthma at 17-18 years of age. Wheezing illnesses with rhinovirus (RV) (OR = 2.9, 95% CI 1.5-5.5, p=0.001) and respiratory syncytial virus (RSV) (OR = 2.4, 95% CI 1.2-4.7, p=0.01) in the first 3 years of life were also associated with increased risk of asthma.

Conclusions: In the high-risk COAST birth cohort, early life environmental tobacco smoke exposure, RV and RSV-induced wheezing, and sensitization to both aeroallergens and food were all associated with increased risk for asthma persistence to early adulthood.

Replacement immunoglobulin trends amongst patients with CVID and concurrent autoimmunity: A report from the USIDNet registry

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Rationale: Common variable immune deficiency (CVID) is a primary immunodeficiency. Autoimmunity complicates approximately 25%. Traditionally IV immunoglobulin (IVIG) is administered to prevent infections but may suppress autoimmune features. Ancedtal reports suggest autoimmunity control may be achieved with subcutaneous immunoglobulin (SCIG). This study aims to evaluate immunoglobulin replacement route trends amongst CVID patients listed on the USIDNet registry.

Methods: A query to the USIDNet registry resulted in 387 CVID patients with a history of autoimmunity (CVID-A) and 399 CVID patients without autoimmunity (CVID-NA). Replacement modality was compared. Additional variables assessed included sex, family history, specific autoimmune disorder and adjunctive immunomodulatory medications. Statistics were significant difference in replacement between CVID-A and CVID-NA was noted (p<0.0001) with more CVID-A patients using SC therapy. The odds of having CVID-NA were 3.14 times higher for patients using IVIG (p<0.001 95% CI [2.19, 4.49]). In the autoimmune population, 67.3% were maintained on SC; 27.7% had at least one cytopenia; 28.7% had at least one gastrointestinal diagnosis. There were no significant differences in modality use in patients with a history of autoimmune cytopenias (p=.396), endocrinologic (p=.108) or dermatologic disorders (p=.540). Autoimmune hepatitis, celiac or inflammatory bowel disease cases were more likely to receive IVIG (p=.0297).

Conclusions: CVID-NA patients were more likely to use IVIG compared to CVID-A patients. Our data suggest against the notion that IVIG outperforms SC therapy in patients with a history autoimmunity. Given the limitations of database analysis, institutional-level, prospective data is required to identify characteristics predictive of success on SCIG.

B cell Activation in Specific Polysaccharide Antibody Deficiency

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Rationale: It is unknown whether the defect in patients with specific antibody deficiency deficiency (SAD) is a single one or if this is a heterogeneous population with multiple defects. Determining B cell activation by a variety of stimuli might address that unknown.

Methods: Peripheral blood B cells of 4 patients with SAD who produced antibody to protein but not polysaccharide antigens, 2 with common variable immunodeficiency (CVID) and 4 normal controls were studied. Lymphocytes were separated from heparinized whole blood by density gradient centrifugation, and mature B cells (CD 20+, CD 27-,CD10-) were stimulated with anti-B cell receptor (Fab’2 anti IgM,G) in a range of doses, ligation of toll like receptor, and mature B cells (CD 20+, CD 27-,CD10-) were stimulated with anti-B cell receptor (Fab’2 anti IgM,G) in a range of doses, ligation of toll like receptor (TLR)2 by PAM 2 cys K4 and of TLR7/8 by ssRNA. B cell activation status was assessed by CD86 (B7-2) expression on flow cytometry.

Results: Patients with SAD were heterogeneous. Two were similar to controls in TLR responses but had lower responses to BCR antibody. One had normal BCR response, but reacted poorly to TLR ligands, and one showed greater responses than control to both BCR and TLR stimuli. Patients with CVID had poor responses to both BCR and TLR stimuli, although the TLR responses were greater.

Conclusions: (1) Patients with SAD are heterogeneous in the integrity of their B cell activation pathways, with impaired BCR activation, impaired TLR activation and hyper activation of both pathways being observed. (2) CVID patients were deficient in Cell activation by both pathways, although some activation via TLR was detected.
RATIONALE: Diagnosis of primary immunodeficiency leads to a 1.42 fold increased risk of cancer compared to the general population, and CVID accounts for 70% of cases of cancer in primary immunodeficiency.

RESULTS: Seventeen percent (35/204) of the CVID patients had a diagnosis of cancer, with roughly half of those cases being leukemia/lymphoma (n = 17). The second most common cancer type was skin malignancies (N = 22, 1.2%). Lymphoid hyperplasia was most commonly reported in 16% (N = 25, 1.6%), followed by non-specific inflammation, lymphocytosis, and gammopathies. The most commonly reported atypical lymphoid hyperplasia was lymphoma (N = 17), with 8% reporting an associated lymphoma. While CVID patients are at increased risk for lymphoma, lymphoproliferation may be appreciated in the absence of a concurrent hematologic or solid tumor malignancy in CVID.

CONCLUSIONS: Lymphoproliferation was commonly reported among CVID patients, with 8% reporting an associated lymphoma. While CVID patients are at increased risk for lymphoma, lymphoproliferation may be appreciated in the absence of a concurrent hematologic or solid tumor malignancy in CVID.
Effect Of Air Cleaners (Intense Pure Air® XL) On Early And Late Asthmatic Response In Asthmatic Subjects Sensitized To Cat In ALYATEC’s Environmental Exposure Chamber (EEC)

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Rationale: Indoor air quality is a growing concern. Air cleaners have been promoted in the treatment of respiratory allergic diseases for several decades. However, no clear clinical proof of their efficacy on allergic asthma has been demonstrated. The aim of the study was to verify the efficacy of air cleaners in cat allergic asthma.

Methods: 24 asthmatics subjects sensitized to cat (GINA 1) were enrolled in a randomized, cross-over, double-blind placebo-controlled study. They were exposed to airborne cat allergen for two hours during baseline exposure in Alyatec® EEC. Afterward, they were randomized in 2 groups exposed to cat allergen either with active or placebo air cleaners with a wash-out period of three weeks.

Results: 100% presented an EAR (20% drop in FEV1) and 25% a LAR (15% drop in FEV1) during baseline exposure. The mean time necessary to obtain an EAR and LAR was 50.3 and 156 min, respectively. In placebo group, the frequency of EAR and LAR was not significantly different from the baseline (91.7 and 29.2% respectively). The time necessary to obtain an EAR and LAR was not significantly different. In active group, only 29.2% had an EAR and 16.7% had a LAR (p=0.0019). In the active group, 62.6% had neither EAR nor LAR.

Conclusions: We have demonstrated that air cleaners Intense Pure Air XL® were able to reduce significantly the frequency of EAR and LAR in Alyatec’s EEC. For the first time, it has been shown that Air cleaners had a clinical effect in subjects allergic to cat.

Wood Smoke Particles increase markers of systemic inflammation in healthy volunteers

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Rationale: Wood smoke particles (WSP) from wildland fires can cause abrupt increases in ambient air PM2.5 levels. PM exposure has been linked to systemic inflammation and cardiovascular morbidity, and this is especially relevant for those with high occupational exposure to WSP, such as firefighters.

Methods: Healthy volunteers underwent exposure to 500μg/m3 WSP for 2 hours. Venipuncture was performed prior to the exposure, and 6 and 24 hours after exposure to evaluate changes in systemic markers of inflammation. Post-exposure values were compared to pre-exposure values using paired t-tests or Wilcoxon signed rank tests, depending on whether or not the normality assumption was met.

Results: Total white blood cell count (WBC), peripheral blood percent neutrophils (%PMN) and platelets (Plt) were significantly increased from baseline at 6 hours post-WSP exposure (WBC: 1300/μL [890-1770]; %PMN: 7% [3.6, 9.8]; Plt: 8000/μL [760-14330]) but returned to near baseline by 24 hour post-exposure. No significant increase was detected in CRP, LDH, or TH1 cytokines (IL-1, IL-6, IL-8, TNFα) at 6 or 24 hours post-exposure. Serum LDL was increased from baseline at 24 hours post-exposure by 4 mg/dL [1.6, 7.1].

Conclusions: Exposure to WSP for 2 hours was associated with significant increase in markers of systemic inflammation in healthy adults. These findings may have important implications for those with high exposure to wood smoke. Further studies are needed to determine if the acute increase in systemic inflammation is associated with cardiovascular dysfunction, and whether pharmaceutical interventions can provide a protective effect against these effects.

The Impact of a Prescribed Burn versus a Wildfire on the Immune and Cardiovascular Systems of Children

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Rationale: Prescribed burns are one method to help reduce and contain wildfires. We investigated whether the health impacts of a prescribed burn are different from that of a wildfire of the same size.

Methods: We retrospectively analyzed data collected from Fresno, CA, where blood, blood pressures and FFTs were collected from 7 year olds. Prior to data collection, there was either a prescribed burn (n=32; 38% [12/32] asthmatic; 70 miles away) or a wildfire (n=36; 25% [9/36] asthmatic; 90 miles away) 3 months prior. Pollution exposures were assessed from central site monitors and distance-weighted to the subject’s home. Peripheral blood mononuclear cells were stained with metal conjugated antibodies for surface markers and CyTOF was performed. Methylation studies were also performed.

Results: Linear regression models were performed to investigate the effect of health outcomes between the 2 groups. Models controlled for age, sex, BMI percentile, race, smoke exposure and asthma status. Th2 cell percentages were increased (Est = 1.88; SE = .94; p = 0.050), but Th1 (Est = -2.13 SE = 0.52; p = 0.00018) and Th17 (Est = -1.10 SE = 0.48; p = 0.027) decreased post wildfire versus prescribed burn. There were also significant differences between groups for CD8+ cells, monocytes and B cells. Foxp3 methylation in the promoter region was increased post wildfire (Est = 2.59; SE = 0.95; p = 0.0088). Pulse pressures were trending towards increased post wildfire (Est = 4.079; SE = 2.35; p = 0.088).

Conclusions: There are significant differences between immune outcomes in 7 year olds after a prescribed burn versus a wildfire.
249 Report of prenatal exposure to pesticide predicts infant rhinitis and watery eyes without a cold

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RATIONALE: Previously we found that infant rhinitis and watery eyes reported without cold (RWWC) predicted school age exercise-induced wheeze, emergency department (ED) visits and hospitalizations for breathing problems. This appeared independent of infant wheeze and allergy. Overall, we theorize that environmental exposures have induced dysregulation in the autonomic nervous system, with increased parasympathetic response, leading to infant RWWC and school age EIW. For these analyses, we test the hypotheses that prenatal environmental organophosphate pesticides (OP) exposure, which can alter infant autonomic nervous system responses, would predict RWWC in the 1st year of life.

METHODS: Within a prospective birth cohort of urban children (n = 390), pregnant women were recruited during between 1998 and 2006 and were queried in the third trimester about pesticide exposure. Child RWWC was queried every 3 months. Relative risks (RR) for RWWC were estimated with multivariable models adjusting for potential confounders and covariates.

RESULTS: RWWC was predicted by mother’s report of prenatal pesticide exposure (RR=1.3, P=0.002). Reported professional application of pesticide was associated with RWWC among children born before 2002 (RR=1.5, P=0.001), but not after (RR=1.1, P=0.68, Pinteraction=0.031), the latter of which corresponds to a time after a ban on OP for residential use. Additionally, effect modification was observed for a common polymorphism in the serum paraoxonase/arylesterase 1 (PON1) gene promoter region (Pinteraction=0.012), which can alter OP detoxification efficiency.

CONCLUSIONS: These results suggest an association between prenatal OP exposure and RWWC in infancy, further supporting a link between infant autonomic dysregulation and RWWC.

250 Effect of prenatal particulate matter exposure on atopic dermatitis in preschool children modified by cord blood vitamin D: COCOA study

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RATIONALE: Maternal particulate matter (PM) exposure during pregnancy is associated with allergic disease of offspring. However, modifying effect of cord blood vitamin D on the relationship between PM exposure during pregnancy and atopic dermatitis (AD) in preschool children is unclear. To investigate the effect of PM2.5 during pregnancy on AD in preschool children and whether cord blood vitamin D modify this effect of PM2.5.

METHODS: This study included 1,183 mother-child pairs from the Cohort for Childhood Origin of Asthma and allergic diseases (COCOA). Levels of PM2.5 during pregnancy were estimated for addresses by land-use regression models based on national monitoring system. The prenatal period was divided into three trimesters; from week 1 through 13 (first), week 14 through 27(second) and from week 28 through week 40 (third). A diagnosis of AD was based on parental report of a physician’s diagnosis. Cord blood 25-hydroxyvitamin D3 was analyzed.

RESULTS: A higher PM2.5 exposure during first trimester of pregnancy was associated with AD at ages 1 and 2 years (aOR 1.579, 95% CI 1.092-2.285 and aOR 1.422, 95% CI 1.002-2.018, respectively). Low cord blood vitamin D increased the effects of PM2.5 exposure during first trimester of pregnancy on AD at ages 1, 2 and 3 years (aOR 2.028, 95% CI 0.984-4.177, aOR 2.354, 95% CI 1.178-4.701, and aOR 2.018, 95% CI 1.041-3.910, respectively).

CONCLUSIONS: PM2.5 exposure during first trimester of pregnancy may increase susceptibility to AD in preschool children. This effect can be modified by cord blood vitamin D.
AB82 Abstracts
FEBRUARY 2019

251 A 5-year Summary of Real-life Dietary Egg Consumption after Completion of a 4-year Egg OIT Protocol

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RATIONALE: Long-term dietary implications of egg OIT (eOIT), including desensitization and sustained unresponsiveness (SU), are not well described.

METHODS: Previously described egg allergic subjects (5-11 yo) were randomized to eOIT (n=40, treated with eOIT up to 4 years) or placebo (n=15, 1 year). Subjects passing a 10g OFC on therapy were considered desensitized and underwent a 10g OFC and open feeding 4-6 weeks after discontinuing therapy to determine SU. Long-term follow-up questionnaires (LFOQ) assessing egg consumption and symptoms were administered annually for 5 years following trial completion.

RESULTS: At study completion, 20/40 (50%) eOIT subjects were classified as SU, 11/40 (28%) subjects desensitized, and 9/40 (22%) not desensitized. Annual LFOQ completion ranged from 76-82% of all subjects (85-95% of the SU group). At year 5, 93% (30/32) of eOIT subjects were ingesting some egg compared to 64% (7/11) of placebo (p=0.029), 100% (19/19) of SU subjects were ingesting both concentrated and baked egg versus 43%, 17%, and 36% in the desensitized, not desensitized, and placebo groups, respectively. Decreased frequency and amount of egg ingestion and increased symptoms were observed in all non-SU groups versus the SU group. Epinephrine was required after concentrated egg ingestion in 3 non-SU subjects.

CONCLUSIONS: Five years after study completion, eOIT treated subjects achieving SU were highly likely to consume and tolerate dietary egg, while other groups had more variable egg consumption and increased symptoms associated with consumption. Further study to develop biomarkers predictive of treatment response is necessary to mitigate risk and assess clinical outcomes with OIT.

252 Successful Desensitisation And Sustained UnResponsiveness Using Modified Peanut: Results From The BOPI Study

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RATIONALE: Boiling peanut results in a modified, hypoallergenic product which can induce desensitisation (JACI 2014;134:751-3). We undertook the BOPI study, a Phase 2b/3 randomized controlled trial to assess efficacy and safety of boiled peanut oral immunotherapy (OIT).

METHODS: Children with peanut allergy confirmed at double-blind, placebo-controlled food challenge (DBPCFC) were randomised (2:1) to receive either oral immunotherapy (updosing using boiled peanut for ~6 months, followed by maintenance with roasted peanut) or standard treatment (allergen avoidance). Participants underwent repeat DBPCFC at 12 months to assess response, following which peanut OIT was stopped and sustained unresponsiveness assessed after 4 weeks (ClinicalTrials.gov NCT02149719).

RESULTS: Forty-seven children (8-17 years, 43% female) were randomised (32 to active treatment). Eight patients in the active group and 1 in the control group withdrew prior to primary outcome assessment, 4 due to treatment-related adverse events following initiation. Median cumulative eliciting dose prior to OIT was 143mg peanut protein (IQR: 43-443mg). 24/32 participants (100% per protocol) achieved the primary outcome of desensitisation to >1.4g peanut protein (P<0.0001); of those 14 tolerated >4.4g peanut protein. 13/24 participants achieved 4-SU. There was no significant change in threshold in the control group (P>0.05). There were 17 episodes of anaphylaxis occurring in 9 patients during home dosing. Boiled peanut OIT had a favourable safety profile, with under 2% of doses associated with gastrointestinal symptoms.

CONCLUSIONS: Oral immunotherapy using boiled peanut is pragmatic and effective, with a favourable safety profile and level of sustained unresponsiveness after 1 year of treatment.

253 Differential Gene Expression Among Infants at High-Risk for Peanut Allergy

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RATIONALE: We sought to identify key differentially expressed genes that may distinguish peanut allergic infants among those at high-risk for peanut allergy.

METHODS: Eight infants aged 4-11 months with egg allergy and/or moderate-severe atopic dermatitis, but not yet eating peanut, were prospectively recruited from a tertiary care allergy clinic. Infants were classified as peanut allergic (PA), peanut sensitized but tolerant (PS-T) or peanut non-sensitized, non-allergic (NA) based on skin test, specific IgE and/or oral food challenge. RNA was isolated from whole blood and samples underwent RNA-seq library preparation and sequencing. Differential expression analysis was performed using DESeq2 R package and p-values were adjusted by FDR.

RESULTS: Median age was 7.5 months and 50% were male. There was differential expression of 197, 198 and 557 unique genes in the PA, PS-T, and NA groups, respectively. Forty-one genes were up-regulated and 7 down-regulated in PA compared to NA (adj-p<0.05). The top 5 enriched genes in PA infants included: HLA-DRB6, CLC, SIGLEC8, SLC29A1 and ALOX15 (log2fold change >2.0, adj-p-value <0.01). Compared to PS-T, 4 genes were up-regulated and 6 down-regulated in PA (adj-p<0.05). There was a distinct subset of genes differentially expressed in PA compared to PS-T on hierarchical cluster analysis. Gene ontology enrichment revealed 138 pathways were differentially enriched between PA and PS-T. Four molecular function pathways (involving carbohydrate binding, neuropeptide binding and oxidoreductase activity) were enriched in PA compared to NA (adj-p<0.05).

CONCLUSIONS: Differential gene expression is present among high-risk peanut allergic infants, which may provide insight on the pathogenesis of early infant peanut allergy.
254 TCR Repertoire Analysis Reveals Public Motifs with High Probability for Allergen Epitope Specificity

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RATIONALE: Allergen-specific memory T cells play a vital role in both IgE- and non-IgE mediated food hypersensitivity. Identifying and analyzing allergen-specific TCRs in affected patients may provide useful targets for therapeutics and diagnostics.

METHODS: PBMCs from peanut-allergic and milk-allergic eosinophilic esophagitis patients were stimulated with peanut and milk protein, respectively. Activated and resting CD4+ memory T cells were sorted based on the expression of CD40L (CD154) and qDNA was used for TCR sequencing to obtain CDR3 sequences from both compartments. An analysis pipeline was developed to select putatively-specific CDR3 sequences (psCDR3s) that were significantly enriched in CD154+ versus CD154− cells using a G-test of independence with FDR q < 0.05. The CDR3 anti-gen-contact residues were further evaluated for motifs, 3-5 amino acids in length, and analyzed for association with antigen-specificity.

RESULTS: 6292 (14.1%) peanut-psCDR3s and 1080 (4.26%) milk-psCDR3s were enriched within the total CD154+ pool. Consistent with antigen-selection, psCDR3s were more homologous, as measured by hamming distance (p < 0.01). The vast majority of psCDR3s are private, however, 23 motifs in milk- and 63 in peanut-psCDR3s were public, highly-enriched in activated cells (q < 0.05, 10-fold higher in enriched) and found in ≥ 3 unique CDR3s, implicating them to be common epitope-specific sequences.

CONCLUSIONS: A small subset of CD154+ clones share sequence homology and are most likely to represent true antigen-specific T cells. Identification of these clones and their homologous sequences in the CDR3 contact residues may be used for improved diagnostics and therapeutics in both IgE- and non-IgE-mediated allergic diseases.

255 IgEhi Endophenotype in Those with Transient Desensitization after Peanut Oral Immunotherapy

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RATIONALE: Peanut-allergic patients who only have transient desensitization (TD) after oral immunotherapy (OIT) are known to generally have higher levels of allergen-specific IgE before starting OIT. We hypothesize that the IgEhi endophenotype is characterized by pre-existing B cell memory that predisposes the post-immunotherapy antibody repertoire to be less protective.

METHODS: Peanut-allergic children, aged 7-13, enrolled in a single-center, open-label peanut OIT trial. After 1 year of OIT, 23 subjects with challenge-proven desensitization (post-OIT) underwent challenge after 1 month of avoidance (post-avoidance). TD was confirmed in 13 patients and sustained unresponsiveness (SU) in 9. Using a fluorescent Arah2 multimer, we isolated Arah2-specific B cells for single-cell immunoglobulin sequencing and recombinant antibody production. We isolated memory B cells (CD19*CD27*) cells by flow cytometry for heavy chain immunoglobulin deep sequencing. We analyzed the repertoires using R/ Bioconductor and the Immcantation framework. Affinity was measured by biolayer interferometry.

RESULTS: TD subjects had higher Arah2-specific IgE levels before OIT (p=0.002). In the subset with high serum Arah2 IgE levels, their Ara h 2 IgG repertoire was more diverse (p<0.05), had high affinity for Ara h2 in the subnanomolar range, and had increased homology with the memory B cell IgE repertoire as opposed to the IgA repertoire in SU patients.

CONCLUSIONS: The IgEhi endophenotype is characterized by increased serum Ara h2 IgE levels and a diverse and high-affinity IgG repertoire related to the IgE repertoire. This suggests increased sequential switching to IgE may drive this endophenotype, dextering the development of protective antibody responses. Targeting this process may enhance the effectiveness of peanut OIT.

256 Family History of Atopy in Food Allergy Development

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RATIONALE: Food allergy (FA) affects 8% of US children. A comprehensive understanding of parental history of FA, and atopy more broadly, may provide insight into underlying heritable mechanisms contributing to the incidence of FA. We hypothesize that having a parental history of atopy and FA will impact FA development.

METHODS: A survey was administered via web and telephone to a sample of US households between 2015-2016, providing parent-proxy responses for 41,341 children. Stringent symptom criteria were developed with FA experts to distinguish respondents with “convincing” FA from those with similar conditions. Post stratification-weighted proportions were estimated to compare FA characteristics and observe family history.

RESULTS: Children were more likely to develop FA if there was a parental history of asthma (15.2% vs. 7.6%; p<0.05), eczema (13.7% vs. 7.6%; p<0.05), seasonal allergy (11.8% vs. 7.6%; p<0.05). This was most pronounced in children with a parent with FA (22.9% vs. 7.6%; p<0.05). When this was analyzed using multiple logistic regression analysis, children with parental history of FA were 5.92 (95% CI: 5.04-6.81, p<0.05) times more likely to develop FA. Children were more likely to develop food allergies if their parents had two or more atopic conditions (17.5% vs. 7.6% (p<0.05) and three or more atopic conditions (26.1 vs. 7.6% p<0.05).

CONCLUSIONS: Children were more likely to develop food allergies as the number of atopic conditions for parents increased, especially in those who had a parental history of FA. Parental history of atopy is a risk factor that may play a significant role in FA development.
AB84 Abstracts

J ALLERGY CLIN IMMUNOL
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257 Characterization of Epinephrine Utilization in Michigan Public Schools 2014-17

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RATIONAL: Michigan Public Act 187 of 2013 requires publicly funded schools to have epinephrine auto-injectors (EAI) and food allergy action plans. In 2015, a collaboration was initiated allowing the ability to collect data on EAI use in Michigan schools and begin training staff to gauge understanding of the policy among school personnel.

METHODS: Survey administered to 538 school districts in Michigan, June 2015 through June 2018 regarding EAI use from 3 prior years (2014-2017). Districts were offered completion of survey via phone, fax, or e-mail. The survey averaged 3-4 minutes to complete via phone. Funding through Blue Cross Blue Shield of Michigan Foundation.

RESULTS: 377/538 (70%) districts completed the survey. Prior to Michigan Public Act 187, 197/364 (54.1%) districts did not have written policies in place regarding EAI use. Of 103 schools with written policy, 36% were for training staff. Majority of schools (80.6%) secured funding to cover EAI cost, with increase in coverage over time. Most schools reported 0-2 total incidents of EAI use, with incidence increasing over 3 years (21% increase). 54/131 (33.4%) of EAI incidents occurred in high schools. Suspected cause of incident was 50/131 (38.2%) food allergy (FA), 37/131 (28.2%) stings; FA incidents increased 13% from 2014-2017. School owned EAI used for 94/159 (59%) incidents, >80% for students.

CONCLUSIONS: Data collection on EAI use in public schools in Michigan is leading to policy changes and legislation to improve incident tracking, access to medication and education around allergic reactions.

258 Implementation, Practices, and Barriers to the 2017 Peanut Allergy Prevention Guidelines Among Pediatricians

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RATIONAL: The 2017 Addendum Guidelines for the Prevention of Peanut Allergy (“Guidelines”) recommend assessment of peanut allergy risk for infants 4-6 months old before early introduction of peanut-containing foods. As pediatricians are the first line of health care for infants, our objectives were to assess Guideline awareness, barriers, and implementation among U.S. pediatricians.

METHODS: Invitations for a cross-sectional, online survey were emailed to a random sample of pediatricians from a sampling frame of 44,578 non-retired, U.S. pediatricians in general practice. From the 6,625 invitation emails that were successfully delivered, 369 pediatricians responded. The survey assessed awareness, implementation, and barriers of the Addendum Guidelines among pediatricians. Descriptive statistics were calculated for each outcome.

RESULTS: Of survey respondents, 92% (95% CI: 89-95) were aware of the Guidelines. Among those aware of the Guidelines, 28% (95% CI: 23-33) were using all Guidelines, 62% (95% CI: 56-67) were using parts, and 11% (95% CI: 8-14) were not using the Guidelines. Barriers among those using all or parts included parental concerns about allergic reactions (41%), understanding the Guidelines (35%), lack of clinic time (30%), novelty of the Guidelines (29%), and conducting an in-office feeding of peanut (28%). Of pediatricians not using the Guidelines, 67% reported insufficient knowledge of the Guidelines.

CONCLUSIONS: Less than one-third of U.S. pediatricians are currently fully implementing Guidelines. Since implementation of the Guidelines has the potential to reduce peanut allergy incidence on a national level, it is imperative to improve Guideline adherence and develop interventions to alleviate barriers to implementation.

259 Improvement in Quality of Life (QOL) in Pediatric Patients with Food Allergy Associated Disease After Initial Clinic Evaluation

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RATIONAL: The Pediatric QOL Inventory™ (PedsQL) survey measures health-related QOL in children with acute and chronic health conditions. The aim of this study was to determine the QOL for pediatric patients with an evaluation of food allergy associated disease 1 and 2 years after their initial clinic visit, which included education about rescue medications and food allergy action plans.

METHODS: The PedsQL survey was given to patients ages 2–18 years referred for food allergies, eczema, eosinophilic esophagitis and/or allergic rhinitis seen for initial consultation in the Texas Children’s Hospital Allergy/Immunology Clinic from October 2014–September 2015. Surveys were distributed at 1 and 2 year follow up visits until September 2017. The measured outcomes of the survey administration included follow up visit compared to initial scores in physical, social, emotional & school functioning domains. Higher scores correlate with better QOL.

RESULTS: PedsQL surveys were initially administered to 207 patients with food-associated disease. The overall initial PedsQL mean score for patients was 77.8/100. At one year follow up, the mean score increased to 84.7/100 (n=82). At the two year follow up, the overall mean scores decreased to 81.6/100 (n=72). The physical, social, and emotional functioning scores improved 6.5, 7.1, and 5.4 points, respectively, at the first follow up visit while the school functioning score decreased 5.4 points. At the two year follow up visit, the school domain score increased 7.2 points from baseline.

CONCLUSIONS: QOL PedsQL survey scores improved in patients with food allergy associated disease one and two years after initial allergy/immunology clinic evaluation.
Factors Associated with Increased Food Allergy-associated Anxiety in Parents of Food-allergic Children

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METHODS: Food Allergy Canada, a not-for-profit organization supporting families with food allergies, emailed parent members in Fall 2017 inviting them to complete an online survey about their FAAA using a visual analogue scale, which measured FAAA on a scale of 0 (not anxious) to 100 (very anxious). Multiple linear regression was performed to determine demographic, clinical, and psychosocial factors associated with FAAA, and standardized coefficients were calculated.

RESULTS: Of 1,244 parents who clicked on the survey, 548 completed it (44.1%). Mean FAAA was 71.2 (95% CI: 69.5, 73.0). Those with higher FAAA had a higher parental burden (beta = 0.51, p < 0.001), higher perception of risk that their child would have a severe reaction (beta = 0.13, p = 0.001) or die (beta = 0.13, p = 0.001) if they were accidentally ingested their food allergen, as well as lower tolerance of uncertainty (beta = 0.14, p < 0.001). The overall model explained 52.8% of the variance (p < 0.001).

CONCLUSIONS: We identified psychosocial factors associated with parental anxiety, including risk perception, intolerance of uncertainty, and parental burden. Parental burden appeared to be most strongly associated with FAAA. This will help us develop a validated diagnostic tool, so that clinicians can more easily diagnose FAAA and provide support/resources to those who need it.

Blocking Histone Deacetylase Activity As A Novel Target For Epithelial Barrier Defects In Allergic Rhinitis

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RATIONALE: A defective epithelial barrier is present in the pathology of allergic rhinitis and asthma, however, the underlying regulatory mechanisms remain poorly understood. Histone deacetylase (HDAC) activity is identified as a crucial driver for maintaining allergic inflammation and tight junction dysfunction. We hypothesized that epigenetic activity is altered in allergic rhinitis and contributes to epithelial barrier dysfunction.

METHODS: Nasal epithelial cells (NECs) of controls and AR patients were cultured at air-liquid interface (ALI) to study trans-epithelial electrical resistance, paracellular flux of FITC-dextran 4kDa, together with mRNA expression and immunofluorescence staining of tight junctions. ALI cultures were stimulated with different concentrations of JNJ-26481585, a broad-spectrum HDAC inhibitor. In vivo, the effect of JNJ-26481585 on mucosal permeability and tight junction function was evaluated in a mouse model of house dust mite-induced allergic airway inflammation.

RESULTS: HDAC activity was increased in nasal epithelial cells from patients with allergic rhinitis and correlated inversely with epithelial integrity. Accordingly, pharmacological treatment of nasal epithelial cells at ALI with JNJ-26481585, restored epithelial integrity by promoting tight junction mRNA expression and protein reorganization. In vivo, house dust mite sensitized mice, treated with JNJ-26481585 had decreased eosinophils and levels of IL-4 and IL-13 and bronchial hyperreactivity compared to saline controls. In vivo, JNJ-26481585 treatment reestablished nasal mucosal function through increased mRNA expression of tight junctions.

CONCLUSIONS: Our findings advocate increased HDAC activity as a novel intrinsic regulatory mechanism for defective epithelial barrier in allergic rhinitis. Blocking HDAC reconstitutes barrier function and appears a promising novel target for therapeutic intervention.

Age-related Endotype in Patients with Chronic Rhinosinusitis

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RATIONALE: Age-related cytokine profile in chronic rhinosinusitis (CRS) should be investigated for precision medicine. The objective of this study was to characterize the immunologic profiles according to age subgroups in each subtype of CRS and suggest clinical implication.

METHODS: Twenty-three inflammatory markers were investigated in nasal tissues using multiplex cytokine assay and ImmunoCAP®. Age-related changes in key cytokines were identified in CRS subtypes. Pediatric (< 18 year-old) and geriatric CRS (≥ 60 year-old) were characterized immunologically.

RESULTS: Control tissues showed a moderate age-related decline in several neutrophil-associated mediators and remodeling markers such as peristin and TGF-β1. Like control tissues, non-Th2 CRS (CRSsNP and non-eosinophilic NP, NENP) also demonstrate a decrease in neutrophil markers. Expression of neutrophil markers such as CXCL-1 and CXCL-8 correlated to CT scores in NENP. Therefore, NENP showed an age-related decline in CT scores. There was a modest positive correlation of age with Th2 mediators including IL-5 in NENP, whereas myeloperoxidase and IL-17A increased in Th2 CRS with ageing. IFN-γ showed age-related increment in all subtypes of CRS. However, these age-related cytokine changes was not associated with disease extent based on CT scores. Pediatric CRSsNP was mostly non-eosinophilic, characterized by upregulation of CXCL-8 and S100A8. In geriatric population, CRSsNP showed upregulation of BAFF and downregulation of TGF-β1, and ENP exhibited downregulation of IL-13.

CONCLUSIONS: There was age-related decline in neutrophil-associated mediators in controls and non-Th2 CRS such as CRSsNP and NENP. These changes may affect disease extent in NENP. Age-related cytokine changes are associated with different endotypes according to age subgroups.
263 Expression and Functional Analysis of CST1 in Intractable Nasal Polyps

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RATIONALE: This study found Cystatin SN (CST1), a type 2 cystatin subfamily member, to be highly expressed in nasal polyps from patients with intractable chronic rhinosinusitis with nasal polyps (CRSwNP), using a whole transcript analysis with next-generation sequencing. Eosinophilic chronic rhinosinusitis (ECRS) involves nasal polyps that are refractory and recurrent immediately after endoscopic sinus surgery. We hypothesized that CST1 may contribute to the pathogenesis of ECRS.

METHODS: The expression of CST1 in nasal polyps from patients with ECRS was examined by mRNA expression levels, using real-time PCR and immunohistochemistry. We examined the function of CST1 using nasal epithelial cells and nasal fibroblasts.

RESULTS: CST1 was significantly expressed in the epithelial cells of the nasal polyps from patients with ECRS, compared with patients who did not have ECRS (non-ECRS). Particularly, CST1 showed very strong expression in patients with severe ECRS. The expression of CST1 may be correlated with the recurring and refractory nature of ECRS. Stimulation by a combination of IL-4 plus dsRNA plus CST1 significantly elevated mRNA expression levels and protein levels of TSLP in nasal epithelial cells. Stimulation by TSLP or IL-33 significantly elevated mRNA expression levels of CST1 in nasal epithelial cells. Stimulation of CST1 significantly elevated mRNA expression levels of CCL11 and POSTN in nasal fibroblasts.

CONCLUSIONS: CST1 could amplify eosinophilic infiltration and Th2 inflammation by interacting with epithelial-derived cytokines and fibroblasts on nasal polyps. CST1 may be involved in the pathogenesis of ECRS, and may contribute to the severity and recurrence of CRSwNP after ESS.

264 Respiratory Virus Detection in Nasal Lavage Fluid of Chronic Rhinosinusitis Patients During Acute Exacerbations

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RATIONALE: Chronic rhinosinusitis (CRS) is associated with poor sleep and higher risk for obstructive sleep apnea (OSA) in retrospective studies. The aim of this prospective study is to find a reliable biomarker to screen CRS patients for sleep disruption and sleep apnea.

METHODS: Patients with CRS were enrolled. All patients completed the Pittsburgh Sleep Quality Index (PSQI) and Functional Outcomes of Sleep Questionnaire. Morning serum IL-6 levels were measured by a high-sensitivity ELISA. Patients were randomly selected for overnight polysomnography. OSA was diagnosed if apnea-hypopnea index (AHI) > 5. Associations between IL-6 levels and sleep disruption were evaluated by ANOVA test and regression analysis.

RESULTS: Sixty CRS patients were enrolled. Serum IL-6 level were significantly higher in patients with OSA compared to those without OSA (4.1ng/dL ± 2.8 vs 1.1ng/dL ± 0.5; mean IL-6 ± SD adjusted P<0.05). IL-6 level was associated with severity of OSA (3.15ng/dL ± 2.0 in mild, 5.15ng/dL ± 1.7 in moderate; 10.49ng/dL ± 3.8 in severe OSA; mean ± SD adjusted P<0.0001). IL-6 level was associated with severity of sleep hypoxemia (1.1 ng/dL ± 0.5 in mild hypoxemia (O2-nadir>88mmHg); 2.5 ng/dL ± 1.8 in moderate hypoxemia (O2-nadir<88 mmHg); 6.9 ng/dL ± 3.3 in severe hypoxemia (O2-nadir<80 mmHg) respectively, P=0.02). PSQI score was higher in patients with OSA compared to those without OSA (5.9 ± 3.2 vs. 7.2 ± 2.8; mean ± SD, adjusted P=0.045), but PSQI was not associated with severity of OSA or hypoxemia.

CONCLUSIONS: Serum IL-6 is associated with severity OSA and hypoxemia in CRS. Serum IL-6 could serve as a screening biomarker for OSA in CRS.
A Low Prevalence of Pediatric Food Allergy (FA) Among Older Order Mennonites (OOM) Is Related to Robust IgA Production in Early Life

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RATIONALE: Farm life is protective against development of atopic diseases, as also shown by our studies in the OOM. However, the effect of farm life on specific FA and development of the IgA responses have not been assessed.

METHODS: 500 surveys were distributed to OOM families. Surveys queried FA in children as adapted from the NHANES 2007-2010 (self-reported FA). Phone contact determined if the child was also avoiding the food (likely/possible FA). Saliva IgA was measured in 31 OOM and 37 Rochester non-OOM infants at 6 months, and immunoglobulin gene repertoire of cord blood B cells from 4 OOM and 4 Rochester infants.

RESULTS: Among 524 OOM children, rates of self-reported allergy to egg, soy, tree nuts, fish, and shellfish, as well as rates of likely/possible allergy to peanut, wheat, fish and shellfish were significantly lower than in NHANES (p<0.01). The weaning foods in OOM include fruits and yogurt at 7 months, with egg and peanut introduced at 8 and 21 months. Saliva IgA was higher in OOM than in Rochester infants (p<0.01). In cord blood, immunoglobulin gene repertoire was dominated by IgM B cells, although contained ~5% IgA B cells. The IgA B cells were substantially restricted in their clonal diversity, and interestingly, OOM cord blood had a higher proportion of IgA among all immunoglobulin transcripts.

CONCLUSIONS: OOM have a robust mucosal IgA production and low rates of FA despite delayed introduction of highly allergenic foods such as peanut. Priming of the immune system towards IgA production in OOM may have prenatal origins.

Gastrointestinal Staphylococcus aureus: immune responses to its enterotoxins and regulatory T cell dysfunction in childhood food allergy

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RATIONALE: Staphylococcus aureus (SA) is associated with disease severity and onset of atopic dermatitis, and SA may be an important trigger of allergic sensitization. Although food allergy (FA) is often co-expressed with atopic dermatitis in early life, the role of SA in FA remains uncertain.

METHODS: Sixty-seven children with and without FA were studied. The presence of SA was detected in the stool by microbial culture, specific circulating IgE and IgA levels and cytokine responses of peripheral blood mononuclear cells (PBMCs) to staphylococcal enterotoxins A and B (SEA and SEB) were assessed. The effect of SEB on Tregs was evaluated by flow cytometry.

RESULTS: SA was detected in the stool in 53.3% of children with FA, compared to 15.4% of children without FA (p=0.04). Food allergic children also had higher levels of IgA against staphylococcal enterotoxins (SEA: 1.35+/-.21 vs 2.21+/1.00 kU/L, p=0.003; SEA: 1.97+/-.70 vs 2.59 +/-1.30 kU/L, p=0.003). Exposure to SEB promoted greater regulatory T cell dysfunction in food allergic children, as evidenced by increased IL-17 expression in CD25+CD127loFoxp3+ cells that express SEB responsive T cell receptors (16.6% vs 5.65%, p=0.01). Additionally, in vitro exposure of PBMC to SA toxins uniquely induced Th2 and Th17 responses and reduced IFNγ responses in children with food allergy compared to non-food allergic children.

CONCLUSIONS: Food allergy was associated with increased presence of SA in the stool, Treg dysfunction, and enhanced Th2 and Th17 cytokine responses. These results suggest that SA may participate in promoting allergic inflammation and Treg dysfunction in food allergy.
268 Peanut Allergy is Induced by Distinct Immunologic Pathways Dependent on the Routes of Allergen Exposure in Mice

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RATIONALE: Environmental exposure to allergens plays critical roles in development of allergic diseases. The goal of this project was to investigate the immunologic mechanisms involved in the development of peanut allergy by using mouse models of exposure to natural peanut allergens through skin or airways.

METHODS: For skin sensitization, naïve BALB/c mice were painted with peanut flour twice a week for 4 weeks. Alternatively, mice were intranasally exposed to peanut flour. No exogenous adjuvants were used. Immunological mechanisms were investigated by using a series of genetic models.

RESULTS: When exposed through skin or airways, naïve mice developed peanut allergy as demonstrated by increased serum levels of peanut-specific IgE and IgG antibodies and by manifestation of acute anaphylaxis symptoms. Mice deficient in follicular helper T (Th) cells were protected from developing peanut allergy in either skin or airway sensitization. Several major differences were observed, however. In wild type mice, airway sensitization produced ~100x higher titers of peanut-specific IgG1, IgG2a, and IgG2b antibodies while IgE antibody titers were roughly comparable. In IL-4RA-deficient mice, IgE antibody was abolished in skin sensitization while IgE was partially inhibited and IgG antibodies increased in airway sensitization. Anaphylactic responses were dependent on IgE and the IL-4RA pathway in skin sensitization while it was independent of them in airway sensitization.

CONCLUSIONS: Irrespective of whether animals are exposed through skin or airways, Th cells play a critical role in development of peanut allergy. While skin sensitization promotes IL-4 and IgE-dependent peanut allergy, airway sensitization promotes the response(s) independent of these molecules.

269 Immune Progression Within the Memory CD4+ T Cell Compartment is a Marker of Heightened Clinical Sensitivity for Patients with Peanut Allergy

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RATIONALE: Individuals with peanut allergy range in clinical sensitivity from those who can consume grams of peanut without any symptoms to those who have multi-system reactions to as little as ~1 mg. This clinical heterogeneity makes informed decisions about who to treat dependent upon better understanding its immunological underpinnings.

METHODS: We compared the TCRβ usage and phenotypes of peanut-activated, CD154+ CD4+ memory T cells in 20 peanut-allergic patients classified as either reactive (10) or hyporeactive (10) based upon a blinded graded peanut protein ingestion challenge with a cumulative dose of 443 mg.

RESULTS: TCRβ analysis of the CD154+ and CD154- fractions to identify significantly enriched sequences revealed >1000 public CDR3s as well as enriched CDR3 amino acid motifs, consistent with the strong selection of peanut-specific clones. These putatively-specific clones were expanded in frequency and diversity among the reactive patients and this expansion occurred within effector, but not regulatory T cell populations. The ratio of putatively peanut-specific effector T cells to regulatory T cells was 1.5-fold higher in reactive than in hyporeactive patients (p<0.01). Transcriptional analysis of peanut-activated T cells revealed an association between clinical reactivity and a gene set associated with strongly polarized Th2 effector cells, including IL-5, IL-9, and HPGDS (p<0.05). Increased expression of Th2 cytokines was confirmed at the protein level, and strongly correlated with peanut-specific IgE.

CONCLUSIONS: Immune progression within the effector T cell compartment is correlated to clinical sensitivity, and this observation may be useful to inform our assessment of disease phenotype and to monitor disease longitudinally.

270 Identification of An Antigenic Region Involved In IgE Cross-reactivity Between Fatty Acid Binding Proteins (FABP) from Shrimp and Human

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RATIONALE: FABP from shrimp Litopenaeus vannamei (LvFABP) and the human (Heart-FABP and Adipocyte-FABP) are functional and structural homologous proteins. This could allow that antibodies from an immune response to shrimp cross-react against the human FABP.

METHODS: Fifty-six sera from individuals sensitized to L. vannamei extract were selected for analysis of IgE and IgG reactivity to LvFABP, H-FABP and A-FABP. Overlapping peptides from LvFABP and human sera were used to map B cell epitopes. Cross-reactivity was explored by ELISA inhibition assays, using pool of sensitized sera, the recombinant FABP and also the peptide sharing 65% of amino acid identity among these FABPs. In addition, modelling by homology was apply to localize cross-reactive regions.

RESULTS: IgE reactivity to LvFABP, H-FABP and A-FABP was found in eleven sera. IgE cross-reactivity was 52% between LvFABP and H-FABP and 48% between LvFABP and A-FABP. Overlapping peptides from LvFABP and human sera were used to map B cell epitopes. Cross-reactivity was explored by ELISA inhibition assays, using pool of sensitized sera, the recombinant FABP and also the peptide sharing 65% of amino acid identity among these FABPs. In addition, modelling by homology was apply to localize cross-reactive regions.

CONCLUSIONS: We identified an antigenic region involved in cross-reactivity between shrimp and human FABP, which suggest that LvFABP could induce, by molecular mimicry, an antibody response to homologous human FABP.
IL33 contributes to diesel pollution-induced increase in experimental asthma severity

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RATIONALE: The mechanisms by which exposure to traffic-related diesel pollution potentiates allergic airway responses remains poorly understood. Exposure to diesel exhaust particles (DEP) induces a Th17 response, whereas exposure to DEP in the context of an allergic response enhances Th2 responses. IL33 and TSLP contributions to this increase in disease severity were investigated using gene deficient mice.

METHODS: Mice lacking either the TSLP receptor or the IL33 receptor were exposed 9 times over a 3-week period to either saline, DEP, house dust mite extract (HDM) or both. Airway hyperresponsiveness (AHR) and pulmonary innate and adaptive immune cells and their cytokines were assessed 24h after the last exposure.

RESULTS: AHR was significantly ablated in ST2 deficient mice but not in TSLPR deficient mice or control mice exposed to HDM+DEP. In these ST2 deficient mice, pulmonary levels of IL5 and IL6, but not IL13 or IL17A, were decreased as well as γδT-cells and pathogenic IL5+IL17A+CD4+γδT-cells, but not classic TH2 cells. Despite similar numbers of pulmonary dendritic cells and TH2 cells, when lung cells from HDM+DEP co-exposed mice were stimulated in vitro with HDM, IL5 and IL13 secretion were ablated in ST2 deficient lung cell cultures.

CONCLUSIONS: IL33 signaling through its receptor ST2 contributes to DEP-induced experimental asthma severity potentially by promoting the accumulation and responsiveness of allergen-specific IL5+IL17A+producing CD4+γδT effector cells.

Nasal Epithelial Brush Cells Generate Cysteinyl Leukotrienes in Response to Aeroallergens and Stress Signals

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RATIONALE: Solitary chemosensory cells (SCCs) and brush cells (BrCs) are cholinergic airway epithelial cells (EpCs) in the upper and lower airway, respectively. They are the dominant source of IL-25, which drives type 2 immune responses in the airways. Unexpectedly, these type 2 responses were further enhanced in CARD9-/- mice. Stimulation of NHBE cells with Alternaria induced extracellular release of IL-33 into cell-free supernatants. SiRNA knockdown of CARD9 in NHBE cells significantly increased IL-33 concentration in the supernatant as compared to those treated with control siRNA.

METHODS: Naïve wild-type (WT) C57BL/6 mice and CARD9-/- mice were exposed intranasally to Alternaria extract. Type 2 immune responses were analyzed at 4.5 hours or 7 days. For an in vitro model, CARD9 expression was knocked down in normal human bronchial epithelial (NHBE) cells by siRNA. The cells were stimulated with Alternaria extract and IL-33 release was analyzed by ELISA.

RESULTS: In WT mice, exposure to Alternaria increased the lung levels of IL-5 and IL-13 and promoted accumulation of eosinophils in the airways. Unexpectedly, these type 2 responses were further enhanced in CARD9-/- mice. Stimulation of NHBE cells with Alternaria induced extracellular release of IL-33 into cell-free supernatants. SiRNA knockdown of CARD9 in NHBE cells significantly increased IL-33 concentration in the supernatant as compared to those treated with control siRNA.

CONCLUSIONS: CARD9 serves as an inhibitory molecule for type 2 immune response to Alternaria, suggesting that type 2 immune responses to fungal allergens are distinct from anti-fungal immunity. The CARD9 pathway may be used as a potential therapeutic target for allergic airway diseases.
**Disease-Associated KIF3A Genetic Variants Alter Gene Methylation And Expression Resulting In Skin Barrier Dysfunction And Increased Risk For Atopic Dermatitis**

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**RATIONALE:** Atopic dermatitis (AD) is a chronic relapsing inflammatory skin disease. Single nucleotide polymorphisms (SNPs) in KIF3A, the gene encoding Kinesin family member 3A, have been associated with AD and asthma, but the mechanistic basis underlying these associations remains unclear.

**METHODS:** We investigated the mechanistic basis of the genetic contribution of KIF3A using human and mouse studies. Individuals carrying 1 or 2 copies of rs11740584 and rs2299007 alternate alleles were recruited and SNP methylation and allele-specific gene expression was determined in nasal airway cells. Skin barrier function was determined in rs11740584 and rs2299007 alternate allele carriers and Kif3a skin specific knockout mice.

**RESULTS:** KIF3A SNPs rs2299007 and rs11740584 generate new CpG sites, which are methylated in individuals carrying the alternate alleles. Allele-specific PCR confirmed lower KIF3A expression from the alternate allele. Methylation levels were associated with unbalanced expression of skin barrier genes FLG and LOR, and with increased transpidermal water loss (TEWL). Kif3aK14 mice had increased TEWL and epidermal thickness, and dysregulation of skin barrier genes Flg and Claudin-1. Further, Kif3aK14 mice demonstrated increased susceptibility to develop AD following cutaneous allergen exposure.

**CONCLUSIONS:** Our data provide a mechanistic basis for the AD disease susceptibility conferred by KIF3A SNPs rs2299007 and rs11740584. The alternate alleles generate novel CpG sites resulting in increased methylation and decreased expression of KIF3A leading to skin barrier dysfunction. KIF3A is required for skin barrier homeostasis, and decreased KIF3A expression in skin causes increased TEWL and dysregulation of skin barrier genes, and promotes development of AD.

**275 Mast cell-dependent adjuvant activity is a key component of the respiratory immune response to inhaled Alternaria**

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**RATIONALE:** Exposure and sensitization to Alternaria alternata (Alternaria) is strongly associated with asthma development, persistence, and exacerbations. Alternaria elicits murine and human mast cell (MC) activation, independent of IgE receptor signaling, but the relevant fungal ligand, mechanism of activation, and potential for adjuvanticity have not been characterized.

**METHODS:** Alternaria fractions were obtained using sequential salting-out fractionation, ion-exchange, and size-exclusion chromatography, and tested for activity on murine bone marrow-derived MCs (BMMCs). Putative MC ligands from active fractions were identified using Mass-spectroscopy and cloned for recombinant expression. WT and Mcpt5/ DTA mice, with diptheria toxin-mediated MC deletion, were treated with intranasal Alternaria and dendritic cell (DC) activation and lung inflammation was assessed at serial timepoints.

**RESULTS:** In response to Alternaria inhalation, IgE-independent MC activation not only potentiates pulmonary inflammation but also regulates the migration of antigen-bearing DCs to regional lymph nodes to mediate the earliest events in aerosolergen sensitization. Partial purification of Alternaria extracts demonstrates that MC degranulation and CysLT generation is elicited by a weakly-anionic heat-labile protein (30-50kDa in size) and is protease-independent. Mass-spectroscopy and cloning have identified several novel fungal candidate proteins that have not been previously characterized.

**CONCLUSIONS:** Although several Alternaria allergens have been identified, the adjuvant activities of most fungal proteins remain poorly characterized. We find that a novel Alternaria Ag acts as a danger signal to initiate innate MC-dependent sensitization and subsequent pulmonary inflammation. These findings highlight the role of innate MC sensing in the respiratory tract and the importance of MC-DC crosstalk in priming for allergen-elicted inflammation.