618 Relationship Between Sputum TWEAK Levels and Childhood Asthma

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RATIONALE: Human Tumor Necrosis Factor-like weak inducer of apoptosis (TWEAK) has been known to play a role in the pathogenesis of various inflammatory diseases. However, there is no previous data elucidating relationships in between TWEAK and childhood asthma.

METHODS: One hundred and one children with asthma and 81 control subjects aged 5-18 years were included. Induced sputum, pulmonary function, and methacholine challenge test were performed. Patients with asthma were stratified according to four levels of asthma severity (mild intermittent, mild persistent, moderate persistent, and severe persistent).

The analysis of TWEAK levels in induced sputum supernatants was performed with the use of a commercially available enzyme-linked immunosorbent assay (ELISA) kit.

RESULTS: TWEAK levels in induced sputum sample were significantly higher in asthmatic children than those in controls [238.6 (36.7-559.0) pg/mL vs. 121.4 (35.6-585.3) pg/mL, P = 0.043]. TWEAK level was elevated in eosinophil-dominant sputum compared to non-eosinophilic sputum in asthma patients [212.2 (113.4-1183.5) pg/mL vs. 66.9 (8.3-187.5) pg/mL, P < 0.001]. In addition, atopic asthma patients showed significantly higher TWEAK levels than non-atopic asthma patients [131.4 (62.8-228.8) pg/mL vs. 45.7 (4.8-162.3) pg/mL, P = 0.016]. Sputum level of TWEAK increased according to severity, mild, moderate, and severe, in persistant asthma group [108.6 (42.6-181.3), 170.2 (68.3-506.5), and 328.0 (60.0-764.8) pg/mL, respectively].

CONCLUSIONS: TWEAK might play a role in airway inflammation of childhood asthma, especially eosinophilic asthma with atopy.

619 Ethnic Differences in Exhaled Nitric Oxide (FeNO) Before, During, and After an Asthma Exacerbation in Children with Asthma

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RATIONALE: Studies have found African American (AA) asthmatics to be less responsive to systemic and inhaled glucocorticoid (GC) therapy, although this finding remains controversial.

METHODS: 131 children (67 Caucasians, 37 Hispanics, 27 AA’s) with moderate asthma had exhaled nitric oxide (FeNO) and spirometry measured before, during and after an acute asthma exacerbation (following a course of prednisone).

RESULTS: At baseline, there was no difference in lung function between Caucasians and AA’s. AA’s were more atopic (15.5±1.5 vs. 9.8±1.1 positive SPT; P = 0.005), required higher dose inhaled GC (998±126 vs. 676±85 mcg/d; P = 0.04) and had higher FeNO levels (42±5 vs. 26±3 ppb; P = 0.008). Hispanics compared to Caucasians had better lung function but similar FeNO levels. During an acute exacerbation, compared to Caucasians, AAs had the greatest increase in FeNO (79±9 vs. 49±6; P = 0.006), while there was no difference in lung function between the groups. Following prednisone therapy, AA’s had the highest FeNO levels (40±2.5 vs. 25±3 ppb; P = 0.01) and fewer had a positive FeNO response (level falling to <25 ppb; 71% vs. 30%; P = 0.003). Hispanics had the greatest improvement in both FEV1 and FEF25-75 following prednisone therapy.

CONCLUSIONS: Compared to Caucasian children with moderate persistent asthma, AA children had higher FeNO levels at baseline, during an acute exacerbation and following a course of prednisone. In addition, fewer AA’s had a positive FeNO response to prednisone. This suggests that AA children have a greater degree of allergic inflammation at baseline, have a greater inflammatory response during an asthma exacerbation, and have a blunted response to prednisone therapy.
**621 Metabolic and Deep Immune Profiling Reveal Coordinate Effects on Immune Function in Asthma and Obesity**

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**RATIONALE:** The connections between asthma and obesity remain poorly understood, particularly in pediatric patients. This is due, in part, to a lack of understanding of how these diseases impact immune function. Asthma and obesity separately, and particularly the challenging to manage subgroup of obese asthmatics, may have distinct immunological imprints.

**METHODS:** Prospective study of pediatric asthma and obesity with four groups of patients (6-18 years): obese asthmatics, non-obese asthmatics, obese non-asthmatics and non-obese and non-asthmatics. Clinical studies included CBC/d, immunoglobulins, vaccine titers, lipids, inflammatory markers and electrolytes. Research studies included water-soluble and lipid-soluble metabolomics, high dimensional flow cytometry, Luminox studies of serum cytokines and adipokines and expression of interferon signature genes (ISGs).

**RESULTS:** Metabolic pathways differentiated our patient groups, with evidence of both possible biomarkers and mechanistic underpinnings. We also found immune dysfunction, with significantly diminished pneumococcal titers in our regular weight asthmatics. Discovery of novel immunophenotypes and evaluation of activation/exhaustion status was undertaken with advanced dimension reduction and cluster discovery tools, yielding differences in activation and exhaustion status and in obese vs. regular weight asthmatics.

**CONCLUSIONS:** By combining many datastreams, including deep immune profiling by high dimensional flow cytometry and metabolomics, we have discovered extremely detailed phenotypes. This has given particular insight into the challenging subgroup of obese asthmatics, with differences in ISGs, metabolic pathways and both T cell activation and differentiation providing biomarkers and perhaps future therapeutic targets. Furthermore, the evidence of impaired pneumococcal protection in our regular weight asthmatics has potential implications for current vaccination strategies.

**622 Effect of Sex and Puberty on Mannitol Airway Responsiveness**

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**RATIONALE:** Airway hyperresponsiveness is associated with the presence of asthma. Puberty results in a shift in asthma prevalence between sexes, with post-pubertal males having a lower prevalence of asthma. Furthermore, methacholine responsiveness has been shown to decrease in pubertal boys with asthma. Our objective was to examine the association of sex and puberty on mannitol airway responsiveness in a high-risk birth cohort.

**METHODS:** Childhood Origins of ASThma birth cohort study children were followed prospectively from birth and assessed annually. Mannitol bronchodprovocation, an indirect airway challenge test, was performed in children pre-puberty (n=144) and post-puberty (n=72). Repeated measures analysis was used to examine the relation of sex and pubertal status on mannitol airway hyperresponsiveness.

**RESULTS:** Among all study children, there was a significant reduction in the rate of positive mannitol challenge post-puberty (OR≈0.38, 95% CI 0.19-0.75, p=0.01). We next examined impact of sex on airway responsiveness. Post-pubertal boys had a reduced rate of positive mannitol challenge (OR=0.26, 95% CI 0.10-0.67), while girls did not have a significant reduction in mannitol responsiveness post-puberty (OR 0.7, 95% CI 0.24-1.98).

**CONCLUSIONS:** Our results demonstrate that there is a reduction in airway hyperresponsiveness as assessed by mannitol challenge post-puberty that appears to be most prominent in boys. This loss of responsiveness may contribute to fewer asthma symptoms among boys during this time frame.

**623 Association of the Presence of Blood Eosinophils in Children with Acute Bronchiolitis and Recurrent Wheezing**

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**RATIONALE:** One of the most common sequelae of acute bronchiolitis is recurrent wheezing leading to asthma. Blood eosinophils are viewed as a risk factor for childhood asthma but no predictor in recurrent wheezing caused by acute bronchiolitis has been identified. The aim of this study was to evaluate the association between blood eosinophils during acute bronchiolitis and recurrent wheezing in young children.

**METHODS:** Young children hospitalized with acute bronchiolitis were retrospectively identified. Complete blood counts at bronchiolitis admission were determined. Data on recurrent wheezing episodes during one year after admission were obtained by medical record and telephone interviews.

**RESULTS:** Patients with the presence of blood eosinophils at the time of acute bronchiolitis hospital admission had a higher rate of recurrent wheezing episodes within 1 year than the group with an absence of blood eosinophils (OR 3.72, 95% CI 1.46-9.77, P-value = 0.002). The absolute eosinophil count was significantly higher in the recurrent group (median 93.8 cells/ul) compared to the non-recurrent group (median 0 cells/ul). In the presence of blood eosinophils, there was a significantly greater number of patients with recurrent wheezing (33/58) than non-recurrent wheezing (11/42). When the effects of gender, history of atopic dermatitis, passive smoking and positive RSV nasal swab test were examined, only the presence of blood eosinophils at the time of bronchiolitis hospital admission demonstrated a statistically significant relationship to the recurrent wheezing episodes during one year from the onset of the disease.

**CONCLUSIONS:** The presence of blood eosinophils at the time of acute bronchiolitis is associated with recurrent wheezing.
Spirometry Considerations in Transgender Patients

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RATIONALE: One of the Department of Health and Human Service’s goals is improving the health and well being of lesbian, gay, bisexual, and transgender (LGBT) individuals. Aside from health disparities, members of the transgender community face challenges related to their public gender identity. In the US, the classification of sex is dictated by the state. Despite legal and physical changes to one’s designated sex, transgender patients may still encounter medical issues that relate to their biological sex.

METHODS: A 46 y/o female presented to Allergy Clinic for management of asthma. The patient reported less than once a month nocturnal awakenings and use of her albuterol about two times per week. She was maintained on fluticasone and montelukast. She had a remote history of PFT’s, however none recently. These were performed in clinic.

RESULTS: Spirometry revealed a FEV1/FVC of 77%, FEV1 as 113%. Upon further history, patient was noted to have undergone gender reassignment surgery and was on hormonal therapy. Repeat spirometry with male sex designation revealed FEV1/FVC 77%, FEV1 97%, which better-estimated patient’s true pulmonary function.

CONCLUSIONS: In reviewing patient’s original PFT’s it should be noted that the sex designation as female over estimated patient’s lung function, as patient’s thoracic cavity is actually male and the predicted should be higher. Whereas gender reassignment dose not alter spirometry, it does alter interpretation, as females have lower predicted flow rates and volumes. This is important to note in an effort to balance appropriate classification of asthma severity, yet maintain respect in honoring a patient’s reassigned gender.

Neutrophilic Steroid-Refractory Recurrent Wheeze and Eosinophilic Steroid-Refractory Asthma at School Age

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RATIONALE: Little is known about inflammatory pathways of severe recurrent wheeze in preschool children and severe asthma at school age. The aim of the “Severe Asthma Molecular Phenotype” (SAMP) cohort was to characterize phenotypes of severe recurrent wheeze and severe asthma during childhood in terms of triggers (allergic or not), involved cells (eosinophil or neutrophil) and corticoid responsiveness.

METHODS: School-age children with moderate to severe asthma and preschool children with moderate to severe recurrent wheeze were enrolled prospectively. They underwent standardized clinical and blood work-up, and broncho-alveolar lavage (BAL) evaluation. Cluster analysis was applied to 350 children with 34 variables.

RESULTS: Three clusters were identified: Cluster 1, Neutrophilic steroid-refractory recurrent wheeze phenotype, with 138 preschool children uncontrolled despite high-dose inhaled corticosteroids (ICS) (92%, p<0.001), with more history of pneumonia (31%, p<0.001), more gastroesophageal reflux disease (37%, p<0.001) and the highest blood neutrophil count (mean 4.524cells/mm3, p=0.05); Cluster 2, Severe recurrent wheeze with sensitization to a single allergen (12%, p=0.002), with 104 preschool children controlled with high-dose ICS (63%, p<0.001); Cluster 3, Eosinophilic steroid-refractory asthma phenotype, with 108 school age children uncontrolled despite high-dose ICS (76%, p<0.001) with more allergic rhinitis, atopic dermatitis and food allergies (82%, 40%, 31%, p<0.001, respectively). They also had a higher blood eosinophil count and a higher percentage of BAL eosinophil (506/mm3, 2.6%, p<0.001 respectively).

CONCLUSIONS: Inflammation pathways of asthma and recurrent wheeze are related to eosinophil cells at school age and neutrophil cells in preschool children. These results could improve personalized treatments.

Asp299Gly Polymorphism of the TLR-4 Gene in Adult Patients with Fixed and with Reversible Airflow Obstruction in the Population of Crimea, Ukraine

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RATIONALE: The TLR4 single nucleotide polymorphism Asp299Gly due to the amino acid substitutions Asp299Gly (RefSNP ID:rs4986790) impacts the amino acid substitutions Asp299Gly (RefSNP ID:rs4986790) impacts inflammatory pathways of severe asthma. The Asp299Gly polymorphism of the TLR-4 receptor gene was the Asp299Gly polymorphism of the TLR-4 receptor gene was studied in 151 patients with fixed and 180 with reversible airflow obstruction assessed by the post-bronchodilator ratio of FEV1 / FVC (<0.7 fixed obstruction). The control group included 285 healthy non-atopic volunteers.

RESULTS: In the control group, the frequency distribution of genotypes (AA – 122 (81%) AG 4.41, (11%), GG – 1 (1%), x2 = 1.65, p = 0.44) and reversible airflow obstruction assessed by the post-bronchodilator ratio of FEV1 / FVC (<0.7 fixed obstruction). The control group included 285 healthy non-atopic volunteers.

Single nucleotide polymorphism of Asp299Gly was detected by PCR.

RESULTS: The TLR4 single nucleotide polymorphism Asp299Gly due to the amino acid substitutions Asp299Gly (RefSNP ID:rs4986790) impacts the extracellular domain of the TLR4 receptor. This polymorphism can modify the receptor’s response to endotoxin, which is an important trigger of severe asthma.

METHODS: The Asp299Gly polymorphism of the TLR4 receptor gene was studied in 151 patients with fixed and 180 with reversible airflow obstruction assessed by the post-bronchodilator ratio of FEV1 / FVC (<0.7 fixed obstruction). The control group included 285 healthy non-atopic volunteers. Single nucleotide polymorphism of Asp299Gly was detected by PCR.

RESULTS: In the control group, the frequency distribution of genotypes (AA – 242 (85%), AG – 40 (14%), GG – 3 (1%) was not significantly different from patients with fixed airflow obstruction (AA – 122 (81%) AG – 28 (18%), GG – 1 (1%), x2 = 1.65, p = 0.44) and reversible airflow obstruction (AA – 139 (77%), AG – 38 (21%), GG – 3 (2%), x2 = 4.41, P = 0.11). The analysis risk of allele G revealed that the frequency of GG genotype in patients with reversible airflow obstruction asthma (23%) was significantly greater (odds ratio = 1.66, p = 0.04) compared to the controls (15%).

CONCLUSIONS: The TLR-4 (Asp299Gly) polymorphism is associated with reversible airflow obstruction asthma in the Crimean population.
628 Differential Effect on the Central and Peripheral Airways of Smoking the First Cigarette of the Day As Measured By Exhaled Breath Temperature

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RATIONALE: Smoking one cigarette has been shown to increase the integral exhaled breath temperature (iEBT) without affecting spirometry indices. A new single breath method can differentially assess EBT from central and peripheral airways (cEBT, pEBT), allowing identification of the location and sequence of airway temperature changes following smoking of one cigarette.

METHODS: Our system employs a computer operated valve system driving expired air from the central and peripheral airways through channels with sensitive temperature sensors, while also measuring iEBT. The EBT indices were measured from 12 volunteer smokers, median age 56.5, range 36 to 58 years, 6 women, before and 1, 15 and 30 minutes after smoking their first cigarette of the day. Air flows and volumes were measured corresponding to the assessed EBT indices.

RESULTS: iEBT increased after smoking one cigarette from 28.42±0.21 (mean ± s.e.m.) to 28.64±0.29°C at minute 1 (P=0.237), to 28.84±0.21°C at minute 15 (P=0.024) and to 29.64±0.29°C at minute 30 (P=0.001). This increase was mostly due to increase of cEBT at minute 15: 26.37±0.34°C versus 25.66±0.34°C at baseline, with the effect seen at the periphery at minute 30: pEBT = 28.46±0.54°C vs. 29.49±0.27°C at baseline, P=0.041. No changes in the respective lung volumes appeared over time.

CONCLUSIONS: This study provides the first description of the kinetics of EBT in the central and peripheral compartments of the lungs after smoking one cigarette showing an initial significant increase in cEBT, followed by a significant increase in pEBT.

629 Comparison of the exercise and mannitol bronchial provocation tests in children with asthma

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RATIONALE: This study compared bronchial hyper-responsiveness (BHR) assessed using exercise and mannitol in children with previously diagnosed asthma.

METHODS: The study included 30 children, from 6 to 15 years old, who had been diagnosed with asthma based on clinical symptoms and BHR to methacholine. Exercise and mannitol bronchial provocation tests (BPTs) were performed and serum periostin levels were measured. The response to mannitol was expressed as the response-dose ratio (RDR) (% fall in FEV1/ cumulative dose).

RESULTS: Seventeen (56.7%) subjects had a positive exercise BPT result. Sixteen (53.3%) subjects had a positive mannitol BPT result. Subjects with a positive exercise BPT result had a significantly lower methacholine PC20, significantly lower FEV1/FVC, significantly higher the fractional exhaled nitric oxide (FENO) levels, significantly higher blood eosinophil count, and significantly higher serum periostin levels. Subjects with a positive mannitol BPT result had a significantly lower methacholine PC20, significantly higher blood eosinophil count, and significantly higher serum periostin levels. There was a positive correlation between the maximum decreases in %FEV1 after exercise and the mannitol RDR. The maximum decrease in %FEV1 after exercise was significantly more closely associated with the serum eosinophil and FENO levels than the mannitol RDR. Periostin levels were significantly correlated with both the maximum decrease in %FEV1 after exercise and the mannitol RDR.

CONCLUSIONS: Those with a positive exercise BPT had significantly more eosinophilic inflammation and higher FENO levels compared with the values seen in subjects with a positive mannitol BPT result. Serum periostin levels were significantly associated with AHR to exercise and mannitol.

630 The Effect of Sleep Duration on Levels of Exhaled Nitric Oxide from Healthy Adults and those with Asthma

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RATIONALE: The daily pattern of allergic asthma disease severity involves exacerbation in the overnight period. As increased nocturnal asthma activity may affect sleep, we determined the association of sleep duration with morning and afternoon exhaled nitric oxide levels.

METHODS: Exhaled nitric oxide (eNO) levels (Niox Vero, Aerocrine) were measured for adults asthmatics (n=6) and healthy controls (n=8) at 10 AM and 4 PM. History of previous night sleep duration was recorded. Spearman coefficients were generated.

RESULTS: Median duration of sleep was 6.6 hrs (min 4.0, max 8.3). Median eNO level in AM was 23.0 ppb (min 8.0, max 81.0); median eNO in PM was 21.0 ppb (min 7.0, max 82.0). There was a significant inverse relationship between sleep duration and AM eNO levels (R=−0.65, p=0.02). The association of sleep duration with PM eNO levels approached significance (R=−0.57, p=0.06).

CONCLUSIONS: Increased duration of sleep is associated with lower airway levels of nitric oxide, both in the morning and afternoon, for both adults with asthma as well as healthy controls. This suggests sleep may suppress airway inflammation.
All abstracts are strictly embargoed until the date of presentation at the 2017 Annual Meeting.

**631** Respiratory impedance measured by forced oscillation technique in young healthy preschool children

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**RATIONALE:** Respiratory impedance measured by Forced oscillation technique (FOT) has been used instead of spirometry in young children. This study was aimed to evaluate respiratory impedance in healthy preschool children.

**METHODS:** 1,053 preschool children aged 3-4 years were screened with ISAAC questionnaire. 955 children were excluded due to having positive question for ISAAC questionnaire, family history of allergy, recent lower respiratory tract infection, and environmental tobacco smoke. Respiratory impedance (resistance and reactance) was measured using FOT method (MostGraph-02; Chest M.I., Co Ltd, Tokyo, Japan).

**RESULTS:** A total of 98 children were enrolled. 40 children (40.8%) were male. 90 from 98 children (91.8%) could perform the measurements with acceptable coefficient of variability. The mean (sd) of respiratory impedance parameters were respiratory resistance at 5Hz (R5): 12.62(2.33) cmH2O/L/s, respiratory resistance at 20Hz (R20): 10.16(1.93) cmH2O/L/s, R5-20: 2.46(0.77) cmH2O/L/s, reactance at 5Hz(X5): -2.07(1.36) cmH2O/L/s, frequency of resonance (Fres): 12.5(4.47) cmH2O/L/s, and area of reactance (ALX): 12.65(12.16) kPa.s. Significant correlation between respiratory impedance (R5, R20, X5, Fres and ALX) has been demonstrated to be correlated with height but not with weight. There was no significant difference in respiratory impedance between male and female in age-matched and height-matched data.

**CONCLUSIONS:** Majority of young preschool children, aged 3-4 years, can performed FOT method. FOT could be used as a tool in diagnosis and monitoring of pulmonary disease.

**632** Bronchodilator Responsiveness of FEF25%-75% As a Predictor for the Loss of Control in Childhood Asthma

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**RATIONALE:** Notwithstanding medication adjustment following Global Initiative for Asthma (GINA) recommendation, it is generally observed that a number of controlled asthmatic children cannot maintain their level. This study attempted to find the parameters of pulmonary function test as predictors of the future loss of control in this type of patients.

**METHODS:** 21 children with controlled asthma, age 6-12 years old, were recruited for prospective study. Baseline allergy testing results, comorbidities and steps of treatment were collected. Pulmonary function test using spirometry were performed. The 10-14 weeks follow-up visit was made without change in medication. At the follow-up visit, the levels of control in asthmatic individuals were evaluated according to standard of GINA by pulmonologist. Eosinophil counts were obtained by CBC. Asthma diagnosis and severity have been classified according to GINA 2015.

**RESULTS:** In this group, but there was an association between serum IgE and eosinophil counts did not correlate to asthma severity.

**CONCLUSIONS:** In this group, but there was an association between serum IgE and eosinophil counts did not correlate to asthma severity.

**633** Eosinophil Counts and Asthma Severity in Children

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**RATIONALE:** Elevated peripheral eosinophil count has been associated to asthma exacerbations and its severity. The objective is to determine whether eosinophil count is higher in severe asthmatics of a tertiary care setting.

**METHODS:** This is a retrospective analysis of 1475 asthmatic patients; we excluded cases with other conditions that might interfere in total serum IgE levels and eosinophil counts, such as helminthiasis. Skin prick tests (SPT) with standardized extracts of 11 allergens, FDA Allergenics®, were obtained in 663 patients. Tests were considered positive if wheal diameter was > 3 mm. Total serum IgE was determined by chemiluminescence. Eosinophil counts were obtained by CBC. Asthma diagnosis and severity have been classified according to GINA 2015.

**RESULTS:** 891 (60.4%) were male, median age 5.6 years (0.2 – 20 years); 86.8% had allergic rhinitis, 8% atopic dermatitis and 20.7% allergic conjunctivitis. 12.4% had no allergy-related comorbidities. Asthma was considered mild in 555 (37.7%), moderate in 610 (41.3%) and severe in 310 (21.1%); 362 (54.6%) had positive skin prick tests, 89.8% to D. pteronyssinus. Eosinophil counts were similar in mild (median 304 cells/mm³), moderate (median 296 cells/mm³) and severe asthma (median 249 cells/mm³) groups (Kruskal-Wallis Anova p = 0.27). ROC curve was generated for total serum IgE and eosinophil counts >400cells/mm³. The area under the curve was 0.66 (95% CI 0.62-0.70; p<0.01) and sensitivity was 70.3% and 1-specificity was 57.3%, for IgE = 186U/L.

**CONCLUSIONS:** Eosinophil counts did not correlate to asthma severity in this group, but there was an association between serum IgE and eosinophil counts.

**634** Exhaled Nitric Oxide Concentration Measured By NO Breath® Correlate with Asthma Severity

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**RATIONALE:** Measurement of fraction of exhaled nitric oxide (FeNO) in the breath of asthma patient is non-invasive and useful method for assessing eosinophilic airway inflammation. However, it is known that results vary with the type of device used. The relationship between FeNO measured by NO breath® (Bedfont Scientific, Maidstone, UK) and asthma severity or asthma control is unknown.

**METHODS:** We included 128 consecutive asthmatics who were using inhaled corticosteroid. They underwent FeNO quantification (NO breath®). The GINA guideline 2015 was used to assess asthma control. Asthma severity was assessed according to the recommendations of “Proceedings of the ATS workshop on refractory asthma” (Am J Respir Crit Care Med 2000).

**RESULTS:** The mean FeNO value was 17.5 ppb in the well-controlled group (95% CI = 9.6 - 26.6) and 37.1 ppb in partly-controlled (95% CI = 36.5 - 53.5; p = 0.0037), and 88.8 ppb in the uncontrolled group (95% CI = 53.0 - 113.3; p = 0.0009). The mean FeNO value was 44.9 ppb in the refractory asthma group (95% CI = 50.0 - 71.1) and 27.6 ppb in the non-refractory asthma group (95% CI = 9.63 - 31.9; p = 0.0289).

**CONCLUSIONS:** Our results demonstrate that FeNO measured by NO breath® reflects asthma control and severity.
635 Delayed Diagnosis of Paradoxical Vocal Fold Motion Results in Increased Morbidity in Patients with or without Asthma

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RATIONALE: Paradoxical vocal fold motion (PVFM), a disorder secondary to inappropriate motion of true vocal folds, is frequently misdiagnosed as asthma. Proper diagnosis is commonly delayed.

METHODS: Ninety-six patients 12 years or older were referred for evaluation to the Voice Center for PVFM between 2008 and 2013. Medical records were reviewed for clinical characteristics, time to diagnosis, treatment and outcome. Institutional review board at the center approved the study.

RESULTS: Of 96 patients referred, 64 met criteria for PVFM and 40 were previously treated for asthma. Forty-six patients (73%) were women. Symptoms included dyspnea (n=56), throat tightness (n=35), chest tightness (n=26), cough (n=23), wheezing (n=17), GERD (n=15) and anxiety (n=15). Symptoms occurred spontaneously (SPVFM) in 55, exercise-induced (EIPVFM) in 8, and in combined. Median time from symptom onset to diagnosis was 1 year (mean 2.6 years). Before diagnosis, 21 patients had ED visits, 11 were hospitalized, and 5 intubated. During evaluation, 21 patients (33%) had laryngoscopic evidence of PVFM/EIPVFM with reproducible symptoms. Respiratory therapy was recommended as primary treatment (n=52); anti-reflux medications were also used in selected patients. In 44 patients with data available, 36 improved, 2 had resolved, but 6 reported no improvement.

CONCLUSIONS: PVFM continues to be undiagnosed or misdiagnosed as asthma, leading to inappropriate therapy and prolonged morbidity. Presence of inspiratory dyspnea and poor response to asthma treatment are indications of possible PVFM. Respiratory therapy remains the mainstay of treatment and often leads to satisfactory outcome.

636 Influence of Sensitization Patterns on Fractional Exhaled Nitric Oxide in Asthmatic Children

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RATIONALE: Fractional exhaled nitric oxide (FeNO) has been suggested as a non-invasive biomarker of airway inflammation. Whether sensitization to particular allergens is a predictive factor for increased FeNO levels is not yet fully understood.

METHODS: From October to December in 2015, the medical documents of 127 mild, steroid-naïve asthmatic children and 34 healthy age-matched children were evolved in retrospective cross-sectional study. The results of the FeNO measurements, skin prick test, and the spirometry were collected for analysis. Sensitization patterns to the 18 aeroallergens (5 categories: Mites, Molds, Animal dander, Pollen, and Other) were determined in study population.

RESULTS: A significant increase in FeNO level was observed in polysensitized asthmatic children (34.7 p.p.b [28.3-41.1 p.p.b]), compared with mono-sensitized asthmatics (30.7 p.p.b [18.3-43.2 p.p.b]) and with non-sensitized asthmatics (17.3 p.p.b [10.8-24.5 p.p.b]). With sensitization to perennial allergens (mites, mold, and animal dander), blood eosinophil counts were significantly associated with increased FeNO (P<0.05 for all). The highest FeNO level was identified in children sensitized to a combination of the perennial, seasonal, and other allergens, when compared with those sensitized to one category of allergen alone (P=0.004).

CONCLUSIONS: Our study provided the evidence that variations in FeNO level were associated with individuals’ sensitization patterns. Being sensitized to some particular allergens might contribute to prompt the airway inflammation.

637 Sex-Differences in Bronchial Reactivity to Exercise Test in Prepubertal Children

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RATIONALE: Exercise-induced bronchoconstriction (EIB) develops during or after exercise in children with and without bronchial asthma (BA). Previous studies reported that the time to maximal bronchoconstriction after exercise, known as the nadir time (Nadir-t) became faster with decreasing age in children. However, sex-differences in Nadir-t have not been investigated. This study aimed to investigate whether sex-differences in bronchial reactivity to exercise exist even in prepubertal children.

METHODS: Fifty-one 5- to 6-year-old children without BA were enrolled in this cross-sectional study. The children underwent the 6-minute free-running test for an exercise challenge. Peak expiratory flow rate (PEFR) was measured before exercise and at 0, 3, 10, and 20 minutes after exercise. At times when post-exercise PEFR most decreased from pre-exercise PEFR, Nadir-t was compared boys and girls. Statistical analysis was performed by Mann-Whitney test using by STATA software.

RESULTS: Among the children (n =23 boys; n =28 girls), the prevalence of EIB was 41.2% (21/51) when a ≥20% decrease in PEFR was used. In children with decreased post-exercise PEFR, any proportions of Nadir-t of 0, 3, 10, and 20 minutes after exercise had no significant differences between boys and girls (21.7%, 21.7%, 21.7% and 21.7% vs. 32.1%, 7.1%, 32.1% and 7.1%, P = .36).

CONCLUSIONS: In prepubertal children, significant sex-differences in bronchial reactivity were not observed. To conclude exactly same-sex-differences, further studies are needed.

638 A Pilot Study of Pediatric Respiratory Assessment (PRAM) Score and Wood’s Asthma Score in Childhood Asthma Exacerbation Assessment

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RATIONALE: Wood’s score, has been used to assess childhood acute asthma severity in Thailand since 19th century. However, PRAM score which is increasingly used in Western countries was not evaluated. Therefore, we aim to determine whether Wood or PRAM score are better predicting asthma severity in childhood exacerbation.

METHODS: 53 Children, 2 - 18 years old, with asthma exacerbation were recruited. PRAM and Wood’s score were measured at emergency department by 2 physicians independently. The patient’s outcome was assessed at 0, 4, 24 hours after admission and the day of discharge.

RESULTS: The admission rate was 27.3 % with the mean length of stay = 3.66 days (SD 3.5). PRAM was correlated with Wood’s score (Pearson’s correlation prior to treatment =0.907, p<0.01). PRAM score had better internal consistency (Cronbach’s α = 0.632) than Wood’s score (Cronbach’s α = 0.375). Both PRAM and Wood’s score also had moderate inter-rater reliability between two physicians (κ = 0.471, 0.44 respectively). ROC indicated similar score (>3), both PRAM and Wood’s score, in the requirement for admission.

CONCLUSIONS: PRAM and Wood’s score are both promising in prediction of severity and outcome of childhood acute asthma.
639 Impact and Seasonality of Respiratory Viral Illnesses: A Retrospective Study

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RATIONALE: We retrospectively evaluated the timing and impact of respiratory viral infections on asthma exacerbations in a children’s hospital.

METHODS: We performed chart reviews of ~4500 patients from February 2012 through January of 2016 of children who received respiratory viral panel PCRs during either emergency department (ED) or inpatient admissions. Based on ICD9 and 10 codes, we found 127 of our cohort had a diagnosis associated with asthma exacerbations. Patient demographics, season of admission, length of admission, and time to viral swab were gathered to evaluate the association of socioeconomic factors, past medical history, county of residence and length of hospital stay with viral infections and asthma exacerbations.

RESULTS: Overall, patients with a diagnosis of asthma exacerbation had higher rates of positive results to all viral tests (p<0.0001). However, when evaluating specific viruses and the association with asthma exacerbations, only rhinovirus (RV) was highly associated with asthma exacerbations (p<0.0001). Enterovirus/RV was most highly associated asthma exacerbations during the summer months, specifically in September (p<0.0001). We found that patients with RV and asthma exacerbations had shorter lengths of stay compared to those with asthma exacerbations in the absence of confirmed viral infection (2.8 days asthma + RV; 5.05 asthma + no virus; p<0.05).

CONCLUSIONS: Viral infections are associated with asthma exacerbations; however, this association does not correlate with longer lengths of stay.

640 Assessment of Heterogeneity of Childhood Asthma Using Medical Informatics Approaches

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RATIONALE: To identify asthmatic children for electronic medical record (EMR)-based large-scale clinical studies, we recently developed natural language processing (NLP) algorithms for two asthma criteria (Predetermined Asthma Criteria (NLP-PAC) and Asthma Predictive Index (NLP-API)). We characterized subgroups of children with asthma using these two NLP algorithms.

METHODS: We utilized the 1997-2007 Mayo Birth Cohort. We applied NLP-PAC and NLP-API algorithms to patients’ EMR and categorized them into 4 groups (Group1: both criteria positive; Group2 or 3: PAC or API only positive; Group4: both criteria negative) to characterize them with regard to demographics and asthma-related variables (i.e. asthma outcomes).

RESULTS: Of the eligible 8,493 subjects, 51% were male, 82% White, and mean age (SD) at last follow-up date was 12.6 years (3.1). We identified 1,668 children (20%) as Group1, 986 (11%) as Group2, 107 (1%) as Group3, and 5,732 (67%) as Group4. As compared to other groups, Group1 were more likely to be male and had more asthma diagnosis, earlier asthma onset date, higher prevalence of allergic rhinitis and eosinophilia (p<.001 for all assessed variables). Group3 had more eczema compared to others (p<.001). Group1 had poorer asthma control defined by ED visit or hospitalization (p<.001) and a higher frequency of pneumonia (p<.001).

CONCLUSIONS: The two NLP algorithms for asthma criteria are useful for assessing heterogeneity of asthma in clinical studies in the EMR era. Also, as these NLP algorithms identify poorly controlled asthmatics and those with asthma-related comorbidity, they are a useful population management tool for asthma care.

641 Risk Factors Associated with Asthma-Related Emergency Department and Urgent Care Visits Among Older Adults

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RATIONALE: Asthma morbidity is increased among older adults. Interventions to improve asthma control in this population are not well-described.

METHODS: We investigated risk factors for asthma-related emergency department and urgent care center visits (ED/UCV) using a sample of older adults (>65 years) with active asthma from 40 states, the District of Columbia, Guam and Puerto Rico who participated in the Behavioral Risk Factor Surveillance System Asthma Call-back Survey, a random-digit dialing survey. We conducted weighted logistic regression analyses using 2006–2010 data to compare older adults with and without asthma-related ED/UCV visits with respect to clinical, environmental, and financial measures. We controlled for sociodemographic and clinical characteristics.

RESULTS: Among 14,076 older adults with active asthma (representing ≥2.6 million persons), 10.6% (95% confidence interval [95% CI]=9.7–11.5%) reported ≥1 asthma-related ED/UCV in the past year. Compared to older adults without asthma-related ED/UCV, adjusted odds were higher among older adults with ≥1 asthma-related ED/UCV for chronic obstructive pulmonary disease (adjusted odds ratio [aOR]=2.26, 95% CI=1.80–2.82), coronary artery disease (aOR=1.53, 95% CI=1.24–1.89), depression (aOR=1.42, 95% CI=1.15–1.76), diabetes (aOR=1.28, 95% CI=1.03–1.59), mold in the home (aOR=1.61, 95% CI=1.18–2.20), and cost as a barrier to accessing asthma-related health care (primary care aOR=1.92, 95% CI=1.31–2.81; specialty care aOR=2.47, 95% CI=1.57–3.90; asthma medication aOR=1.87, 95% CI=1.41–2.46).

CONCLUSIONS: Among older adults, asthma-related ED/UCV were associated with medical comorbidities, mold in the home, and financial barriers to asthma-related health care. Interventions addressing modifiable factors could reduce asthma-related ED/UCV among older adults.

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RATIONALE: Childhood allergic diseases have increased in prevalence worldwide, particularly eczema among younger children, and rhinoconjunctivitis among children of all ages. However, recent findings suggest a plateau in the rate of wheeze in areas previously reporting a high prevalence. We conducted a nation-wide school-based survey to investigate any change in the prevalence of allergic diseases.

METHODS: In 2005, 2008, and 2015, questionnaires were distributed to 6-7-year-old, and 13-14-year-old, children (approximately 40,000 children in each age group) among randomly selected schools in each prefecture in Japan. We used the Japanese version of the ISAAC questionnaire to evaluate the prevalence of allergic diseases.

RESULTS: The prevalence of current wheeze among 6-7-year-olds was 13.8% in 2005 and 13.7% in 2008, and decreased to 10.2% in 2015. Among 13-14-year-olds, it was 8.7% in 2005 and 9.5% in 2008, decreasing to 8.1% in 2015. The prevalence of current rhinoconjunctivitis increased from 14.5% in 2005 to 15.7% in 2008 and to 18.6% in 2015 among the 6-7-year-olds, and from 20.1% in 2005 and 21.1% in 2008 to 26.4% in 2015 among 13-14-year-olds. Current eczema was present in 15.9%, 16.5% and 14.7% of the 6-7-year-olds, and in 9.8%, 10.6% and 9.7% in the 13-14-year-olds for the respective years examined.

CONCLUSIONS: The prevalence of wheeze showed a decrease similar to that recently reported in other developed nations. While the prevalence of eczema also showed a similar trend, the number of children with allergic rhinoconjunctivitis continued to increase in line with previous reports.

643 Blood Cadmium and C-Reactive Protein Levels As Risk Factors for Allergic and Respiratory Diseases in Early Childhood: The Mothers and Children's Environmental Health Study

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RATIONALE: Recent studies have shown that inflammatory process induced by cadmium exposure during pregnancy may affect the fetal immune response and the risk of allergic or respiratory diseases. We examined whether cadmium and CRP levels in mother–offspring pairs are associated with allergic or respiratory diseases in early childhood.

METHODS: 917 mother–offspring pairs were studied. Allergic and respiratory outcomes were obtained from questionnaires by the mothers at postnatal months 6, 12, and 24. Cadmium and C-reactive protein (CRP) levels were measured in pregnant women, cord blood (CB) and at 24 months of age. Total IgE, eosinophil counts, and IL-10 levels were measured in CB and at 24 months of age. At 24 months data of 462 children were available.

RESULTS: Cadmium levels in CB are significantly positively correlated with maternal cadmium and CRP levels at late pregnancy. Cadmium levels during pregnancy and in CB were dichotomized into low and high group using median value. High cadmium group at late pregnancy had significantly higher levels of total IgE and IL-10 in CB and 24 months of age compared to low cadmium group. High levels of cadmium and CRP at late pregnancy were associated with increased risk of atopic dermatitis (AD) at 24 months (aORs 2.91, 95% CI (1.13 to 7.49), p=0.027). However there was no relationship between maternal and offspring cadmium or CRP levels and respiratory diseases.

CONCLUSIONS: Maternal cadmium and CRP levels may contribute to increase the risk of AD in early childhood.

644 Phenotype Determined By Cluster Analysis in Asthmatic Children

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RATIONALE: Asthma phenotype can facilitate understanding of disease pathogenesis and potential targeted therapies. Objective is to characterize the distinguishing features of phenotypic groups in asthmatic children examined by bronchial provocation test.

METHODS: The provocation tests for bronchial hyperresponsiveness (BHR) using acetylcholine (Ach) were performed in 377 patients (Female 149, range 5-17, mean 11.0-year-old). We obtained the provocation concentration of Ach producing a 20% decrease in FEV1 (PC20). FeNO measurement were performed before Ach provocation test. Analyzed variables included age, sex, obesity, age of asthma onset, treatment, atopy, FeNO, BHR and % predicted FEV1. We determined number of phenotypic groups by cluster analysis with Ward minimum variance method. Cluster analysis used kmeans method as the principal clustering technique.


CONCLUSIONS: Children’s asthma examined by BHR test can be classified into distinct 4 phenotypes. Better understanding of phenotype in asthmatic children could facilitate better later respiratory health.
645 Risk of Developing Glioma among People with Asthma: A Population-based Case-control Study

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RATIONALE: The reported relationship between asthma and risk of glioma has been inconsistent, in part due to methodological inconsistency in sampling frame and asthma and/or glioma ascertainment. The true nature of the association is unknown.

METHODS: We conducted a retrospective population-based case-control study, which enrolled all eligible biopsy-proven incident glioma cases (1995-2014) and 2 sets of controls among Olmsted County, MN residents, matched to birth-year and gender (1st set: community controls without ICD9 codes for glioma; 2nd set: MRI (brain)-negative controls from the same community). We performed comprehensive medical record reviews to ascertain asthma status of cases and controls using predetermined asthma criteria. Frequency of history of asthma prior to index date was compared between glioma cases and their matched controls using conditional logistic regression models.

RESULTS: We enrolled 135 glioma incident cases [19 (14%) age <18 years] and 270 controls. The median ages (IQR) at the index date were 52 years (32-67) for glioma cases. Of the glioma cases, 21 (16%) had a history of asthma, compared to 17 of community controls (13%) and 36 of MRI controls (27%) [OR (95%CI): 1.28 (0.63-2.58), p = .48 for community control vs. 0.48 (0.25-0.91), p = .02 for MRI control]. Overall, there was no association between asthma and risk of glioma [OR (95%CI): 0.74 (0.41-1.31), p = .30].

CONCLUSIONS: A history of asthma does not increase the risk of Glioma overall. As different source populations for controls may draw different conclusions suggesting a potential detection bias, choosing appropriate reference group in a case-control study is critical.

646 Overweight And Obese Inner City Asthmatics (BMI: 25-40 Kg/m²); High IgE (HC, 30-700 IU/ml) Vs. Low IgE (LC, <30 IU/ml) Cohorts

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RATIONALE: Immunoglobulin E (IgE) and obesity are known risk factors for asthma. Our previous studies on our inner-city patients showed more severe symptoms in super-obese asthmatics (SOA, BMI≥40 Kg/m², mean 47Kg/m²) vs. normal BMI (BMI 18-25Kg/m²). Also, sensitivities to subclasses of seasonal allergens and certain molds were significantly higher in an ultra-high IgE cohort (UHC, IgE >700; mean 2,600 IU/ml) vs. a high cohort (HC,30-700; mean 182 IU/ml). However, these studies did not delineate differences in characteristics of a LC vs. HC of overweight/obese asthmatics (OOA; BMI: 25-40Kg/m²).

METHODS: We examined our Drexel Pulmonary outpatient LC vs. HC of urban OOA for differences in allergen sensitization (ImmunoCAP®), obstruction indices, exacerbations and eosinophil counts. Subjects were matched for age, gender and BMI. Exclusion criteria included age <18 years, >10 pack years, ABPA and COPD.

RESULTS: The HC included more African Americans (AA), had significantly worse air trapping RV/TLC >40 (p = 0.0001) and FEV1 <80% predicted (p=0.03). However, FEV1/FVC < 80 (p=0.06) and FEF25-75% < 65% (p=0.05) were not different. The HC had higher eosinophil counts (p=0.02) and increased frequency of exacerbations (p=0.04) vs. LC. Enhanced allergen sensitization was confirmed among the HC (e.g. dog, timothy grass, maple, cedar, elm, walnut tree, sycamore, and ragweed (p <0.05 for each). Cat (p=0.2), cockroach (p=0.1) and molds were not different.

CONCLUSIONS: HC vs. LC inner city OOA tend to be more African-American, suffer worse obstruction, higher eosinophilia, exacerbations and higher sensitization to dog, grass, trees and ragweed though surprisingly not to molds, cat and cockroach.

647 Asthmatic Patients Perception of Their Weight and Its Impact on Their Asthma

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RATIONALE: Obesity has emerged as a major modifier of asthma. We sought to gain insight about how patients perceived their weight and relation to asthma, and to identify patients that were interested in weight loss interventions.

METHODS: A 5-question survey was given to a cohort of asthmatics to assess their perception of their weight, its role in their asthma control, and their willingness to pursue weight loss. The survey was distributed to 50 consecutive patients seen in our asthma clinic, regardless of BMI. The results of the survey were compared to clinical characteristics of asthma and BMI.

RESULTS: The survey was completed by 49/51 patients. Mean (±SD) BMI for participants was 34.0±11.0. Our cohort had a mean (±SD) FEV1 % predicted of 69.6±19.24%. Most (78%) felt that their weight was “too heavy”, and 55% answered “yes” when asked whether they thought that their weight worsened their asthma control. Mean BMI (±SD) was higher in these patients compared to the responders who answered “no” (39.5±10.7 vs. 27.8±7.6, p=0.0002), and FEV1 was lower (2.38±0.84L vs 1.90±0.71L, P=0.046). Fifty-nine % felt that weight loss would help with their asthma, and 63% was interested in either a web-based/app or other study participation to help them lose weight.

CONCLUSIONS: Obesity is common in our asthma clinic. Most patients believe that it has a negative impact on their asthma, and this was supported by higher BMI and lower FEV1 in this group. Obese patients are interested in weight loss interventions, particularly those that utilize technology-based approaches/apps.
648 Geographical Distribution of Asthma in Mexico and Its Ecological Association with Other Conditions

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RATIONAL: Asthma prevalence greatly varies worldwide. The Instituto Mexicano del Seguro Social provides medical care to >50% Mexican population in 758 from 2456 counties nationwide; thus, data from this institution may yield valuable information to determine asthma frequency and to identify potential risk factors.

METHODS: Data about asthma and other diseases diagnosed by family physicians from 2007 to 2012 were gathered for each county. This data corresponds to first-time diagnoses, thus it is a surrogate of incidence when adjusted by insured population. Information about counties’ latitude, altitude, temperature, population, marginality, and %insured population was also obtained.

RESULTS: Asthma incidence (x100,000 insured subjects) from all counties varied from 16.2 to 403.8 (median, 296.2). Asthma incidence was higher in locations in or near coasts, and was kept relatively constant until ~1539 m altitude (piecewise regression analysis), with a progressively decline thereafter. The Spearman correlation between asthma incidence and altitude for counties located above this cut-off point was rs = -0.52, p < 0.001. Average maximum temperatures strongly correlated with asthma incidence (rs = 0.51, p < 0.001). Asthma was also associated with upper respiratory tract infections (rs = 0.53), diabetes (rs = 0.44), helminthiasis (rs = 0.29), and with marginalization (rs = 0.26), all with p < 0.001. There was an inverse correlation between asthma and the county’s total population (rs = -0.31, p < 0.001). All these correlations persisted when population was divided in males and females, in 0-19 and ≥20 years old, and in counties with 10,000 or more inhabitants.

CONCLUSIONS: Altitude was the main factor inversely associated with asthma incidence, specifically in counties at ≥1539 m altitude. Other factors associated with asthma were also identified.

649 Prevalence of Allergic Rhinitis, Atopic Dermatitis and Asthma among school children in Hyderabad, India

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RATIONAL: Prevalence of allergic diseases is increasing in both developed and developing countries worldwide. Earlier, we observed a four fold increase in prevalence of allergic rhinitis and asthma over 15 years in Mysuru, India. There is a paucity of data of prevalence of allergic rhinitis, atopic dermatitis, asthma and associated factors among children in Hyderabad, India.

METHODS: Four schools in 2 administrative wards in Hyderabad with a population of 50,000 were randomly selected from 16 schools. ISAAC Questionnaire was used to estimate the prevalence of Allergic Rhinitis, Atopic Dermatitis and Asthma in children aged 3 to 15 years.

RESULTS: A total of 1047 children (M 585, F 462) responded out of 1300 (response rate of 80.5%). Most of the children (94.27%) were born in hospital and majority were breast fed between 6 to 12 months (65.9%). The estimated prevalence of allergic rhinitis is 304 (29.04%), atopic dermatitis is 103 (9.84%) and asthma is 89 (8.5%).

650 Allergen Sensitization Is Associated with Increased Rates of Exacerbations, Oral Corticosteroid (OCS) Use, and Asthma-Related Healthcare Services in Children with Severe or Poorly Controlled Asthma

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RATIONALE: Allergen sensitization (AS) may worsen asthma symptoms. We investigated the association between AS and asthma exacerbations, OCS use, and asthma-related healthcare use in children insured through private (PI) or Medicaid (MD) plans, separately.

METHODS: Children aged 6-11 with severe or poorly-controlled asthma (thereafter = asthma; ≥2 asthma medical claims [ICD-9-CM 493.x; 1st diagnosis = ID], ≥2 asthma medication claims, and ≥1 claim for high-dose ICS or chronic OCS or ≥2 claims for SABA in 3 successive months in 12 months after ID) were identified. AS was defined as extrinsic asthma (ICD-9-CM 493.0x) and an allergic-condition diagnosis (allergic rhinitis, anaphylaxis, conjunctivitis, eczema, dermatitis, food allergy, urticaria, angioedema). Outcomes included asthma exacerbations (<15-day OCS burst, asthma-related hospitalization or ER visit) asthma-related healthcare use (with asthma-diagnosis claims), and OCS-use days. Per-patient per-year rates were compared using multivariable models, controlling for demographics (age, sex, plan type, region [PI] or state [MD], and race [MD]) and baseline corticosteroid use.

RESULTS: PI children with (n=11,448) vs without AS (n=7,744) experienced: asthma exacerbations (1.23 vs 0.90), OCS-use days (11.81 vs 9.78), inpatient admissions (0.08 vs 0.05), inpatient days (0.22 vs 0.18), ER visits (0.26 vs 0.20), MD children with (n=10,800) vs without AS (n=6,535) experienced: asthma exacerbations (1.71 vs 1.10), OCS-use days (11.65 vs 8.34), inpatient admissions (0.12 vs 0.08), inpatient days (0.60 vs 0.42), ER visits (0.60 vs 0.42). All p-values were <0.01.

CONCLUSIONS: PI and MD children with severe or poorly controlled asthma with AS experienced more asthma exacerbations and used more healthcare services and OCS than those without AS.
651 Uncontrolled Asthma in Specialized Centers in Latin America: Findings from the Asthma Control in Latin America (ASLA) Study

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RATIONALE: There is no multi-country study in specialized centers investigating uncontrolled asthma and associated factors in Latin America.

METHODS: Cross-sectional study, including subjects ≥12 years with a diagnosis of asthma and prescription for asthma medication at 18 public/private outpatient specialised centres in Argentina, Chile, Colombia and Mexico. The Asthma Control Test (ACT) was used to classify the patients as controlled (ACT: 20-25) or uncontrolled (ACT < 19). Multivariate logistic regression was applied to assess the association between hospital admission/exacerbation/emergency visit and uncontrolled asthma.

RESULTS: 594 patients were included. The frequency of uncontrolled asthma was 56.6% (95%CI 52.5-60.5%). In the multivariate analysis, the uncontrolled patients were more likely to be women (62.3% vs 41.4%, ORadj: 1.8, p<0.001), non-white (68.3% vs 45.2%, ORadj: 2.01, p=0.057), monthly family income lower than $668.5 (67.8% vs 45.6%, ORadj: 1.71, p<0.05) and obese (70.1% vs 29.9%, ORadj: 1.63, p=0.057). The patients with uncontrolled asthma were more likely to have severe/moderate asthma exacerbations (28.0% vs 10.9%, ORcrude: 3.31, p<0.001), hospital admissions (6.8% vs 3.1%, ORcrude: 2.30, p=0.047) and emergency visits (34.5% vs 15.9%, ORcrude: 2.79, p<0.001) due to asthma.

CONCLUSIONS: Even in specialised services, more than half of the patients were classified as uncontrolled. Poorly controlled asthma was associated with an increase in the demand for healthcare in Latin America. The uneven distribution of control relative to race/ethnicity and income points to the emerging role of social factors influencing the burden of asthma.

652 The Spectrum and Prevalence of Reactions to Marijuana in a Colorado Allergy Practice

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RATIONALE: Since the legalization of medical marijuana (MJ) and recreational marijuana in certain states in the US, an increasing number of allergic patients are presenting due to MJ exposure. The majority have significant exposure in the grow industry or heavy consumers, indicating that cannabis sativa is a mild allergen. We surveyed our allergy practice patients’ experience with MJ and reactions to it.

METHODS: We composed a voluntary questionnaire addressing our patients’ exposure to MJ, active or passive, and types of reactions.

RESULTS: 134 Questionnaires were handed out, and 132 patients answered, 2 declined. 28 of 132 total patients experienced symptoms (21%). Patients who had never smoked 69 (52%), of these 8 had symptoms from passive exposure (12%). Patients who had smoked in the past 47 (35%), of these 12 (26%) had experienced symptoms. Patients who actively smoke 16 (13%), of which 8 (50%) experienced symptoms. Symptoms ranged from respiratory, followed by ocular, then skin.

CONCLUSIONS: Although cannabis sativa may be a mild allergen for most, increasing exposure and especially active use result in increased adverse effects in the allergic population.

653 Prevalence of Symptoms of Asthma and Rhinitis in Adult General Population of Rosario, Argentina

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RATIONALE: The increase of allergic diseases in the world is essential to develop a deeper understanding of the epidemiology of asthma and allergic rhinitis in general population samples knowledge. Our objective was to assess prevalence of symptoms of asthma and allergic rhinitis in adult population of the city of Rosario.

METHODS: A descriptive cross-sectional study with 1053 individuals living in Rosario, Santa Fe, of both sexes (52.5% women), aged between 18 and 88 years (x = 41.50 ± 17.01), who attended at six municipal districts and randomly responded ISAAC questionnaire validated for asthma and rhinitis, during November and December 2011 were included.

RESULTS: 8.4% of individuals reported having experienced symptoms of asthma in the past year and 15.3% of the sample reported symptoms of asthma ever in life. The prevalence of nasal symptoms during the last year was 31.2% and at some point in the life of 36.4%. For none of the two cases was a significant gender differences regarding age found. A significant degree of comorbidity between symptoms of asthma and rhinitis was found during the last year (OR = 3.79; 95% CI: 2.35 to 6.11) and once in life (OR = 3.40; CI95 %: 2.36 to 4.90).

CONCLUSIONS: These data of general adult population of Rosario show a high rate of nasal and bronchial symptoms of allergic etiology. The medical community should be aware of this alarming epidemiological situation in allergic respiratory diseases.
ASSOCIATION OF INTERLEUKIN-6 SINGLE NUCLEOTIDE POLYMORPHISMS WITH JUVENILE IDIOPATHIC ARTHRITIS

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RATIONALE: Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in children. Genetics and inflammatory elements seem to act as major underlying factors in its pathogenesis. The aim of this study is to identify the associations between interleukin-6 (IL-6) gene polymorphisms and individuals susceptibility to JIA in a group of Iranian pediatric patients.

METHODS: A case-control study was conducted on fifty four patients with JIA and 139 healthy unrelated controls. Using polymerase chain reaction with sequence-specific primers, cytokine genotyping was performed. The allele and genotype frequency of two single nucleotide polymorphisms (SNPs) within the IL-6 gene at -174 and +565 positions were assessed.

RESULTS: A significant positive association was observed for IL-6 -174 G allele in the patient group (P value=0.02). Furthermore, a positive association was observed in patients with JIA for the GG genotype at same position (P value<0.01), thus revealing a predisposing effect in JIA patients. On the other hand, a significant negative association was found for IL-6 -174 CG genotype (P value<0.01) in the case group. No significant difference was discovered in both the allelic and genotypic frequencies of IL-6 +565 position between patients and controls. Additionally, haplotype analysis divulged over representation of IL-6 GG haplotype in patient group (P value<0.01) as well as IL-6 CG haplotype in healthy controls (P value<0.01).

CONCLUSIONS: Certain allele, genotype, and haplotype in IL-6 gene were over expressed in patients with JIA, which probably could render individuals more susceptible to this disease.

HUMORAL IMMUNE RESPONSE AFTER A FOUR-SITE INTRADERMAL RABIES BOOSTER VACCINATION IN PREVIOUSLY RABIES IMMUNIZED HIV-INFECTED ADULTS

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RATIONALE: Repeated rabies exposures sometimes occur with HIV-infected individuals. In healthy, a single visit 4-site intradermal (ID) rabies booster vaccination has shown superior immunogenicity than conventional intramuscular (IM) regimen, along with the convenient, and economical advantages. The randomized controlled study was conducted to assess immune response after a 4-site ID injection in HIV patients.

METHODS: We compared rabies neutralizing antibody titers (Nab) after a 4-site ID regimen with 0.1 mL of purified Vero cell rabies vaccine (PVRV) per inoculation site distributed at both deltoids and thighs vs. standard intramuscular injection using an ampule (0.5 mL) of PVRV at the deltoid on day 0 and 3 in thirty-eight previously rabies immunized HIV-infected participants who were on antiretroviral therapy and had CD4+ ≥ 200 cells/mL. Baseline Nab, CD4+/CD8+ counts and HIV RNA were analyzed prior to immunization. On day 7 and 14, Nab was sequentially monitored by Rapid Fluorescent Focus Inhibition Test.

RESULTS: All recipients elicited protective Nab level by day 7. Four-site ID could evoke higher Nab than IM protocol, of which the geometric mean titers in ID vs. IM group were 14.9 vs. 12.9 IU/mL (p=0.67) and 31.3 vs. 19.8 IU/mL (p=0.18) on day 7 and 14 respectively. The statistical significance was demonstrated only among patients whose CD4+ ≥ 500 cells/mL. A correlation between CD4+/CD8+ ratio and Nab titers on day 7 was found. Having been primary rabies immunized during AIDS conditions had affected subsequent booster immunization despite quantitative CD4+ T-cell recovery.

CONCLUSIONS: WHO-approved 4-site ID rabies booster vaccination was immunogenic in asymptomatic HIV-infected adults.

RISK FACTORS FOR RSV BRONCHIOLITIS DO NOT INCLUDE SECONDARY IMMUNODEFICIENCY

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RATIONALE: Acute bronchiolitis is a virally mediated inflammation of the bronchioles occurring in children younger than age 2 years. Frequent organisms isolated are rhinovirus and respiratory syncytial virus (RSV). Risk factors include prematurity, congenital heart disease and chronic lung disease. The association between RSV bronchiolitis and human immunodeficiency virus (HIV) is poorly described. We aimed to assess the correlation between RSV bronchiolitis in HIV-infected and HIV-uninfected children admitted between January and July 2016.

METHODS: We retrospectively assessed all children less than 2 years with a clinical diagnosis of bronchiolitis admitted to our centre. Using polymerase chain reaction (PCR) multiplex testing, nasopharyngeal aspirates were tested for respiratory viruses. All patients were assessed for human immunodeficiency virus status (HIV).

RESULTS: Between January and July 2016 there were 103 cases of bronchiolitis. The peak incidence was in June with 30 cases. RSV was identified in 39% of cases. The peak incidence occurred between 1 and 3 months of age. Of the total admissions, 21% went to PICU. Although all cases admitted had a known risk factor (prematurity, CHD, chronic lung disease or smoking member at home) there were no infants who were HIV infected.

CONCLUSIONS: RSV was not identified in any HIV-infected children. RSV in HIV-uninfected cases caused marked morbidity. Of the 40 children admitted with a confirmed RSV viral bronchiolitis, 22 (55%) were ventilated for severe disease. The association between RSV bronchiolitis and HIV disease is poorly understood, and further research is required to understand the immune mechanisms in HIV that protect against RSV viral bronchiolitis.
657 Treatment of Maternal Lupus Resulting in a Positive Newborn TREC Screen

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RATIONALE: T-cell receptor excision circles (TRECs) are used in the screening of newborns for severe combined immunodeficiency (SCID). We present a case of a strong-positive newborn TREC screen as a result of treatment of maternal lupus with immunosuppressive agents.

METHODS: TREC screen was performed by quantitative PCR at the Michigan Newborn Screening Laboratory.

RESULTS: A 13 day-old boy was found to have a strong-positive TREC screen (0-7 TRECs) at full-term birth. There was no family history of immunodeficiency. His mother was being treated for systemic lupus erythematosus (SLE) with daily prednisone 10mg and azathioprine 50mg in addition to hydroxychloroquine 200mg twice daily. She was given prednisone 100mg intravenously at the time of delivery. By 3-weeks of age T cell numbers were improving, but had not normalized. At follow up at 7-months of age they had normalized, without any interval infections and he was discharged from our Immunology clinic.

CONCLUSIONS: Causes of abnormal TREC screens in newborns include SCID, syndromes associated with T cell lymphopenia such as DiGeorge, lab artifact, and, as with our patient, secondary causes such as immunosuppressants. Notable about this case is the severity of reduction which has not been seen in the five years our state has been screening for SCID. With the ever increasing number of states screening via TRECs, better understanding of these secondary causes of low values will help in identifying true cases of SCID.

658 A Case of Familial Invasive Aspergillosis of Unknown Etiology

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RATIONALE: Invasive aspergillosis is typically seen in those with weakened immune systems. This report details a case of a patient and mother who both developed invasive, life-threatening Aspergillus infection without a history of immunosuppression or inciting factors.

METHODS: Lymphocyte antigen and mitogen proliferation panel.

RESULTS: 47-year old male with an 8-month history of sinus infections presents with new onset of diplopia. Emergent MRI noted abnormal enhancement of extracocular muscles (left medial and inferior recti) and infiltrative changes involving the bony structures of the skull base. Surgical biopsies revealed necrotizing granulomatous inflammation and fibrosis with invasive fungal organisms. Fungal cultures grew Aspergillus fumigatus.

Immune work-up: WBC 8.2 K/mcL. Lymphocyte subsets: CD3+ (2233/ mcL), CD4+ (1499/mcL) cells, and CD8+ cells (734 /mcL). Quantitative immunoglobulins were normal. Neutrophil oxidative burst assay was normal. Of interest, lymphocyte antigen and mitogen proliferation assay revealed a normal response to Tetanus antigen and 3 non-specific mitogens, but a low response to Candida antigen. Of note, the patient’s mother died in early adulthood of a disseminated Aspergillus infection that began as a primary pulmonary infection.

CONCLUSIONS: A familial history of invasive Aspergillus infection with abnormal T cell proliferation response to Candida is indicative of a decreased adaptive immune response to fungal elements. We hypothesize there is an underlying, likely inherited, deficiency in the development of fungal specific CD4+ memory T cells, a mechanism yet to be described in the literature. We are hopeful that future testing, including gene sequencing of patient and affected parent DNA will provide further answers.
660 Successful Utilization of Costimulatory Blockade in a Refractory Pediatric Autoimmune Enteropathy Patient

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RATIONALE: Autoimmune enteropathy (AIE) is a rare disorder involving a T cell regulatory defect, resulting in enteroocyte destruction and small intestinal mucosal atrophy with anti enteroocyte antibodies. Clinical manifestations include severe chronic diarrhea and malnutrition. We present a pediatric male with autoimmune enteropathy who failed standard immunosuppressive therapy. It was hypothesized that T cell activation may be playing a role in his severe disease and costimulatory blockade might be an effective therapy as it is useful in severe Rheumatoid arthritis.

METHODS: A 19 month old with milk protein allergy, eczema, chronic diarrhea, failure to thrive and TPN dependency was evaluated. Treatment including steroids, cyclosporine, tacrolimus, and enteral immunoglobulin failed to yield any improvement. Sirolimus was found to be marginally effective; however, patient required multiple readmission for diarrhea and dehydration. Extensive infectious workup was negative and biopsies were consistent with autoimmune enteropathy with anti enteroocyte antibodies. Immune evaluation revealed normal T cell function, IPEX sequencing as well as PID microarray were negative for common mutations. An ablative stem cell transplant was considered for a definitive therapy of his severe enteropathy. Alternative immunomodulatory agents were considered.

RESULTS: Abatacept, a selective modulator of T cell activation was initiated at 10mg/kg at weeks 0, 2 and 4 then administered monthly. At week 4, his diarrhea resolved and patient was weaned off TPN therapy.

CONCLUSIONS: This is the first reported case of a pediatric patient with refractory autoimmune enteropathy successfully treated with costimulatory blockade. This treatment protocol may prove to be helpful for similar challenging patients with autoimmune conditions.

661 Relationships Among Depression and Levels of Cytokines and Testosterone in Patients with Chronic Abacterial Prostatitis

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RATIONALE: Chronic prostatitis/chronic pelvic pain syndrome (CP/ CPPS) is a common chronic condition largely unresponsive to medical intervention. Comorbid depression and chronic pain are highly prevalent in patients with chronic abacterial prostatitis. The impact on CP/CPPS of depression, inflammatory cytokines and testosterone was assessed in this study.

METHODS: The National Institutes of Health (NIH) - Chronic Prostatitis Symptom Index (CPSI) for severity of CP/CPPS, and Patient Health Questionnaire-9 (PHQ-9) for depression were administered to 27 patients with CP/CPPS. Cytokine levels and testosterone levels in semen were determined by ELISA.

RESULTS: There were significantly positive correlations between NIH-CPSI total scores and PHQ-9 alone, and when compared to pro-inflammatory cytokines (IL-1β, TNF-α, IL-8). A significant negative correlation was seen between anti-inflammatory cytokines (IL-10, TGF- β) and depression and symptoms of CP/CPPS. In CP/CPPS patients, the level of testosterone in blood decreased (p<0.001).

CONCLUSIONS: The imbalance of immune function seen in CP/CPPS chronic prostatitis occurs concurrent with a decline in testosterone production. Immune dysfunction associated with increased inflammatory cytokines depression and lower testosterone relate to CP/CPPS symptoms and may be integral to the pathogenesis of this condition.
663  Neuroinflammatory biomarkers in Chronic Fatigue Syndrome (CFS)

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RATIONALE: Neuroinflammation provides a unifying mechanism for fatigue, exertional exhaustion, cognitive, sleep, nociceptive (pain, tenderness) and interoceptive (dyspnea, nonallergic rhinitis, irritable bladder and bowel) dysfunction in CFS. Hypotheses of causation include central sensitization; chronic or noncytolytic neurotrophic infections; autoreactive immune dysfunction with neural targets; brainstem atrophy with autonomic dysfunction; metabolic; mitochondrial and psychosomatic dysfunction.

METHODS: Sedentary control (SC) and CFS subjects were diagnosed by history and physical (1994 CDC criteria) before submaximal bicycle exercise testing on 2 days, fMRI before and after exercise, lumbar puncture, and heart rate variability testing.

RESULTS: Ceiling and floor effects significantly distinguished CFS from SC on SF-36, McGill Pain, Fatigue, depression, anxiety, catastrophizing, and other psychometric instruments. CFS and SC had comparable performance on exercise DAYs 1 and 2 with no incremental deficits in VO2, peak heart rate, or post-exercise fatigue. Cerebrospinal fluid (csf) metabolomes showed subtle variations between SC and CFS, but csf and plasma cytokines, and csf microRNA profiles were equivalent. Exercise testing on 2 days, fMRI before and after exercise, lumbar puncture, and other psychometric instruments. CFS and SC had comparable performance on exercise DAYs 1 and 2 with no incremental deficits in VO2, peak heart rate, or post-exercise fatigue. Cerebrospinal fluid (csf) metabolomes showed subtle variations between SC and CFS, but csf and plasma cytokines, and csf microRNA profiles were equivalent. Exercise caused transient postural orthostatic tachycardia in half of CFS, but sympathetic (low frequency) and parasympathetic (high frequency) heart rate variability were not altered. CFS had lower thresholds for pain with normal stimuli such as light (photophobia), sound (phonophobia), hyper-ventilation (dyspnea), orthostasis (vestibular intolerance), light pressure (systemic hyperalgesia) and nasal irritation (nonallergic rhinopathy).

CONCLUSIONS: Neural mechanisms of central sensitization modulate the amplitude of sensory inputs and enhance conscious perception of nociceptive and interoceptive stimuli. Objective biomarkers and mechanisms remain elusive for explaining the disabling fatigue, exertional exhaustion and cognitive incapacitation. R01NS085131.
Leukocytoclastic Vasculitis Associated with Epstein–Barr virus, Increased IgE with Atopy and NSAID Intolerance

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RATIONALE: Leukocytoclastic vasculitis (LCV) can be due to drugs, infections, connective tissue diseases, allergens, or be idiopathic.

METHODS: A medical report of LCV induced by unknown cause was reviewed for possible causative factors.

RESULTS: A 26-year female had conjunctivitis, pruritic dermatitis for 8 months with use of Diclofenac and prednisolone due to joint symptoms. Two years before she had birch pollen allergy without skin symptoms. The new rash did not respond to antihistamines. NSAIDS were used for the joint symptoms but worsened the rash. The patient had pruritic erythematous rashes on the face and extremities and conjunctival erythema. Leukopenia, moderate eosinophilia (1.9 G/L), increased erythrocyte sedimentation rate and fibrinogen, increased total IgE (1198 IU/ml), and increased levels of specific IgE (>0.35 kU/l) to D. pteronyssinus, D. farinae, rBetv1 and rBetv2, positive antinuclear antibody and cANCA (anti-proteinase-3) were noted. EBV was found in the pharynx, blood and saliva. Skin biopsy showed leukocytoclastic vasculitis with eosinophils and lymphocytes within the vessel walls. According to the definitions of the Chapel Hill Consensus Conference and ACR Criteria LCV was diagnosed associated with EBV, IgE and NSAIDS. Antiviral drugs, prednisolone, and antihistamines provided decreased skin and eyes findings.

CONCLUSIONS: EBV in association with allergens may be associated with development of LCV. Detection of triggers of vasculitis allows etiological treatment and prevention of complications.

Management of Churg-Strauss Syndrome (CSS) in the setting of Disseminated Histoplasmosis

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RATIONALE: Churg-Staruss Syndrome (CSS), also known as Eosinophilic Granulomatosis with Polyangiitis, is characterized by asthma, chronic rhinosinusitis, eosinophilia and vasculitis. We describe a case of CSS management in the setting of disseminated histoplasmosis.

METHODS: A 60-year-old male with CSS was admitted with fever, pancytopenia and transaminitis. He was on prednisone, methotrexate (MTX) and Cellcept. Given concern for infection MTX and Cellcept were discontinued. Patient had recently torn down a deck with numerous bird droppings. Infectious work up revealed elevated Fungitell, Histoplasma antigen and antibody levels. Bone marrow biopsy and blood cultures were positive for Histoplasma Capsulatum confirming the diagnosis of disseminated histoplasmosis. Patient was treated with Amphotericin and Voriconazole.

One month later patient had uncontrolled rhinosinusitis and asthma despite maximal therapy including oral and inhaled corticosteroids. Cellcept and MTX could not be resumed with disseminated histoplasmosis. He was treated with high dose IVIG and Omalizumab with significant improvement in symptoms.

RESULTS: The mainstay of CSS treatment is corticosteroids. However, cytotoxic drugs are required for refractory disease. The patient described was on immunosuppressants prior to developing disseminated histoplasmosis, which precluded continuation of immunosuppression, thus leading to uncontrolled disease. This presented a challenge in management. High dose IVIG has been found to be effective in EGPA patients with cardiomyopathy or mononeuritis multiplex. The activation and induction of Treg cells is responsible for this efficacy. Our patient’s asthma and rhinosinusitis improved with IVIG and Omalizumab therapy.

CONCLUSIONS: High dose IVIG and Omalizumab could be used to treat asthma and rhinosinusitis in CSS patients when immunosuppressants are contraindicated.
668 Effects Of An 8-Week Lifestyle Education Program On Participants with Autoimmune Disease

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RATIONALE: Autoimmune patients have a higher incidence of mental health problems. We evaluate the effect that a lifestyle education program had on these participants.

METHODS: The Nedley clinic trained and certified facilitators that operated a depression program in 5 continents. Out of 5998 participants that finished an 8-week educational program, 453 had an autoimmune disease. This group was 54.7 years old and 84.5% were females. Demographics, medical history and depression levels were measured using a depression test that included a modified PHQ-9 (Patient Health Questionnaire). The non-profit program meet once a week for a two hour facilitated session, a 45 minute DVD lecture and small group discussions. No doctor patient relationship was established. The program focused on health education such as plant based nutrition, exercise, sleep, and other health principles.

RESULTS: Participants with autoimmune disease had a mean PHQ-9 score of 14.4 (moderate), st dev 7.3, median 15, mode 21. While participants without an autoimmune disease had an mean PHQ-9 of 11.9 (low moderate), st dev 7.5, median 12, mode 0. By the end of the 8 weeks participants with an autoimmune disease had a mean PHQ-9 of 7.8 (mild), st dev 6.3, median 6, mode 0. Those without an autoimmune disease had a mean PHQ-9 of 6.4 (none). ST dev 5.9, median 5, mode 0.

CONCLUSIONS: Participants with autoimmune disease had a higher baseline depression. Both groups benefited from the 8-week program but those without an autoimmune condition improved more. Long term follow up is advised.

669 Role of Tubulointerstitial Lesions in Predicting Renal Outcome among Pediatric onset Lupus Nephritis – A Retrospective Cohort Study

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RATIONALE: Raising evidence supported a prognostic utility of tubulointerstitial lesions in lupus nephritis (LN). The exact prevalence of tubulointerstitial abnormalities and its predictive value among pediatric onset systemic lupus erythematosus (pSLE) cases, however, remained unknown.

METHODS: Sixty-seven pSLE subjects diagnosed with LN with initial renal samples available were enrolled and followed for an average of 6.43 ± 3.06 years. Renal histology was evaluated according to the International Society of Nephrology/Renal Pathology Society classification, National Institute of Health classification and tubulointerstitial activity index (TIAI).

RESULTS: Tubulointerstitial injuries were observed in 38.81% of all LN cases, including 13.33% with non-proliferative lupus nephritis (nPLN) and 46.15% of with proliferative lupus nephritis (PLN). Tubulointerstitial injuries occurred solitary in cases with nPLN (13.33%), but always associated glomerular changes and significantly impacted renal survival (p = 0.032) among those with PLN. TIAI associated glomerular abnormalities (p = 0.031) but did not correlate renal performance or subsequent outcome (p = 0.445). Among the chronicity index, it was the chronic tubulointerstitial lesions which provided prognostic information (p = 0.012). We observed a synergistic effect of all tubulointerstitial abnormalities rather than an individual factor attributed the prognostic utility (p = 0.025 vs. p = 0.083, 0.055, 0.354). Finally, considering tubulointerstitial injuries in PLN further discriminated subsequent renal outcome (p = 0.006).

CONCLUSIONS: The prevalence and clinical significance of tubulointerstitial abnormalities were similar among the pSLE and the adult population. With its importance in identifying those at risk of renal failure, histologic classification considering tubulointerstitial lesions may potentially assist outcome prediction.

670 Measuring Circulating Complement Activation Products in MPO and PR3 ANCA Vasculitis

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RATIONALE: The mouse model of anti-myeloperoxidase (MPO) vasculitis indicated an unexpected, possible role of complement activation in ANCA-associated vasculitis (AAV). We investigated complement activation in human MPO-AAV and proteinase 3 (PR3)-AAV. We also studied effects of futhan, a broad-specificity protease inhibitor, on measuring complement activation.

METHODS: Subjects included 31 active AAV (14 MPO/17 PR3), 36 remission AAV (15 MPO/21 PR3), and 27 age- and gender-matched healthy controls (HC). Plasma samples were obtained on ice in EDTA tubes including no or 100 mcg/ml of futhan. Properdin (Hycult) and Bb, C3a, C5a, and sc5b-9 (Quidel) were measured by ELISA. Wilcoxon two-sample test and Pearson’s correlation were used when appropriate. After Bonferroni correction, p<0.0083 was considered statistically significant.

RESULTS: In PR3-AAV, Bb, C3a, and sc5b-9 were higher in active disease compared to HC. Bb and C3a were higher in remission compared to HC. C3a in remission was lower than in active disease, but Bb did not differ by disease state. C5a was not different. In MPO-AAV, C3a, C5a, and sc5b-9 were higher in active disease compared to HC. Bb and C3a were higher in remission compared to HC. There was no difference in properdin among groups. Bb levels were higher in samples without futhan than with, but the difference was systematic (r²=0.83).

CONCLUSIONS: We provide further evidence of complement activation in AAV, and the profile differs by disease activity and between MPO-AAV and PR3-AAV. Further study is needed on whether addition of futhan is required to accurately measure complement activation.
An association between IL-1ß production and mitochondrial functions in patients with autism spectrum disorders (ASD)

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RATIONALE: Innate immune abnormalities and mitochondrial dysfunction are frequently reported in ASD subjects, indicating a possible association between immune-mediated inflammation and mitochondrial dysfunction in ASD.

METHODS: Inflammatory cytokine such as IL-1ß generated by innate immune cells affect mitochondrial functions. In 71 ASD subjects, cytokine production by purified peripheral blood mononuclear cells (PBMCs) were examined.

RESULTS: A positive association between OCR and IL-1ß production was observed with TLR4 and TLR7/8 agonists in both ASD and controls. Because of variable responses to zymosan, a TLR2/6 agonist, ASD samples stimulated with zymosan were divided into three groups defined by the IL-1ß/IL-10 ratio results based on the reference values from 33 non-ASD controls. ASD cells with higher IL-1ß/IL-10 ratio (N=15) showed no association between OCR and IL-1ß production. Cells with lower IL-1ß/IL-10 ratio (N=7) showed a negative association, while those with normal IL-1ß/IL-10 ratios (N=49) revealed a positive association (r=0.506 vs. 0.37, r=-0.466 vs. 0.344 for ATP linked and maximal OCR, respectively, for these 2 groups). Non-ATP linked OCR which is associated with oxygen burst revealed the similar tendency in these 2 groups (r=-0.455 vs. 0.385).

ASD subjects with higher or lower IL-1ß/IL-10 ratio with zymosan had chronic gastrointestinal (GI) symptoms.

CONCLUSIONS: Our results indicates an association between IL-1ß production by innate immune cells and mitochondrial function of immune cells. Altered its association in some ASD subjects may be associated with their chronic GI symptoms.

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Alzheimer’s disease could be preventable and ameliorated by DNA vaccines made from cytokines, brain derived nerve growth factor and Apo E 2 gene

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RATIONALE: Alzheimer’s disease (AD) is an irreversible, progressive brain disease. The risk of AD increases with age developing. AD is not a part of aging, caused by a disease that affects brain. We propose the amyloid plaques are formed in the brain in the hippocampus and it is causing autoimmune reaction to host., thus brain tissue damaged by autoimmune injuries. The vascular structure is also contributing factors Thus the AD could be both preventable and could be ameliorated by repairing damaged neuronal system by brain derived nerve growth factor, improve vascular structure by APO gene, improve immune regulation by providing T reg cells derived cytokine IL-10 gene and Th2 cytokine gene IL-4 to dampen TH 1 response to amyloid gene.

METHODS: Using transgenic mice model, they were given the three cytokine genes, brain derived nerve growth factor gene, as well as APOE2 gene alone or combinations and as positive control, Interferon gamma gene were given. Water maze tests were performed for the functional assay and brain was dissected and immunostaining were performed.

RESULTS: Water maze test results showed that the gene vaccine especially, IL-10, IL-4 received mice improved markedly and the immunostaining of hippocampus, the presence of amyloid marked decreased, where as the interferon gamma gene received mice did not improved the water maze test result as well as immunohistology.

CONCLUSIONS: We have now proved that proper DNA gene vaccines could both prevent and ameliorate AD in animal model and needs clinical trials.

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Long-Lasting Remission of Severe Refractory Henoch-Schonlein Purpura Nephritis with Rituximab

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RATIONALE: Henoch-Schönlein purpura (HSP) is an immunoglobulin A vasculitis. The symptoms include cutaneous purpura, arthralgia, enteritis and nephritis. HSP nephritis (HSPN) can be severe and refractory to treatment. Steroids and azathioprine are used in combination in refractory cases. The role of B cells in HSPN is not clearly defined. However, the concept of depletion of antibody producing B cell makes Rituximab (anti-CD20 monoclonal antibody) appealing. Two HSPN pediatric cases treated with Rituximab have been reported, and a short remission period (5 months) is described in these cases. We describe a pediatric patient with HSPN refractory to steroid and azathioprine treatment with remission after Rituximab treatment for 36 months as of September 2016.

METHODS: Medical record and literature review were conducted.

RESULTS: This 7 year old patient presented with persistent proteinuria, vomiting and abdominal pain. Renal biopsy confirmed the diagnosis of HSPN with diffuse membranoproliferation and crescents and IgA deposits. He initially was treated with intravenous high-dose Methylprednisolone and all the symptoms improved. However, steroid dose tapering was ineffective with acute worsening of proteinuria so Azathrioprine daily was started. Afterwards, he had three episodes of relapse. However, after two doses of intravenous Rituximab he has been in remission for 36 months as of September of 2016.

CONCLUSIONS: This is the first reported pediatric case with a long-lasting period of remission after Rituximab treatment for refractory HSPN and without complication. Rituximab is a treatment modality that can be considered in severe, refractory cases of HSPN.
**ABSTRACT**

**674 Idiopathic CD4 T Lymphocytopenia and the Association of Autoimmunity Involving the Nervous System**

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**RATIONALE:** Idiopathic CD4 T lymphocytopenia (ICL) is a rare immunodeficiency defined as absolute CD4 T-lymphocyte count <300/μL, without evidence of infection with HIV or HTLIV. ICL patients have susceptibility to opportunistic infections and associated autoimmunity. Functional T-cell lymphocytopenia can result in a variety of organ-specific autoimmune diseases in animal models; autoreactive T cells undergo expansion as a mechanism of compensation for lymphopenia. Defects in T regulatory cells (CD4+CD25+) correlate with disease severity in myasthenia gravis and multiple sclerosis. We report two cases of patients with ICL who also had autoimmune disease involving the nervous system.

**METHODS:** A retrospective chart review was performed.

**RESULTS:** Patient A is a 59 year old female with multiple sclerosis diagnosed at the same time that lymphocytopenia was reported. Her CD4+ T cell quantities range from 25-51 cells/μL and CD8+ 38-106 cells/μL. Review of medications did not reveal any associated with bone marrow suppression and bone marrow biopsy was also normal. Patient B is a 49 year old female with Sjögren’s Syndrome, pulmonary Mycobacterium avium complex, and ICL that developed myasthenia gravis 1 year after ICL was diagnosed. Her CD4+ T cell quantities have ranged from 227-297 cells/μL, CD8 has ranged from 180-240 cells/μL. T regulatory cell repertoire is being examined in both patients.

**CONCLUSIONS:** Although, lymphopenia is a common finding in autoimmune diseases it is not well described in those with neurologic autoimmune, specifically multiple sclerosis and myasthenia gravis. Testing of lymphocyte subsets and proliferative studies is warranted in this population, as those results may affect management.

**675 Two patients with multiple sclerosis presenting with symptomatic selective IgM deficiency**

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**RATIONALE:** Multiple sclerosis (MS) is a heterogeneous disorder thought to possibly be autoimmune in nature. Per the literature, MS has been identified in a small number of patients with common variable immunodeficiency but has not been reported in selective IgM deficiency or combined immunodeficiency.

**METHODS:** Patients seen in outpatient clinic; previous records reviewed. Work-up included CBC, immunophenotyping, CH50, quantitative immunoglobulins, protein- and polysaccharide-based vaccine titers, and lymphocyte mitogens/antigens.

**RESULTS:** Patient 1 is a 60 year-old female diagnosed with MS at age 44. She presented with a history of multiple episodes of bronchitis, pneumonia, and sinusitis in addition to hypothyroidism. CD3+ total T cells and CD3+CD8+ subsets were both low. CH50, IgG, and IgA were within normal limits but IgM was decreased (30 – 33 mg/dL) with a poor pneumococcal vaccine response as well as a decreased response to in vitro tetanus recall antigen despite intact tetanus antibody titers. Patient 2 is a 41 year-old female diagnosed with MS and optic neuritis at age 39. She presented with a history of Hashimoto’s thyroiditis, recurrent nonmenstrual toxic shock syndrome, recurrent sinusitis, and acute episodes of thrush, shingles, cellulitis, and gastroenteritis. CD19+CD27- transitional B cells were decreased but lymphocyte mitogen/antigen stimulation was normal. IgM was decreased (27 – 36 mg/dL) with a poor pneumococcal vaccine response. CH50, IgG, IgA, and protein-based vaccine response were normal.

**CONCLUSIONS:** These patients may represent a subset of patients with MS suffering from co-morbid impaired immune systems including selective IgM deficiency, combined immunodeficiency, and immune dysregulation.
Amicrobial pustulosis associated with autoimmune disease (APAD) responsive to mycophenolate and dapsone

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RATIONALE: Amicrobial pustulosis associated with autoimmune disease (APAD) is a rare diagnosis that typically presents in females with hypergammaglobulinemia and positive ANA. Patients have a chronic relapsing course that improves mainly with protracted courses of systemic steroids.

METHODS: A case of adult-onset, severe chronic pustular pruritic dermatosis with disseminated lymphadenopathy, immune dysregulation and severely elevated IgE levels is presented.

RESULTS: A 42-year-old male with a history of seropositive Sjogren’s syndrome presented with a 2 year history of diffuse pustular dermatosis and lymphadenopathy. Notable findings included a serum IgE level of 7,719 mg/dL, absolute eosinophil count of 1,500, and polyclonal pan-hypergammaglobulinemia. Ofuji’s eosinophilic or neutrophilic pustular folliculitis, lymphoma and HIV folliculitis were initially considered diagnoses.

Skin biopsies were sterile and demonstrated non-specific subacute spongiotic dermatitis with non-specific immunofluorescence. Tryptase, CRP, TTG, H. pylori IgG, RF, neutrophil oxidative burst, IL-10 suppression, galactomannan, HIV PCR and stool O&P serologies were normal. CT scan showed extensive adenopathy. Lymph node biopsy was dermatopathic and bone marrow biopsy demonstrated polytypic plasmacytosis with normal cytogenetics. Flow cytometry demonstrated increased activated CD4 and CD8 T cells and reduced unswitched memory B cells.

The rare diagnosis of APAD was ultimately considered. Patient responded transiently to a prolonged oral corticosteroid regimen, but failed antibiotic, antifungal, antistaminie, topical steroids, indomethacin, ivermectin and dapsone monotherapy. Patient experienced marked improvement of the dermatosis, lymphadenopathy, and pruritus with mycophenolate and dapsone.

CONCLUSIONS: APAD is a rare clinical condition of uncertain pathogenesis. This case of novel and successful use of mycophenolate and dapsone may offer a steroid sparing option.

Combination Omalizumab and Intravenous Immunoglobulin (IVIG) as successful treatment of common variable immunodeficiency (CVID) and severe persistent asthma

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RATIONALE: A subset of patients with CVID have concurrent allergy and asthma. The efficacy of omalizumab in these patients has not been established. Omalizumab is thought to improve asthma control through both anti-allergic and anti-viral immunomodulation suggesting a potential role for some immunodeficient patients. We report a case of CVID with concurrent severe persistent asthma successfully treated with combination omalizumab and IVIG.

METHODS: Laboratory assessments were performed at University of Washington Medical Center.

RESULTS: A 50-year-old female was referred for recurrent respiratory infections and poorly controlled asthma including multiple ICU admissions. She had a history of mild asthma and allergic rhinitis but her clinical symptoms worsened significantly in her 40’s. Her total IgE was 425 mg/dL and specific IgEs were positive to multiple environmental allergens. Her FEV1 was 57% predicted. Omalizumab was started for her severe asthma with improvement in severity of exacerbations, however she continued to have respiratory infections and intermittent need for corticosteroids and antibiotics. Further workup revealed hypogammaglobulinemia (IgG 428 mg/dL) with poor pneumococcal vaccine response. She was diagnosed with CVID and started on IVIG in addition to omalizumab with resolution of respiratory infections and further improved asthma control.

CONCLUSIONS: Patients with CVID may also have allergic disease and asthma. Combination IVIG and omalizumab therapy has not been previously described. Here we report a patient with severe asthma, elevated IgE, and CVID with clinical benefit from combination omalizumab and IVIG. Treatment with omalizumab should be considered in patients with CVID and asthma who have multiple risk factors for progressive pulmonary disease.
**680** Similar Efficacy and Pharmacokinetic Behavior of Intravenous Immunoglobulin (Privigen®) in Primary and Secondary Immunodeficiency

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**RATIONALE:** Both primary and secondary immunodeficiency disorders (PID and SIDs) are treated with immunoglobulin G (IgG) replacement therapy. We aimed to determine the relationship between IgG dose, IgG trough (IgGt) levels, and infection rate in PID and SID patients treated with intravenous IgG (IVIG; IgPro10 [Privigen®]).

**METHODS:** Pooled clinical study data from 90 PID and 98 SID patients who completed the study; none of the discontinuations (n = 9) were treatment-related systemic or local AEs. There was no association between the rate of causally-related local AEs during onboarding was low, which decreased and remained low over time. The rate of local AEs was not associated with fast infusion rates or large volumes per site with this new SCIG 20% treatment.

**RESULTS:** Mean (standard deviation [SD]) plasma IgGt levels during IVIG therapy were higher in PID (9.1 [3.2] g/L) than in SID (6.1 [1.9] g/L), corresponding to the higher mean (SD) monthly IgG doses in PID (451 [132] mg/kg vs 218 [105] mg/kg in SID). Mean (SD) annualized infection rates were within the same near-normal range in PID (2.97 [3.30] infections/patient) and SID (1.69 [2.88]). Higher IgGt correlated with lower infection rates in both indications. Efficiency index was inversely proportional to IgGt, for both PID and SID, with comparable efficiency at the same IgGt levels.

**CONCLUSIONS:** Low infection rates can be achieved with IVIG therapy in both PID and SID patients. IVIG doses and IgGt levels necessary to maintain a low infection rate appear lower in PID than in SID.

Individualized dosing based on the patient’s clinical condition may be appropriate in both disorders.

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**682** A New Subcutaneous Immunoglobulin 20% Formulation (SCIG 20%) with Individualized Infusion Parameters Resulted in a Positive Safety and Tolerability Profile in Patients with PIDD in Europe and North America

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**RATIONALE:** Cuvitru, a new human immune globulin (Ig) subcutaneous, 20% (SCIG 20%) ready-for-use, liquid preparation of highly purified human IgG, was well tolerated based on data from a combined analysis of two phase 2/3 studies in patients with primary immunodeficiency diseases (PID) in Europe and North America. Improved tolerability of this new SCIG 20% allows for increased dose/site (up to 12 g/site) and fast infusion rates (up to 60 mL/hr/site), while demonstrating a low rate of local adverse reactions (LARs).

**METHODS:** The rate of LARs was assessed in patients with PIDD aged ≥2 years, who at screening were receiving Ig replacement therapy (300-1000 mg/kg every 3-4 weeks) ≥3 months and had a serum IgG trough level of ≥500 mg/dL.

**RESULTS:** Overall, 112 (91.8%) of 122 patients aged 2-83 years who were treated with SCIG 20% completed the studies (median of 365 days). Only one discontinuation was due to mild infusion-site pain. The LAR rate was 0.034/infusion; almost all were mild (0.033/infusion) and 0.001/infusion were moderate in severity. No treatment-related LARs were reported in 65.6% (80/122) of patients; 3.1% of infusion were associated with non-serious LARs. Most infusions were completed in <1 hour (n = 3,445; 53%) or <2 hours (n = 6,005; 92.4%). Overall, 99.8% of 6,665 infusions were completed without any administration changes, such as slowing, interrupting, or stopping the infusion.

**CONCLUSIONS:** A positive safety and tolerability profile of a new SCIG 20% was demonstrated in patients with PIDD at increased doses/site, large infusion volumes/site, and relatively fast infusion rates.

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**681** Review of the Onboarding Experience of a New 20% Human Immune Globulin for Subcutaneous Administration (SCIG 20%): Correlation of Infusion Parameters and Adverse Events (AEs)

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**RATIONALE:** Data from a phase 2/3 North American clinical trial provided an opportunity to understand the onboarding experience of a new SCIG 20% in patients with PIDD. This new highly-concentrated SCIG 20% allows for fast infusion rates and large infusion volumes resulting in shorter infusion durations.

**METHODS:** Patients (3-83 years) received weekly SCIG 20% for >1.3 years. As tolerated, volumes up to 60 mL/site and rates up to 60 mL/hr/site were infused. Associations between the rate of causally-related local AEs and the infusion parameters were investigated.

**RESULTS:** Of the 77 enrolled patients, 53 (69%) had no previous SCIG experience. Overall, 91% (67/74) of patients treated with SCIG 20% completed the study; none of the discontinuations (n = 7) were due to treatment-related systemic or local AEs. There was no association between the rates of causally-related local AEs (0.4%, 1.4%, 1.1%, and 0.3%, respectively) and the infusion volume/site (30-39, 40-49, 50-59, and ≥60 mL/site, respectively). At infusion 1, 13% of patients reported ≥1 causally-related local AEs, which decreased and remained low throughout the study.

The median total infusion time was 0.95 hours (53% and 94% of infusions were delivered in <1 and <2.0 hours, respectively). The median maximum infusion rate (60 mL/hr/site) was used by 71.6% (53/74) of patients and during 57.3% of infusions.

**CONCLUSIONS:** The percent of patients who experienced causally-related local AEs during onboarding was low, which decreased and remained low over time. The rate of local AEs was not associated with fast infusion rates or large volumes per site with this new SCIG 20% treatment.
683 Longitudinal Data from a Prospective Observational Study of Hypogammaglobulinemia After Lung Transplantation (LT)

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RATIONAL: Immunosuppressive therapies have led to vast improvements in survival in LT recipients but these therapies can lead to hypogammaglobulinemia resulting in increased risk of infection.

METHODS: This is a single center prospective study of LT recipients at the University of Pittsburgh Medical Center. Pre- and post-transplant IgG levels were measured and related to pneumonias and survival. Analysis was performed using non-parametric tests (Wilcoxon rank-sum).

RESULTS: 135 LT recipients were evaluated. The mean age was 56.8 years and 62.2% were males. The primary reasons for transplant were IPP, COPD, and CF. 66.7% were induced with Alemtuzumab and 33.3% with Basiliximab. Median IgG levels increased from 496.5 mg/dl 1 week post-transplant to 675 mg/dl at 18-months post transplant. 10 subjects were deceased by 18 months (7.4%). Post-transplant subjects receiving Basiliximab had significantly lower IgG levels at 3, 6, and 9 months than those induced with Alemtuzumab, but those differences were absent at 12, 15 and 18 months after transplant. In subjects who had one or more incidence of pneumonia in the first 12 months after transplant, there was a negative correlation between IgG level and the number of pneumonias (Spearman’s rho = -0.31, p = 0.05), though that relationship was absent at 15 and 18 months post-transplant. In addition, one-year and 18-month mortality were associated with lower IgG levels at 3 months post-transplant.

CONCLUSIONS: Our results suggest that LT recipients with lower IgG levels may be at risk for developing recurrent pneumonias at 1 year and increased mortality at 12 and 18 months.

684 Evaluation of Physician-Patient Interactions Regarding Route of Administration for Immunoglobulin Therapy in Primary Immunodeficiency Disease

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RATIONAL: Immunoglobulin(IG) is standard therapy in treating primary immunodeficiency disease (PIDD) and can be infused intravenously (IV) or subcutaneously (SC). These routes of administration (RoA) have differentiating characteristics, including frequency and duration of infusions, number of needle sticks, and the nature of side effects. Communicating these RoA differences is important for the patient to make an informed decision in choosing which RoA best fits their lifestyle.

METHODS: We conducted IRB-approved online surveys with 100 board-certified allergists/immunologists treating PIDD patients, and 158 PIDD patients currently receiving IVIG or SCIG. Similar questions were asked of physicians and patients to evaluate their perceptions of therapeutic dialogue during a patient’s initial IG-prescribing visit.

RESULTS: Twenty-three patients (15%) feel their provider explained the different RoAs in a hurried, unclear or confusing manner. Physicians report discussing concerns or issues with the different RoAs less frequently compared to physician self-report (77% vs 95%). Additionally, physicians overestimate how often they ask questions in an open-ended format to patients (95% vs 73%) and how frequently they discuss the risks associated with each RoA (95% vs 73%). Nearly all (84%) physicians report they make the final RoA decision together with the patient; however, less than half (48%) of patients believe this is a joint decision. Only 6% of physicians believe they made the final RoA decision; however 23% of patients felt the provider made the decision.

CONCLUSIONS: These data suggest a discrepancy exists between physicians’ and patients’ perceptions of the initial IG-prescribing visit. In order to bridge this gap, improved physician/patient communication regarding the different IG routes of administration may be warranted.

685 Analysis of Safety and Tolerability Data in Pediatric Patients with Primary Immunodeficiency Diseases from Two Phase 2/3 Studies of Human Immunoglobulin Subcutaneous, 20%

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RATIONAL: Two phase 2/3 studies of Cuvimru (human SCIG 20%) in patients with primary immunodeficiency diseases (PIDD) were conducted in North America and Europe. We present the combined safety and tolerability data in pediatric patients.

METHODS: A total of 39 patients (2-<16 years) received weekly SCIG 20% infusions for ~1 year. Serious adverse events (SAEs), rates of local/systemic adverse reactions (ARs) defined as causally-related AEs, and infusion characteristics were analyzed.

RESULTS: Patients received a total of 2118 SCIG 20% infusions. No SAEs related to SCIG 20% were reported. All ARs were mild or moderate. In the age groups 2-<6 (n=6), 6-<12 (n=22), and 12-<16 years (n=11), the local AR rates/infusion were 0.010, 0.037 (95% mild), and 0.057 (0.180 including one patient who reported 72% of local ARs in this age group, 100% mild), and the systemic AR rates/infusion were 0.010, 0.003, and 0.024, respectively. All infusions were tolerated well; > 99% of them did not require any rate reduction or interruption. In North America, for the age groups 2-<6 (n=1), 6-<12 (n=14), and 12-<16 years (n=6), median infusion rates were 15.0, 30.0, 50.0 mL/hr/site, and median infusion volumes were 14.5, 19.5, and 42.7 mL/site, resulting in median infusion durations of 0.95, 0.73, and 1.18 hours, respectively. Per infusion, 1 or 2 infusion sites (median) were used.

CONCLUSIONS: SCIG 20% treatment was safe and well tolerated at high infusion rates and volumes per site with short infusion durations, offering a favorable Ig treatment option in pediatric patients.
AB218 Abstracts

**686** Intravenous Immunoglobulin (Privigen®) Has Similar Pharmacokinetic Properties in Primary and Secondary Immunodeficiency

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**RATIONALE:** Immunoglobulin G (IgG) pharmacokinetics (PK) and dosing recommendations are well established for primary immunodeficiency (PID), but under-investigated in secondary immunodeficiency (SID). We compared PK characteristics of intravenous IgG (IVIG; IgPro10 [Privigen®]) in PID and SID patients using a population PK approach.

**METHODS:** Data on demographics, IgG dose, and plasma IgG concentration (including trough level [IgGtrough]), were collected from 90 PID and 98 SID patients, and pooled for analysis in each indication. A covariate analysis of IgG PK parameters (including weight, disease type, age, etc.) was performed to determine the cause of variability in IgG PK parameters.

**RESULTS:** Mean (standard deviation [SD]) monthly IVIG doses in PID and SID were 451 (132) mg/kg and 218 (105) mg/kg, respectively, resulting in mean (SD) serum IgGtrough levels of 9.1 (3.2) g/L (PID) and 6.1 (1.9) g/L (SID). Higher IVIG doses correlated with higher IgGtrough. Logistic regression analyses showed significant effects of weight on clearance was observed. When accounting for the difference in weight between the PID and SID populations, the difference in clearance values was within 1%.

**CONCLUSIONS:** PK analyses indicate that the disposition of IVIG Privigen® during IgG replacement therapy is similar, irrespective of whether the defect is inherited or acquired, supporting the use of similar therapy approaches in PID and SID.

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**687** Subcutaneous Immunoglobulin (SCIG) Therapy during Pregnancy in a Woman with Hyper-IgM (HIGM) Syndrome

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**RATIONALE:** HIGM syndromes are rare disorders distinguished by quantitative deficiencies of IgG and IgA with normal or elevated IgM resulting from defective antibody class-switching. Patients with immunodeficiency require special consideration of immunoglobulin replacement strategies during pregnancy, and IgG trough levels with decrease during pregnancy due to such physiologic factors as plasma volume expansion and increased catabolism. SCIG product inserts recommend periodic monitoring of total IgG levels during maintenance therapy, although high-quality evidence is lacking. We present an empirically successful management strategy for SCIG maintenance therapy during pregnancy for a patient with HIGM.

**METHODS:** Beginning at the end of the first trimester, trough total serum IgG Levels were monitored monthly and weekly SCIG doses (Hizentra, CSL Behring) adjusted as clinically indicated or to approximate 700 mg/dL.

**RESULTS:** Incremental dosage increases of 1 to 3 grams of SCIG were required beginning in the second trimester of both pregnancies. A UTI during the first trimester of the second pregnancy resolved with oral nitrofurantoin. She had two spontaneous, term deliveries at ages 29 years and 33 years, respectively. She continued the final SCIG dose for 4 weeks post-partum and then resumed the ante-partum dose.

The first child has Down syndrome, which we do not attribute to immunoglobulin replacement; the second child has no discernible development defects.

**CONCLUSIONS:** We believe this is the first report of a specific SCIG strategy during pregnancy for a patient with HIGM. Further pregnancy registry data are needed.

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**688** Is Oral Route an Option for Intravenous Human Immunoglobulin As an Adjunctive Treatment for Recurrent Diarrhea in Immunocompromised Pediatric Patients? Extended Follow-up

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**RATIONALE:** Immunocompromised patients (IP) often suffer recurrent episodes of diarrhea associated with poor clinical outcome. Mucosal and humoral immunity seem to play an important role in its resolution. We hypothesized that oral use of intravenous human normal immunoglobulin (IgOR) could help to eliminate pathogens diminishing the consequent chronic epithelial inflammation if able to reach their target in pediatric IP with recurrent infectious enteropathy.

**METHODS:** Retrospective study of gastroenteritis due in IP who required admission from November 2014-March 2016 in whom standard therapy failed and received adjunctive therapy with IgOR.

**RESULTS:** Four males were included; mean age: 2.7 years (2.0-3.1). They have undergone heart (2), kidney (1) and bone marrow (1) transplantation. Three were hypogammaglobulinemic during the infectious episode. All four were still on immunosuppressive regimen. Norovirus (2) and Campylobacter spp. (3) were the causative agents (one patient had a coinfection). All of them received antibiotics and 2 intravenous IgG replacement therapy. All four received IgOR treatment between 17 and 60 days from the symptoms’ onset. Microbiological clearance was observed in only 1 patient and 3/4 presented a transient clinical outcome. After a median follow-up of 16 (6-22) months 2 patients remain asymptomatic. The other 2 continued with milder episodes of recurrent diarrhea treated with supportive therapy.

**CONCLUSIONS:** Despite transient clinical improvement, microbiological clearance remains a challenge leading to recurrences. Although several significant limitations, our study highlights the importance and difficulty to treat of chronic infectious enteropathy in IP. A multicenter prospective study to assess the usefulness of IgOR is needed.
689 Improved Treatment Satisfaction with a New Human Subcutaneous Immunoglobulin (SCIG 20%) in Patients Previously Treated with IVIG

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RATIONALE: Treatment satisfaction is an important consideration for immunoglobulin therapy. This analysis compares the treatment satisfaction during the IVIG and Cuvitru (SCIG 20%) treatment periods of clinical studies conducted in North America and Europe among patients who entered the study from IVIG therapy.

METHODS: Two phase 2/3 prospective studies evaluated patients with PIDD treated with SCIG 20% for approximately 12 months subsequent to 3 months of treatment with either IVIG (North American study) or IVIG or SCIG (European study). This analysis assessed treatment satisfaction using the Life Quality Index (LQI) instrument at the end of the IVIG period and after the completion of the SCIG 20% period in both studies among patients entering the studies from IVIG therapy. Higher LQI scores indicate greater satisfaction. Median scores were reported. Statistical significance was evaluated with Wilcoxon Signed Rank test.

RESULTS: Patients reported significant improvements from the IVIG period to the SCIG 20% period in both studies among patients entering the studies from IVIG therapy. Higher LQI scores indicate greater satisfaction. Median scores were reported. Statistical significance was evaluated with Wilcoxon Signed Rank test.

CONCLUSIONS: After 12 months on the new 20% SCIG, patients reported improvements in treatment satisfaction compared with IVIG. Clinicians should consider improved satisfaction in offering the new 20% SCIG to patients receiving IVIG.

690 Personalized Approach to Subcutaneous Gammaglobulin Infusion with Flexible Dosing Regimens

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RATIONALE: Subcutaneous Immunoglobulin (SCIg) therapy for Common Variable Immunodeficiency (CVID) is often implemented on a weekly, biweekly or monthly schedule. Flexible individualized dosing would achieve better patient outcomes including tolerance and adherence to treatment and thus decreased infections.

METHODS: A retrospective analysis of 20 patients between the ages of 15 - 80 were treated over a 2 year period with variable high dose 20% SCIg therapy in a private community allergy practice. Most patients had secondary CVID and associated concomitant diseases such as SLE, post CLL, and bronchiectasis. All had previous hospitalizations for serious infections.

RESULTS: Prior to initiating SCIg therapy a team was formulated to review the best treatment approach. This included physician, patient and patient’s family, nursing and specialty pharmacist. Review of patient’s concomitant diseases, medications and renal, cardiac and pulmonary function helped guide decision on dosing with weekly or biweekly therapy. Older patients with decreased renal function and cardiac disease were initiated with weekly infusions and gradually increased to biweekly or every 10 day regimens. Younger patients tolerated a biweekly regimen with larger volumes of infusion per site and fewer sites of infusion. Patient outcomes were improved including decreased infection rates and side effects of treatment. Two patients required hospitalization, one with pneumonia and another with shingles.

CONCLUSIONS: Treatment with an individualized, flexible dosing regimen can achieve successful outcomes in SCIg therapy. A thorough team discussion of treatment options, concerns and preferences with the patient prior to initiation of therapy can provide a personalized approach to SCIg therapy.

691 Oral Immunoglobulin Controls Chronic Diarrhea in Common Variable Immunodeficiency (CVID)

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RATIONALE: Gastrointestinal manifestations in CVID are usually not controlled with intravenous immunoglobulin (IVIG).

METHODS: We report two cases of successful oral IVIG treatment of CVID-associated chronic diarrhea.

RESULTS: Case 1: 8y/o boy, had several admissions for pneumonia and diarrhea, one in pediatric ICU. Additionally, he had recurrent otitis media, chronic rhinosinusitis and bronchiectasis. At the age of 1: IgG 273mg/dL, IgA and IgM undetectable, no BTK deficiency. IVIG was introduced right after the diagnosis. Because of persistent chronic diarrhea and severe malnutrition, oral IVIG (5g/month) was initiated and after 2 months, the diarrhea ceased, remaining so after 16 months of use.

Case 2: 36 y/o woman diagnosed with CVID in 1998, laboratory tests : IgG 253mg/dL, IgA 37mg/dL and IgM 16mg/mL. Chest CT showing bronchiectasis. She began to receive IVIG right after the diagnosis and remained stable, with occasional use of antibiotics for rhinosinusitis. By the age of 34, she started with persistent diarrhea, > 20 episodes/day, weight loss (10 pounds) and impairment of daily activities. Stool culture did not show any pathogenic bacteria. Oral IVIG was initiated (5g/month) with complete resolution of diarrhea. After 6 months of treatment, she remained with no diarrhea.

CONCLUSIONS: Oral IVIG demonstrated benefit in CVID-associated chronic refractory diarrhea. Further controlled studies are needed to confirm the optimal dose and mechanisms of such route of IVIG.
Paradoxical Effect of Epinephrine Administration During Anaphylaxis

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RATIONALE: Bradycardia is an unexpected effect of epinephrine administration. Clinical factors that predispose to this paradoxical reaction are infrequently appreciated by healthcare providers and patients administering epinephrine.

METHODS: Three patients presented here were referred for outpatient Allergy evaluation following episodes of anaphylaxis.

RESULTS: History of anaphylaxis was the presenting concern in all cases. The cause of anaphylaxis was identified as tree nut (n = 1) and unknown (n = 2). Peak tryptase levels were 2.6ng/ml (tree nut anaphylaxis), 26.2ng/ml, and 72.6ng/ml (normal <11.5 ng/ml). Management of anaphylaxis was complicated by bradycardia ensuing within 15 minutes of epinephrine administration. Heart rate nadir was 33-42 bpm. EKGs showed no underlying conduction abnormalities. Glucagon (n = 1) and atropine (n = 2) were administered with resolution of arrhythmia shortly. Chart review was significant for use of non-selective beta-blockers (NSBB; oral: n = 2; ophthalmic: n = 1) at the time of reaction. NSBB use was for anxiety (n = 1), headache prophylaxis (n = 1), and glaucoma (n = 1). Discussion with patients’ care providers was undertaken to assess alternatives to beta-blocker use.

CONCLUSIONS: Paradoxical bradycardia following epinephrine administration is well-documented but rare. NSBB use can be a likely modifiable factor. Once paradoxical bradycardia is recognized, discussion with other healthcare team members may prevent future episodes by finding alternatives to NSBBs where permitted, or having risk-benefit discussions when beta-blocker use is mandated. Allergists are in a unique position to educate patients and other providers about potential adverse effects of epinephrine.

Trends in Reporting of Physician-Diagnosed Food Allergy in New York City Schools

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RATIONALE: Food allergy (FA) prevalence appears to have increased, but the reporting rate of medically documented FA to schools is not well established.

METHODS: Medically-documented reporting of FA (“cases”) in the New York City (NYC) public school system, which includes over 1 million students, was retrospectively reviewed for the school years 2007-08 to 2012-13. Cases included students whose FA was entered into schools’ electronic health records (EHR), which require physician documentation on a health examination form, medication administration form, or other communication. Collated and de-identified data from citywide school EHR were provided to investigators by the NYC Department of Health and Mental Hygiene.

RESULTS: Prevalence of medically-documented FA increased each year from 0.4% (4,007/1,037,560) in 2007-08 to 1.4% (15,944/1,116,346) in 2012-13. Reporting was higher for younger children: 1.3%, 0.8%, and 0.4% in elementary, middle, and high schools, respectively. Overall, there was a male predominance (OR 1.33, p<0.001). Cases were more likely to be white (OR 2.4), Asian (OR 1.1), or identifying as “other” (OR 1.3) than black (OR 0.8) or Hispanic (OR 0.64; all preceding p<0.001). Those eligible for free lunch (proxy socioeconomic status) were less likely to have medically-documented FA (OR 0.53, p<0.001). Only 48% of those with medically-documented FA provided an epinephrine auto-injector (EAI) to the school.

CONCLUSIONS: Medically-documented FA has increased among NYC students, and varied with age, gender, race/ethnicity, and socioeconomic status. Additional study is needed to explore differences in medically-documented and undocumented FA, as well as the unexpectedly low rate of families providing EAs for school emergencies.
**695 Are There Racial and Socioeconomic Disparities in School Peanut-Free Policies?**

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**RATIONALE:** Racial and socioeconomic disparities exist in school food allergy emergency preparedness and epinephrine access. Peanut-free policies exist in some schools. We sought to determine the association of race and socioeconomic status with school peanut-free policies.

**METHODS:** Massachusetts public school nurses were surveyed on their schools’ peanut-free policies in the 2010-2011 academic year. Racial and socioeconomic data were compared for schools with and without peanut restrictive policies.

**RESULTS:** Four hundred and thirty-four public schools in rural, suburban, and urban settings throughout the state of Massachusetts provided data for this study. Schools banning compared to those permitting peanuts from home had a higher proportion of low-income (24.1% v. 17.0%, p < 0.05) but similar proportion of minority (12.5% v. 13.7%, p = 0.56) students. Schools with peanut-free policies compared to those permitting peanuts being served in school had a higher proportion of low-income (24.3% v. 10.3%, p < 0.0001) but similar proportion of minority (12.5% v. 12.6%, p = 0.75) students. Schools banning compared to those permitting peanuts being served in school had a higher proportion of low-income (31.7% v. 16.8%, p < 0.0001) and minority (24.6% v. 11.1%, p < 0.0001) students. Schools with peanut-free classrooms compared to without had higher proportions of low-income (44.0% v. 21.0%, p < 0.0001) and minority (42.3% v. 15.4%, p < 0.0001) students.

**CONCLUSIONS:** This is the first study correlating racial and socioeconomic disparities with specific food restrictive school policies. Schools with more restrictive and potentially protective policies had higher proportions of racial minority and low-income students.

**696 Locations of Anaphylactic Events in Schools As Observed in the 2014-2015 EPIPEN4SCHOOLS® Survey**

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**RATIONALE:** The EPIPEN4SCHOOLS® program provides stock EpiPen® (epinephrine injection) Auto-Injectors to >60,000 qualifying schools across the United States. A survey of these schools was conducted to determine how anaphylactic events are managed in schools.

**METHODS:** A cross-sectional, web-based survey of schools participating in the EPIPEN4SCHOOLS® program during the 2014-2015 school year was conducted.

**RESULTS:** During the 2014-2015 school year, 12,183 responding schools reported 2191 anaphylactic events. The majority of events with data on location of where symptoms developed occurred in 3 areas of the school: 46.6% (928/1992) of events occurred in the classroom, 19.9% (396/1992) occurred in the cafeteria, and 9.7% (194/1992) occurred on the playground. Among the schools that provided information on which types of staff were permitted to administer epinephrine, 89.8% (10,968/12,213) permitted the school nurse; 73.2% (8940/12,213) permitted at least some teachers, and 44.9% of those schools (4007/8934) permitted all teachers. Additionally, 35.1% of schools (4292/12,213) permitted students to self-administer epinephrine.

**12,183 indicated there was a full-time nurse available at the school, while 32.0% (3899/12,183) had a part-time nurse.

**CONCLUSIONS:** As anaphylactic events occurred in various locations throughout schools, there is a need to make sure that a range of staff members are trained to recognize anaphylaxis and administer epinephrine. However, less than half of schools allowed all teachers to administer epinephrine and nearly half did not have a full-time nurse available, indicating that students suffering an anaphylactic attack may not encounter a staff member permitted to administer epinephrine.

**697 Current State of Food Allergy Education and Training in Schools: School Nurse Survey Study**

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**RATIONALE:** Food allergy prevalence is rising, and children spend a significant amount of time at school. Little is known, though, about the present state of school food allergy education. Thus, this study aimed to assess current practices, in order to garner more information for improvement.

**METHODS:** An anonymous electronic survey was distributed via the email list serve for the National Association of State School Nurse Consultants. The state school nurse consultants had the option to share with school nurses in their states.

**RESULTS:** 92.1% of 1486 respondents were RNs with a median of 11-15 years of school nursing experience. 99.3% report students with food allergies at the school(s) they serve and 34% covered >2 buildings. Nearly half report that >75% of their school staff receive food allergy education, but 15% report <10% of their staff receive training. 50.8% of responders received food allergy education within the past 12 months, whereas 14.6% report never receiving any training. School nurses provided a majority of food allergy education for other staff members (92.7%) and students (75.5%), 94.9% and 74.2% state that teachers and administrators, respectively, participate in training but only a small number of substitute teachers (18.5%) and volunteers (5.2%) do.

**CONCLUSIONS:** Despite the potential severity of food allergy reactions there are many schools where the nurse may not be onsite at all times and where many of the staff is not trained. Training a wider population of school workers may be beneficial and extend the school nurses ability to manage students with food allergies in schools.
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RATIONALE: Food allergy affects 3-6% of school age children. Consensus guidelines on the management of food allergy in the school setting recommend food allergic students have an individualized emergency care plan (ECP) as well as epinephrine available at all times. This study examined whether food allergic children (K-12) had ECPs and epinephrine at school.

METHODS: Data regarding ECPs, epinephrine auto injectors, and type of food allergies was collected for the 2015-2016 school year from the school nurses at each school in the district.

RESULTS: Data was available for 5,015 of 5,738 students in the district. 418 (8.33%) students reported food allergies. From kindergarten through 7th grade, the percentage of students with ECPs was 71.8% (171/238), and the percentage of students with epinephrine auto-injectors was 83.6% (199/238). From 8-12 grade, the rate of students with ECPs decreased to 5.0% (9/180), and the rate of epinephrine auto-injectors decreased to 47.2% (85/180). These figures accounted for students who had documentation of permission to self-carry epinephrine in the district, including grades 8-12.

CONCLUSIONS: In this suburban school district, there was a significant decrease in the percentage of students with ECPs and epinephrine auto-injectors from grades 8-12 compared to grades K-7. Adolescence and delayed administration of epinephrine are risk factors for poor outcomes from food allergy anaphylaxis. This data highlights a gap in anaphylaxis preparedness in the school setting, and suggests an opportunity for targeted educational efforts towards this high risk population.

Michael Pistiner, MD, MMS1, and Julie Wang, MD2; 1Harvard Vanguard Medical Associates, Boston, MA, 2Icahn School of Medicine at Mount Sinai, New York, NY.

RATIONALE: New regulations addressing epinephrine in school are now widespread throughout the U.S.

METHODS: An anonymous electronic survey was distributed via the email list serve for the National Association of State School Nurse Consultants. The State School Nurse Consultants had the option to share with school nurses in the states that they represent.

RESULTS: 1486 responders started the survey, 1,285 (86%) completed all survey questions. The majority represented 9 states (≥20 participants from each), but other states were also represented. 41.4% reported having ever administered epinephrine.

For the 2015-2016 (2014-2015) school year 15% (24%) of participants reported that at least one dose of epinephrine was administered in their School(s) by anyone, themselves included. 2.7% (4.3%) reported that epinephrine was administered by unlicensed staff. Epinephrine was administered by a licensed school nurse to someone without a known prior allergy in 4.8% (8%); unlicensed staff administered epinephrine to someone without a known history in 0.98% (1.6%). 1.7% (2.9%) reported >1 dose of epinephrine was needed for a single event of anaphylaxis before EMS arrival.

CONCLUSIONS: Epinephrine use in schools is significant, and is being given by both licensed and unlicensed school staff for individuals with known and unknown histories of allergies. Although epinephrine use by unlicensed staff is less frequent than by licensed school nurses, these results support the importance of staff training.

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RATIONALE: The purpose was to understand and evaluate patient characteristics, concordance with post discharge care, health care resource utilization and repeated events among adults and children with an inpatient or Emergency Department (ED) claim for anaphylaxis in the United States.

METHODS: For retrospective analysis the Truven Healthcare MarketScan® database was used to assess pre- and post-event epinephrine auto-injector (EAI) prescriptions and Health Care Resource Utilization associated with these prescriptions.

RESULTS: The study comprised 10189 adults (age >18) and 3891 pediatric patients (age <18). 11.7% of patients seen in the ED were admitted to inpatient care and spent 2.7 days on average in the hospital. At the time of the index event 83.3% of patients did not have a prescription for an EAI filled. Only 12.1% of patients had the minimum of 1 EAI prescription refill. The mean number of days from last prescription to anaphylactic event was 2350 days.

CONCLUSIONS: A significant portion of patients are transitioned to inpatient care from the ED resulting in greater healthcare utilization. The data indicate that patients demonstrate suboptimal maintenance of EAI prescriptions placing them at risk for life threatening events and questioning the preparedness of patients and caregivers for the management of an anaphylactic event. Given the low active prescription level it appears patients are not proactively prepared for an anaphylactic event which may lead to costly ED visits and hospital admissions.

Juhee Lee, MD, Bonnie Rodio, BSN, RN, CEN, CPHQ, Jane Lavelle, MD, Megan Ott Lewis, MSN, RN, CPNP. Jennifer Molnar, CRNP, Cynthia Jacobstein, MD, Sarah Hadley, RN, Rachel English, Lisa Zielinski, RN, Nicholas Tsarouhas, MD, and Terri F Brown-Whitehorn, MD FAAAAI; The Children’s Hospital of Philadelphia, Philadelphia, PA.

RATIONALE: Recommended durations of observation following anaphylaxis have been widely variable, with many ranging from 8 to 24 hours. Prolonged durations often prompt admission for ongoing observation.

METHODS: We revised the anaphylaxis clinical pathway of the Emergency Department (ED) of the Children’s Hospital of Philadelphia to decrease the recommended length of observation from 8 to 4 hours. We reviewed the medical records of ED patients diagnosed with anaphylaxis between April 2013 and April 2016 and compared rates of admission and return visits between the 18 months prior to (baseline cohort) and the 18 months following (update cohort) the pathway revision.

RESULTS: A total of 439 patients (median age 6 years) were diagnosed with anaphylaxis over 3 years, with 182 patients in the baseline cohort and 257 patients in the update cohort. Overall admission rate decreased from 58.2% (106/182) in the baseline cohort to 24.5% (63/257) in the update cohort (p<0.0001). Patients discharging from the ED had epinephrine auto-injectors in hand. Following discharge, 1.3% (1/76) of the baseline cohort and 2.6% (5/194) of the update cohort returned to the ED within 72 hours (p=0.52). None of the revisions in either cohort were for severe symptoms or anaphylaxis.

CONCLUSIONS: Decreasing the recommended length of observation following anaphylaxis from 8 to 4 hours in a pediatric ED resulted in a near 60% reduction in the overall admission rate while the rate of return visits remained similar. A 4-hour length of observation appears safe and could drastically improve ED patient flow and decrease hospitalization rates.
702 An Analysis of Anaphylaxis Cases at a Single Pediatric Emergency Department in Over One Year

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RATIONALE: Case series of anaphylaxis can vary regarding causes, treatments, and follow up of patients. We sought to define these variables at a pediatric ED over a single calendar year.

METHODS: We identified all ED visits with the following ICD-9 codes: 995.XX (allergic reactions) and 989.5 (sting or venom reaction) for one calendar year (1/1/2014 through 12/31/2014). Cases were reviewed by an allergist (JAL) and an emergency medicine physician (ML) to identify true anaphylaxis cases using Sampson criteria. Any questionable or disputed case was reviewed and ruled on by an expert in anaphylaxis (PL).

RESULTS: We identified 927 unique ED visits. Of which, 40 were determined to definitively meet anaphylaxis criteria. Median age of cases was 6.5 years. 70% of cases were male, and 89% were African American. The most common trigger was foods (65%) and other triggers included venom/insect sting (12.5%) and medications (5%), while 18% were idiopathic. All cases had multi-organ involvement with 98% of cases having skin involvement, 78% having lower respiratory symptoms, and 40% having GI symptoms. There were no deaths. Only 33% of cases received epinephrine at some point in their care. Only 12 cases (30%) mentioned referral or were referred to an allergist and only 4 of these were actually seen by an allergist in follow-up care.

CONCLUSIONS: At our center, true anaphylaxis remains rare, and foods are the most common trigger. Cases seem to continue to be undertreated and follow up with an allergist was very rare.

703 Dispensing Patterns of Epinephrine Auto-Injectors for Treatment of Anaphylaxis in Manitoba Children and Uptake of Allerject (Auvi-Q)

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RATIONALE: Epinephrine is the first-line medication for treatment of anaphylaxis. We evaluated dispensing patterns for epinephrine auto- injectors (EAIs) in Manitoba from the time Allerject (Auvi-Q) became available until its recall.

METHODS: Using the Drug Programs Information Network (DPIN) administrative pharmaceutical claims database in Manitoba, Canada, we analyzed dispensing data for EAIs among children ages 0-16 years from February 2013 to May 2015, inclusive. We evaluated the absolute number and percent of EAIs dispensed overall and as first dispensions (EAIs dispensed for children with no previous EAIs dispensed). Using multivariable logistic regression, we calculated the change in Allerject dispensing over the study period.

RESULTS: In 2 years, EAIs were dispensed 15,755 times for 7390 children. The total number of EAIs dispensed increased in each year studied. In 2013, 2014, and 2015, Allerject dispensions accounted for an increasing proportion of EAI dispensions (17%, 38%, and 47% for the 0.3-mg dose and 13%, 30%, and 40% for the 0.15-mg dose, respectively, p<0.0001). Similarly, when considering only first EAI dispensions, the percent of dispensed Allerjects increased each year; among new 0.3-mg EAI prescriptions in 2015, more Allerjects (52%) were dispensed than EpiPens (48%). Significantly more Allerjects were dispensed in 2015 versus 2013 (OR 4.46, 95% CI: 4.02-4.95), after adjustment for age, sex, family income, urban versus rural residence.


704 Provider Barriers to Epinephrine Autoinjector Prescription in Patients with Anaphylaxis

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RATIONALE: Epinephrine is the first line of treatment for anaphylaxis; delayed administration of epinephrine is associated with an increased risk of hospitalizations and fatal reactions. Little data exists on provider barriers to the proper prescribing of epinephrine autoinjectors. Our objective is to identify what barriers exist among physicians for prescribing epinephrine autoinjectors, appropriate patient education of epinephrine autoinjectors, and anaphylaxis recognition.

METHODS: An anonymous physician survey was conducted in the Emergency Department, Internal Medicine, Pediatrics, Surgery, and Subspecialties. When inquiring about epinephrine autoinjectors we focused specifically on EpiPen®, the most widely recognized and prescribed device.

RESULTS: A total of 167 physicians responded to the survey. Emergency room physicians were 5.59 (95% CI: 1.64 – 19.04) times more likely to properly identify anaphylaxis than other physicians (p = 0.01). Among the 124 physicians who reported comfort with diagnosing anaphylaxis, none correctly identified all five of the anaphylactic reactions in a list of patient scenarios. Physicians were significantly more likely to identify anaphylaxis if cutaneous symptoms were present. Physicians with medical training on epinephrine autoinjectors were 3.37 (95% CI: 1.74 – 6.55) times more likely to report comfort teaching a patient how to use one, but 26.95% of physicians reported no training on epinephrine autoinjectors. The most commonly reported barrier to using an EpiPen® was unfamiliarity with how to use it.

CONCLUSIONS: Many non-ER physicians do not accurately identify anaphylaxis. Several physicians report lack of proper training on the EpiPen® and unfamiliarity with how to use the device.
705 Rate and Management of Anaphylaxis in Adult Patients at a Tertiary Care Centre Emergency Department

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RATIONALE: To compare the rate, triggers and management of anaphylaxis between adult emergency departments (ED) in Western and Eastern Canada.

METHODS: As part of the Cross-Canada Anaphylaxis Registry (C-CARE), we conducted a chart review of adults presenting with allergy-related ICD-10 codes to a tertiary care centre ED in Western Canada (Edmonton, Alberta) between March 1, 2011 and February 28, 2012. Anaphylaxis cases were defined as those that fulfilled the published consensus definition for anaphylaxis. Clinical and management data were collected and compared to published data from an ED in Eastern Canada (Montreal, Quebec).

RESULTS: Among 59,195 presentations to the Edmonton ED, 0.22% (95% CI 0.19%, 0.27%) were due to anaphylaxis. Food was the trigger in 57.1% (48.3%, 65.7%), mainly tree nut (21.0% (12.5%, 31.9%) of food-triggered cases). Epinephrine was used in 54.9% (46.0%, 63.5%) and 41.3% (32.9%, 50.2%) were prescribed an auto-injector. In Montreal, 0.26% (0.21%, 0.32%) of ED presentations were due to anaphylaxis, and 63.3% (52.9%, 72.6%) were triggered by food, primarily shellfish (12.9% (6.1%, 24.4%) of food-triggered cases). Epinephrine was used to treat 49.0% (38.8%, 59.2%) of patients and 67.1% (55.3%, 77.2%) were prescribed an auto-injector.

CONCLUSIONS: In Western and Eastern Canada, anaphylaxis accounted for over 0.2% of adult ED visits and was mainly due to foods. Tree nuts rather than shellfish were the main food triggers in Western Canada. Given the poor adherence to guidelines stipulating epinephrine use in all anaphylaxis cases, education programs promoting early epinephrine use are required across the country.

706 Adequacy of Current Epinephrine Autoinjector Needle Length to Reach Muscle Under Simulated Compression in Adults

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RATIONALE: The needle length of epinephrine autoinjectors (EIA) is not adequate for IM injection in some patients, but pressure on an ultrasound transducer in previous reports, to mimic activation pressure, decreased the skin-to-muscle distance. We have extended these observations by using a standardized method of compression to confirm that compression can change the skin-to-muscle distance.

METHODS: Convenience sample of adult patients who consecutively agreed to participate in the study. The protocol was approved by the IRB. Demographic data were obtained, including height and weight. The skin-to-muscle distance at a consistent location on the right anterolateral thigh was calculated with and without addition of a 7 lb weight to an endovaginal ultrasound transducer which was a similar size to an EIA.

RESULTS: Eighty-three consented to participate: 58 female, 25 male, mean age 49.7 years (5 African-American, 4 Asian, 57 Caucasian, 3 Filipino, 11 Hispanic, 3 Other). Thirty-three of 83 (40%) had a calculated BMI >30. At baseline without compression, 39 of 83 (47%) had a skin-to-muscle distance >1.59 cm, but this decreased to only 7 of 83 (8.4%) with compression. All 7 were female, with a mean calculated BMI of 33.9, range 25-51.5.

CONCLUSIONS: With the addition of a 7 pound weight to the transducer to mimic the force needed to activate an EIA, 32 of the 39 patients (82%) with a baseline skin-to-muscle distance >1.59 cm now were in the range for intramuscular penetration of the most commonly prescribed EIA containing a 0.3 mg dose in the United States.


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RATIONALE: Awareness about food allergy and food-induced anaphylaxis has increased dramatically over the past decade. However, it remains unclear whether concordance with guidelines for the management of food-induced anaphylaxis has improved over time. Our objective was to describe changes in emergency department (ED) concordance with guidelines for the management of food-induced anaphylaxis.

METHODS: We performed chart review for patients with food-induced acute allergic reactions seen in one of twelve EDs during two time periods: 1999-2001 and 2013-2015. Visits were identified similarly across years – e.g., using ICD-9-CM codes 693.1, 995.60, 995.61-995.69, 995.0, and 995.3. Anaphylaxis was defined as an acute allergic reaction with involvement of 2+ organ systems or hypotension. We compared concordance between time periods for four guideline recommendations: 1) treatment with epinephrine, 2) referral to an allergist/immunologist, 3) instructions to avoid offending allergen, and 4) discharge prescription for epinephrine auto-injector (EAI).

RESULTS: The analytic cohort included 980 patients (380 from 1999-2001 vs. 600 from 2013-2015). Overall, 530 patients had food-induced anaphylaxis (199 [52%] vs. 331 [55%], respectively). Any treatment with epinephrine (pre-ED or in the ED) increased over time (37% vs. 58%; P<0.001). While documentation for referral to an allergist/immunologist and instructions to avoid the offending allergen did not change (both P>0.05), prescriptions for EAI at discharge increased from 27% to 62% (P<0.001). Receipt of 3+ guideline recommendations remained low but tripled over the study interval (9% vs. 26%; P<0.001).

CONCLUSIONS: Over the ~15-year study interval, we observed clinically and statistically significant increases in ED concordance with epinephrine-related guidelines for food-induced anaphylaxis.
708 Longitudinal Differences in Treatment of Anaphylaxis Presenting To Pre-hospital Emergency Services in Rural Quebec

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RATIONALE: As part of the Cross-Canada-Anaphylaxis-Registry (C-CARE), we aimed to assess data collected prospectively over three years on pre-hospital anaphylaxis cases managed by paramedics in Outaouais, rural Quebec.

METHODS: A software program prospectively recorded clinical characteristics and management of anaphylaxis cases. Univariate and multivariate logistic regression were compared to identify factors associated with reaction severity and administration of epinephrine.

RESULTS: Amongst a total of 101,136 ambulance calls of which 81,640 required transport, 345 cases of anaphylaxis were identified - 0.34% [95% CI, 30.1%, 38.8%] among all ambulance calls and 0.42% [95% CI, 38.0%, 47.0%] among those requiring transport. The median age among all cases was 47.3 years and 61.7% were females. Common triggers included food (36.8% [95% CI, 31.8%, 42.2%]), drugs, (22.0% [95% CI, 17.8%, 26.8%]) and venom (18.2%, [95% CI, 14.4, 22.8%]). Older age, male gender and a venom trigger were associated with severe reactions (ORa=1.0 (1.0,1.02), 2.0(1.2,3.3), and 2.0 (1.1,3.6) respectively). Among all reactions, 28.1% [95% CI, 23.5, 33.2]) were severe, defined when hypotension or hypoxia (saturation ≤92%) developed. Of patients with severe or moderate anaphylaxis (crampy abdominal pain/diarrhea/recurrent vomiting/dyspncea/stridor/cough/wheeze), 21.5% [95 CI, 17.1, 26.8] were not administered epinephrine. Cases in which antihistamines were given prior to paramedic arrival were more likely managed without epinephrine (odds ratio adjusted: ORa =2.0 [95% CI 1.2,3.4]).

CONCLUSIONS: Given that antihistamines may mask symptoms but not the progression of anaphylaxis, the study highlights a need for increasing awareness among those delivering pre-hospital care regarding the recognition and appropriate use of epinephrine.

709 Disparities in Pre-Emergency Department Epinephrine and Antihistamine Use for Anaphylaxis

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RATIONALE: Anaphylaxis is a potentially life-threatening reaction requiring prompt treatment. Most pediatric patients present to the emergency department (ED) but factors that affect pre-ED administration of essential medications are not well understood.

METHODS: One year after developing an ED reporting tool for anaphylaxis, we analyzed associations between patient characteristics and receipt of pre-ED epinephrine and diphenhydramine using descriptive statistics, chi-square tests, and Fischer’s exact tests.

RESULTS: 209 cases were identified. Fewer Hispanic children received pre-ED epinephrine compared to other children (3.5% vs 19.7%, p =0.002), while age, sex, and type of allergic exposure were not significantly different. Additionally, more white children received pre-ED epinephrine compared to children of color (23.0% vs 8.3%, p =0.003). Children with Medicaid also received pre-ED epinephrine less compared to children with private insurance (2.1% vs 19.6%, p =0.006). Children younger than 12 years of age received pre-ED diphenhydramine less compared to older children (26.6% vs 52.9%, p=0.001), while sex, race, and insurance type were not significantly different. Only 19.3% of Hispanic children received diphenhydramine compared to 38.2% of other kids (p=0.01).

CONCLUSIONS: In this cohort ethnicity, race, and insurance status were associated with pre-ED epinephrine use while ethnicity and age were associated with pre-ED diphenhydramine use. In an ED where greater than 50% of the population has Medicaid and/or is Hispanic, this study highlights striking disparities in pre-ED administration of potentially life-saving medications.

710 Serum tryptase levels among Brazilian patients: correlation with severity of anaphylaxis

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RATIONALE: A relationship of elevated serum basal tryptase(sBT) and severity of anaphylaxis, and association of high sBT with mastocytosis have been shown. Our aim was to correlate sBT level with severity of anaphylaxis and type of trigger factor among Brazilian patients.

METHODS: Twenty-five patients (14 men) attending a hospital-based Allergy and Immunology Clinic were selected by having had at least one episode of anaphylaxis and were divided into 4 groups, according to the trigger factor responsible for their first episode of anaphylaxis: food, drugs, Hymenoptera venom and idiopathic. Ages varied from 5 to 67 years, with median of 26 years-old. sBT levels were assessed by the Immuno-CAP Tryptase immunoassay. According to signs and symptoms, the first anaphylactic episode was classified into four grades of severity (I-IV), according to Ring J et. Al, Lancet, 1977.

RESULTS: Tryptase levels ranged from 2.74 to 8.58µg/L. There were no significant differences of sBT levels according to the trigger factor. Mean levels of sBT were: 5.38; 6.44; 4.85 and 4.53µg/L for patients who had anaphylaxis to foods, drugs, Hymenoptera venom and idiopathic, respectively. Severity was classified as grade II (3 patients), III (17 patients) and IV (5 patients). Significantly lower levels of sBT were observed in patients with disease severity grades III/IV, as compared to grade I, p<0.05.

CONCLUSIONS: Among Brazilian patients with anaphylaxis, higher sBT were found in patients with more severe anaphylaxis. None of the patients presented sBT levels which prompted us to investigate mastocytosis.
Increasing the Accuracy of Notification of Anaphylaxis Deaths in Brazil through the International Classification of Diseases (ICD)-11 Revision

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RATIONALE: In 2012, an analysis of the Brazilian mortality database demonstrated under-notification of anaphylaxis deaths due to difficult coding under the International Classification of Diseases (ICD)-10. This work triggered a cascade of strategic international actions supported by the Joint Allergy Academies and the ICD World Health Organization (WHO) representatives to update the classifications of allergic disorders for the ICD-11 revision. These efforts have resulted in the construction of the new “Allergic and hypersensitivity conditions” section under the “Disorders of the Immune system” chapter. We propose to analyze the capacity of the new ICD-11 revision to capture anaphylaxis deaths.

METHODS: We re-estimated the anaphylaxis deaths that occurred in Brazil during the period 2008 to 2010, utilizing this new framework and the database of the Brazilian mortality information system that had initially been extracted in May 2011. However, in 2016, a manual review of each of the 3,638 records was performed.

RESULTS: We identified 639 anaphylaxis deaths, of which 95% were classified as “definite anaphylaxis deaths”. In contrast to the 2012 published data, we found a higher number of cases; moreover, all 606 definitive anaphylaxis deaths would be considered as underlying causes of death utilizing the ICD-11 revision. This work, therefore, represents a significant improvement to the current classification of allergic disorders and an important step forward in classifying anaphylaxis deaths.

CONCLUSIONS: Clearer was the effect on the accuracy reaching 95% for definite anaphylaxis when ICD11 was used. This study is the first real-life example of how the new “Allergic and hypersensitivity conditions” section of the forthcoming ICD-11 can improve the quality and accuracy of official vital statistics data and the visibility of an important public health concern.

Anaphylaxis During Exercise In A Pediatric Population

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RATIONALE: Exercise may be the sole trigger of anaphylaxis (Exercise-Induced Anaphylaxis [EIA]), it can co-trigger anaphylaxis with food allergens (Food-Dependent Exercise-Induced Anaphylaxis [FDEIA]) or it can be a cofactor in anaphylaxis regardless of trigger. We aimed to determine sociodemographic, clinical characteristics and management of exercise-related anaphylaxis cases (ERAC) in a pediatric anaphylaxis cohort recruited at the Montreal Children’s Hospital Emergency Department (MCHED).

METHODS: Between April 2011 and 2016, data was collected through a standardized questionnaire. Post-ED follow-up records were reviewed when available and consenting parents were contacted regarding post-ED follow-up with an allergist.

RESULTS: Among 1262 anaphylaxis cases presenting to the MCHED, 70 occurred during exercise and were defined as ERAC [5.5% [95%CI, 4.4%, 7.0%]. The mean age was 11.6 years and 55.7% were males. Epinephrine was administered prior to ED arrival in 37.1%, in the ED in 41.4% and in both settings in 5.7% of ERAC.

Thirty-nine cases were followed-up with chart reviews or phone calls. Four (10.3%) were diagnosed as EIA, three (7.7%) as FDEIA and eight (20.5%) as idiopathic. Exercise was found to be a cofactor with: food 17/39 (43.6%), pollen 3/39 (7.7%), venom 2/39 (5.1%), and other precipitants 2/39 (5.1%). Only 2 of 39 (5.1%) ERAC underwent an exercise challenge but no cases diagnosed as EIA underwent exercise challenge.

CONCLUSIONS: Exercise was more frequently a cofactor than a direct trigger of anaphylaxis. Diagnosis of EIA or FDEIA was rarely established through the use of appropriate confirmatory tests.
ABSTRACTS

714 Management of Exercise-Induced Anaphylaxis with Omalizumab

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RATIONALE: Omalizumab is a monoclonal antibody against immunoglobulin E used for management of moderate to severe allergic asthma. Exercise induced anaphylaxis is a rare condition characterized by diffuse pruritis, urticaria, and wheezing that can progress to life threatening laryngeal edema and hypotension with continued physical activity. We present a patient with exercise-induced anaphylaxis successfully treated with omalizumab.

METHODS: The patient underwent skin prick testing and pulmonary function testing. IgE and tryptase levels were collected.

RESULTS: An adolescent male presented with recurrent urticaria, facial edema, and wheezing after riding his bicycle and playing soccer, improving with discontinuation of activity. Skin prick testing was positive for allergies to several types of grass pollen. He tried sublingual immunotherapy and antihistamines with no improvement. His condition limited him in making friends and participating in school. Testing revealed elevated IgE level at 158 (range 0-100 U/mL) and normal tryptase level at 3.3 (normal <10.9 µg/L). Pulmonary function tests were normal. He was treated with fexofenadine 180 mg daily, but his symptoms continued. He started doxepin 10 mg at bedtime and fluticasone 110 µg 2 puffs twice a day with albuterol therapy as needed, but continued to experience recurrent urticaria and wheezing with activity. He was started on omalizumab therapy 300 mg subcutaneously every 28 days. After two doses, he noted significant improvement in symptoms.

CONCLUSIONS: Few reports describe the use of omalizumab in preventing episodes of exercise-induced anaphylaxis. The utility of this immunomodulator with exercise-induced anaphylaxis needs to be further evaluated.

715 Food-dependent exercise-induced anaphylaxis in children: A single center experience

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RATIONALE: Food-dependent exercise-induced anaphylaxis (FDEIA) is a specific form of exercise induced anaphylaxis that develops only when exercise combined with ingesting a specific food. Clinical features and diagnostic results of FDEIA in children are investigated in this study.

METHODS: The medical records of 13 patients younger than 18 years old diagnosed with FDEIA at Asan Medical Center from January 2003 to August 2016 were reviewed.

RESULTS: Demographics of 13 patients with Food-dependent exercise-induced anaphylaxis showed that 13 to 17-years-old patients (mainly male (n=10)) had 1 to 7 episodes of FDEIA before diagnosis. The most dominant causative foods were wheat (46%). Other causative factors were rice, celery, cabbage, soybean, mungbean, and fish. The most common symptoms were angioedema and urticaria. The skin prick tests and immunoCAP tests for suspicious foods were positive in 4 of 8 patients and 9 of 12 patients, respectively. The provocation tests were positive in 7 of 8 patients. The 3 of 7 patients described severe symptoms such as hypotension, dypnea and were injected epinephrine intravenously. The average interval between exercise and symptoms was approximately 21.6 minutes.

CONCLUSIONS: The diagnosis of FDEIA is based on either causality between symptoms and causative factors or tests such as lab, prick test and provocation. To make exact diagnosis and treatment plan, provocation test should be conducted. Awareness of medical staffs and patients to diagnosis and treatment is also important features of FDEIA.

716 Hymenoptera Venom Hypersensitivity Evaluation (HVHE): Preliminary Results From A Prospective Study Comparing Skin And In Vitro Testing

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RATIONALE: Hymenoptera venom hypersensitivity is diagnosed based on a clinical history of a systemic reaction to hymenoptera coupled with positive skin and/or in vitro testing. Robust data on the concordance between skin and serum testing is currently lacking in the literature. This study investigates the concordance between skin and serum specific IgE (sIgE) to each of the five specific venoms in patients being evaluated for hymenoptera venom hypersensitivity.

METHODS: Seventeen patients with a history of a systemic reaction to hymenoptera stings and 42 controls were recruited from the allergy clinic. Intradermal skin testing (IDST) was performed and serum sIgE to each of the five specific venoms and a baseline tryptase were measured.

RESULTS: Preliminary data shows an overall higher discordance between IDST and serum sIgE testing in cases than controls (6.7% vs. 16.5%, p=0.001, CI=3.88-22.94). This discordance was observed with all hymenoptera venom except honey bee. Sensitivity was slightly higher with serum testing (53% vs. 47%) but specificity was higher with IDST (95% vs. 79%).

CONCLUSIONS: Preliminary results reveal higher discordance between IDST and serum sIgE in cases versus controls for all hymenoptera venoms except honey bee. These initial results do not support or refute the current guidelines of pursuing serum sIgE testing to patients with negative IDST with a positive history. Further investigation and data is necessary to clarify the role of sIgE testing and its relationship to IDST in all patients with a positive history of venom hypersensitivity.
Clinical Characteristics, Immediate Treatment, and Long-Term Management of Venom Allergic Reactions Presenting to Canadian Pediatric Emergency Departments and out-of-Hospital Emergency Services

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RATIONALE: There is little Canadian data on the short and long-term treatment of allergic reactions due to Hymenoptera venom. This study examines the characteristics and short and long-term management of venom triggered anaphylaxis cases (VTAC).

METHODS: The Cross-Canada Anaphylaxis Registry (C-CARE) enrolls anaphylactic cases presenting to emergency departments (EDs) and out-of-hospital emergency medical services (EMS). We utilized C-CARE to identify VTAC that presented to EDs at the Montreal Children’s Hospital and Sacre-Coeur Hospital, and to EMS in Western Quebec from June 2013 to May 2016. ED physicians and EMS paramedics documented characteristics, triggers, and management using standardized forms. Consenting patients were contacted regarding long-term management. Multivariate logistic regression was used to identify factors associated with epinephrine treatment and severe reactions.

RESULTS: Among 83 VTAC cases, 49.4% (95%CI 38.3%, 60.5%) were moderate and 37.3% (95%CI 27.2%, 48.7%) were severe. Epinephrine was administered to 81.9% (95%CI 70.7%, 89.7%) of moderate/severe VTAC and to 77.1% (95%CI 66.3%, 85.3%) of all VTAC. Reactions occurring at home were more likely managed without epinephrine (OR adjusted 4.6; 95%CI 1.1, 18.79) and older patients had more severe reactions (OR adjusted 1.03; 95%CI 1.01, 1.06). Twenty-one patients were contacted in follow-up: 87.5% (95%CI 62.6%, 96.2%) were prescribed an epinephrine auto-injector, 47.6% (95%CI 26.4%, 69.7%) saw an allergist who confirmed the allergy, and 54.5% (24.6%, 81.9%) of confirmed allergies received venom immunotherapy.

CONCLUSIONS: In the majority of VTAC providing long-term data, the diagnosis is not confirmed and immunotherapy is not prescribed. Hence, educational programs promoting referral to allergists and subsequent immunotherapy are required.

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RATIONALE: Changes in emergency department (ED) concordance with guidelines for the management of insect sting-induced anaphylaxis are not known. Building on prior work (Clark et al. JACI2005;116:643-9), we describe temporal changes in ED concordance with guidelines for the management of insect sting-induced anaphylaxis.

METHODS: We performed chart review for patients with insect sting-induced acute allergic reactions seen in one of ten EDs during two distinct time periods: 1999-2001 (prior study) and 2013-2015 (new study). Visits were identified similarly across studies – e.g., using ICD-9-CM codes 989.5, 995.0 and 995.3. Anaphylaxis was defined as an acute allergic reaction with involvement of 2+ organ systems or hypotension. We compared concordance between time periods with four guideline recommendations: 1) treatment with epinephrine, 2) referral to an allergist/immunologist, 3) instructions to avoid the offending allergen, and 4) discharge prescription for epinephrine auto-injector (EAI).

RESULTS: The analytic cohort included 959 patients (510 from 1999-2001 vs. 449 from 2013-2015). Overall, 283 patients had insect sting-induced anaphylaxis (158 [31%] vs. 125 [28%], respectively). Any treatment with epinephrine (pre-ED or in the ED) increased during over time (33% vs. 47%; P=0.02). While documentation of instructions to avoid future stings did not change (23% vs. 26%; P=0.65) and documentation for referral to an allergist/immunologist decreased (29% vs. 13%; P=0.003), prescriptions for EAI at ED discharge increased from 34% to 60% (P<0.001).

CONCLUSIONS: Over the ~15-year study interval, we observed increased ED concordance with epinephrine-related guidelines for the management of insect sting-induced anaphylaxis. Reasons for the decline in allergy/immunology referrals merits further study.

719 Severe Anaphylactic Reactions after Stopping Hymenoptera Venom Immunotherapy: a Clonal Mast Cell Disorder Should be Suspected

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RATIONALE: Up to 75% of patients with systemic anaphylactic following hymenoptera sting are at risk for further reactions when restung. Venom immunotherapy (VIT) is effective in preventing systemic reactions in hymenoptera venom allergy (HVA). After VIT lasting 3-5 years, most patients with previous anaphylactic symptoms remain protected after discontinuation. A long treatment should be considered in high-risk patients. Many case showed that patients with mastocytosis and HVA, protected during VIT, can have severe reactions after VIT discontinuation. This study confirmed that VIT should be continued life-long in patients with mastocytosis, and that most patients who lost protection after VIT discontinuation are suffering from mastocytosis.

METHODS: This is retrospective multicentre study performed in patients receiving VIT. Patients who underwent a 3-5 years course of VIT and restung with reaction after VIT discontinuation were evaluated. Out of them, those with tryptase levels >11.5 ng/mL or anaphylaxis with hypotension without urticaria and/or angioedema underwent a bone marrow biopsy, kit mutation, expression of aberrant CD25 assessment.

RESULTS: 24 patients with the above mentioned characteristics were evaluated. All received a 5-year VIT course, all resulted to be protected during VIT. After VIT they were again restung and had severe reactions: 16 anaphylaxes, 8 with loss of consciousness and without urticaria/angioedema and 8-I-III Mueller grade reactions. All patients who had severe anaphylaxis at resting resulted then to have mastocytosis (6 with normal tryptase).

CONCLUSIONS: Independently of tryptase level, in patients with previous anaphylaxis, VIT should be discontinued only after exclusion of mastocytosis. Consequently, patients with mastocytosis and HVA should be treated with VIT life-long.

720 Further Classification of the Angioedema without Urticaria Attended in the Emergency Department

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RATIONALE: The angioedema is a common disease not often well classified in the Emergency Department (ED).

METHODS: Patients over 15 y/old, were referred from the ED with AE without urticaria (Jan-2013 to Dec-2015). After a meticulous anamnestic, biochemistry, cells blood count, total and Anisakis IgE, parasitic serology, complement and allergy tests, AE attacks were classified according to Cicardi et al. 2014.

RESULTS: 663 AE were attended in the ED. 266 were later studied in the Allergy Service. Mean age 52 y±19.2. F/M: 1.4, 42% had recurrent episodes. 138 attacks were classified as Histaminergic-AE (H-AAE): Idiopathic-H-AAE (69.5%), Allergic (30.1%); Anisakis simplex (12.3%), drugs (12.3%) and food (5.5%). 62 had a non-histaminergic-AE (nH-AAE): ACE-I-AAE (82.2%), HAE (9.6%), Idiopathic (8.2%). Twenty-two AE could not yet be classified. Facial AE was present in 72.4% of H-AAE vs 59% in nH-AAE (p=0.05). Oro-pharyngolaryngeal: 39.8% vs 77.14% (n.s), peripheral: 10.1% vs 0.1% (n.s) and genitals 5.3% vs 1.6% (n.s). Erythema was present in 18.8% vs 6.4% (p<0.05), pruritus: 19.6% vs 12.9% (n.s), breathing difficulties in 15.2% vs 23.5% (n.s). Antihistaminics/corticosteroids were given to 69.5% vs 41%, C1 INH/Icatibant to 1.4 % vs 16.1%. 44 were finally diagnosed with edema (infection: 31.8%, GRE 20.4%, inflammatory, 9%, contact dermatitis 11.3%, macroglisia 6.8%). Correlation between the etiology suspected at the ED and the final diagnosis was only coincident in 18.4%.

CONCLUSIONS: Differences between H-AAE and nH-AAE are minimal at the ED which difficulty its rapid classification. A conscientious allergologic study is crucial to better classify and direct future treatments.
721 Switch from Intravenous C1-Inhibitor C1-INH(IV) to Subcutaneous C1-Inhibitor [C1 INH(SC)] for Routine Prevention of Hereditary Angioedema (HAE) Attacks: Subgroup Findings from the Compact Trial

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RATIONALE: The COMPACT (Clinical Studies for Optimal Management of Preventing Angioedema with low-volume subcutaneous C1-Inhibitor Replacement Therapy) trial evaluated the safety and efficacy of a low-volume C1-INH(SC) as routine prevention in patients with HAE. This subgroup analysis was designed to compare HAE attack rates in patients who stopped their prior C1-INH(IV) as routine prophylaxis to start C1-INH(SC) routine prevention during the COMPACT trial.

METHODS: This was a pre-specified subgroup analysis of 22 subjects who used C1-INH(IV) for routine prophylaxis of HAE attacks prior to using C1-INH(SC) during COMPACT trial participation. The time-normalized rate of HAE attacks (number/month) during pre-study C1-INH(IV) prophylaxis was determined for the 3 month period prior to COMPACT trial entry and compared against the time-normalized attack rate during study treatment with C1-INH(SC), 40 or 60 IU/kg.

RESULTS: The mean (SD) time-normalized HAE attack rate (number/month) during pre-study use of C1-INH(IV) prophylaxis (n=22) was 2.56 (2.579), compared with 1.73 (2.013) while using C1-INH(SC) for routine prevention in the COMPACT study. Following a switch to C1-INH(SC), the mean (SD) percentage reduction in HAE attack rate compared to prophylactic C1-INH(IV) use was 52.1% (63.64%). The corresponding mean (SD) percentage reductions in HAE attack rates by C1-INH(SC) dose were 48.8% (68.37%) for C1-INH(SC) 40 IU/kg, and 53.7% (64.23%) for C1-INH(SC) 60 IU/kg.

CONCLUSIONS: This subgroup analysis of COMPACT trial data suggests that patients previously using C1-INH(IV) prophylaxis and switched to C1-INH(SC) (40 or 60 IU/kg) for routine prevention may experience a lower attack rate than experienced during routine prophylaxis with C1-INH(IV).

722 Preclinical Characterization of BCX7353, an Oral Plasma Kallikrein Inhibitor, for the Treatment of Hereditary Angioedema (HAE)

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RATIONALE: HAE, an autosomal dominant disorder resulted from deficiency of C1 esterase inhibitor, is characterized by episodic swelling of the skin, pharynx, larynx, GI tract, genitals and extremities. Bradykinin, generated from plasma kallikrein-mediated cleavage of high molecular weight prekallikrein (HMWK), is the major mediator of acute attacks in HAE. BCX7353 is a small-molecule human plasma kallikrein inhibitor that is currently under evaluation as an oral drug for prophylactic use in HAE patients in a phase 2 study. The present study describes its effects on kallikrein activity both in vitro and ex-vivo and on kallikrein-mediated bradykinin release from endothelial cells.

METHODS: In vitro and ex vivo kallikrein activities were evaluated using a colorimetric substrate S2302 or a fluorometric substrate Z-FR-AMC respectively; and bradykinin levels were determined by an Elisa kit.

RESULTS: BCX7353 potently inhibits isolated human plasma kallikrein activity with an inhibition constant (K_i) of 0.44 nM. BCX7353 also inhibits kallikrein activity in activated human plasma with an effective concentration (EC_{50}) value of 5.83 nM. BCX7353 potently inhibited kallikrein activity in plasma from 14 HAE patients with an EC_{50} value of 15.9 nM. BCX7353 is highly specific for plasma kallikrein with IC_{50}s of BCX7353 against a range of other serine proteases approximately 4,500 to 56,000-fold higher. Western blot analysis showed that BCX7353 inhibits cleavage of HMWK in activated human plasma. Incubation with BCX7353 inhibits kallikrein-dependent bradykinin release from the surface of endothelial cells with an EC_{50} of 5.56 nM.

CONCLUSIONS: These data suggest that BCX7353 potently inhibits kallikrein activity and suppresses bradykinin production.

723 Age-Related Influence on the Clinical Course of Hereditary Angioedema Due to C1-Inhibitor Deficiency (HAE-C1-INH) – A Retrospective Study in 150 Adult Patients

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RATIONALE: Hereditary angioedema / C1-inhibitor deficiency (HAE-C1-INH) is a rare autosomal dominant inherited disease. The recurrent symptoms are subcutaneous edema and colic-like abdominal pain. Laryngeal edema is rare, but potentially life-threatening. Age-related hormonal changes (i.e during puberty, pregnancy) could have a negative influence on the clinical course of HAE-C1-INH. Our aim was to investigate the age-related influence on the clinical course in adult patients with HAE-C1-INH.

METHODS: Clinical course of HAE-C1-INH in 150 adult patients (i.e. triggers, first signs, localization, severity and frequency of attacks) and age-related influence have been analyzed retrospectively over an observation period of 12 months in a single-center study. This analysis also included patient characteristics, concomitant diseases and the individual management of HAE-C1-INH.

RESULTS: A total of 150 patients with HAE-C1-INH were enrolled: 97 females (64.7%) and 53 males (35.3%). Mean patient age was 44.2 years (range: 18 - 86 years). The 150 patients (134 patients <65 years, 89.3%; 16 patients >65 years) experienced a total of 5658 attacks. The majority of patients had moderate (36.0%) or mild (31.1%) attacks with no relevant difference between men and women. The percentage of severe attacks was higher in patients <65 years of age compared to patients >65 years (11.5% of attacks versus 3.8%).

CONCLUSIONS: Our data indicate a trend towards less severe HAE-C1-INH with milder attacks in older patients compared to younger patients. The age-related influence may have an impact on the clinical course of HAE-C1-INH, but more data are needed to confirm our results.
Intravenous C1-INH [C1-INH(IV)] Use Among Patients with Hereditary Angioedema (HAE) in the United States (US) and Associated Health Care Resource Utilization (HCRU)

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RATIONALE: Limited data are available regarding C1-INH(IV) treatment for HAE in the US. We characterized HAE medication consumption and HCRU in patients treated for HAE using a large US claims database.

METHODS: Retrospective cohort design using LifeLink Health Plan database records between 1/1/06 – 12/31/14. Subjects with HAE (ICD-9 code 277.6) ≥1 claim for an HAE-specific medication, and continuous insurance enrollment for ≥3 months following first (index) HAE prescription claim were included. Subjects included in a separate HCRU analysis were required to have enrollment data for ≥3 months pre- and ≥1 month post-index date.

RESULTS: 434/631 (68.8%) HAE patients used C1-INH(IV) (Cinryze® and/or Berinert®) during follow-up. 521/631 (82.6%) were included in the HCRU analysis, 336/521 (64.5%) of whom had claims for C1-INH(IV) treatment at any time. In unadjusted analyses, 68/336 (20.2%) of patients using C1-INH(IV) were hospitalized and 191/336 (56.8%) visited the emergency department (ED), compared to 11/185 (5.9%) and 80/185 (43.2%), respectively, of patients using only subcutaneous (SC) HAE medications. In the HCRU analyses, 18 patients had a central venous access device (CVAD) placed; 5/18 (27.7%) required hospitalization and 14/18 (77.7%) required an ED visit, compared to 79/521 (15.2%) and 271/521 (52.0%), respectively, among patients without a CVAD. The adjusted RR risk of hospitalizations and/or ED visits with a CV AD was 2.6 (95% CI: 0.17, 39.23) compared with no CV AD.

CONCLUSIONS: This study found high HCRU among C1-INH(IV) patients compared to patients using SC HAE medications, suggesting that venous access for HAE medication is associated with treatment complications in US HAE patients.

Recombinant Human C1 Inhibitor (rHC1INH) Is Efficacious and Well Tolerated As Prophylaxis for Prevention of Hereditary Angioedema (HAE) Attacks: A Randomized, Phase 2 Trial

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RATIONALE: rHC1INH is currently administered for the treatment of acute HAE attacks. Repeat rHC1INH treatment for recurrent attacks during open-label extension studies have maintained efficacy while being well tolerated, supporting a potential role for rHC1INH in prophylaxis.

METHODS: A randomized, double-blind, 3-period, crossover study was conducted in patients ≥13 years of age with functional C1INH levels <50% of normal and ≥4 HAE attacks during the previous 3 months. Patients received rHC1INH 50 IU/kg (max, 4200 IU) once or twice weekly or placebo in three, 4-week periods; each treatment was separated by 1 week and symptoms monitored by a daily diary. Primary endpoint was number of HAE attacks per 4-week period. Additional endpoints included percentage of patients with ≥25%, ≥50% (clinical response), or ≥75% reduction in number of HAE attacks versus placebo and number of days with HAE symptoms.

RESULTS: Thirty-two patients were randomized (mean age, 45.9 years [range, 16.9–73.5 years]). Mean number of HAE attacks was reduced from 7.2 (placebo) to 4.4 (rHC1INH once weekly; P=0.0004) and 2.7 (rHC1INH twice weekly; P<0.0001). Percentage of patients with ≥25%, ≥50%, and ≥75% reduction in HAE attacks versus placebo was 64.5%, 41.9%, and 19.4% for rHC1INH once weekly and 80.6%, 74.2%, and 41.9% for rHC1INH twice weekly, respectively. Number of days with HAE symptoms was lower with rHC1INH twice weekly (5.1 days) and once weekly (8.0 days) versus placebo (10.2 days).

CONCLUSIONS: rHC1INH was efficacious for the prevention of HAE attacks and data support continued investigation of rHC1INH as prophylaxis.

Hereditary Angioedema with Normal C1 Inhibitor: An Italian Case Series

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RATIONALE: Hereditary angioedema with normal C1-inhibitor (nC1-INH-HAE) with and without factor XII mutations (FXII-HAE and U-HAE respectively) are familial disorders. We present the genetic and clinical features of patients with nC1-INH-HAE followed up in centers of the Italian Network for Angioedema (ITACA).

METHODS: 97 patients with personal or family history of angioedema and normal plasma levels of C1 inhibitor were studied. All patients were investigated for mutations in the whole F12 gene coding region by direct DNA sequencing.

RESULTS: 80 patients had angioedema symptoms. Of these patients, 20 females (median age 42.2 years, range 12-78), belonging to 8 unrelated families, had the same mutation in F12 gene, leading to the most common disease-causing aminoacid substitution, p.Thr309Lys. They were diagnosed as FXII-HAE. The haplotype analysis by using intragenic SNPs confirmed the hypothesis of a common founder. 17 subjects (9 males) in 7 FXII-HAE families were asymptomatic carriers of the same mutation. 60 patients (38% males; median age 45 years, range 12-81) had history of angioedema in their 36 families and no mutation in F12 gene. They were diagnosed as U-HAE. Sequencing analysis revealed the presence of different SNPs that have been previously described as not affecting protein activity or function.

Accordingly, the minimum prevalence of FXII-HAE and U-HAE in Italy in 2016 is 37.59.394.000 inhabitants and 60.59.394.000 respectively, equivalent to 1:1.605.243 for FXII-HAE and 1:989.900 for U-HAE.

CONCLUSIONS: We present an homogeneous geographical distribution of nC1-INH-HAE among European countries.
727 Autonomic Modulation and Contact System in Patients with Hereditary Angioedema Due to C1 Inhibitor Deficiency

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RATIONALE: Attacks of Hereditary Angioedema due to C1-inhibitor deficiency (C1-INH-HAE) are often triggered by stressful events/hormonal changes. Our study evaluates the relationship between autonomic nervous system (ANS) modulation and contact/complement system activation.

METHODS: In 23 HAE patients (6 males, 47.5±11.4 years) during remission and 24 healthy volunteers (8 males, 45.3±10.6 years) ECG, beat-by-beat blood pressure (BP), respiratory activity were continuously recorded during rest (R; 10’) and 75-degrees-head-up tilt (T; 10’). C1-INH, C4, cleaved high molecular weight kininogen (HK) were assessed; in 16 patients and 11 controls plasma catecholamines were evaluated. Spectral analysis of heart rate variability allowed to extract low-(LF) and high-(HF) frequency components, markers of sympathetic and vagal modulation respectively.

RESULTS: HAE patients showed higher mean systolic arterial pressure (SAP) (134.0±19.0 vs 112.0±17.4 mmHg, p=0.001 at R, 141.4±29.0 vs 121.7±17.3 mmHg, p=0.01 during T). Only in volunteers T induced a significant increase in mean SAP (121.7±17.3 vs 112.0±17.4 mmHg, p=0.02) and SAP total power-variance (54.0±48.9 vs 27.0±36.3 ms², p=0.05). Despite sympathetic modulation (LFnu) increasing after T (69.7±26.1 vs 57.7±24.9, p=0.03 in patients, 78.0±20.7 vs 51.5±21.2, p=0.001 in controls), only in controls LF/HF ratio, index of sympathovagal balance, increased significantly (16.5±18.7 vs 2.7±3.0, p=0.003). At R patients showed higher noradrenaline values (301.4±132.9 pg/ml vs 210.5±89.6 pg/ml, p=0.05). Only in patients T induced increased HK cleavage, marker of contact system activation (49.1±7.6 vs 46.1±8.0, p=0.02).

CONCLUSIONS: Our data are consistent with an alteration of ANS modulation in HAE patients, who show increased sympathetic activation at rest and blunted response to orthostatic challenge. Tilt test-induced increased HK cleavage suggests a link between stress and bradykinin production.

728 Acquired angioedema due to C1-inhibitor deficiency: a survey of 101 Italian patients

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RATIONALE: Acquired Angioedema due to C1-inhibitor deficiency (C1-INH-AAE) is rarer than Hereditary Angioedema (HAE), usually associated with lymphoproliferative disorders and/or C1-INH-autoantibodies and characterized by late onset and lack of family history. We report data on a large population of C1-INH-AAE Italian patients included in ITACA database.

METHODS: The following data were collected: vital status (alive/death), age and sex, time of symptoms’ onset and diagnosis, plasma levels of antigenic and functional C1-INH/C4/C1q, presence of C1-INH-autoantibodies, concomitant lymphoproliferative diseases, location of attacks, on-demand therapy and long-term prophylaxis (LTP).

RESULTS: 101 patients (54% female; median age 71 years) were diagnosed from 1976 to 2015. Median age at onset of symptoms and diagnosis was 58 and 63 years respectively, with a median delay in diagnosis of 2 years. During follow up 19 patients died (one for laryngeal involvement). Facial edema was the most common location (82%). C1q levels were reduced in 70% of patients, C1-INH-autoantibodies were found in 68% and a lymphoproliferative disease was present in 37%. 70% of patients used on-demand treatment: pdC1-INH (N=63) and/or icatibant (N=31). 9/63 patients receiving pdC1-INH became non-responsive, all with detectable C1-INH-autoantibodies. 36 patients received LTP with tranexamic acid (effective in 31), and 21 with androgens (effective in 9).

CONCLUSIONS: We found a ratio of C1-INH-AAE/C1-INH-HAE patients of 1:9.7. Diagnostic delay (2 years) was lower than for HAE (>10 years in ITACA cohort). On-demand treatments for C1-INH-AAE were effective, although a reduction of effectiveness of pdC1-INH may be observed. Tranexamic acid was more effective than androgens for LTP.

729 Ibrutinib, a BTK inhibitor used for treatment of lymphoproliferative disorders, eliminates both allergic reactions to aeroallergens and basophil activation test reactivity in allergic cancer patients receiving drug

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RATIONALE: Bruton’s tyrosine kinase (BTK) is critical for FceRI signaling and allergen reactivity in human mast cells and basophils. We therefore sought to determine the effect of ibrutinib, an irreversible BTK inhibitor that is FDA-approved for various B cell malignancies, on allergen reactivity.

METHODS: Using an IRB-approved protocol, we initiated a pilot study in patients prescribed ibrutinib for treatment of their lymphoid malignancy. Subjects were screened prior to ibrutinib treatment for aeroallergen reactivity by prick skin test followed by basophil activation test (BAT) and underwent repeat skin testing and BAT after 7 days and ≥30 days of treatment with ibrutinib 420mg daily.

RESULTS: Over two years, 22 of 27 screened patients met entry criteria and were enrolled. One had a positive skin test to cat and one was positive to ragweed; both had a positive BAT. One week after starting ibrutinib, there was an almost complete loss of allergen skin test reactivity as assessed by wheal size and basophil activation measured by the BAT in both subjects, although histamine reactivity was maintained. The loss of skin test and BAT responses was maintained at ≥30 days of treatment. Total and specific IgE levels were unchanged over this same time period. Finally, BAT responses to a non-IgE-dependent stimulus, formyl-methionyl-leucyl-phenylalanine, were unaffected or minimally altered.

CONCLUSIONS: These results suggest that through inhibition of FceRI-dependent basophil and mast cell activation, ibrutinib may be able to block allergic reactions. Use of this pharmacological agent may make it possible to eliminate allergic reactivity in humans.
730 Early Versus Late Administration of Icatibant in Patients With Hereditary Angioedema

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RATIONALE: Relationship of the timing of icatibant self-treatment to demographic and treated-attack characteristics for patients with hereditary angioedema due to C1-inhibitor deficiency are poorly understood.

METHODS: Data from the Icatibant Outcome Survey was used to evaluate early versus late icatibant self-treatment (defined as patients with median time-to-first injection <1hr versus ≥2hr from attack onset, respectively).

RESULTS: Of 229 patients analyzed, 89 (38.9%) had median time-to-first injection <1hr (median [Q1,Q3] for 482 icatibant-treated attacks, 0.25h [0.0, 0.5]) with no gender differences. Early self-treatment varied across countries, ranging from 77.1% (Germany/Austria) to 11.6% (France). Early (versus late)-treaters treated skin attacks at a higher rate (50.2% vs 34.6% respectively, P=0.0098); conversely, late (versus early) treaters treated abdominal attacks at a higher rate (66.6% vs 49.7% respectively, P=0.0078). Laryngeal attack frequency was not significantly different (P=0.6064), nor was grouped attack severity (very mild/mild/moderate vs severe/very severe; P=0.313). Significant reduction (P<0.001) in median (Q1,Q3) time to resolution [3hrs (0.8, 9.3) versus 7hrs (3, 19.3)] and attack duration [4hrs (1, 10.3) versus 12.5hrs (6.0, 26.0)] was observed between early versus late treatment, respectively (206 patients; 913 attacks).

CONCLUSIONS: Early treaters had shorter time to resolution and attack duration compared to late treaters, possibly indicating the importance of early access to icatibant in the face of HAE attacks. Differences in local practice patterns, icatibant availability, and tendency of early treaters to treat any symptoms without delay may drive prevalence of early use across countries. These and other findings from this analysis are hypothesis generating and should be further evaluated.

731 Risk for Attacks in Hereditary Angioedema (HAE) Population Correlates with C1-inhibitor Functional Activity (C1-INHact)

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RATIONALE: Routine prophylaxis with C1-inhibitor (C1-INH) is an established treatment option for patients with HAE, and C1-INH<sub>act</sub> >40% is assumed to prevent attacks. An analysis was conducted to relate the risk of an HAE attack to C1-INH<sub>act</sub> in patients with HAE.

METHODS: Data from the COMPACT (Clinical Studies for Optimal Management in Preventing Angioedema with Low-Volume Subcutaneous C1-inhibitor Replacement Therapy) program were used to develop population PK (POPFPK) and pharmacokinetic-pharmacodynamics (PK/PD) models. An interval-censored repeated time-to-event model was developed that enabled the C1–INH<sub>act</sub> to be directly related to the HAE attack event. The final model included 2 components, a baseline hazard and a non-linear drug effect.

RESULTS: The PK/PD model demonstrated a strong exposure-response (E-R) relationship, with increasing C1-INH<sub>act</sub> decreasing the risk of experiencing an HAE attack. Based on the POPFPK model, the predicted mean (95% CI) trough C1-INH<sub>act</sub> after twice-weekly subcutaneous C1-INH [C1-INH(SC)] 40 IU/kg was 40.2% (22.2, 77.9) and after twice-weekly C1-INH(SC) 60 IU/kg was 48.0% (25.1, 102). Furthermore, the mean trough C1-INH<sub>act</sub> after subcutaneous administration was predicted to yield a 70% reduction in the relative risk of an HAE attack after C1-INH(SC) 40 IU/kg dosing and an 81% reduction after 60 IU/kg dosing. Simulations based on the E-R model predicted that higher C1-INH<sub>act</sub> significantly lowers the risk for HAE attacks in a greater proportion of patients with maximal effect occurring near normal C1-INH<sub>act</sub>.

CONCLUSIONS: Simulations based on data from the COMPACT program suggest that the prevention of HAE attacks is maximized when C1-INH<sub>act</sub> are restored to the normal range (>70%).
Placebo-Controlled Trials of C1-Inhibitor (C1-INH) Replacement Therapy for Routine Prevention of Attacks in Patients with Hereditary Angioedema (HAE)

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Rationale: Currently, only intravenous C1-INH [C1-INH(IV)] is approved for prophylaxis of HAE attacks (1000 IU twice-weekly). C1-INH(IV) and subcutaneous C1-INH (C1-INH(SC)) were each independently evaluated in similarly-designed randomized, double-blind, placebo-controlled trials with similar HAE patient populations (CHANGE [NCT01005888] and COMPACT [NCT01912456] trials).

Methods: Both studies applied placebo-crossover designs and included subjects with type I/II HAE who experienced at least 1 HAE attack/month. In COMPACT, 45 patients were randomized to twice-weekly C1-INH(IV) 40 or 60 IU/kg for 16 weeks, preceded or followed by placebo for 6 weeks. The change trial included 22 patients who received 12 weeks each of C1-INH(IV) 1000 IU twice-weekly and placebo. Reduction in HAE attack rate, responder rates (≥50%/≥90% reduction) and use of rescue medication were descriptively compared between trials.

Results: The reduction in mean-time-normalized number of HAE attacks versus placebo was 89% and 95% with C1-INH(IV) 40 IU/kg and 60 IU/kg, respectively, compared with 53% for C1-INH(IV). The percentages of subjects with ≥50% reductions in HAE attack rate versus placebo were 76% [C1-INH(IV) 40 IU/kg], 90% [C1-INH(IV) 60 IU/kg] and 50% [C1-INH(IV)]. The percentages of subjects with ≥90% reductions in HAE attack rate versus placebo were 43% [C1-INH(IV) 40 IU/kg], 58% [C1-INH(IV) 60 IU/kg] and 18% [C1-INH(IV)]. Mean monthly use of rescue medication was 1.2 and 0.3 with C1-INH(IV) 40 and 60 IU/kg, respectively, and 1.8 with C1-INH(IV).

Conclusions: Within the limitations of an indirect study comparison, it appears that C1-INH(IV) provides a higher percentage of responders and higher magnitude of attack reduction compared to standard C1-INH(IV) routine prophylaxis.

Subcutaneous C1-Esterase Inhibitor [C1-INH(SC)] to Prevent Hereditary Angioedema (HAE) Attacks: Subject and Investigator Assessments from the Compact Trial

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Rationale: The COMPACT trial established the safety and efficacy of routine prevention with C1-INH(SC) in subjects with HAE. This analysis presents subject- and investigator-reported assessments of treatment effectiveness.

Methods: Subjects (n=90) were randomized to 1 of 4 treatment sequences: twice-weekly C1-INH(IV) (40 or 60 IU/kg) for 16 weeks, preceded or followed by placebo for 16 weeks. Assessments using the Treatment Satisfaction Questionnaire for Medication (TSQM), the Investigator’s Global Assessment of Response to Therapy (IGART), and the Subject’s Global Assessment of Response to Therapy (SGART) were conducted after 14 weeks of C1-INH(IV) and after 14 weeks of placebo. A post hoc comparison of the mean (within-subject) difference in TSQM scores was performed. The percentage of subjects with responses of none, poor, fair, good, or excellent was determined using the IGART/SGART.

Results: C1-INH(SC) (40 and 60 IU/kg, combined) had a larger effect on TSQM Effectiveness compared with placebo (mean difference [95% CI], 37.07 [24.86, 49.28]). For both the IGART and the SGART, the percentages of subjects with a “good or excellent” response to therapy were higher during treatment with C1-INH(IV) than placebo. For the IGART, 80.0% (72/90) of subjects on C1-INH(IV) (40 and 60 IU/kg, combined) received a rating of “good or excellent” versus 12.2% (11/90) on placebo. For the SGART, 75.6% (68/90) of subjects on C1-INH(IV) (40 and 60 IU/kg, combined) indicated a rating of “good or excellent” versus 23.3% (21/90) on placebo.

Conclusions: These findings provide further evidence that C1-INH(SC) is an effective attack prevention option for the management of HAE.

Acute attacks in patients with Hereditary Angioedema (HAE): analysis of frequency, characteristics, treatment and direct costs in 133 patients observed prospectively for one year

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Rationale: frequency and severity of attacks varies widely in patients with HAE modifying therapeutic approaches and related costs. We studied prospectively patients with HAE to evaluate attack variability and the direct costs derived from the treatment of attacks.

Methods: a cohort of 133 HAE patients (age 42.5±17.6, 64% female) prospectively recorded all angioedema attacks over the period of one year reporting in specific diaries information on severity, acute treatment, presence of long term prophylaxis (LTP), admission to emergency room. Results: 1504 attacks were reported with mean number of 11 attacks per patient. (minimum 1, maximum 126, median 22). Twenty-nine of 133 patients were on attenuated androgens for LPT; 1132 (75%) attacks occurred in patients not receiving LTP. Attacks were located to the head (6.3%), peripheral skin (48.6%), bowel (40.2%), neck (4.9%). They were severe in 26.5%, moderate 49.5%, mild 24%. The frequency of severe attacks was higher for the cutaneous locations (chi-square 71.6, p<0.001); there were not differences in severity comparing patients with or without LTP (chi-square=1.84; p=0.17). Visits to ER were more frequent in patients without LTP (chi-square 16.14; p<0.001). Overall annual direct cost of attacks was 1,564.395 (1.058 /attack) mainly attributable to on demand drugs. Per attack cost was higher in patients without LTP (average cost +235/attack vs LTP) due to the fact that in patients on prophylaxis attacks remained more frequently untreated (chi-square 4.56, p=0.03)

Conclusions: these data confirm that patients with HAE present elevated number of angioedema attacks carrying elevated costs. LTP reduces attack frequency and per attack direct cost.
Efficacy of Recombinant Human C1 Esterase Inhibitor (rhC1INH) Across Anatomical Locations in Acute Hereditary Angioedema (HAE) Attacks

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RATIONALE: rhC1INH is efficacious for acute HAE attacks. It is important to understand if differences in time to symptom relief may vary by anatomical attack location.

METHODS: Data were pooled from 2 randomized, double-blind, placebo-controlled studies with open-label extensions. Patients ≥12 years of age with an acute HAE attack received rhC1INH 50 U/kg or placebo. Time to beginning of symptom relief was defined as first timepoint that severity visual analog scale (VAS) score at an attack location decreased by ≥20 mm versus baseline, with persistence to next timepoint. Data reported as mean (95% confidence interval).

RESULTS: For all attack locations assessed, rhC1INH treatment shortened time to beginning of symptom relief. Time to beginning of symptom relief for an abdominal attack for rhC1INH (n = 194) was 60.0 minutes (47.0, 62.0) and for placebo (n = 15) was 240.0 minutes (45.0, 720.0). For a peripheral attack, the time to for rhC1INH (n = 169) was 105.0 minutes (90.0, 120.0) and the time to for placebo (n = 17) was 303.0 minutes (180.0, 720.0). Time to beginning of symptom relief for an oro-facial-pharyngeal-laryngeal attack for rhC1INH (n = 36) was 64.5 minutes (60.0, 720.0) and for placebo (n = 6) time to was 306.0 minutes (30.0, 495.0). For a facial attack, the time to for rhC1INH (n = 24) was 158.0 minutes (90.0, 330.0); placebo (n = 2) could not be determined. For a urogenital attack, rhC1INH (n = 13) was 119.0 minutes (40.0, 270.0), and for placebo (n = 1) was 320.0 minutes.

CONCLUSIONS: Treatment with rhC1INH 50 U/kg was efficacious in shortening time to symptom relief of acute HAE attacks, regardless of attack location.

An International Registry for Angioedema without Urticaria

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RATIONALE: Patients with recurrent angioedema without urticaria are often categorized into hereditary, acquired, drug-induced or other forms. However, up to 40% of patients with angioedema are idiopathic. Unfortunately, little is known about the natural history of idiopathic angioedema. Therefore, we sought to analyze several clinical characteristics and disease frequency and severity in patients with idiopathic angioedema.

METHODS: In an IRB-approved protocol, the University of Wisconsin electronic medical record was accessed to identify patients who received an ICD-9 diagnostic code of angioedema over a five-year period. Patients with hereditary angioedema or identifiable triggers were excluded from the analysis. Data collected included symptom duration, tissues involved, prednisone usage, and whether or not emergency care was sought.

RESULTS: Of the 160 patients examined with an exclusive ICD-9 code for angioedema, 99 had a history consistent with idiopathic angioedema (61 patients had hereditary angioedema or an identifiable trigger). 55% of the patients had recurrent episodes of angioedema for greater than one year, while 35% had episode(s) lasting less than a year. The episodes of angioedema predominantly involved the face (69%), oral cavity (54%), and limbs (16%). Just over half of these patients (52%) reported at least one visit to an emergency room or urgent care clinic and 55% of patients required a steroid burst.

CONCLUSIONS: Patients with idiopathic angioedema tend to experience recurrent episodes, typically persisting for years. Tissue involvement is primarily of the face and oral cavity, and symptoms are often severe enough to provoke emergency evaluation and necessitate prednisone usage.
739 Safety Of Plasma-derived C1-inhibitor Treatment In Pediatric Patients With Hereditary Angioedema Due To C1-inhibitor Deficiency – A Long-term Survey

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RATIONALE: Plasma-derived C1-inhibitor concentrate (pdC1-INH, Berinert®) is the only approved drug for treatment of hereditary angioedema with C1-inhibitor deficiency (C1-INH-HAE) in pediatric patients of all age groups.

METHODS: In the prospective, long-term survey, real-life data of pdC1-INH use in patients, diagnosed and followed up under the age of 18 years in the Hungarian Angioedema Centre were analyzed.

RESULTS: Of 70 pediatric patients (33 boys and 37 girls; mean age at diagnoses: 7.73 years; 26 boys and 28 girls were below the age of 12 years) experienced a total of 759 cases of 1835 peripheral, 141 facial, 72 genital, 74 upper airway attacks during the observation period. Thirty-two of 70 received one or more vials of pdC1-INH in case of edematous attacks (352 vials) or for prophylaxis (27 vials). 379 vials of pdC1-INH (1 vial = 500 IU) were administered (on average 11.8 vials/patient). First administration of pdC1-INH was on average at the age of 11.59 years (min.: 1 year, max.: 17.8 years). The distribution of used pdC1-INH in different age groups were the following: 1 vial (0-1 years), 2 vials (1-3 years), 18 vials (3-6 years) 167 vials (6-12 years) and 171 vials (12-18 years).

No systemic allergic reactions, viral transmission and thromboembolic events occurred. Only one patient had urticaria, developed within few minutes after administration of pdC1-INH, but it was not related to the drug.

CONCLUSIONS: Real-life data from our long-term survey confirm that pdC1-INH is a safe and effective treatment for pediatric patients with C1-INH-HAE of all age groups.

740 Hypercoagulability Study in Patients with Angioedema.

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RATIONALE: Angioedema can be caused by histamine/bradykinin release. We studied thrombophilia in adult angioedema patients candidate to treatment with tranexamic acid.

METHODS: Retrospective, cross-sectional study (EC approval PI-1654).

Adult angioedema patients with thrombophilia study were included. Patients were classified into 4 subgroups: A) angioedema with hereditary/acquired C1-inhibitor deficiency; B) hereditary angioedema with normal C1-inhibitor; C) other bradykinergic angioedema; D) histaminergic angioedema.

RESULTS: Eighty-eight patients were included (A 55, B 9, C 6, D 18 patients; mean age 39.7±15.5y; 69.3% female). Platelets were high in 5, low in 1 patient. Fibrinogen was low in 1, high in 29 patients. Partial thromboplastin time (ratio) was low in 12 patients and significantly shorter in group A [Median-Interquartile range (IR): group A (0.83-0.07), group B (1.04-0.11), group C (0.98-0.15), group D (1.00-0.095); χ²(K-W)=46.18, gl=3, p<0.001]. Antithrombin was high in 17 patients. Protein S was low in 5, high in 21 patients. Protein C was high in 11 patients. Functional FXII was low in 2, high in 20 patients. Lupus factor was positive in 4 patients. One patient carried mutation G1691A in coagulation factor V Leiden gene (heterozygous); three patients carried mutation G20210A in prothrombin gene (heterozygous); forty-one patients carried mutation C677T in MTHFR gene (10 homozygous). Homocystein was high in 12 patients and significantly higher in males [Median–IR: male (9.95-4.47), female (7.60-2.80) (M-W=378.00, Z=-3.07, p=0.002)].

CONCLUSIONS: Mutations in coagulation promoting genes have been found, being C677T in MTHFR gene the most predominant. Partial thromboplastin time was lower in patients with C1-inhibitor deficiency.

K-W: Kruskal-Wallis; M-W: U Mann-Whitney

741 Clinical characteristics and response to attack treatment with Berinert® of drug induced angioedema in the French Cohort COBRA.

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RATIONALE: The Cobra registry reports clinical data and treatment response with Berinert® in the French population of patients with bradykinin mediated angioedema (AE): hereditary AE with and without C1Inhibitor deficiency, idiopathic non histaminergic AE, drug induced AE (DIAE).

METHODS: The study covers all data available from 2007 to July 2016. The analysis included retrospective data extracted from patients’ medical record and prospective data directly recorded in the electronic registry.

RESULTS: Among the 233 bradykinin mediated AE (BMAE) patients included in the registry 16 (6.9%) patients had a DIAE. They are 67.4±9.8 years old and 56.3% of them are male. AE etiology is essentially linked to ACE inhibitors (56.2%), AHRAs (31.2%), and by both of them (6.3%). The first crisis appeared when they were 63.9±10.3 y.o. 73.3% were previously treated with corticosteroids and a first treatment with Berinert® occurred when they were 66.4±9.7y.o. These patients are older and had a sex ratio M/F close to 1/1 rather than close to 1/2 for the other AE. 15 of them had at least an attack treated with Berinert® which were essentially located at upper respiratory tract only (n=9), at face only (n=2) and multilocated (n=4). 92.3% of the upper tract respiratory attack were rated as severe and 60% of those located at the face. Symptoms disappeared in less than 6 hours in 50% of the patients and in less than 12 hours in 93.3%. One failure was reported.

CONCLUSIONS: Attack treatment with Berinert® of drug induced angioedema is efficient and fast acting.
Effect of long term prophylaxis with attenuated androgen (AA-LTP) on the risk for cardiovascular and neoplastic diseases in a cohort of 289 patients with Hereditary Angioedema (HAE) due to C1 inhibitor deficiency.

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RATIONALE: Late decades of life are less populated in patients with HAE than in normal subjects suggesting reduced life expectancy. We investigated a role for AA-LTP through modification of incidence for cardiovascular and neoplastic diseases.

METHODS: ITACA database was integrated adding data about patient’s characteristics collected through a telephone-interview using a standardized questionnaire administered by a doctor.

RESULTS: 289 patients, 158 female (55%), >18 y.o. (mean age of 49.4 ± 16.4) participated in the study. 140 patients (48.4% total) did never received LTP, 129 (44.6%) were on AA-LTP, 19 (6.6%) on LTP with tranexamic acid, 7 (2.4%) on LTP with C1-INH. Hypertension was more common in patients on >10y/AA-LTP (OR 2.3; 95%CI 1.1-4.2) and hypercholesterolemia in those on >15y AA-LTP compared to patients without LTP (OR 2.4; 95%CI 1.0-5.4). Thirty seven patients (12.8%) had cardiovascular diseases, compared to 3.7% of the general Italian population without age correction. The prevalence of neoplasms (n=17/289, 5.9%) was lower in the AA-LTP vs no AA-LTP (3/17 neoplasms; OR 0.02; 95%CI 0.05-0.72).

CONCLUSIONS: HAE patients on AA-LTP appear to have increased risk for cardiovascular disease, but reduced number of neoplasms.

Gender Influence on Hereditary Angioedema with C1-inhibitor Deficiency

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RATIONALE: Hereditary Angioedema (HAE) is a severe, heterogeneous, underdiagnosed and inadequately treated disease. We assess the influence of gender on HAE with C1-inhibitor deficiency phenotype.

METHODS: Cross-sectional study characterizing patients with HAE with C1-inhibitor deficiency in a reference center, assessing differences according to gender.

RESULTS: Ninety patients with HAE, 95% type I and 5% type II, were included, 66% being female and 34% male. Family history was observed in 74%. The average-ages of disease onset and diagnosis were 13 and 25 years, respectively. The average duration of attacks was 67 hours in men and 78.3% reported spontaneous attacks; 64.5% stress; 72% trauma or injury; 37% and 34% menstrual cycles, 40% with exogenous estrogen intake, and 84% with pregnancy. Long-term prophylaxis was prescribed for 81.5% of patients, 85% with danazol, 57.7% with tranexamic acid, and 24.6% with both. Among women, 21% were taking progesterone, 5% progesterone and danazol, 57.7% with tranexamic acid, and 24.6% with both. Among women, 21% were taking progesterone, 5% progesterone and danazol, 57.7% with tranexamic acid, and 24.6% with both. Among women, 21% were taking progesterone, 5% progesterone and danazol, 57.7% with tranexamic acid, and 24.6% with both. Among women, 21% were taking progesterone, 5% progesterone and danazol, 57.7% with tranexamic acid, and 24.6% with both. Among women, 21% were taking progesterone, 5% progesterone and danazol, 57.7% with tranexamic acid, and 24.6% with both. Among women, 21% were taking progesterone, 5% progesterone and danazol, 57.7% with tranexamic acid, and 24.6% with both. Among women, 21% were taking progesterone, 5% progesterone and danazol, 57.7% with tranexamic acid, and 24.6% with both. Among women, 21% were taking progesterone, 5% progesterone and danazol, 57.7% with tranexamic acid, and 24.6% with both. Among women, 21% were taking progesterone, 5% progesterone and danazol, 57.7% with tranexamic acid, and 24.6% with both. Among women, 21% were taking progesterone, 5% progesterone and danazol, 57.7% with tranexamic acid, and 24.6% with both. Among women, 21% were taking progesterone, 5% progesterone and danazol, 57.7% with tranexamic acid, and 24.6% with both.

CONCLUSIONS: HAE with C1-inhibitor deficiency have higher phenotypic expression in women, but with similar severity in both sexes. We observe clinical worsening during pregnancy and with exogenous estrogen intake.

Angioedema Without Urticaria in The Emergency Department

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RATIONALE: To determine the incidence and characteristics of angioedema without urticaria (AE) at the Emergency Department (ED) of a third-level Hospital in Madrid.

METHODS: A retrospective-descriptive study including patients older than 15y/o diagnosed with AE at the Emergency Department (ED) from Jan-2013 to Dec-2015 was conducted.

RESULTS: 455,937 patients were attended to at the ED in 3 years. AE was diagnosed in 639 (Incidence 0.14%). Mean age of 48.6y ± 20, median: 47, 59.9% females. The facial location was present in 90% (34.59% lips, 34.43% eyelids, 21.91% others) and oropharyngolaryngeal edema appeared in 42% (24.73% uvula, 14.55% tongue). 32% of whom suffered breathing difficulties and 27.2% swallowing difficulties. Only 4.54% had peripheral involvement (2.82% extremities, 1.41% genital organs and 0.31% trunk). Pruritus was present in 15.34%. 31.3% had previous episodes of AE. The suspected etiology was unknown in 48.83%, followed by drugs (25.51%; NSAID intolerance 6.73%, ACE inhibitor-AE 6.42% and others 12.36%), foods (12.21%), other allergies (6.42%), hereditary AE (1.1%) and other causes of AE (1.87%). 54.6% were treated with antihistamines and 62.4% with corticosteroids. These drugs were prescribed for several days at discharge to 70.6% of the patients, 59.1% were referred to the Allergy Department for further studies.

CONCLUSIONS: The incidence of Angioedema without urticaria at the ED was low, more common in women. The mayor location was facial, a third had airway compromise, and the peripheral involvement was very uncommon. Pruritus was not frequently associated to AE. A third of patients had recurrent episodes.
AB238 Abstracts


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RATIONALE: To describe clinical characteristics of patients with both HAE and AAE at a private practice in Puerto Rico (PR), their response to newer acute and prophylactic therapies available, the impact on complications in an observational study.

METHODS: Patients referred to our practice for evaluation and management of recurrent angioedema. Once the diagnosed treatment (tx) with s/c Icatibant or Ecallantide were offered as rescue therapy and a C1 Inhibitor (human), was offered if the patient had ≥1 attacks of angioedema per month, as prophylactic therapy.

RESULTS: Overall 46 patients; 37 (80%) were females. Age range 5 to 68yo. Current tx for HAE: prophylaxis with C1 INH 16 (35%), acute tx with Icatibant or Ecallantide 28 (61%). Effect of tx on attacks/month: no attacks from 3 to 41%, 1-2 attacks from 31 to 37%, 3 to 4 attacks from 45 to 9%, and ≥5 from 21 to 13%. Effect of treatments ER visits in last 6mo: no ER visits from 38 to 63%, 1-2 from 31 to 37%, 3 to 4 from 23 to 4%, and ≥5 from 19 to 2%. Effect of tx Hospitalizations in last 6mo: no Hospitalizations from 27 to 87%, 1-2 from 4 to 11%, 3 to 4 from 12 to 5 from 21 to 13%. Effect of treatments ER visits in last 6mo: no ER visits from 38 to 63%, 1-2 from 31 to 37%, 3 to 4 from 23 to 4%, and ≥5 from 19 to 2%. Effect of tx Hospitalizations in last 6mo: no Hospitalizations from 27 to 87%, 1-2 from 4 to 11%, 3 to 4 from 12 to 2%, and ≥5 from 4 to 0%.

CONCLUSIONS: There has been a dramatic burst of HAE in PR; therefore, it is crucial to expand diagnostic testing to different parts of the island to identify undiagnosed patients, for prompt differentiation to receive pertinent and cost-effective therapeutic interventions.

Scratching in Atopic Dermatitis Has Circadian Rhythm

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RATIONALE: Nocturnal eczema flares are severely pruritic and sleep disturbing, yet timing of flares is not well established. Our hypothesis is that eczema has a circadian rhythm, with scratching episodes peaking within the first few hours after sleep onset.

METHODS: Case control study with children ages 6-17 years with moderate/severe AD, controlled asthma and AR (n=19), and age matched controls (n=11). Scratch and sleep were assessed via validated actigraphy (Actiwatch Spectrum) measured for 5-7 consecuitive days/ nights. Generalized least squares models, with cubic spline for smoothing, were fit to the data.

RESULTS: Children with AD (65% male, SCORAD μ=58±22(mean±SD)) versus controls had significantly more minutes of wake after sleep onset (μ=98±53 vs. 50±30, p<0.01). However, the interaction between group and timing was not significant (p=0.37). Yet, the average amount of movement (scratch) in children with AD was increased compared to controls (p<0.0001) and had a clear timing pattern that differed from control patients (p<0.01). These activity bouts clustered in AD around 2-5 hours after sleep, with peak scratch 3 hours after sleep onset.

CONCLUSIONS: Most nocturnal scratch behavior in AD is 2-5 hours after sleep onset, peaking at 3 hours. Overnight awakenings did not have a specific rhythm in AD. This pattern of timing in nocturnal eczema suggests a circadian rhythm to pruritus. Further research into the circadian rhythm of AD might answer the fundamental question about the etiology of AD flares.

CD300a: A New Player in Atopic Dermatitis?

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RATIONALE: CD300a is an inhibitory receptor expressed by mast cells (MCs) and eosinophils. We have previously shown that its expression on eosinophils is upregulated by hypoxia and GM-CSF, hallmarks of inflammation. Atopic Dermatitis (AD) is a chronic inflammatory disease characterized by MCs and eosinophil activation. Therefore, we aimed to investigate a possible involvement of CD300a in AD.

METHODS: Skin biopsies and blood leukocytes from AD patients and normal volunteers were stained for CD300a and biopsies also for hypoxia (HIF1α) and blood vessels (PECAM). Human cord blood (CBMC) and mouse bone marrow (BMMC) derived MCs and human peripheral blood eosinophils were incubated under hypoxia or with S. aureus exotoxins for CD300a expression (FACS, WB, RT-PCR). AD (SEB+OVA/skin tape stripping) or peritonitis (SEB) were induced in CD300a-/- and WT mice and disease characteristics followed.

RESULTS: AD skin showed increased expression of CD300a particularly in eosinophils and macrophages, hypoxia and increased vascularity. Dermal blood vessel numbers correlated with CD300a+MCs and macrophages. CD300a expression was significantly decreased on blood NK cells and increased on B cells. In vitro CD300a expression on MCs and eosinophils was increased by both hypoxia and exotoxins. In CD300a-/- mice epidermal/dermal thickness and eosinophilia was increased in AD and overall inflammation and characteristic eosinophil infiltration were enhanced in SEB-peritonitis.

CONCLUSIONS: CD300a expression is modulated in human AD and its absence in a mouse model of AD and of SEB peritonitis increases inflammation. Targeted activation of CD300a on MCs and eosinophils can be a novel therapeutic approach in AD.

CD300a: A New Player in Atopic Dermatitis?
Eosinophil Peroxidase Contributes to the Induced Inflammation Occurring in Mice following Skin Exposure to TMA

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RATIONALE: Allergic dermatitis induces skin inflammation and increased itch response. The non-classical allergen toxicant trimellitic anhydride (TMA) results in an eosinophil-dependent increase in inflammation and sensory nerve growth as well as associated itch response. This study expands on our previous finding to demonstrate the importance of the eosinophil secondary granule protein eosinophil peroxidase (EPX) activity in inducing these responses in mouse models of allergic dermatitis.

METHODS: Wild type mice or mice deficient in eosinophils (PHIL) or eosinophil secondary granule proteins (eosinophil-peroxidase (EPX−/−) and major basic protein-1 (MBP-1−/−)) were assessed for responses to allergen induced atopic dermatitis TMA treatment. Additional experiments included inhibition of eosinophil peroxidase activity in wild type mice by treatment with two independent drugs: resorcinol and anti-thyroid drug methimazole. End point measurements of inflammation included ear thickness measurements, histological assessments, and qRT-PCR of cytokine and chemokine gene expression and itching events.

RESULTS: Specifically, EPX peroxidase activity was critical in inducing skin inflammation and itch response. Moreover, EPX−/− mice as well as mice inhibited of their EPX activity by drug treatments resorcinol and methimazole were significantly decreased in their Th2 cytokines IL-4, IL-13 and MCP-1 expression when treated with TMA. Itching events were dramatically reduced as well in these mice.

CONCLUSIONS: The peroxidase activity of EPX is a critical mediator of inflammatory events in mouse models of allergic atopic dermatitis. The function of eosinophils and EPX appears to induce Th2 inflammatory events in mouse models of allergic atopic dermatitis. The peroxidase activity of EPX is a critical mediator of inflammatory events in mouse models of allergic atopic dermatitis. The peroxidase activity of EPX is a critical mediator of inflammatory events in mouse models of allergic atopic dermatitis. The peroxidase activity of EPX is a critical mediator of inflammatory events in mouse models of allergic atopic dermatitis. The peroxidase activity of EPX is a critical mediator of inflammatory events in mouse models of allergic atopic dermatitis. The peroxidase activity of EPX is a critical mediator of inflammatory events in mouse models of allergic atopic dermatitis.

Skin Barrier Impairment during Early Infancy Precedes Sensitization to Respiratory Allergens at 5 Years of Age

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RATIONALE: Allergic dermatitis is a common manifestation of atopy, but human based mechanistic, epigenetic, and genomic studies are limited by the lack of reliable, non-invasive methods for collection of samples from skin. Our objective was to develop a non-invasive, reliable, and sensitive method of collection of RNA from lesional and non-lesional skin of children with atopic dermatitis.

METHODS: Tape was utilized to collect samples from non-lesional skin from patients using sequential adhering and removal of strips from the same location. Strips 1-7 were saved for microbiome and genomic analysis (not discussed), and 8-14 for RNA collection. Variables examined included 1) tape and adhesive type, 2) size of tape, 3) number of sequential tape samples (proxy for penetration into dermis), 4) purification technique. Yield (quantity and quality) was estimated using Nanodrop and fluorescent dye. Usability was gauged through RTqPCR to quantify expression of GAPDH, Keratin1 (keratinocyte-specific), and atopy related genes (S100A8, KIF3A). Non-invasiveness was subjectively measured by appearance of rash or discomfort.

RESULTS: All collection methods were well tolerated. Masking tape produced higher yield and consistent results than Tegaderm™. Larger tape results in improved yield, however, resulted in less consistent results. Additional sequential tape samples improved yield and consistency. Purification through column-based methods were more consistent than trizol but similar yield. RTqPCR showed high-level expression of GAPDH, intermediately of S100A8 and Keratin1, low-level expression of KIF3A.

CONCLUSIONS: Our data reveal a novel tape-based method for non-invasive sampling of skin from children with atopic dermatitis. This method reliably yields RNA that is of high-quality and enables genomic and epigenetic studies.

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Reduced Risk of Atopic Dermatitis in Infants from Wisconsin Farm Versus Non-Farm Families

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RATIONALE: Exposures on traditional European dairy farms reduce the risk of atopic dermatitis (AD) in young children. Whether dairy farm environments in the United States have similar effects is unknown. The Wisconsin Infant Study Cohort (WISC) in Marshfield, Wisconsin is a birth cohort with prenatal enrollment of participants stratified into dairy farm and non-farm groups. Based on European findings, we hypothesize that children born into farm families in the WISC cohort will be less likely to develop AD compared to non-farm children.

METHODS: Parents reported by questionnaire if a health care provider had diagnosed the child with AD. Parents completed between 1 to 8 questionnaires at clinic visits (2, 9, 12, 18, 24 months) and phone calls (6, 15, 21 months). The target enrollment is 100 per group, and to date there are 170 subjects (farm n=73; non-farm n=97) and 686 subject visits (farm n=324; non-farm n=362). Fischer’s exact test was used to evaluate group-related differences in AD.

RESULTS: Median follow-up time was similar for the two groups (farm=13.44 months; non-farm=11.25 months). Cumulative prevalence of AD in farm subjects was 11% (n=8) and 23% (n=22) in non-farm (p<0.036). Percent of visits with current AD reported in farm subjects was 7% (n=3) and 12% (n=43) in non-farm (p<0.022).

CONCLUSIONS: Wisconsin farm children are about half as likely to develop AD during infancy compared to non-farm children. These findings suggest that environmental factors found in Wisconsin dairy farms reduce the risk of developing AD.

Chronic Urticaria in a Pediatric Cohort: Resolution and Associated Factors

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RATIONALE: To assess the natural history of chronic urticaria in a cohort of children and to determine factors associated with resolution.

METHODS: As part of the pediatric chronic urticaria registry at the Montreal Children’s Hospital data was collected through a standardized questionnaire from consenting parents on demographic characteristics, history of comorbidities, use of medications and clinical characteristics of hives. In addition, we assessed basophil count and basophil activation (measured by CD63 by flow cytometry) at study entry. Cox model was used to assess resolution (defined as absence of hives for at least one year with no medications) and sociodemographic, clinical and laboratory parameters associated with resolution.

RESULTS: Among 139 patients followed up to 30 months, there were 48.90% males and the average age was 8.77 years old. A total number of 43 cases were resolved and the resolution rate was 10 per 100-patient-year. Resolution was more likely if CD63 levels were higher and less likely if basophil count was higher [Hazard ratio adjusted(HRA):2.20 (95%CI, 4.70,1.01) and HRA:0.41 (95%CI,0.92, 0.18)].

CONCLUSIONS: Our findings indicate low rate of resolution and that laboratory parameters such as basophil count and CD63 are useful prognostic factors.

The Impact of Exposure to Air Pollutants on 1023 Adult Atopic Dermatitis Patients – a Nationwide Population-Based Cross-Sectional Study.

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RATIONALE: There is a trend toward an increased worldwide prevalence of allergic diseases. It is speculated that industrialization with resultant air pollution plays a role. Atopic dermatitis (AD) is a disease mostly of childhood but some AD patients still suffer from their disease in the adulthood. Nevertheless, there is scarce epidemiological data with respect to the relationship between air pollution and AD in adults.

METHODS: We conducted a cross-sectional study based on the data from the National Health Insurance Research Database (NHIRD) in Taiwan. A total of 1023 adult AD patients (≥ 20 years old) were identified in a random 1,000,000 sample population in 2011. We also utilized monitoring data of the air pollutants from 71 Environmental Protection Agency (EPA) monitoring stations across Taiwan to calculate the average concentrations of these air pollutants. A multivariate logistic regression analysis, adjusted for age, gender, levels of urbanization, family income and levels of exposure to air pollutants, was performed.

RESULTS: The mean age of adult AD patients in Taiwan was 44 years old and a slight female predominance (57%) was present. We found a modest association between particulate matter (PM2.5 or Pollutant Standards Index (PSI, the highest sub-index of the concentrations of main air pollutants after transformation), and the development of adult AD. The adjusted odds ratios were 1.05 (95% confidence interval [CI]: 1.02-1.08) and 1.02 (95% CI: 1.01-1.03), respectively.

CONCLUSIONS: Our results demonstrated that air pollution, represented by PM2.5 or PSI, is modestly associated with the development of AD in adults.
755 Ambient Nitrogen Dioxide Aggravates the Acute Symptoms of Atopic Dermatitis in Young Children

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RATIONALE: We evaluated the effect of nitrogen dioxide (NO2) on atopic dermatitis (AD) symptoms in children based on high-resolution exposure assessment of ambient NO2.

METHODS: A total of 128 patients (78 boys and 50 girls aged under 6 years) with AD living in Seoul Metropolitan Area, Korea were enrolled and followed between April and July in 2014. Daily AD symptoms were recorded to describe the degree of itching, sleep disturbance, erythema, dryness, oozing, and edema with a scale of 0 to 4. We assessed daily NO2 level for residential area using Community Multi-scale Air Quality (CMAQ) modeling system with spatial resolution of 1 km. Generalized linear mixed model was used to evaluate the effect of NO2 on the AD symptom after controlling for age, sex, outdoor temperature, outdoor humidity, ambient particulate matters (PM10), ambient ozone (O3), the presence of fever, and the use of topical corticosteroid.

RESULTS: The symptom records of 8,410 person-days were collected. CMAQ-modeled NO2 levels were well agreed with measured NO2; Index of agreement was 64.4%. An increase in NO2 by 10 ppb was significantly associated with an increase in 13.2% (95% CI: 2.5 to 25.0) of AD symptoms on the same day and 11.5% (95% CI: 1.5 to 22.4) on the previous day. AD symptoms in boys increased by 21.5% (95% CI: 6.7 to 38.3) per 10 ppb of NO2 increase, while an increase in girls was not statistically significant.

CONCLUSIONS: Our results suggest that exposure to NO2 aggravates AD symptoms in children.

756 Phenotypic Differences Between Asthmatic Children with and without Atopic March

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RATIONALE: Atopic dermatitis (AD) in infancy followed by allergic rhinitis (AR) and asthma in later childhood is known as atopic march. However, a significant number of children and adults develop asthma without history of preceding atopic dermatitis. The aim of this study was to delineate the clinical characteristics of asthmatic children with and without atopic march.

METHODS: Data on 198 asthmatic children aged 3-18 years were collected. The study subjects were divided into two groups. Group A (N=98) comprised of asthmatic children with history of atopic dermatitis. Group B (N=100) comprised of asthmatic children without any history of atopic dermatitis.

RESULTS: Group A: Male: Female 65:33. Race, Caucasian: Other race 46:52. Family history of atopy in 78.5% subjects. Allergic Rhinitis (AR) 83.6%. Food Allergy (FA) 63.5%. Gastro esophageal reflux (GER) 6%. Associated ENT issues (Adenoid hypertrophy, Eustachian tube dysfunction) 9%. Average Intake of oral steroid/year/Patient was 1.26. Average number of hospitalization for asthma/year/patient was 1.0

Group B: Male: Female 68:32. Race, Caucasian: Other race 59:41. Family history of atopy in 50% subjects. AR 49%. FA 6%. GER 26%. Associated ENT issues 33%. Average Intake of oral steroid/year/Patient was 0.43. Average number of hospitalization for asthma/year/patient was 0.09.

CONCLUSIONS: These data suggest that family history of atopy, food allergy, allergic rhinitis and asthma morbidity (increase use of systemic steroids and hospital admissions) were significantly more common phenotypic features (p<0.01-0.03) in group A (asthmatic children with atopic march). ENT pathologies and GER were significantly more prevalent(p<0.0001-0.0003) in group B (children without atopic march). Early identification of phenotypic features may help in developing strategies to reduce the asthma morbidity.

757 Characterization and Natural History of Skin Testing in Children with Persistent Atopic Dermatitis

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RATIONALE: Skin testing (ST) is utilized in Pediatric Atopic Dermatitis (AD) to help identify potential food avoidance. Frequently, ST are positive without history of exposure; the significance of this sensitization is unknown.

METHODS: A retrospective chart review in a community allergy practice (2008-2012) identified children (<10 years) with chronic AD who were seen >1 time over 5 years with repeated ST. Results of ST (mm) over time with clinical correlation.

RESULTS: A total of 125 children were seen. Eighty two of 125 (66%) had positive ST identified to 16 foods. Twenty-four of 82 (29%) children with positive ST to foods had a history of true food allergic reaction. Sensitization to foods was found in 72 of 82 (88%) with some overlap in children with true food allergy (FA). The most common foods testing positive were egg (57/82, 70%), peanut (56/82, 68%), tree nut (43/82, 52%), milk (30/82, 37%) and wheat (10/82, 12%) at initial allergy visit. Over 5 years, ST to egg (25/57, 44%) resolved over an average of 31 months, followed by milk (12/30, 40%) over 29 months, wheat (3/10, 30%) over 13 months, tree nut (6/43, 14%) over 31 months and peanut (6/56, 11%) over 30 months. The majority of children (77/82, 94%) improved with allergen avoidance in combination with medical plan.

CONCLUSIONS: ST to foods is positive in the majority of children with chronic AD, reflecting both true FA and sensitization. Resolution of FA/sensitization varied between foods over 2.5 years and is an optimistic finding for children with AD and FA.
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**758** Insufficient physical activity is a risk factor of atopic dermatitis in Korean adolescents

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**RATIONALE:** Regular physical activity (PA) has been known as beneficial that it reduces the risk of chronic diseases including allergic diseases. However, little has known regarding the relationship between PA and allergic diseases in Korean adolescents. We analyzed the national data whether PA is related to the prevalence of allergic diseases in the population of Korean adolescents.

**METHODS:** Data from sixth Korean National Health and Nutrition Examination Survey (2013 to 2014) that included 1,272 adolescents from 12 to 18 years old was analyzed. We defined regular PA according to Physical Activity Guidelines for Americans. Multivariate regression analysis was performed to find whether insufficient PA could be a risk factor for allergic diseases.

**RESULTS:** The prevalence of asthma, allergic rhinitis (AR) and atopic dermatitis (AD) were 1.3%, 9.3% and 5.2% in Korean adolescents, respectively. After adjusting for factors, PA was not associated with asthma and AR, but was significantly related to AD in Korean adolescents (adjusted odd ratio 3.254, 1.202-8.810, p = 0.021)

**CONCLUSIONS:** This study suggests insufficient PA is a risk factor of atopic dermatitis in Korean adolescents. These findings may be helpful for management and improving the quality of life in AD of Korean adolescents.

**759** Allergen Sensitivity in Adults with Atopic Dermatitis

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**RATIONALE:** Atopic dermatitis (AD) is a chronic inflammatory disease characterized by significant barrier disruption and increased allergen sensitivity. Approximately 80% of patients with AD have evidence of sensitivity to one or more environmental or food allergens. We hypothesized that the frequency and distribution of allergen sensitivity would identify potential subsets of AD patients.

**METHODS:** Serum was collected from 39 healthy controls with no history of skin disease and 76 subjects with AD and analyzed for allergen sensitivity to a panel of 119 environmental and food allergens using the ImmunoCAP Solid-Phase Allergen Chip (ISAC) test. Extrinsic AD (EAD) was defined as a total IgE level ≥ 150 kU/L.

**RESULTS:** Total IgE levels were significantly greater (p<0.001) in subjects with AD (1372.52 kU/L) compared to healthy controls (13.68 kU/L). Additionally, the number of positive allergens was statistically greater for patients with EAD compared to both intrinsic AD (IAD, p<0.001) and healthy controls (p value <0.0001). Interestingly, the number of positive allergens correlated with total serum IgE levels for EAD (r=0.7832, p<0.01) and all AD (r=0.7042, p<0.0001). Overall, there were significantly more positive results to both environmental and food allergens in the EAD group compared to IAD and healthy control groups. A greater prevalence was observed for dust mite, cat, and horse allergens in all AD subjects (p<0.05).

**CONCLUSIONS:** These findings support the hypothesis that determination of allergen sensitivity in patients with AD may allow identification of patient subsets which may have implications for future therapeutic approaches.

**760** Patch Testing for Evaluation of Allergic Contact Dermatitis in a Single Academic Allergy Practice

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**RATIONALE:** Allergic contact dermatitis (ACD) is frequently encountered by allergists. Patch testing is the “gold standard” to identify culprit allergens causing ACD, but there are limited studies on patch testing in allergy practices. Our objective was to report on patch testing findings in an outpatient allergy practice.

**METHODS:** A retrospective chart review of patients referred for patch testing from July 2013-May 2016 was performed. Data collected included a history of atopy, location of dermatitis, if referred from a dermatologist, and positive patch test results.

**RESULTS:** Of the 387 patients (mean age 49.2, 73% female) who were patch tested over a 34 month period, 241 (62.3%) had a positive reaction. Of those who tested positive, 59.4% reported an atopic history and 55.3% were referred from a dermatologist. The extremities were the most common involved site (53.7%), followed by the head/neck (47.2%) then trunk (29.7%). The five most common positive allergens were gold sodium thiosulfate, nickel sulfate, methylchloroisothiazolinone, thimerosal and bacitracin. One hundred twenty five patients (51.8%) were positive to at least 1 Thin-Layer Rapid-Use Epicutaneous (T.R.U.E) test allergens, 49 (20%) were positive on both T.R.U.E test and additional allergens from the North American Contact Dermatitis (NACDG) panel. 17 (7%) were positive to the additional NACDG allergens alone and 8 (3.3%) were positive only to supplemental allergens provided.

**CONCLUSIONS:** Patch testing is a valuable diagnostic tool for the practicing allergist. Performing a more extended series such as the NACDG and/or supplemental allergens is higher yield when compared to limited standard series in evaluating ACD.
Prediction of Infectious Complications in Children with Atopic Dermatitis

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RATIONALE: The purpose of the study is to develop criteria for the prognosis of infectious complications (IC) in children (Ch) with moderate to severe atopic dermatitis (M-SAD).

METHODS: Ninety-four Ch aged 5-17 years with M-SAD and a disease duration of 1-15 years in the remission stage were comprehensively clinical and immuno-allergological examined. A control group included 30 practically healthy Ch. Clinically, the AD had multiple and extensive inflammation with exudation or infiltration, lichenification, excoriation and severe itching, which led to the accession of secondary infection. The severity of clinical symptoms was assessed according to the SCORAD scale.

RESULTS: In Ch with AD were identified immune imbalances: re- ductions of phagocytic activity of neutrophils (PhAN) - phagocytic index (PhI) and the phagocytic number (PhN); IL-4 and IL-13 in serum, local and systemic specific IgE were increased and IFN-γ-decreased with worsening of the clinical course of the disease. The SCORAD index before treatment of M-SAD was 42.57±3.41 - 48.2±5.7 points. The inclusion of allergen-specific immunotherapy (AIT) in the comprehensive treatment (CT) of immunocompromised Ch with AD and impaired function of the PhAN, led to the development of IC in 78% of the cases. There were no complications or worsening of the clinical course of AD in the group of Ch with AD in plans that included AIT and an immunomodulator that activates PhAN.

CONCLUSIONS: Thus, monitoring of the blood levels of PhI and PhN in IgE-mediated AD predicts the development of IC in Ch with AD.

Patch Testing for Metal Hypersensitivity Evaluation in Patients With Metal Implants

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RATIONALE: As the use of metal implants is increasing, along with the concern for hypersensitivity to implanted components, allergists are receiving referrals for metal patch testing (PT). Our objective was to examine PT results in patients with suspected metal hypersensitivity with relation to medical implants both pre-implantation (pre-impl) and post-implantation (post-impl).

METHODS: We conducted an IRB-approved, 10-year retrospective chart review of patients that underwent PT for metal implant related hypersensitivity. Data gathered included patient demographics, clinical characteristics and PT results. PT was performed with metal and bone cement components.

RESULTS: Patients were divided into 2 groups: pre-impl (n= 30) and post-impl (n=14). Implants included orthopedic (n=12), dental (n=1), and cardiac (n=1). The pre-impl group was referred for a history of metal hypersensitivity. In this group, 60% of patients had at least 1 positive metal PT (18/30). Patients in the post-impl group presented after development of symptoms indicating most commonly pain (n=9) but also rash, swelling, itch, joint loosening and failure. In this group, 29% of patients had at least 1 positive PT (4/14), with 3 out of 4 also reporting a history of metal hypersensitivity. Two patients had a positive PT to an implant component (cobalt, methyl methacrylate).

CONCLUSIONS: In our population, a history of metal hypersensitivity was a strong predictor of a positive PT to metal as the pre-implantation group had the highest rate of positive PT overall. Large prospective studies are warranted to further delineate the relevance of positive PT in symptomatic post-implantation patients.

Role of Patch Testing in Assessing Allergic Risk of Orthopedic Implants: Pre- and Post- Surgery

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RATIONALE: Type IV hypersensitivity is a potential contributor to orthopedic implant failure.

METHODS: A retrospective chart review of patients for assessment of metal or bone cement allergy in both pre and post surgical populations was completed from 2013 to mid-2016. Information on patch test (PT) results along with available post surgical outcomes was recorded.

RESULTS: Twenty three patients were identified. In the pre-surgical population with history of metal allergy risk, 9 of 11 were PT positive to metals (Nickel, Palladium, Gold, Cobalt), antibiotics (Bactracin, Gentamycin, Neomycin, Tobramycin), and bone cement (Epoxy resin). To date, 4 of 9 have post operative outcomes available. PT results impacted surgical decision in 3 of 4 with favorable outcomes. Two of 4 were allergic to metals, resulting in nickel free implant; surgical decision of the remaining 2 was to a cementless joint. In the post operative joint failure population, 7 of 10 patients had positive PT. Positives included metals (Nickel, Cobalt, Tin, Palladium), antibiotics (Gentamycin) and components of bone cement (N,N-Dimethyl-p-toluidine, Methyl methacrylate, Benzoyl peroxide). To date 5 of 7 have undergone joint revision, with 4 of 5 surgical decisions based on allergen profile from PT, these 4 with favourable outcome.

CONCLUSIONS: In the pre-surgical patient, history of metal hypersensitivity predicts allergy in the majority (9/11) with discovery of non-metal allergens (ie bone cement/antibiotic) in 4/9. Both allergen results directed surgical decisions. In the post-operative patient with joint failure, the majority (7/10) were found to have positive PT with resultant surgical revisions dictated by newly found allergens.

PREVALENCE AND CLINICAL FEATURES OF PATIENTS WITH CHRONIC SPONTANEOUS URTICARIA FROM A COMMUNITY CLINIC

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RATIONALE: We observed that several patients with chronic spontaneous urticaria were displaying previously unreported phenomenon of urticaria in the shape of their tattoo or scar. The prevalence and long-term significance of this is unknown.

METHODS: Initially, 5 patients were identified with this phenomenon. On the basis of this, records of 50 consecutive patients who have chronic spontaneous urticaria from an academic outpatient clinic were reviewed.

RESULTS: 16/50 patients had either tattoos and/or surgical scars. 9/50 had tattoos and 5/9 developed urticaria in the shape of the site. Two of the original 5 patients had a reaction of their scar, but none of the consecutive cases. Between episodes or on antihistamines, the sites were unremarkable with no evidence of chronic inflammation or of contact dermatitis. One patient had a biopsy of the involved tattoo revealing coarse, granular pigment within macrophages with no increase in mast cells or signs of inflammation. In all cases, adequate treatment of the systemic urticaria was also effective for the tattoo-site associated urticaria.

CONCLUSIONS: As the popularity of tattoos rises, we believe that this will be increasingly reported. The lack of inflammation between episodes, complete resolution with antihistamines, lack of inflammation on biopsy and of inflammatory sequelae over decades indicate that this is not contact dermatitis. The involvement of surgical scars, albeit at a lower frequency, suggest that scarring rather than a response to the pigment may underlie its pathogenesis. The identification of this phenomenon necessitates cautionary advice to patients with chronic spontaneous urticaria who are interested in obtaining tattoos.
The Significance of Anti-Fc Epsilon RI Antibodies in Chronic Idiopathic Urticaria: The Role of Autoimmunity in the Differential Response to Treatment

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RATIONALE: Autoimmunity is thought to play a role in the disease process of chronic idiopathic urticaria (CIU) as 30-40% of patients with CIU have clinical autoimmune disease or circulating autoantibodies. However, the role of autoimmunity in the clinical course of CIU is unclear. This study assesses the differential response to CIU therapies as stratified by anti-FcεRI antibody status.

METHODS: A retrospective review of electronic health records of patients aged ≥12 years with CIU evaluated for anti-FcεRI antibodies was conducted at Duke University Medical Center. Patients were characterized by response to treatment as well as clinical and laboratory characteristics. Univariate analysis followed by multiple logistic regression was performed.

RESULTS: Of the 230 patients identified, 50 (22%) tested positive for anti-FcεRI antibodies. There were no significant differences in age, gender, race, thyroid disease or autoimmune disease between those with positive vs negative anti-FcεRI antibodies. Mean monocyte count was significantly higher in patients with negative anti-FcεRI antibodies (529 vs 393 per mm³, p<0.0001). In patients with negative anti-FcεRI antibodies, there was a higher odds ratio of response to antihistamines (OR 1.50 [95% CI 1.12 – 2.03]) and omalizumab (OR 6.00 [2.32 – 20.4]). Negative ANA (<1:160) and the absence of clinical autoimmune disease were associated with a higher odds ratio of response to omalizumab (OR 9.50 [2.76 – 59.63] and 4.67 [2.07 – 12.48], respectively).

CONCLUSIONS: CIU patients with negative anti-FcεRI antibodies may respond more favorably to treatment with antihistamines and omalizumab than those with positive anti-FcεRI antibodies. CIU patients with evidence of autoimmunity may have more treatment resistant disease.

Clinical Predictors of Response to Omalizumab for Treatment of Chronic Urticaria

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RATIONALE: Omalizumab, an effective treatment for chronic urticaria, has not been well-studied in patients with associated conditions and comorbidities like anaphylaxis, angioedema, and dermatographism, or in urticaria refractory to multiple second-line treatments. We sought to determine if these clinical variables predict response to treatment.

METHODS: We conducted a retrospective chart review of 52 patients over age 18 who received omalizumab for severe chronic urticaria through the Northwestern University Allergy-Immunology clinic (approved by NU IRB, STU#IRB00037899). Clinical variables predicted to affect treatment response were extracted from the electronic medical record. The outcome measure was treatment response, graded as complete, partial, or none, based on the attending physician’s assessment of disease activity. Chi-square and one-way ANOVA were used to evaluate the data.

RESULTS: 86.5% of patients responded partially or completely to omalizumab. There was a significant difference in number of prior medications tried in each group (mean 5.6, 6.8, 7.4 in complete, partial and non-responders, respectively; p=0.039). Patients with eczema were less likely to respond (64% vs 93%, p=0.012). There was a trend towards decreased response in patients with neutrophilic urticaria (70% vs 90%, p=0.088). Treatment response was not affected by angioedema (p=0.72), anaphylaxis (p=0.17), dermatographism (p=0.18), or steroid use (p=0.35). Response was not correlated with disease duration.

CONCLUSIONS: Greater number of prior medications was associated with lack of response to omalizumab, but anaphylaxis, angioedema, dermatographism, steroid use, and disease duration were not. Omalizumab appears to be an effective treatment for severe or complicated disease. It is unclear why eczema is associated with lack of response.

Withdrawn
**768 Comparative Study of Basophil Activation Marker Testing and Basophil Histamine Release in Subjects with Chronic Spontaneous Urticaria**

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**RATIONALE:** Basophil IgE receptor function is altered in chronic spontaneous urticaria (CSU). Two basophil phenotypes have been described - CSU responders (CSU R) and CSU non-responders (CSU NR), based on the degree of basophil histamine release (BHR) to anti-IgE antibody. We now assess the utility of BAT (basophil activation test) to reflect these basophil phenotypes.

**METHODS:** Adults with CSU underwent blood sampling after informed consent. We conducted assays in parallel for BHR and BAT. Percoll isolated leukocytes were utilized for BHR while whole blood was utilized for BAT using CD63. Both assays were conducted using the same stimulants. BHR was analyzed by automated fluorometry and BAT analyzed on a FACs calibur, gating on the basophils (CD123+ and CCR3+). BAT assays were compared to BHR using both % positive shift and net mean MFI.

**RESULTS:** A total of 12 CSU subjects were compared (10 CSU R and 2 CSU NR). BAT testing followed the pattern of histamine release in the subjects tested (both CSU R and NR). Either metric of BAT reflected the net BHR profiling, with no statistical difference in % of maximum curves between either of the BAT metrics and BHR. One exception to the accuracy of BAT compared to net BHR occurred in a subject with high spontaneous BHR.

**CONCLUSIONS:** Preliminary data supports that BAT testing reflects the altered BHR phenotypes existing in CSU. However, a limitation of both assays is their inability to detect syk deficiency. Since BAT is more widely available, it may serve as a viable surrogate for BHR.

**769 Adaptation and Validation of the Korean Version of Urticaria Control Test**

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**RATIONALE:** A 4-item Urticaria Control Test (UCT, 0-16) was previously developed and validated in German and English. We sought to investigate the validity, reliability, and responsiveness to change of the Korean version of UCT (K-UCT) for assessing chronic urticaria (CU).

**METHODS:** A structured and linguistically validated translation of the German UCT into the Korean language (K-UCT) was validated in 80 Korean patients with CU before and after 4-week treatment. Correlations between K-UCT and Physicians’ assessment of urticaria severity and control status, and general assessment of symptom scores by patients were analyzed by a generalized estimating equations model adjusted for age, sex and treatment step.

**RESULTS:** Strong correlations between the K-UCT and disease severity including UAS (OR 0.54, P <0.001), physicians’ global assessment of urticarial control (OR 101.8, P <0.001) and patients’ assessment of symptom severity (OR 0.008, P <0.001), and CU-specific quality of life (OR 53.64, P <0.001). Excellent internal consistency and intra-class reliability were obtained. K-UCT score of ≥12 (sensitivity 81.8% and specificity 63.8%, AUC on ROC analysis 0.816) was found to be optimal for determining well-controlled CU. Perceived stress scale, a patient-oriented inventory to estimate the perceived stress levels in daily life, was significantly correlated with UAS (OR 1.93, P <0.001) and K-UCT (0.47, P <0.001).

**CONCLUSIONS:** This study demonstrates the clinical utility of the K-UCT to assess control status of CU and to detect clinical response to urticaria treatment in the Korean patients. Urticaria severity and control status impact significantly on individual perceived stress levels in patients with CU.

**770 Sustained Effect and Clinical Outcomes in Chronic Spontaneous Urticaria in Patients Receiving Omalizumab for Several Years**

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**RATIONALE:** No studies exploring the natural course of the disease and OmAb control for several years.

**METHODS:** We analyzed the data of 15 patients treated with OmAb for 3 to 7 years. We assessed the Urticaria Control Test (UCT), Urticaria Activity Score average of seven days (UAS7) in 2012 and in 2015 plus the Quality of life specific for CU (CU-Q2OL).

**RESULTS:** Out of the 15 patients, 6 went on complete remission after second, third or fourth dose. One patient received 5 OmAb doses and 1-year cyclosporine due to the non-reimbursement of OmAb. None of the patients who received OmAb for several years lost response with time. Two patients went on remission for 5 years but have to reintroduce OmAb due to CU relapse, both patients showed the same good response to OmAb. 3 patients received a monthly administration and the rest from every 6 to 14 weeks. We did not find any significant differences in UCT, UAS7, or CU-Q2OL when comparing monthly vs “on demand” administration. All the patients received 300mg except for 2 patients who went to 150 mg due to good response. These two showed worse scores prior to the administration of OmAb (UCT = 0, UAS7 =32, CU-Q2OL=79) and are scheduled to receive 300mg thereafter.

**CONCLUSIONS:** 40% of patients went on remission upon OmAb treatment. OmAb maintains a complete CSU control response along several years and is also effective on re-introduction. Clinical severity and quality of life scores are similar when administering OmAb on a regular basis or upon appearance of symptoms.
771 Patient demographics and real-world use of omalizumab for the treatment of chronic spontaneous/idopathic urticaria in Canada

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RATIONALE: As there are limited publications on real-life use of omalizumab in chronic idiopathic urticaria in Canada, there is a need to generate data on its and characteristics of patients using it. The study aims to describe demographics and treatment patterns of patients to whom omalizumab was prescribed.

METHODS: Following regulatory approval, a patient support program (PSP) was made available to all Canadian patients prescribed omalizumab. Baseline demographics and treatment information were collected for patients who provided consent, enrolled between August 2014 and 15 June 2016; patient reported information was collected as of Nov 2015.

RESULTS: 1522 patients enrolled in the PSP received at least one dose of omalizumab (71% women; average age: 46). Most patients (73%) were prescribed omalizumab 300mg q4wks while 15% were prescribed 150mg q4wks; 12% of patients were treated with other dosing regimens. Treatment history was reported by 377 patients; 84% reported being treated with ≥1 H1-antihistamine while 31% received montelukast. Prednisone was used in 20% of patients; use of cyclosporine was uncommon. Angioedema history was reported by 307 patients, 65% reported having a history of angioedema; 29% had not experienced angioedema; 6% did not know. Average omalizumab treatment persistency is 13 months.

CONCLUSIONS: In a real-world Canadian setting, omalizumab is prescribed to a population comparable to that of the Phase 3 clinical program. Treatment history and history of angioedema were likely underestimated as data were patient reported and collected as of November 2015. There requires a need to further collect and disseminate data to understand the use of omalizumab in a real-world setting.

772 Chronic Spontaneous Urticaria: Response to Antileukotriene

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RATIONALE: Around 30% of patients with chronic spontaneous urticaria (CSU) show symptoms exacerbation after nonsteroidal anti-inflammatory drugs (NSAIDs) intake. The aim of this study was to compare the efficacy of antileukotriene in NSAID-intolerant and NSAID-tolerant CSU patients.

METHODS: This retrospective study assessed CSU outpatients in a tertiary hospital. All patients were questioned about the history of CSU exacerbation or not by NSAIDs. An antileukotriene, montelukast, was added to AH1 treatment for all patients, at some time of follow up. We evaluated the response to antileukotriene and compared its efficacy according to the history of exacerbation with NSAIDs.

RESULTS: Sixty-two patients participated in the study. The mean age was 48.4 years, and 82.3% were female. Thirty-five patients (56.5%) reported NSAID intolerance and, 77.1% of them improved their symptoms after adding antileukotriene. Twenty-seven patients had no history of exacerbation with NSAIDs and 48.1% of these patients had a favorable response to antileukotriene association. The response to antileukotriene was higher and statistically significant (p=0.031) in NSAID-intolerant CSU patients.

CONCLUSIONS: Although second generation AH1s are the first choice for treatment of CSU, about 40-50% do not respond adequately to these drugs, some of these patients may be NSAID-intolerant. NSAID are cyclooxygenase inhibitors resulting in an overproduction of leukotrienes. The association of antileukotriene to AH1 would be an option for NSAID-intolerant CSU. This study showed that 65% of the patients responded to this association and this option became even more relevant for NSAID-intolerant CSU patients (77.1%).
774 The Relationship Between Chronic Urticaria and Serum Vitamin D Level

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RATIONALE: The vitamin D has an immunomodulatory action. The relationship between chronic urticaria and inflammatory process and serum vitamin D levels is controversial, and the information of them is scarce.

METHODS: We performed a descriptive, observational, cross sectional study. We selected 27 patients of which presented chronic episodes of hives, (chronic urticaria) and compared with normal healthy matched controls. In both groups we were performed the intradermal autologous serum test (IDAST) and serum vitamin D levels by ELISA as well as total IgE by ELISA.

RESULTS: The age was 47.3 ± 3.54 years in chronic urticaria and 45.9 ± 3.54 in controls. The predominant gender was female (n: 18) and male (n: 9). The IDAST was positive in 13 of 27 cases and negative in 14 of 27 cases in chronic urticaria as well as in controls. In chronic urticaria the vitamin D levels was deficient in 8 of 27 cases, insufficient 11 of 27 cases and normal level in 4 of 27 cases; the control group presented normal level in 11 of 16 cases, insufficient in 4 of 16 cases and deficient in 1 of 16 cases; p<0.0001. The serum IgE level was in chronic urticaria 216 ± 43 kU/L and in control 30.75 ± 4.129 kU/L.

CONCLUSIONS: These results indicated that the predominant gender in chronic urticaria was female. The predominant levels of serum vitamin D in chronic urticaria were deficient and insufficient. Probably indicated the important immune-modulatory role of this vitamin D in chronic urticaria.

775 Omalizumab Administration for Refractory to H1-antihistamines Chronic Urticaria Prevents Respiratory Illnesses

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RATIONALE: There is evidence suggesting that omalizumab administration in asthmatic individuals reduces viral induced asthma exacerbation. We sought to determine if omalizumab administration in refractory to H1 antihistamines chronic urticaria (CU) patients prevents respiratory illnesses, in general.

METHODS: All respiratory illnesses from all CU patients under regular omalizumab administration (300mg Q4-weeks) from at least September 2015 until August 2016 were prospectively recorded. Patients with history of asthma, allergic rhinitis, chronic rhinitis/rhinosinusitis or any type of immunodeficiency were excluded. All patients were followed up every 4 weeks at each omalizumab administration. The closest in age household member (spouse, partner, relative, roommate etc), when available and fulfilling the exclusion criteria, was used as a control individual.

RESULTS: Thirty three patients (21 women) 45 ± 16.6 years old and 30 age-matched control subjects (9 women, 46.4 ± 9.6 years old) were enrolled. The CU-patients reported significantly less respiratory illnesses as compared with the control subjects (median: 0 vs 1, inter-quartile range 0-1 vs 1-1, min-max: 0-3 vs 0-4, respectively, p-value=0.01). All but 3 patients and all but 2 controls were vaccinated for influenza between October and December 2015.

CONCLUSIONS: Omalizumab administration reduces common respiratory illnesses even in individuals having neither respiratory disorders nor allergic sensitization profile. This finding suggests the potential role of omalizumab in preventing the clinical expression of a respiratory infection at least in CU patients and raises questions of the role of IgE in infections independently of the atopic environment, at least as the last has been defined until now.
**777** Translating Chronic Urticular Guidelines to Clinical Practice: A Study Assessing How Allergists and Dermatologists Apply Guidelines Recommendations in Argentina

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**RATIONALE:** Chronic spontaneous urticaria (CSE) is a frequent condition which affects patients’ quality of life. In 2014 Argentine national guidelines and WAO guidelines for the management of urticaria were released, an important national dissemination campaign took place. Our objective was to assess if, after a year of guidelines release, allergists and dermatologists followed the recommendations in real life.

**METHODS:** A standardized clinical case of CSE was developed and presented to the audience at National Allergy and Dermatology meetings. An interactive technology was applied to allow participants to answer 7 questions related to diagnosis or management of the clinical case. Statistical significance was assessed using the chi-square test with Epi-Info 6.22d.

**RESULTS:** 120 allergists and 150 dermatologists entered the pool. The answers to the questions during the development of the clinical case are expressed as % of correct answers for allergist vs dermatologists. Question topic: 1) Diagnosis, 65% vs 38.8% (p<0.00001); 2) Evolution, 27.5% vs 40% (p=0.03); 3) First diagnostic procedure, 4.2% vs 6% (p=0.49); 4) Severity markers, 14.2% vs 8% (p=0.10); 5) First treatment step, 51.7 vs 38% (p=0.03); 6) Second treatment step, 50% vs 66% (p=0.07); 7) Third treatment step, 10% vs 18.3% (p=0.06). The average percent of correct answers was 31.8% for allergists and 50.7% for dermatologist.

**CONCLUSIONS:** More than two thirds of allergists and dermatologists do not follow the updated chronic urticaria guidelines. More efforts are needed to disseminate guidelines and assess their instrumentation.

**778** How does experience affect Management of Chronic Spontaneous Urticaria? A cross sectional study in Latin America

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**RATIONALE:** Chronic spontaneous urticaria (csU) affects 0.5–1 % of the global population at any given time and has a considerable burden on patients, healthcare systems and society. Management of csU can have different approaches among physicians and specialists. This study aimed to find associations related to variable management of csU in Ecuador.

**METHODS:** Physician based survey study from March 2015 to March 2016 in Ecuador using a standardized questionnaire (3). Descriptive statistics were employed. Adjusted logistic regression was employed among physicians that knew urticaria guidelines, practicing years, specialties and location. A p value <0.05 was significant for all tests.

**RESULTS:** 740 surveys were collected and analyzed. 64.7% of physicians had less than 20 years of experience, 24.7% less than 30 years and 10.5% more than 30 years. Only 26% of physicians with >30 years experience knew the current EAACI/GA2LEN/EDF/WAO guideline, being the group with the highest rate. The logistic regression showed physicians with >30 years practice in medicine use four times more regular doses of nsAHs than physicians with less experience (OR 4; CI, 1.7 -10.12). Prescription of oral steroids was associated with years of practice and physicians with >30 years of practice used them more frequently (OR 3.5, CI 95% 1.5 - 8.6).

**CONCLUSIONS:** Management of csU among experienced physicians showed some contradictions, despite guidelines recommendations. Variable management of csU patients is not only associated with knowledge of guidelines, but also with location and physicians experience.

**779** Persistent Diffuse Skin Eruption and Tingling in the Extremities of Unknown Etiology Diagnosed As Mercury Poisining and Vit B-6 Toxicity

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**RATIONALE:** Diffuse eruptive non urticarial rash non responsive and not identified by skin biopsy

**METHODS:** Physical exam showed diffuse eruptive rash, non urticarial, no hyperpigmented residual, spread on the trunk and extremities.

**RESULTS:** Mercury Poisining and Vitamin B-6 toxicity

**CONCLUSIONS:** Often patients present after multiple evaluations with non specific rashes that have non diagnostic skin biopsies. Eating Sushi has become very popular and it is known that there is the risk of mercury exposure in fish. When evaluated for food allergy the patient stated “I eat sushi almost every day”. Her labs showed elevated mercury levels but this didn’t account for the tingling in her extremities. She mainly ate Tuna which is high in both mercury and Vitamin B-6 as are spinach and avocado, her other daily foods. Tuna is the third highest B6 containing food, spinach and avocado are 9th and 10th. Vitamin B-6 is not water soluble and can cause toxicity with associated neuropathy. Many patients with rashes that persist are evaluated for autoimmune diseases but if that workup is negative it is important to look for, among other things, metal toxicity especially mercury which is common in some fish with Tuna having the highest mercury content.
780 Best Possible Treatment for All Patients with Primary Immune Deficiency (PID) in Sweden Regardless of Social Factors, Sex, Age or Residence

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RATIONALE: To create equal treatment for individuals living in Sweden with PID.

METHODS: Since 1999 SLIPI (Swedish Association for Physicians Interested in Immunodeficiency Diseases) in close cooperation with SSSI (Swedish Nurses Association for Primary Immunodeficiencies) and PIO (Patient Organization for PID) have implemented standard procedures for diagnostics, treatment and follow up of various PIDs. There are biennial meetings to develop guidelines and consolidate treatment. A web-based register for healthcare professionals is used since 2012. A web-based Health Journal for the patients began February 2016. The screen-combination of the two registers mentioned above will be shown.

RESULTS: As of August 25, 2016 there were 1637 patients with 16 different diagnoses registered. Most common diagnoses requiring IgG substitution dose was median 115 mg/Kg/bodyweight and week (IQR 100 - 146 mg/Kg/bodyweight and week). Only 8 patients were substituted with less than the recommended dose of ≥100mg/Kg/bodyweight and week (range 80-99mg). Ninety-eight patients have been using the web-based patient diary and they are now registering symptoms such as cough, pain, fever, medication, days with infections and sickness leave as well as patient reported outcome (PRO) and patient reported experience (PREM).

CONCLUSIONS: The strength of having both the patient’s hospital file and her/his own health journal at the same screen being able to discuss all relevant finding at the visit will hopefully result in improved care, lead to better health related quality of life, and increased survival of the patients.

781 Preferences in social media in patients with obstructive lung disease

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RATIONALE: Social Media (SoMe) is broadly used worldwide. In recent years, the amount of pulmonary related apps have risen. Our aim is to determine the frequency of use and the interest in receiving or seeking information about disease through SoMe. Descriptive statistics were employed, as well chi square for comparisons among age: adolescents (<18 y-o), young-adults (18 – 40 y-o) and adults (>40 y-o).

RESULTS: Enrolled patients were 712. Mean age was 52.3 (20.9), 58.8% were females, 61.8% Hispanics. Cellphone ownership was high (86.3%), but not Internet Access (59.6%), neither smartphone (45.7%). Most preferred SoMe was SMS by 59.4% of patients (54.0% in adults, p<0.001). Also, Internet was commonly used (43.5%), Facebook (39%), and email (37.7%), and more in patients under 40 y-o (p<0.001). Twitter, Youtube, LinkedIn and Skype was fairly used. High interest in asking information by SMS was reported by 57.7%. Otherwise, Facebook and email (36.4%), with predominance in patients under 40 y-o (p<0.001). Whatsapp preferences asking or receiving information was similar (50%).

CONCLUSIONS: SMS is a useful communication tool across all ages. Otherwise, Facebook, email and Whatsapp constitute excellent social networks to be communicated with our younger patients (< 40 y-o).

782 The Impact of the Algorithmic Software Tool to Help Manage Asthma (ASTHMA) Educator Mobile Health Application on Asthma Knowledge in Patients with Atopy and/or Eosinophilia

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RATIONALE: The Algorithmic Software Tool to Help Manage Asthma (ASTHMA-Educator) mobile health application has been developed at Montefiore and pilot tested among severe asthmatics. We describe the impact of the ASTHMA-Educator on patients with atopy and/or eosinophilia.

METHODS: Study participants were divided into groups based on whether or not they had atopy (at least 1 positive skin and/or specific IgE test), and the same was done for patients with eosinophilia (absolute eosinophil count > 0.4 K/L). Pre-and post-intervention asthma knowledge scores following the ASTHMA-Educator intervention were compared with scores following the nurse-delivered education for atopic and non-atopic patients and patients with/without eosinophilia. Comparisons were performed through the 2-sample t-test.

RESULTS: The study had 50 patients in total. There were 26 atopic patients and 2 non-atopic patients. There were 10 patients with eosinophilia, and 40 without eosinophilia. Mean asthma knowledge scores pre- and post intervention increased for both groups: using the ASTHMA Educator, both atopic (9.96 vs 12.2, p=0.0003), and non-atopic patients (10 vs 12 p=0.500) had increased scores. Atopic patients had significantly increased scores (10.15 vs 14, p=0.0040) with the nurse-delivered education. Patients with eosinophilia (9.5 vs 11.83, p=0.0751) and patients without eosinophilia (9.92 vs 12.32, p=0.0032) had increased scores using the ASTHMA-Educator. Through nurse-delivered education, both patients with eosinophilia (10.4 vs 14.6 p=0.0032) and patients without (10.13 vs 13.8 p=0.0004) had increased scores.

CONCLUSIONS: Patients with atopy and those with eosinophilia demonstrated improved asthma knowledge through the ASTHMA-Educator and nurse-delivered interventions. Additional larger studies are needed to further evaluate the ASTHMA-Educator.
CONCLUSIONS: When asked if they would utilize a website database of case reports on drug allergy, 95% said they would, with the majority saying yes. A need among North American allergists for this database and what features are important to them was assessed. A semi-structured survey was created and administered to members of the AAAAI and CSACI. The questions were split into two parts: demographics and database design. The demographics section of the survey strives to ascertain the types of drugs commonly consulted for and the frequency of these consults. The last part of the survey tries to gauge if there is a need among North American allergists for this database and what features are important to them.

METHODS: A semi-structured survey was created and administered to members of the AAAAI and CSACI. The questions were split into two parts: demographics and database design. The demographics section of the survey strives to ascertain the types of drugs commonly consulted for and the frequency of these consults. The last part of the survey tries to gauge if there is a need among North American allergists for this database and what features are important to them.

RESULTS: 262 North American Allergists answered the survey. When discussing which drugs patients are consulted about- the vast majority (95%) said they had been consulted for Penicillins, and Cephalosporins. When asked if they would utilize a website database of case reports on drug hypersensitivity reactions and desensitization protocols among North American allergists. An online survey was administered to American allergists, who are members of the American Academy of Allergy, Asthma and Immunology (AAAAI) as well as the Canadian Society of Allergists and Immunologists (CSACI).

CONCLUSIONS: There is widespread support among North American Allergists for the creation of a database of drug allergy. Most respondents feel it would be useful and would be interested in submitting case reports.

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**Self-injectable Epinephrine Prescription Trends in a Tertiary Referral Center**

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**Rationale:** There has been significant publicity on self-injectable epinephrine in light of recent price increases. Our study investigated the prescribing indications at the West LA VA Medical Center.

**Methods:** A retrospective chart review of prescribed self-injectable epinephrine prescriptions at the West LA VA medical center and satellite clinics. Data was collected pertaining to initial prescribing clinic, length of active prescription, and indication for prescriptions.

**Results:** There were a total of 268 prescriptions within a one-year period. There were a total of 172 unique prescriptions after removal of prescriptions filled multiple times by patients. Average length of prescription per patient was 1.45 years. The majority of prescriptions originated from either Allergy clinic (40.7%) or primary care clinic (37.2%). The two leading indications for self-injectable epinephrine were venom hypersensitivity (41.3%) and food allergies (19.8%). 24 (14%) self-injectable epinephrine prescriptions were written for angioedema of which 8 were ACE-inhibitor or ARB induced angioedema.

**Conclusions:** The majority of self-injectable epinephrine prescriptions were prescribed for venom and food allergies, mostly originating from Allergy and primary care clinic. 4.7% (8) of the prescriptions were for ACE-I/ARB induced angioedema for which self-injectable epinephrine is not indicated. This serves as a reminder self-injectable epinephrine should only be prescribed when indicated and appropriate particularly in light of its significant cost.

**Fruit Intake Significantly Reduces the Onset of Allergic Symptoms in Schoolchildren**

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**Rationale:** To evaluate the effect of diet on allergic symptoms in schoolchildren.

**Methods:** Questionnaires regarding allergic symptoms (International Study of Asthma and Allergies in Childhood) and diet (brief-type self-administered 10-year diet history questionnaire for schoolchildren) were distributed to the caregivers of all 759 7-year-old children in every primary school in Omihachiman City, Shiga, Japan in 2011. Questionnaires were distributed for 4 consecutive years, until the children were 10 years old in 2014. The 520 children (68.5%) whose caregivers responded all 4 years were included in the analysis. Food intake was categorized as low, medium or high, depending on the intake amount during the study period.

**Results:** The rate of allergic symptoms (asthma, eczema or rhinitis) at age 10 was significantly lower in children with high fruit intake, compared to those with low or medium intake (25.8% vs 48.0%, p=0.001). Among those with no allergic symptom at age 7, the onset of allergic symptoms during the study period was significantly lower in those with high fruit intake compared to those with low or medium intake (14.3% vs 29.0%, p=0.02). No such trend was observed for the intake of other supposedly allergy-suppressive foods, such as fish, vegetables or soybeans. Moreover, multivariate analysis showed that the effect of fruit intake was independent of intake of other foods.

**Conclusions:** Schoolchildren with high fruit intake showed significantly lower onset of allergic symptoms, suggesting that encouraging schoolchildren to consume high amounts of fruit can prevent the onset of new allergic symptoms.

**Posthoc Analysis Demonstrates Oral Cetirizine 10mg Effectively Relieves Subjects’ Worst Seasonal Allergy Symptom(s)**

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**Rationale:** A posthoc analysis of data from randomized controlled trials (RCTs) was conducted to evaluate the efficacy of oral cetirizine 10mg for the relief of subjects’ worst seasonal allergic rhinitis (SAR) symptom(s).

**Methods:** Subjects (aged ≥12 years), pooled from four studies, rated severity for 5 or 6 symptoms, including sneezing, runny nose, postnasal drip, itchy eyes, watery eyes, and itchy mouth, daily in 2-week RCTs of cetirizine 10mg or placebo for SAR symptom relief. Of these symptoms, those with the highest baseline score were predefined as the individual’s worst symptom(s) in the posthoc analysis. When multiple symptoms shared the same highest (worst) baseline score, the daily average of ratings was calculated to represent the post-baseline rating of subjects’ worst symptom(s). Daily ratings of worst symptom(s) were averaged over 2 weeks. The change from baseline was the efficacy endpoint. Data from subjects with baseline symptom severity scores ≥1 (0=none, 3=severe) were analyzed.

**Results:** In these subjects, mean baseline worst symptom scores were 2.45 (SD=0.53; range 0.7-3.0, N=859) for cetirizine and 2.43 (SD=0.54; range 0.7-3.0, N=755) for placebo, with no significant difference between groups (P=0.559). Over 2 weeks, the LS mean change from baseline worst symptom score for cetirizine was -1.19 (SE=0.02, N=859) and -0.90 (SE=0.03; N=751) for placebo (P=0.001). The percent difference in relief achieved with cetirizine 10mg was 32.8% compared with placebo.

**Conclusions:** Cetirizine 10mg effectively relieves subjects’ worst symptom(s), including sneezing, runny nose, postnasal drip, itchy eyes, watery eyes, itchy nose, and itchy mouth, in adults with SAR.
**790** Intra-Nasal Theophylline for the Treatment of Chronic Anosmia and Hyposmia

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Allergic Disease Associates, PC, Philadelphia, PA; Drexel University College of Medicine, Philadelphia, PA; Allergic Disease Associates, PA; Allergic Disease Associates, PA; Allergic Disease Associates, PA.

**RATIONALE:** To evaluate the efficacy of intra-nasal theophylline therapy (ITp) in improving smell in subjects with chronic hyposmia/anosmia.

**METHODS:** Ten subjects with chronic hyposmia/anosmia were evaluated for smell loss, with history and physical, nasopharyngolaryngoscopy, laboratory tests, allergy skin tests, paranasal sinus CT, prensinone challenge, and brain MRI. Subjects completed a University of Pennsylvania Smell Identification Test (UPSIT) Monell-Jefferson Taste and Smell Questionnaire (M-JTSQ) pre and post-ITp to evaluate smell function quantitatively and qualitatively. Subjects consented to an open-label pilot study with 20μg theophylline/0.4mL saline solution administered by 4 sprays in each nostril daily for 1 month. Complete responders (CR) and partial responders (PR) to ITp continued on long-term ITp.

**RESULTS:** Two of 10 subjects dropped out of the study with limited exposure to ITp and were excluded from analysis. Post-ITp, 2 of 8 subjects were considered CR; these subjects showed improvement in their UPSIT score and M-JTSQ responses. Two of 8 subjects were considered PR; these subjects showed improvement in either UPSIT score or M-JTSQ responses. CR’s and PR’s were monitored on long-term ITp and reported persistent improvement. CR’s and PR’s did not differ significantly from non-responders in pre ITp clinical or laboratory characteristics or response to prednisone challenge. No adverse effects to ITp were reported by any subjects.

**CONCLUSIONS:** ITp improved smell in 50% of subjects after 4 weeks of ITp; continued ITp improved smell for up to 27 months. Pre-treatment subject phenotype did not predict treatment response. Response to prednisone did not predict response to ITp (r = 0.58).

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**791** Oral Cetirizine 10mg Significantly Improves Highest Perennial Allergic Rhinitis Symptom Severity Scores(s) in Posthoc Analysis

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**RATIONALE:** The effect of oral cetirizine 10mg on subjects’ highest (worst) perennial allergic rhinitis (PAR) symptom severity score(s) was evaluated in a posthoc analysis of randomized controlled trial (RCT) data.

**METHODS:** Subjects (aged ≥12 years) rated severity for 6 or 7 PAR symptoms, including sneezing, runny nose, itchy nose, postnasal drip, itchy eyes, watery eyes, and itchy mouth, in daily three RCTs of cetirizine 10mg or placebo. Symptom(s) with the highest baseline score were predefined as the individual’s worst symptom(s) in the posthoc analysis. When multiple symptoms shared the same highest baseline score, the daily average of ratings was calculated to represent the post-baseline rating of subjects’ worst symptom(s). Daily ratings of worst symptom(s) were averaged over 4 weeks. The efficacy endpoint was the change from baseline worst symptom severity score(s). Data from subjects with baseline symptom severity scores ≥1 (0 = none, 3 = severe) were evaluated.

**RESULTS:** In these subjects, mean baseline worst symptom scores were 2.39 (SD=0.49; range 1.0-3.0, N=308) in the cetirizine group and 2.40 (SD=0.50; range 1.0-3.0, N=313) in the placebo group (P=0.691 between groups). Over 4 weeks, the LS mean change from baseline worst symptom score(s) for cetirizine was -1.03 (SE=0.04, N=307) and -0.82 (SE=0.04; N=312) for placebo (P<0.001 versus placebo). The percent difference in relief achieved with cetirizine 10mg was 26.1% compared with placebo.

**CONCLUSIONS:** Oral cetirizine 10mg significantly improved the severity of subjects’ worst symptom(s), including sneezing, runny nose, itchy nose, postnasal drip, itchy eyes, watery eyes, and itchy mouth, in adults with PAR.

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**792** Intranasal Azelastine and Mometasone Exhibit a Synergistic Effect on a Murine Model of Allergic Rhinitis

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**RATIONALE:** The purpose of this study was to compare the anti-allergic effects of the combination of azelastine and mometasone with those of either agent alone in a Dermatophagoides farinae (Derf)-induced murine model of allergic rhinitis (AR).

**METHODS:** Forty BALB/c mice were divided into five groups: azelastine (A), mometasone (M), a combination of azelastine and mometasone (MA), Derf, and control. Derf served as the allergen. Allergic symptom scores, eosinophil counts, and serum Derf-specific IgE levels were measured. The mucosal levels of mRNAs encoding interferon (IFN)-γ, T-bet, interleukin (IL)-4, GATA-3, Foxp3, IL-17, and ROR-γt were determined by real-time polymerase chain reaction. The T-bet, GATA-3, Foxp3, and ROR-γt results were confirmed by Western blotting.

**RESULTS:** Nose-rubbing motions; the levels of mRNAs encoding IL-4, GATA-3, and ROR-γt; and tissue eosinophil count were reduced in the MA compared with those in the Derf group (all P values <0.05). The levels of mRNAs encoding GATA3 and IL-4 mRNA [synthesized by T helper (Th)2 cells] were reduced and that of mRNA encoding Foxp3 was increased in the MA compared with those in the Derf and A groups. Western blotting confirmed these findings.

**CONCLUSIONS:** We found that the combination of intranasal azelastine and mometasone synergistically suppressed Th17 responses and (reciprocally) elevated Treg responses. Therefore, this combination not only ameliorated allergenic inflammation by suppressing Th2 responses, but also usefully modified the Treg/Th17 balance.

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**793** Efficacy Analysis of MP-AzeFlu Compared with Fluticasone Propionate Nasal Spray in Children 6 through 11 Years of Age with Allergic Rhinitis

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**RATIONALE:** MP-AzeFlu (Dymista®) is a novel intranasal formulation of azelastine hydrochloride (AZE) and fluticasone propionate (FP) for treatment of allergic rhinitis. The objective of the current analysis was to evaluate the efficacy of MP-AzeFlu compared to FP administered 1 spray per nostril twice daily in children 6 through 11 years of age.

**METHODS:** This was a randomized, open-label, 3-month safety study in patients 4 through 11 years of age. Qualified patients had a history of AR, were in good health, and had no evidence of nasal mucosal erosion, nasal ulceration, nasal septum perforation, or any significant nasal disease. Randomization was in a 3:1 ratio (MP-AzeFlu [n=304]:FP [n=101]). Efficacy was not a pre-specified study objective but was evaluated by self-assessment of overall allergy symptom severity in a subset of patients 6 through 11 years (MP-AzeFlu [n=264]:FP: n=89). Symptom severity was scored on a 4-point scale from 0 to 3 (0 = none; 1 = mild; 2 = moderate; 3 = severe).

**RESULTS:** Total symptom score at baseline was 1.73 in the MP-AzeFlu group and 1.80 in the FP group (max score: 3). Over the entire study period, patients treated with MP-AzeFlu experienced a -0.68 pt reduction in overall symptom score (corresponding to a -5.44 change from baseline in AM + PM reflective total nasal symptom score [rTNSS; max = 24], significantly greater relief than that afforded by FP (-0.54 pt reduction; Diff: -0.14; 95% CI: -0.28, -0.01; p=0.04).

**CONCLUSIONS:** MP-AzeFlu provided significantly greater relief of AR symptoms than FP in children 6 through 11 years of age.
**Time Course of Improvement in Individual Nasal Symptoms During a 2-Week Study of MP-AzeFlu in Patients with Seasonal Allergic Rhinitis (SAR)**

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**RATIONALE:** MP-AzeFlu (Dymista®), a novel single-spray intranasal formulation of fluticasone propionate (FP, 50 μg/spray) and azelastine hydrochloride (AZE, 137 μg/spray) for treatment of allergic rhinitis (AR), was evaluated in a 2-week study in patients with allergy to Texas Mountain Cedar pollen. This post-hoc analysis assessed improvement in individual nasal symptoms with MP-AzeFlu compared to FP, AZE, and placebo on each study day.

**METHODS:** 610 patients 12 years and older were randomized. Treatments were 1 spray/nostril bid; total daily doses of FP and AZE were 200 μg and 548 μg, respectively. The primary efficacy variable was change from baseline in the 12-hr reflective total nasal symptom score (tTNSS) consisting of nasal congestion, runny nose, sneezing, and itchy nose scored twice daily on a 0-point scale (0-3) such that the maximum daily score was 6 for any individual symptom. Treatment group comparisons for the change from baseline for each individual symptom on each day of the study were determined using analysis of covariance (ANCOVA).

**RESULTS:** MP-AzeFlu was statistically superior to FP for nasal congestion on all study days (P<0.05) with statistical superiority for itching (P<0.04) and sneezing (P<0.03) on the majority of study days. MP-AzeFlu was statistically superior to AZE for nasal congestion (P<0.04), sneezing (P<0.02), itching (P<0.03), and runny nose (P<0.009) on each day of the study except a single day for itching and runny nose.

**CONCLUSIONS:** There was consistent and progressive improvement in all individual symptoms of the tTNSS over 14 study days with MP-AzeFlu compared to FP, AZE, and placebo.

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**Characterization and Induced Cytokine Expression in PBMC of an Alternaria alternata Depigmented-Polymerized Extract**

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**RATIONALE:** Alternaria alternata is the most relevant allergenic fungi worldwide. Numerous studies have demonstrated that subcutaneous allergen immunotherapy with chemically modified allergen extracts of pollen and mites is safe and efficacious, due to their reduced allergenicity and maintained immunogenicity. However, there is little evidence about fungi. The objective was to develop and characterize an A. alternata depigmented allergen extract.

**METHODS:** Depigmented-polymerized extracts of A. alternata (Dpg-Pol) were manufactured from native extracts (NE). Protein and allergenic profiles were determined by SDS, immunoblot and HPLC. The presence of relevant allergens was confirmed by mass spectrometry. ELISA-competition was performed to evaluate the reduction of the allergenicity. The capacity of NE and Dpg-Pol to stimulate cytokine production in PBMCs from Alternaria atopic donors was investigated at 72h and 120h by Miliplex.

**RESULTS:** Dpg-Pol characterization showed a range of high molecular weight components, most of them higher than 1,500 kDa and demonstrated the presence of Alt a 1, Alt a 3, Alt a 6 and Alt a 8. As a result of the polymerization process, the IgE-binding capacity of Dpg-Pol was reduced more than 99% respect to NE. After the stimulation of PBMCs, Dpg-Pol induced significant higher levels of IL-10 (72h) and similar IFN-γ, IL-6, IL-4 and TNF-β levels than NE.

**CONCLUSIONS:** This is the first time that a Depigmented-polymerized allergen extract of A. alternata is developed and characterized. The immunological activity and the reduction of the allergenicity suggest that it is a good alternative to be used in humans for the treatment of Alternaria allergy.
797 Relative Allergen Content of Commercial Aspergillus Fumigatus Extracts Determined by Human Monoclonal IgE

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RATIONALE: Sensitization to Aspergillus spp. is associated with severe asthma, as well as other allergic respiratory disease. Allergen immunotherapy with non-standardized Aspergillus extracts is commonly used as therapy in these patients. Asp f 1 content has been reported to markedly vary, both among extract manufacturers, and between lots from a single manufacturer. We hypothesized that newly developed human monoclonal IgE directed against Aspergillus spp. would allow for better characterization of the variability of relevant human allergenic epitopes among currently available commercial Aspergillus fumigatus extracts.

METHODS: Patients with allergic bronchopulmonary aspergillosis were recruited from within the Vanderbilt system. Peripheral blood mononuclear cells were isolated, and IgE specific B-cells were immortalized using standard electrophoresis techniques. Antibody was isolated from hybridoma supernatants and used for western blot and ELISA assays of commercial allergen extract of Aspergillus fumigatus.

RESULTS: Approximately half of Aspergillus specific IgE antibodies function in western blots. Of the antibody targets so far analyzed, none have been present in detectable quantities in every extract assayed. When targets are detected in multiple extracts, the concentration varies between ten and one thousand fold between manufacturers.

CONCLUSIONS: The Aspergillus fumigatus extract currently used in immunotherapy in the US is highly variable in relation to the content of component allergens. This degree of variability is almost certain to affect the efficacy of these reagents. Human monoclonal IgE represents a novel tool for evaluation of content of relevant human allergenic epitopes within these extracts, which may assist the development of standardized mold extracts in the future.

798 Defining the Extent of Allergenic Cross-reactivity among Mold Species

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RATIONALE: It is important to understand the scope of cross-reactivity among mold extracts when prescribing allergen immunotherapy (AIT) for mold allergic patients. Due to the large proportion of poly-sensitized patients in the clinical setting, we hypothesize that a high degree of cross-reactivity occurs between species within closely related taxonomic groups (e.g., Class, Order, and Family). Furthermore, we hypothesize that the potential for cross-reactivity exists between separate mold classes, due to protein homology. Therefore, we investigated commercial AIT extracts to better define the cross-reactivity relationships among clinically-relevant molds.

METHODS: The protein content and diversity of mold extracts were established by Bradford and gel electrophoresis assays. We evaluated cross-reactivity among 15 commercial mold extracts (ALK, Inc) using mono- and poly-sensitized sera derived from both rabbits and humans. Mold proteins were separated by SDS-PAGE, immobilized on nitrocellulose membranes, and immunoblotted using the above-mentioned sera. Human sera samples were purchased from Plasma Labs and screened for mold sensitivity by Thermo Fisher ImmunoCAP. Rabbit sera specific to single or dual mold species produced strong banding patterns in multiple extract lanes. Cross-reactivity was consistently observed between related species within the same Class; sera reactive to Alternaria, Aspergillus, Cladosporium or Epicoccum reacted to all extracts present from molds in the class Dothideomycetes.

CONCLUSIONS: Our results suggest an overlap in allergenic content of closely-related mold species. This finding may support the simplification of AIT formulations for treatment of mold sensitized patients.

797.1 Purified Allergens for Molecular Diagnostics: Strive for Purity

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RATIONALE: Highly purified allergens are the core components of in vitro molecular diagnostics. The absence of any allergenic or host cell-derived impurities is a fundamental quality criterion for diagnostic purposes. The aim of this study was to use high resolution mass spectrometry (LC-MS/MS) to establish criteria of purity and to validate purified allergens for use in molecular diagnostics.

METHODS: Natural and recombinant food, dust mite, pollen and animal allergens were purified by affinity and/or gel-filtration chromatography and analyzed by SDS-PAGE, LC-MS/MS, ELISA, and FEIA or chimeric IgE ELISA. Real time stability data were collected from frozen allergens.

RESULTS: Monoclonal antibody and IgE reactivity of recombinant allergens was strongly correlated with that of the respective natural allergen counterpart (r=0.94, p<0.001). Allergen purity, assessed by LC-MS/MS after trypsin digest and silver-stained SDS-PAGE, was >95%. Trace contaminants were readily identified by LC-MS/MS. Allergens retained their potency in real time stability tests over 24 months in ELISA, with no signs of degradation on SDS-PAGE.

CONCLUSIONS: Optimized, ISO-9001 compliant, bioprocessing pathways have been established to yield high purity allergens. The sensitivity provided by mass spectrometry is critical to confirm allergen purity. Highly purified allergens have applications in molecular allergy diagnostics and as reference standards for monitoring the potency of allergy diagnostics and of vaccines used for immunotherapy.
Salivary IgG4 Increases during Milk Oral Immunotherapy

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Rationale: Cow’s milk allergy (CMA) is a frequent cause of severe allergic reactions and anaphylaxis in children. Oral immunotherapy (OIT) has shown promising results with immunological changes occurring during desensitization. Our team at the Research Institute of McGill University Health Centre has demonstrated an increase in serum IgG4 during the escalation and maintenance phases of milk OIT. We assessed the changes in salivary IgG4 during milk OIT, as a potential non-invasive biomarker of desensitization.

Methods: We performed an interim analysis at baseline (prior to the start of treatment) and at the end of escalation phase (200ml dose) of the milk OIT protocol in subjects who successfully completed the escalation phase. Milk protein component (α-lactalbumin, β-lactoglobulin, casein) specific salivary IgG4 were assessed at baseline and 200ml.

Results: There was an overall increase in salivary IgG4 from baseline to 200ml for all three milk proteins. The mean salivary IgG4 concentration at baseline was 0 ng/mL (SEM 0 ng/mL), 0.5 ng/mL (SEM 0.3ng/mL), and 177.4 ng/mL (SEM 126.1ng/mL) for α-lactalbumin, β-lactoglobulin, and casein respectively; compared to the mean salivary IgG4 concentration at the 200ml dose of escalation phase: 424.1 ng/mL (SEM 265.2ng/mL), 1142 ng/mL (SEM 858.5ng/mL), and 3367 ng/mL (SEM 2443ng/mL) for α-lactalbumin, β-lactoglobulin, and casein respectively.

Conclusions: Successful escalation phase of milk OIT in IgE-mediated CMA in children is associated with an increase in salivary milk protein-specific IgG4. This suggests it could be used as a potential non-invasive biomarker of desensitization in OIT in children. Further assessment with a larger sample size is underway.

Identification of B-cell Epitopes of Peanut Ara h 2

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Rationale: Peanut oral immunotherapy induces allergen-specific memory B-cell (IgG and IgA class switched) populations (Patil et al. JACI 2015; 136:125-134). This study utilized phage display technology to identify epitopes recognized by monoclonal antibodies derived from these B cells.

Methods: Direct ELISA and inhibitory ELISA assays were used to detect the binding of Ara h 2-specific human IgG monoclonal antibodies to native or reduced/alkylated Ara h 2 and Ara h 6. A phage peptide library displaying 12-mer peptides was screened with the monoclonal antibodies by biopanning and phage ELISA. The bound peptides were sequenced.

Results: All of 19 monoclonal antibodies, selected with Ara h 2, are cross-reactive with Ara h 6. Seventeen (89%) of them bind to conformational, but not linear, epitopes of Ara h 2 and Ara h 6, as determined by inhibitory ELISA. By screening the phage library, twenty-five individual mimotopes have been identified. Twenty-three of the mimotopes are recognized by more than 3 monoclonal antibodies and sixteen of nineteen antibodies can recognize more than 2 mimotopes. The pattern of binding of the mAbs to the mimotopes identifies 5 distinct epitopes of Ara h 2/6. mAbs with divergent sequence homology in some cases appear to recognize the same epitope.

Conclusions: Conformational epitopes are major targets of the Ara h 2-specific B-cells induced by peanut oral immunotherapy. Furthermore, the humoral response to Ara h 2/6 appears to be constrained to a small number of epitopes. This may have implications for better understanding the variability of IgE-blocking activity – a potential mechanism of immunotherapy.

Foxp3+ CD62L+ Tregs induced by EPIT have the potency to suppress effector T cells proliferation in specific and bystander conditions

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Rationale: Epicutaneous immunotherapy (EPIT) in sensitized mice significantly increases Foxp3+ Tregs and induces a higher rate of Foxp3+CD62L+ Tregs in comparison to oral or sublingual immunotherapies. The adoptive transfer of EPIT-induced Tregs protects mice from further sensitization and anaphylaxis (bystander effect). Here, we aimed to analyze the suppressive properties of CD62L+ and CD62L- Tregs in specific and bystander conditions.

Methods: k sensitized FOXP3-GFP mice were treated with milk-EPIT. CD4+FOX3+CD62L+ or CD4+FOX3+CD62L- Tregs from EPIT and effector T cells (CD4+CD25+) from milk or peanut sensitized mice were sorted and co-cultured for 4 days at different ratio, using allergen stimulation and allergen-pulsed CD11c+ antigen-presenting cells. Suppression was calculated by tracking divided CD4+CD25+ with a proliferation probe (VDP450) by flow cytometry.

Results: Effector T cells proliferate up to 34%-58%, respectively, with milk or peanut stimulation without Tregs. CD4+FOX3+CD62L+ Tregs have a higher potency to inhibit effector T cells proliferation in specific condition than CD4+FOX3+CD62L- Tregs (47% vs 38% of proliferation suppression at ratio 1:2). In bystander condition, CD4+FOX3+CD62L+ EPIT-induced Treg more efficiently maintain suppressive properties in comparison to CD4+FOX3+CD62L-. Tregs (18% vs 4% of proliferation inhibition at ratio 1:4). Interestingly, the turnover of CD4+FOX3+CD62L-Tregs is lower in bystander conditions, suggesting a crucial role of this Tregs subset in preventing further sensitization.

Conclusions: FOXP3+CD62L+ EPIT-induced Tregs inhibit effector T cell proliferation more efficiently and have a better maintenance of suppressive properties in specific and bystander conditions. The induction of persistence of this Tregs subset by EPIT may be involved in the sustainability of the desensitization process.
AB256 Abstracts

FEBRUARY 2017

MONDAY

SAFETY, TOLERABILITY AND EFFICACY OF CAT-PEPTIDE ANTIGEN DESENSITISATION (CAT-PAD) IN CAT-ALLERGIC CHILDREN – FINDINGS FROM A PILOT STUDY

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RATIONALE: This was a pilot efficacy, safety and tolerability study of Cat-PAD in children.

METHODS: Multicentre, single-blind, placebo run-in study in cat allergic children, with or without controlled asthma, aged 5-11 years. Two doses of placebo intradermally (ID) two weeks apart were followed by eight ID doses of Cat-PAD biweekly. All doses were given with a Micronject™ 600 microneedle.

RESULTS: 16 subjects were enrolled, 14 completed all visits; one withdrew consent, one was withdrawn due to asymptomatic reductions in peak expiratory flow (PEF) >8 hours after three of six doses of CAT-PAD. There were no acute allergic reactions, changes in vital signs or differences in adverse events between placebo and Cat-PAD treatment periods. More small asymptomatic decreases in PEF were observed several hours after Cat-PAD than after placebo but these were inconsistent within and between subjects. Injection site pain scores (Wong & Baker FACES scale) were generally low, with lower scores in older subjects and a tendency to reduce with repeated dosing. Flare and occasional itching occurring following Cat-PAD dosing but there were no injection site adverse events.

On the global impression of change, Investigators and parents assessed all subjects as having an improvement in their symptoms overall following Cat-PAD, and all except two subjects rated their symptoms as improved. Symptom scores recorded in daily diaries were lower after Cat-PAD than after placebo. Rescue medication use was low throughout the study.

CONCLUSIONS: Cat-PAD was well tolerated with an acceptable safety profile. Preliminary evidence of efficacy supports further evaluation in this age group.

DOSING ADHERENCE DURING CHARACTERIZED ORAL DESENSITIZATION IMMUNOTHERAPY (CODIT) FOR PEANUT ALLERGY

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RATIONALE: AR101, a pharmaceutical-grade peanut protein formulation, was well tolerated and demonstrated robust activity in Phase 2, double-blind, placebo-controlled trial in 4-21 year olds. We now report results on at-home dosing adherence.

METHODS: Subjects took their daily dose at home by mixing the capsules’ content in non-allergenic food, and consuming the entire serving. Subjects documented doses taken at home using diary logs and returned unused capsules to the clinic at every visit.

At-home adherence, defined as full, partial (at least ½ dose was taken), and missed home doses, was expressed as a percentage of planned at-home doses.

RESULTS: 55 subjects (AR101, n = 29; Placebo, n = 26) received at least 1 dose of randomized study treatment. The number of days of planned at-home doses was 139.8 days (SD: 38.63) for the overall group. The mean number of days (% [SD]) with any at-home dose (either a full or partial dose) was similar for AR101 and Placebo groups (94.7 [6.80] vs 96.9 [3.37], respectively), as was the percentage of days with full doses (93.6 [6.86] for AR101 and 96.7 [3.41] for Placebo, 95.1 [5.68] overall). The mean number of days (% [SD]) with partial doses was higher for AR101 than Placebo (1.1 [1.94] vs 0.2 [0.50], respectively) as was the mean number of days (% [SD]) with missed doses (4.7 [6.84] for AR101; 2.4 [2.84] for Placebo).

CONCLUSIONS: At-home dosing adherence during ARCo01 was very high, both for AR101 and matching placebo, as the full dose was taken more than 95% of the days.

DOSE DEPENDENT INCREASE OF BET V1 SPECIFIC IgG4 AFTER Bet v 1 COP THERAPY

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RATIONALE: In previous studies we demonstrated that a two month, single course immunotherapy with Betv1 Contiguous Overlapping Peptides (COPs) at a dose of 50 µg induces Betv1 specific IgG4 antibodies in birch allergic patients (NCT01720251). Betv1 specific IgG4 levels remain elevated after the second season and persist over the period of up to four seasons without further treatment (NCT01728519, NCT02143583). In this study, 213 patients were treated with three doses of Betv1 COPs (50 µg, 25 µg and 10 µg) in a double blind, placebo controlled, phase II study (NCT02271009) and immunoglobulin responses were followed during treatment period and one month after last injection.

METHODS: Blood samples were collected before each treatment and one month after treatment termination. Betv1 specific IgG4 were measured by ELISA.

RESULTS: Repeated injection (day 1, 7, 14, 28, and 56) of Betv1 COPs induced Betv1 specific IgG4 as early as one month after the 4th injection in all treatment groups. Betv1 specific IgG4 levels were maximally increased 30-, 24- and 6-fold (median) one month after treatment (after 5th injection) in 50 µg, 25 µg and 10 µg treatment groups respectively. In 90% and 76% of patients Betv1 specific IgG4 had increased by at least 3-fold in the 50 µg and 25 µg groups respectively compared to 61% in 10 µg treatment group.

CONCLUSIONS: Betv1 COPs are highly efficacious in stimulating Betv1 reactive B and T cells and induce Betv1 specific IgG4 early during therapy in a dose dependent manner.
805 Crucial Role of Langerhans Cells in Allergen Uptake and Regulatory T Cell Induction in Epicutaneous Immunotherapy

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RATIONALE: Allergen applied to the skin during epicutaneous immunotherapy (EPIT) induces tolerance in sensitized mice. In our previous work, we have shown that EPIT induces Tregs, including CD62L+ Tregs. The role of Langerhans cells (LCs) and other dendritic cell (DC) subsets in this skin-induced tolerance need to be clarified.

METHODS: LANG-eGFP-DTR mice were sensitized by 2 subcutaneous injections of OVA with Alum. The depletion of LCs was achieved by i.p. injection of Diphtheria Toxin. The migration of LCs (Epcam+ CD11b+) and CD11b+ dDCs (Epcam- CD11b+) were analyzed in inguinal lymph nodes (iLN) after 48h application of a patch containing OVA-A647, and the induction of Tregs was analyzed in iLN and spleen after 2 weeks of treatment with a patch containing OVA in LC-depleted and non-depleted sensitized mice.

RESULTS: The application of one patch containing OVA-A647 resulted in migration of both LCs and CD11b+ dDCs into iLN. These 2 populations induced proliferation and Foxp3 expression in CD4+ cells in vitro. However, only LCs induced LAP+ cells and CD62L+ Foxp3+ Tregs. In vivo, the depletion of LCs dramatically decreased the number of total OVA+ DCs but also the number of OVA+ CD11b+ dDCs in iLN. Whereas 2 weeks of EPIT in non-depleted mice induced Foxp3+ Tregs, especially CD62L+ and LAP+ Tregs in iLN and spleen, no induction of Tregs was observed in LC-depleted mice.

CONCLUSIONS: Although both LCs and CD11b+ DCs could upregulate allergen and induce Tregs, absence of LCs impaired the induction of Tregs in vivo indicating their crucial role in skin-induced tolerance during EPIT.

806 Allergen Capture by DCs during epicutaneous immunotherapy is Enhanced by Modulating the Dose and Surface Area of the Patch

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RATIONALE: Epicutaneous immunotherapy for the treatment of food allergy is effective and safe in animal models and in humans, as recently shown in a Phase II trial demonstrating the crucial role of the dose. In the present study, we aimed to investigate whether increasing the dose and/or the size of the patch may be a way to further modulate the immune response in animal models.

METHODS: Mice were sensitized to ovalbumin or peanut and then received one epicutaneous-delivery patch loaded with allergen labelled with alexa-488 (A-488). Different doses were tested from 10µg to 500µg on a fixed surface (1cm²). In a second experiment, sensitized mice received an application of patches loaded with the same range of doses on a surface up to 5cm². In the 2 experiments, the kinetics of allergen capture by dendritic cells (DCs) was analyzed in the epidermis and lymph nodes (LN) by flow cytometry.

RESULTS: After the 1cm²-patch application, the allergen capture and migration by DCs did not increase beyond the dose of 100µg (17.7±4.0% of A-488+ DCs vs 1.99±0.4% in sham, p<0.001). However, increasing the surface area of the patch from 1–5cm² enhanced by 2-fold the allergen capture by DCs and their migration to LNs (respectively 15.0±6.5% vs 30.9±9.5%, p<0.001).

CONCLUSIONS: Allergen uptake by skin DCs and their migration to LNs are increased with larger surfaces of application and are dependent of quantity of allergen per surface area. The immune response induced by EPIT may thus be modulated by altering the combination of allergen dose and surface area.

807 Dual assessment of peanut-specific effector and regulatory T cells in patients undergoing oral immunotherapy

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RATIONALE: The clinical application of food immunotherapy would greatly benefit from the development of reliable immune monitoring assays that could address the complexity and functional heterogeneity of food allergy. Antigen-specific assays for effector T cells are well characterized, however similar assays for regulatory T cells are still lacking.

METHODS: Coded samples (n=50) to the operator were provided during a randomized, double-blinded, placebo-controlled trial (ARC003) of characterized oral desensitization immunotherapy (CODIT) in peanut-allergic patients. Eligible subjects reacted to ≤ 100 mg peanut protein during a screening double-blind placebo-controlled food challenge (DBPCFC). The magnitude and quality of baseline peanut-specific T-cell responses were determined ex vivo using both CD154 and CD137 upregulation assay.

RESULTS: Highly heterogeneous effector CD4+ T cell responses were observed in peanut-allergic subjects, raising important questions regarding the pathophysiological role of each allergen specific CD4+ T-cell subset in food allergy. In subjects reacting to DBPCFC, we observed two distinct phenotypes in the effector CD4+ memory populations, a classical allergic TH2A phenotype (CD27- CRTH2+ CCR4+ CCR6+) and a Th17-like phenotype (CD27- CRTH2- CCR4+ CCR6+). Conversely, non-reactive subjects had low frequency of peanut-reactive T cells with a profile similar to non-allergic individuals (CD27+ CRTH2- CCR4- CCR6+). Interestingly, for each group we observed low frequencies of antigen-specific regulatory T cells that have an extremely stable phenotype (CD27+ Helios+ CTLA-4+ Foxp3+).

CONCLUSIONS: Heterogeneity of baseline peanut-specific effector T cell responses suggests that cellular phenotypes may associate with or predict clinical treatment outcomes following CODIT in subjects with peanut allergy.
**808 In Vitro Safety Profile of a Depigmented-Polymerized Peanut Allergenic Extract**

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**RATIONALE:** Several alternatives have been developed for the treatment of peanut allergy. Safety is the most challenging issue and the main reason why subcutaneous immunotherapy has not been more extensively studied. This study aims to develop and characterize a depigmented-polymerized peanut extract designed according to their safety profile.

**METHODS:** Peanut native extract (NE) was manufactured after the extraction of the protein fraction from roasted peanuts. This fraction was dialyzed and freeze-dried. Afterwards, the NE was purified (mild acid extraction of the protein fraction from roasted peanuts. This fraction was polymerized with glutaraldehyde (PE). Both extracts were characterized by: Size exclusion chromatography to determine their protein profile. Allergenic activity was compared by ELISA inhibition. IgE-binding stability was measured by surface plasmon resonance (Biacore T100) using sera from allergic patients. Allergenic activity was compared by ELISA inhibition. IgE-binding stability was measured by surface plasmon resonance (Biacore T100) using sera from allergic patients.

**RESULTS:** The chromatogram of the NE showed the presence of several peaks in a distribution between 9 to 100 kDa while the PE showed a clear excellent profile of safety has been developed. The in vitro results demonstrated a reduction of the allergenicity while maintaining the allergen profile. Further studies are under development to confirm the safety profile in animal models.

**CONCLUSIONS:** A depigmented-polymerized peanut extract with an excellent profile of safety has been developed. The in vitro results demonstrated a reduction of the allergenicity while maintaining the allergen profile. Further studies are under development to confirm the safety profile in animal models.

**809 Fraction of Exhaled Nitric Oxide (FeNO) As A Predictor Of GI Symptoms During Food Allergen Updosing**

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**RATIONALE:** FeNO is used as a marker for eosinophilic inflammation in the management of asthma. An elevated FeNO has also been shown to be a predictor of abdominal pain and vomiting in double-blind placebo-controlled food challenges. The purpose of this study was to determine if FeNO could be used to predict patients who would experience GI symptoms during the updosing phase of an oral immunotherapy clinical trial.

**METHODS:** Twenty-seven patients who consented to participate in an IRB-approved oral immunotherapy clinical trial conducted at the Sean N. Parker Center for Allergy Research were included in this study. We measured FeNO prior to the patient’s scheduled updosing in clinic during the desensitization period of the trial. FeNO was obtained according to ATS guidelines using Niox Mino.

**RESULTS:** Twelve (44%) of the twenty-seven patients experienced at least one GI symptom defined as nausea, vomiting, and/or abdominal pain. FeNO was significantly higher in patients with GI symptoms than in patients without these symptoms as revealed by a two-sample t-test ($p = 0.04$). Mean FeNO was 40 ppb in patients with GI symptoms compared to 20 ppb in patients without GI symptoms. The Wilcoxon rank-sum test revealed no significant differences between groups in regards to sex, age, history of asthma, and history of allergic rhinitis ($p > 0.05$).

**CONCLUSIONS:** These results suggest that an elevated FeNO may be associated with abdominal pain, nausea, and/or vomiting during updosing. If confirmed by a larger sample, this study would indicate that FeNO can be used to guide updosing decisions.

**810 "Real Life" Outcome of Oral Immunotherapy for Severe Food Allergy**

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**RATIONALE:** Oral immunotherapy (OIT) is expected to be a promising intervention for severe food allergy and recent clinical studies have demonstrated high achievement of sustained unresponsiveness by OIT. The results, however, obtained under well-designed, strict protocol. “Real life” outcome after off-protocol of OIT is not well known.

**METHODS:** The study initially enrolled 45 and 32 children (5-15 years old) with severe IgE-mediated hen’s egg and milk allergy, respectively, to prove desensitization induction by rush OIT in a randomized delayed control fashion. Protocol-based allergenic food intake was maintained for 12 months, then the subjects were allowed to take “freely” the food under vigilance of anaphylaxis. We surveyed actual daily intake of the food at 2, 3, 4 and 5 years off-protocol and measured specific IgE and IgG4 levels.

**RESULTS:** On protocol at 1 year of maintenance OIT, 82% of egg allergy patients were able to eat half-boiled egg and 66% of milk allergy patients ate 200ml of milk. At 2 years off-protocol, the number decreased to 42% and 43% in egg and milk allergy, respectively. At 3 years and thereafter, about 30% and 35% maintained initially achieved doses, respectively. All other patients maintained small amount of the allergenic food. No patients experienced anaphylaxis requiring epinephrine. Many patients admitted that the food tasted “bad”. There were no differences in specific IgE and IgG4 levels between patients with high and low intake.

**CONCLUSIONS:** OIT hardly induced high-dose unresponsiveness in real life but achieved small but safe intake levels of allergenic food.
811 Structural and immunological characterisation of a broad-spectrum grass allergoid vaccine

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RATIONALE: Immunological and structural characterisation of a complex broad-spectrum grass allergoid vaccine was sought. Mapping IgG epitopes and their functional capacity to induce blocking antibodies for one of the major grass allergens (Lol p1) allows further insights into the mechanism of action for allergoid SIT and provides steps toward standardising allergoid vaccine formulations.

METHODS: Reduced allergenicity and maintained immunogenicity potential of a grass allergoid vaccine was determined using an ELISA inhibition platform. Specificity of immunogenic determinants including Lol p1 IgG-binding epitopes were identified via ELISA inhibition experiments with Lol p1 specific synthetic peptides. The blocking capacity of Lol p1 induced IgG was assessed via IgE ELISA specificity and SDS-PAGE/Western blotting.

RESULTS: Attenuation of IgE immunoreactivity and maintenance of IgG immunoreactivity following glutaraldehyde modification of the mixed-grass native extract was confirmed. Retention of six Lol p1 IgG-binding epitopes on a solvent exposed area of the N-terminal domain of Lol p1 homology model was demonstrated. A novel IgG epitope was identified, not previously characterised, and was classified as immune-dominant. Lol p1 specific IgG antibodies exhibited functional capacity to block 50% of IgE binding sites from the native grass extract.

CONCLUSIONS: Structural and immunological characterisation of the mixed-grass allergoid vaccine formulation demonstrated a high degree of preservation of Lol p1 IgG binding epitopes. It supports the concept of using an allergoid vaccine for treatment of grass allergies and provides further insights of its immunogenicity potential. The blocking function of IgG antibodies reaffirms the protective function of immunotherapy induced antibodies.

812 Isoallergen Distribution of Der p 1 in Mite Extracts and in the Highly Purified Allergen

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RATIONALE: Highly purified, well-characterized allergens can be used for molecular allergy diagnostics and as reference materials. Reference materials are important for standardization of allergen extracts, determination of potency of allergy vaccines and validation of molecular diagnostics. The objective of this study was to analyze purity and isoallergen distribution in affinity-purified dust mite allergen Der p 1.

METHODS: Isoform distribution of Der p 1 in mite culture, during bioprocessing and in preparations of purified Der p 1 was compared by LC-MS/MS. Data from digestes were analyzed against individual Der p 1 isoform sequences. Der p 1 was lyophilized using different buffer conditions. Real time stability data were collected from frozen liquid allergens and lyophilized allergens.

RESULTS: Patterns of Der p 1 isoforms were identical in mite culture and purified allergens. Based on diagnostic peptides, five isoforms of Der p 1 (0101, 0102, 0106, 0108, and 0124) were identified and 17 Der p 1 isoforms could be excluded. Purified Der p 1 was free of contaminants. Real time stability tests of frozen liquid allergens and of frozen lyophilized allergens showed comparable potency in allergen-specific ELISA and no signs of degradation on SDS-PAGE.

CONCLUSIONS: Mass Spectrometry is a valuable tool to assess purity and isoform composition of purified allergens. Affinity-purification of natural Der p 1 does not affect the original isoform distribution found in mite culture. Bioprocessing pathways have been established to yield high purity mite allergens with homogenous isoform profiles. Purified natural Der p 1 can be used as molecular reference material for allergen standardization.

813 Allergen VLPs


RATIONALE: The use of antigenic VLPs has recently impacted the vaccine industry by allowing the development of efficacious, safe and low cost recombinant vaccines. We are currently investigating the potency of allergens presented in the form of recombinant VLPs for immunotherapy.

METHODS: Transient expression of a fusion protein made of a natural non-immunogenic carrier peptide fused to an allergen component was used to produce VLP particles harboring spikes of either homotrimers or homotetramers of a major dust mite allergen. These VLPs were purified and characterized in preparation for a head-to-head mouse efficacy study in comparison with the same allergen in a soluble form and whole dust mite commercial extracts.

RESULTS: VLPs were readily formed with both trimeric and tetrameric forms of the the antigen. Their purification was performed with a succession of simple filtration and ion-exchange chromatography steps. The particles were between 130 and 180 nm in diameter, harboring an average of 900 spikes of the homopolymers on their surface. Their membrane was made of lipids typical of membrane rafts. Their production showed high reproducibility both in yield and quality. They are currently under efficacy trial in mice. This combination of a new manufacturing technology and a new 3D antigen display technology is GMP compliant, low cost and has unlimited capacity. Its functionality has now been tested with some of the major allergens.

CONCLUSIONS: This new technology has the power to bridge the gap between the rapidly increasing knowledge of the immunological basis of allergy and the manufacturing of therapeutic allergens.

814 Do Human Mite Allergen Extracts Contain the Relevant Allergens for Treating Canine Atopic Dermatitis?

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RATIONALE: Der f 15 and Der f 18 are major allergens in dogs, while the human major allergens, Der f 1 and Der f 2, are considered minor allergens. However, canine atopic dermatitis is being treated with the same allergen extracts used for humans. This study aims to demonstrate and quantify the presence of relevant Dermatophagoides farinae allergens for dogs in conventional immunotherapy used in veterinary practice.

METHODS: A native allergen extract of D. farinae was manufactured from a mites culture (body content >80%). The protein profile was analyzed by SDS-PAGE. Concentration of each allergen was calculated by scanning densitometry, according to the whole protein content. The presence of relevant allergens was identified by mass spectrometry (amino-acid sequencing). Allergenic profile was studied by immunoblot using individual serum samples from 18 Spanish-residing dogs, suffering from atopic dermatitis.

RESULTS: The extract showed a protein concentration of 220 mcg/mg. Der f 15 (119 and 96 kDa), Der f 18 (57 kDa), Der f 14/Der f 11 (43 kDa), Der f 3/Der f 14 (34 kDa), Der f 1 (30 kDa) and Der f 2 (15 kDa) were identified. The allergenic profile showed that dogs were mainly sensitized to Der f 15, Der f 18, Der f 1 and Der f 2. The concentration of these allergens was 18, 9.5, 17 and 21 mcg/mg freeze-dried material respectively.

CONCLUSIONS: The commercial D. farinae extract (Laboratorios LETI, Madrid, Spain) contains the major allergens for dogs, being a good candidate for treating allergen-dependent canine atopic dermatitis.
The Effect of Protein Methylation on Binding of IgE to Profilins Bet v 2, Art v 4 and Amb a 8.

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RATIONALE: To evaluate the effect of protein methylation on IgE binding of profilins Bet v 2, Art v 4 and Amb a 8.

METHODS: ELISA and inhibition ELISA with recombinant birch, mugwort and ragweed profilins and their methylated counterparts were performed using sera from allergic rhinitis patients. The reductive methylation protocol led to modification of all profilin lysine residues. The methylation was confirmed using mass spectrometry. The crystal structure of methylated rAmb a 8 was determined.

RESULTS: In 32 patients with positive ELISA the intensity of IgE binding to individual profilins was different. In 15 patients, IgE binding to rBet v 2 was significantly less (30-60%) than to mugwort or ragweed profilins. In those patients, soluble rBet v 2 abolished IgE binding to birch but only attenuated (30-50%) binding to mugwort or ragweed profilins. IgE binding to methylated profilins was significantly less (25-60%) than to the corresponding counterparts. Inhibition with rBet v 2 completely blocked IgE binding to all three methylated profilins. Amino acid sequence analysis revealed the unique substitution of Q37 in Bet v 2 by K37 in Art v 4 and Amb a 8. The analysis of 3D structures of profilins allowed for identification of highly conserved and variable fragments on the surface of these allergens.

CONCLUSIONS: In profilins, lysines participate in formation of IgE epitopes. K37 may participate in formation of IgE epitopes specific for weeds. Mapping of the sequence conservation on profilin structure also suggests that a region of the molecule containing K54 may be responsible for binding species specific IgE’s.

First Naturally Occurring Human IgE Antibody Against Mite Allergen Der p 2

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RATIONALE: The identification of molecular determinants for IgE binding on environmental allergens is limited because IgE antibodies are polyclonal, are present at low concentration in serum, and the frequency of circulating IgE B cells is exceedingly low. The goal was to isolate and analyze naturally occurring human monoclonal IgE antibodies to mite group 2 allergens for molecular analysis of allergenic epitopes.

METHODS: Human B cells from peripheral blood of allergic patients were cultured and fused with a human myeloma cell line (HMMA2.5) using electrical cytofusion. Allergen-specific IgE antibodies were identified by ELISA, expressed and purified. The relative position of epitopes for IgE and three mouse monoclonal antibodies (mAb), and the IgE recognition of isoforms were analyzed by ELISA.

RESULTS: A high affinity Der p 2-specific IgE mAb 2G1 was isolated, which bound allergen with an EC50=7.1 ng/ml. The IgE mAb bound Der p 2.0101, Der p 2.0103 and Der f 2. Two mAbs that bind to opposite sides of Der p 2 (1D8 and 7A1) did not interfere with the IgE binding by two-site ELISA. The IgE mAb 2G1 and murine mAb oDpX (which recognizes both isoforms and Der f 2) appeared to bind to overlapping epitopes.

CONCLUSIONS: The first human anti-Der p 2 IgE antibody that has the natural pairing of heavy and light chains was isolated by human hybridoma technology. This unique tool facilitates mapping of allergenic epitopes recognized by naturally occurring human IgE antibodies, geared to produce new hypoallergens for immunotherapy.
817 Mapping of conformational IgE epitopes on prostate specific antigen

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RATIONALE: Systemic Seminal Plasma Hypersensitivity (SPH) is caused by specific IgE to human prostate specific antigen (hPSA). Pre-sensitization to dog PSA (Can f 5) was reported to be associated with SPH in women sensitized to dog due to cross-reactivity. Conformational epitope mapping of hPSA is required to elucidate this cross-reactivity and to design hypoallergenic derivatives for desensitization.

METHODS: Sequence- and structure-based bioinformatic analyses were performed to identify potential hPSA epitope(s). Sequences of hPSA and other known serine protease allergens were retrieved from the uniprot database. The hPSA structure was obtained from its monoclonal antibody-bound form (2ZCH.pdb) to study its antigenic surface and to model the Can f 5 structure. Site-directed mutagenesis of top solvent-exposed residues was performed to assess their role in IgE binding.

RESULTS: About 45% (5054.97 Å2) of hPSA surface is polar. Four areas, including a region Arg85- Ser99 (containing the mAb binding site) have been identified as potential epitopes. A close evolutionary relationship between hPSA and Can f 5 (57% sequence identity; 89% sequence similarity) was noted. The alpha-C backbone superimposition (global RMSD =1.1 Å) indicated an over-all structural similarity, while conserved surface-exposed patches indicated possible cross-reactivity between hPSA and Can f 5. Preliminary results of site-directed mutagenesis indicated the importance of specific surface exposed residues (e.g. R85) in IgE binding.

CONCLUSIONS: Epitope residues are dispersed on hPSA surface. Conserved patches might be responsible for cross-reactivity between hPSA and Can f 5 in some patients. Peptide microarray-based epitope mapping and detailed characterization of mutant hPSA proteins are ongoing to confirm these findings.

818 Real-life study assessing the clinical diagnosis of allergy and sensitization in atopic patients using the ISAC method (molecular allergology)

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RATIONALE: The usefulness of ImmunoCAP ISAC has been validated in multiple allergic diseases like asthma, allergic rhinoconjunctivitis, atopic dermatitis, cosinophilic eosinophilia, food allergy and anaphylaxis. It provides information on specific and cross-reactive sensitizations that facilitate diagnosis and risk assessment. In the era of precision medicine, developed diagnostic tools such as ISAC is useful for ultimate disease management.

METHODS: Study population consisted of 200 patients of all ages visiting the Allergy/Immunology department. ISAC test (Phadia ImmunoCAP system; Thermo Fisher Scientific) is performed when clinically indicated. Participants are considered sensitized if the test shows a value of allergy-specific IgE greater than 0.35 KUA/L. Clinical diagnosis and correlation are done accordingly.

RESULTS: Patients are found to be sensitized to D. pteronyssinus (38%), D. farina (30%), insects venom (4%), molds (6%), latex (2%), cats (8%), dogs (8%), tree pollens (43%), weed pollens (18%), grass pollens (38%) and food (23%); half of the latter are LTP (lipid transfer protein) and the rest are cross-reactive components. 20% have no sensitization by ISAC despite a positive history, their sensitization is confirmed by subsequent allergy skin prick testing.

CONCLUSIONS: The ISAC method (molecular allergology) is a useful quantitative diagnostic allergy test. It assists the physician in allergy management in particular for starting specific immunotherapy or advising for complete food avoidance. Yet, in a non-negligible percentage it fails to show sensitization despite a positive skin prick testing and clinical correlation.

819 Crystal structure of cocosin, a potential food allergen from coconut (Cocos nucifera)

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RATIONALE: Coconut allergy cases have been reported, but only one coconut allergen has been identified. The 11S seed storage proteins belong to one of a few protein families that contain known food allergens in many food of plant sources. Cocosin, the 11S protein from cocosin remains to be characterized as a potential food allergen.

METHODS: Cocosin was purified from coconut meat. Its characterization was carried out by crystallization any x-ray crystallography studies.

RESULTS: The crystal structure of cocosin was determined by molecular replacement. Information on likely linear IgE epitopes was inferred from sequence and structural comparison with other 11S food allergens.

CONCLUSIONS: Cocosin is likely to be a food allergen and its potential linear epitopes need to be further studied with patient sera when available.

820 Impact of allergen-specific IgG antibodies and FcyRIIb on food allergic responses

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RATIONALE: Food allergy is an increasing health problem with no approved treatments or cures. The role of immunoglobulin (Ig)G antibodies in allergen-specific immune responses is poorly understood, but specific IgG responses have been shown to correlate with clinical tolerance.

METHODS: IgG treatment was used to interrogate mouse and human immune cell responses to allergen, to modulate food allergy models.

RESULTS: Application of allergen-specific IgG inhibited allergen-induced anaphylaxis and mast cell activation. IgG treatment suppressed the generation of IgE switching and T helper 2 polarization, favoring regulatory T cell responses via the inhibitory Fc receptor. The expression and function of Fc receptors in murine and human mast cells was assessed.

CONCLUSIONS: IgG antibodies have the ability to suppress allergic sensitization as well as immediate hypersensitivity, and may facilitate the restoration of immune tolerance.
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RATIONALE: Prior reports have indicated that low molecular weight pollen-derived factors such as phytosterone E1 can directly stimulate class switch of B-cells to IgE secreting cells. Cat dander is a potent allergen that sensitizes a large percentage of the population. However the ability of cat dander extract (CDE) to directly stimulate IgE class switch has not been reported. We hypothesized that CDE can also directly stimulate naïve B-cell class switch to IgE in the presence of T-cell help and IL-4.

METHODS: Purified B cells from the spleen of wild type (WT) C57BL/6 mice or Myd88KO mice were cultured with CDE in the presence of IL-4 and/or anti-CD40 antibody. Total IgE in cell culture supernatants were measured by ELISA. Real-time PCR were performed to assess IgE class switch.

RESULTS: In the presence of IL-4 and anti-CD40 antibody, CDE provided a strong signal to vigorously promote IgE class switch in naïve B cells from WT mice, and increased expression of Nr1t3, GLE (germ-line e) and GLy (germ-line y). Disruption of Myd88 in B-cells blocked CDE-stimulated IgE production and the increase in mRNA expression of Nr1t3, GLE and GLy.

CONCLUSIONS: CDE directly stimulates B cells to induce IgE class switch through a Myd88-dependent signaling mechanism in the presence of IL-4 switch factor (IL-4) and T-cell help (anti-CD40).

822 Relation of hepatitis B virus infection in Brooklyn immigrants to allergic responses and asthma

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RATIONALE: Hepatitis B virus (HBV) is an immunomodulatory virus and has been linked to IgE responses in Brooklyn immigrants from HBV-endemic countries.

METHODS: Serology testing (ELISA, Abnova) was performed on immigrants with (n=167) and without (n=175) asthma, allergic rhinitis, and food allergies. Patients who tested positive for HBV surface antibody (anti-HBs) were tested for HBV core antibody (anti-HBc) to identify natural infection versus vaccination. Anti-HBs negative subjects were further tested for HBV surface antigen (HBsAg) to identify infection prior to seroconversion. Serum IgE levels and exhaled nitric oxide (eNO) (Niox, Aerocrine) measurements were obtained on all patients. Chi-square tests were performed for associations between HBV groups [(1) non-vaccinated, non-infected; (2)vaccinated only; (3)past/current infection] and allergic diseases. Kruskal-Wallis tests were performed to compare distribution of serum IgE and eNO between HBV groups.

RESULTS: 66% (n=226/342) of the sampled Brooklyn immigrant patient population was found to have past or current HBV infection. The prevalence of allergic diseases in HBV infected patients was 50.4% (n=114). We did not find significant association between natural HBV infection and development of seasonal allergies (p=0.39), asthma (p=0.25), food allergies (p=0.15), IgE (p=0.59), or eNO (p=0.24). Furthermore, there was no association of these factors with vaccination or non-infected/non-vaccinated status (p=NS).

CONCLUSIONS: There is no significant association between HBV infection and the development of IgE responses in this Brooklyn immigrant patient cohort.

823 Gamma Tocopherol Inhibits Ozone-Induced Epithelial Cells

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RATIONALE: Allergic airway inflammation can be further exacerbated by exposure to environmental pollutants such as ozone (O3). γ-Tocopherol (γT), the primary dietary form of Vitamin E, possesses an array of anti-inflammatory properties; because airway epithelial cells are direct targets of O3-induced injury, we sought to investigate the potential anti-inflammatory effects of γT and one of its major metabolites, γ-CEHC, on airway epithelial cells using an in vitro O3-exposure model.

METHODS: Immunolized human bronchial epithelial cells (16HBEs), were grown at air liquid interface and exposed to 0.4ppm O3 for 4 hours with a 1 hour recovery. Cells were incubated with DMSO or γT overnight, or γ-CEHC 1 hour prior to exposure. Fold changes in inflammatory gene expression were quantified using qRT-PCR. Statistically significant differences were determined by one way ANOVA with a Kruskal-Wallis post-test.

RESULTS: O3-exposure, in comparison with clean air-exposure, significantly increased expression of IL-6 (4.3 ± 0.8 vs 0.9 ± 0.1, p=0.005) and IL-8 (4.1 ± 0.7 vs 0.9 ± 0.1, p=0.005) in DMSO vehicle control-treated cells. Treatment with either 40μM γ-CEHC or γT blunted O3-induced expression of IL-8 compared to clean air (2.5 ± 0.1 vs 1.0 ± 0.2, p=0.2 vs 0.1 and 2.1 ± 0.5 vs 1.3 ± 0.07, p=0.85 respectively).

CONCLUSIONS: This study is the first to demonstrate that γT can abrogate inflammatory gene expression in airway epithelial cells in response to O3-exposure. Epithelial-derived O3- is integral for recruitment of neutrophils in response to airway injury, suggesting that γT is a candidate therapeutic for reducing neutrophilic airway inflammation.

824 Gastric Juice DirectlyEnhanced IL-13-Induced CCL26 Expression in Human Bronchial Epithelial Cells in Vitro

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RATIONALE: Gastroesophageal reflux disease (GERD) reportedly correlates with difficult asthma, but the mechanisms of how GERD affects asthma pathogenesis remain obscure. In the present study, we investigated the direct effects of gastric juice on chemokine expression in human bronchial epithelial cells in vitro.

METHODS: An immortalized human bronchial epithelial cell line (BEAS-2B) and normal human bronchial epithelial cells (NHBE) were exposed to acidic medium (pH 2) alone or with pepsin (gastric juice), followed by culture in normal medium in the presence or absence of IL-13. CCL26 (eotaxin-3) mRNA in the cell lysates and its protein in the culture supernatants were measured by qPCR and ELISA, respectively.

RESULTS: In both BEAS-2B and NHBE, gastric juice induced significant CCL26 mRNA but its protein was undetectable, whereas the acidic medium alone showed much weaker effects. The gastric juice showed significant synergistic enhancement of IL-13-induced CCL26 mRNA and protein production. Gastric juice did not induce phosphorylation of intracellular STAT6 in BEAS-2B.

CONCLUSIONS: Our results suggest that microaspiration of gastric juice directly exacerbates type 2 inflammation through enhancement of CCL26 production in the airway epithelial cells, perhaps leading to asthma exacerbation.
825 IL-4Ra Promotes Airway Hyperresponsiveness Exclusively Through Effects On Smooth Muscle And Airway Epithelium

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RATIONALE: Asthma is defined by airway hyperresponsiveness (AHR). While mouse models of allergic airway disease (AAD) demonstrate critical roles for IL-4Ra, the required component for responsiveness to both IL-4 and IL-13 and the induction of AHR, the relative importance of this receptor on different airway cell types is unclear.

METHODS: Lung disease was induced by intratracheal administration of house dust mite extract (HDM) or IL-13. We compared BALB/c mice that expressed IL-4Ra on all cell types, or that selectively lacked IL-4Ra on smooth muscle cells (SMC), on airway epithelial cells (EC) or on both of these cell types. We measured AHR (invasively by forced oscillation), bronchoalveolar lavage (BAL) eosinophils, goblet cell metaplasia and cytokine production.

RESULTS: In HDM-inoculated mice, peak airway resistance (PAR) following methacholine inhalation was: 9.1±0.7 when IL-4Ra was expressed on all cell types, 7.8±1.0 when IL-4Ra was lacking on SMC, 3.4±0.5 when IL-4Ra was lacking on EC and 2.0±0.4 when IL-4Ra was lacking on both these cell types. The PAR of mice treated with saline was 1.4±0.2. When disease was induced by IL-13, PAR was 12.3±1.4 in mice that expressed IL-4Ra on all cell types and only 6.2±0.8 when IL-4Ra was lacking on SMC. Selective expression of IL-4Ra did not affect pulmonary eosinophils.

CONCLUSIONS: IL-4Ra expression by EC and SMC almost totally accounts for the contribution of this receptor to AHR. However, EC IL-4Ra is considerably more important when AAD is induced by HDM, while EC accounts for the contribution of this receptor to AHR. However, EC IL-4Ra expression by EC and SMC almost totally accounts for the induction of AHR. While mouse models of allergic airway disease (AAD) demonstrate critical roles for IL-4Ra, the required component for responsiveness to both IL-4 and IL-13 and the induction of AHR, the relative importance of this receptor on different airway cell types is unclear.

826 Regulation of Cadherin-related Family Member 3 Expression in Primary Human Bronchial Epithelial Cells and Respiratory Organ Cultures

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RATIONALE: Rhinovirus C (RV-C) infection was reported to have significant association with asthma exacerbations in children. These viruses were not culturable in standard cell culture until the identification of cadherin-related family member 3 (CDHR3) as its receptor. We hypothesize that cellular distribution of CDHR3 in the human airways was associated with host susceptibility to RV-C infection. This study aimed to investigate changes in CDHR3 expression and the susceptibility of host cells to RV-C upon exposure to asthma-related stimuli.

METHODS: Well-differentiated human bronchial epithelial cells (wd-HBEC) from asthmatic and non-asthmatic patients and ex vivo cultures of human bronchial and lung tissues were subjected to challenges with Th2 cytokines, allergens and respiratory virus (influenza and rhinovirus) infection. CDHR3 expression levels were determined at gene and protein levels using qPCR and western blot. The localization of the CDHR3 was detected by immunofluorescence staining. The effects of these stimuli to RV-C infection were evaluated by a subsequent inoculation of RV-C isolate, and its replication kinetics by titrating the culture supernatant using CDHR3-expressing H1-HeLa cell.

RESULTS: Rhinovirus A16 infection down-regulated the CDHR3 gene expression by 56% - 75% while rhinovirus C17 infection induced less than 2-fold changes. In contrast, influenza infection upregulated CDHR3 by an average of 3 folds in wd-HBEC from non-asthmatic adult patients at 24-hour post infection.

CONCLUSIONS: Rhinovirus infections did not increase gene expression of CDHR3, suggesting that the pathways induced by infection alone would not play a major regulatory role in CDHR3 expression.

827 Systemic imbalance in hormone levels associates with epithelial barrier dysfunction in allergic disease

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RATIONALE: Epithelial barrier dysfunction similarly afflicts patients with different allergic diseases, and is implicated in the origins of allergy. However, systemic drivers of barrier dysfunction in allergy are poorly understood.

METHODS: To identify common genes and signaling pathways underlying disruption of epithelial barriers in multiple allergic diseases, we used an unbiased systems biology approach to directly compare gene expression profiles of asthma and atopic dermatitis, using NCBI GEO microarray repository data (3 studies per disease). As a validation step, we measured pre-pubertal hormone levels in plasma from 54 children with and without food allergy, asthma or atopic dermatitis. We further tested the association between serum hormone levels and markers of barrier dysfunction in patients with asthma and chronic rhinosinusitis.

RESULTS: Gene network analysis of transcriptionomes shared by barriers in asthma and non-lesional atopic dermatitis suggested that metabolic hormone imbalance may underlie systemic susceptibility to epithelial dysfunction. In support of bioinformatics findings, significant decreases in plasma levels of insulin (598±118.96 vs 108.29±18.74 pg/mL, p<0.01) and C-peptide (1292.81±254.06 vs 422.94±73.76 pg/mL, p<0.05), as well as increased triiodothyronine (0.63±0.14 vs 1.83±0.34 ng/mL, p<0.01) and growth hormone (368.60±109.53 vs 5663.90±1448.09 pg/mL, p<0.01), were detected in allergic children. Serum insulin levels were inversely correlated with airway expression of markers of barrier remodeling and type 2 allergic disease (including SERPINB2 and POSTN; R=-0.585,-0.581, respectively, p<0.01) in asthma/chronic rhinosinusitis.

CONCLUSIONS: Hormonal imbalance represents an unexpected and previously unrecognized systemic feature of allergy. Such hormonal dysregulation has the potential to disrupt epithelial homeostasis and predispose to allergic response at different barrier sites.
**AB264 Abstracts**

**Expression of Lipoxin A4 Receptor: FPRL1 in Human Nasal Mucosa**

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**RATIONALE:** Lipoxins(LXs) are a group of lipoxigenase derived eicosanoids which in contrast to other eicosanoids including leukotrienes, are recognized to have potent anti-inflammatory and pro-resolution properties. Formyl peptide receptor-like receptor 1(FPRL1) also called LXA4 receptor, functions as a component of the inflammatory response. To date, only a few reports have shown the existence of this receptor in the airway. The purpose of this study was to investigate the expression and the localization of FPRL1 protein in human nasal mucosa by western blotting and immunohistochemical analysis.

**METHODS:** Human turbinates were obtained after turbinectomy from 6 patients with nasal obstruction refractory to medical therapy. The expression of FPRL1 protein was evaluated by western blotting. To identify the cells expressing FPRL1 protein, immunostaining was performed using anti-human FPRL1 antibody.

**RESULTS:** A single band of approximately 38kDa was detected in human turbinates and primary cultured nasal epithelial cells by western blot analysis using anti-FPRL1 antibody. The immunohistochemical studies revealed that anti-FPRL1 antibody mainly labeled epithelial cells, submucosal glands and some inflammatory leukocytes in nasal mucosa.

**CONCLUSIONS:** These results may have an important clinical implication for understanding the role of LXA4 receptor on upper airway diseases such as allergic rhinitis and non-allergic rhinitis.

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**Sting Regulates Innate and Allergic Airway Inflammation**

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**RATIONALE:** Sting is a component of the interferon regulatory factor (IRF) 3,7,9 reporter activity was quantitated. WT RAW and Sting KO RAW cells were stimulated with diverse allergenic extracts, and interferon regulatory factor (IRF) 3,7,9 reporter activity was quantitated.

**RESULTS:** A single RWPE or CDE intranasal challenge in naive WT mice stimulated neutrophil recruitment into the airways. Compared to WT mice, in Sting KO mice both RWPE (52% reduction) and CDE (75% reduction) induced reduced neutrophil recruitment. Repeated-challenge with RWPE or CDE in WT mice induced allergic inflammation, characterized by recruitment of eosinophils in BALF and levels of total IgE and antigen-specific IgE in serum. Compared to WT mice, in Sting KO mice both RWPE (45% reduction) and CDE (55% reduction) induced reduced eosinophil recruitment and total IgE and antigen-specific IgE in serum.

**CONCLUSIONS:** Sting mediates RWPE and CDE-induced innate and allergic inflammation in the lungs. Sting stimulates RWPE, firebush, pigweed, CDE, and house dust mite extract induced IRF activation in cells. Our data suggest that sensing of damaged DNA in cytosol by Sting may play a role in allergen-induced innate and allergic inflammation.

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**Expression of Nasal Epithelial Platelet Activating Factor Receptor (PAFR) and in vivo Exposure to Air Pollution**

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**RATIONALE:** Vulnerability to pneumococcal infection is increased by exposure to particulate matter (PM) air pollution. Bacterial adherence to host cells is key to infection. A mechanism by which pneumococci adhere to airway cells is by co-opting the platelet activating factor receptor (PAFR). We previously reported that in vitro PAFR expression is increased by PM (1). In this study, we sought evidence that nasal PAFR expression is associated with urban PM exposure in vivo.

**METHODS:** Nasal biopsies from healthy volunteers were taken 1h before and 1h after moving though high pollution areas in London. Exposure was validated by personal black carbon (BC) monitoring (ng/m³). Nasal epithelial PAFR expression was assessed by PAFR monoclonal antibody and flow cytometry. Data are expressed as median fluorescence intensity (MFI) adjusting for isotypic control. The study was approved by a local research ethics committee. Data were analysed by paired t test, and Pearson correlation.

**RESULTS:** Three paired nasal biopsies were obtained from two individuals. Personal BC was increased during exposure to a high pollution area (mean BC ng/m³: 369 vs 10298 p<0.01). Nasal PAFR increased 1h after high pollution exposure (MFI: 654 vs 7289, p<0.05). Overall, there was an association between PAFR expression and 1 h back carbon exposure (r = 0.8284, p<0.05).

**CONCLUSIONS:** Nasal epithelial PAFR expression in vivo is increased by air pollution. We speculate that this alters vulnerability to both airway infection and infection-triggered asthma exacerbations.

References:


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**Serum ST2, but Not IL-33, Is Elevated in Children with Food Allergy Due to Low Dose Baked Milk**

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**RATIONALE:** Most of the children with milk allergy tolerate baked milk. Tolerance of baked milk is a marker of transient IgE mediated milk allergy. IL-1 receptor family member ST2 was an isolated receptor, IL-33 was an association between PAFR expression and 1 h back carbon exposure (r = 0.8284, p<0.05).

**METHODS:** We performed a retrospective study of patients with low dose milk allergy. The subjects of the present study are 132 patients aged from 11 to 96 months. (average 31.2 months) who performed oral food challenge in our department in 2015-2016. The patients ate low dose baked milk; using muffin contained 3mL of milk (protein 102mg) and it was baked at 180°C for 30 minutes. We classified the groups according to physical examinations with allergic symptoms in 3 hours as positive group and investigated blood examinations compared to negative group. Blood examination contains of their serum levels of total IgE, milk-specific IgE, casein-specific IgE, IL-33, ST2.

**RESULTS:** We confirmed that median milk IgE levels did not change. But a significantly higher concentration of ST2 level was detected in positive group compared with negative group, suggesting the influence of in allergic reaction due to low dose milk. Interestingly, the elevation of IL-33 was not observed in allergic group.

**CONCLUSIONS:** We concluded that ST2 is an important factor in milk allergy and speculated that it is because the relationships ST2 and IL-33 played an important role in food allergy due to low dose allergens.
**Endogenous PGE2 Amplifies IL-33 Production By Macrophages through an EP2/EP4-cAMP-Epac-Dependent Pathway**

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**RATIONALE:** Macrophages activated through toll-like receptors can generate IL-33, an IL-1 family cytokine that induces innate immune responses through its receptor, ST2. Lipopolysaccharide (LPS) induces macrophages to generate prostaglandin-E$_2$ (PGE$_2$), a cyclooxygenase (COX)-2 and dominantly microsomal PGE$_2$ synthase-1 (mPGES-1) product. The effects of PGE$_2$ on IL-33 production by macrophages are not known.

**METHODS:** We studied IL-33 production by bone-marrow derived murine macrophages (bMMF) by LPS in absence of endogenous PGE$_2$ and in presence of exogenous PGE$_2$. We elucidated underlying mechanisms using pharmacological approaches in bMMFs from mice respectively lacking mPGES-1 and EP$_2$ receptors.

**RESULTS:** IL-33 production by bMMFs requires endogenous PGE$_2$ and intrinsic expression of EP$_2$ receptor to amplify NF-kB-dependent LPS-induced IL-33 expression via exchange protein activated by cAMP (EPAC). Selective agonists of EP$_2$ and to a lesser extent EP$_4$, but not of EP$_1$ or EP$_3$, potentiated LPS-induced IL-33 generation from mPGES-1-null and WT bMMFs. Exogenous PGE$_2$ enhances IL-33 mRNA expression via a cAMP dependent pathway and its effect was also mimicked by an EPAC-selective agonist, but not by a PKA-selective agonist, and was attenuated by an EPAC-selective antagonist or knockdown. Although both p38 MAPK and NF-kB activations were needed for IL-33 production, they occurred independently of PGE$_2$.

**CONCLUSIONS:** Our data demonstrate that endogenous PGE$_2$ is required to amplify LPS-induced IL-33 expression in mouse bMMFs, involving cAMP dependent pathway involving EPAC. The ubiquitous induction of mPGES-1-dependent PGE$_2$ may be crucial for innate immune system activation during various IL-33 driven pathologic disorders.

**Environmental Adjuvants Induce Neuropilin-2 Expression in Human and Murine Alveolar Macrophages**

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**RATIONALE:** Neuropilin-1 (NRP1) and -2 (NRP2) are transmembrane receptors expressed by lung macrophages, but their functional importance is unclear. Here, we investigated the effect of environmental adjuvants on NRPI and NRP2 expression in human and murine alveolar macrophages (AM).

**METHODS:** Human AM or murine bone marrow-derived macrophages (BMM) were treated ex vivo with Toll-like receptor (TLR) ligands, house dust extract (HDE) or proteases, and NRPI and NRP2 expression was evaluated by real-time quantitative PCR and confocal microscopy. NRP2 reporter mice were also exposed to HDE or endotoxin (TLR4 agonist) in vivo, and NRP2 expression by AM was determined by flow cytometry.

**RESULTS:** Ex vivo stimulation of human AM or murine BMM with endotoxin resulted in increased NRP2 but decreased NRPI expression. NRP2 was also induced in BMM treated with HDE and agonists for TLR2, TLR3 and TLR9. In contrast, protease treatment of BMM did not induce significant NRPI expression. Expression of the NRPI co-receptors, pleckstrin A3 and vascular endothelial growth factor (VEGF) receptor 3, was increased in endotoxin- and HDE-stimulated BMM. In vivo airway exposure to HDE or endotoxin induced NRP2 expression in murine AM. Furthermore, quantitative PCR analysis revealed expression of NRP2 ligands (VEGF and semaphorin 3F) in lungs of HDE-exposed mice.

**CONCLUSIONS:** Stimulation of innate immune receptors by TLR ligands and HDE induces NRP2 expression in human and murine AM. Given the importance of AM in maintaining immune homeostasis in the lungs, our findings suggest that NRP2 may play a role in regulating airway inflammation in response to environmental adjuvants.
**Use of Proteomic and Flow Cytometry Assays to Characterize Innate Anti-Viral Immune Responses Using Cord Blood in a Birth Cohort Study**

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**RATIONALE:** Farm exposure is protective against asthma and our preliminary findings suggest viral respiratory illnesses (VRIs). Type I interferon responses are immature in neonates, however the relationship between varied immune maturation markers has not been studied. Proteomic and flow cytometry assays were used to characterize neonatal immune responses to rhinovirus (HRV-A16) and viral-associated TLRs, and the results of these two assays were compared.

**METHODS:** In a prospective birth cohort study, cord blood was collected from farm and non-farm neonates. 19 study subjects (10 farm and 9 non-farm) were analyzed. Blood mononuclear cells were isolated and stimulated with HRV-A16 and viral-associated TLR agonists (R848 & OpGA). Multi-parameter flow cytometry and multiplex, bead-based assays were used to determine innate and adaptive immune responses. Spearman’s rank coefficient was calculated to determine correlation between assays.

**RESULTS:** For HRV and R848 agonists, IFNα2 supernatant levels were positively correlated with plasmacytoid dendritic cell (pDC) IFNα integrated fluorescence intensity (iMFI, \( r_s = 0.560, p = 0.013 \) and \( r_s = 0.512, p = 0.025 \), respectively) and were not correlated with pDC maturation (CD40+CD86+). IP-10, important in effector T cell recruitment, was secreted by stimulated cord blood cells with the highest levels detected with HRV stimulation (\( p < 0.0001 \)). HRV stimulation demonstrated IP-10 correlation with B cells and conventional dendritic cells maturation (\( CD40+CD86+ \)). IP-10, important in effector T cell recruitment, was secreted by stimulated cord blood cells with the highest levels detected with HRV stimulation (\( p < 0.0001 \)). HRV stimulation demonstrated IP-10 correlation with B cells and conventional dendritic cells maturation (\( CD40+CD86+ \)). IP-10, important in effector T cell recruitment, was secreted by stimulated cord blood cells with the highest levels detected with HRV stimulation (\( p < 0.0001 \)). HRV stimulation demonstrated IP-10 correlation with B cells and conventional dendritic cells maturation (\( CD40+CD86+ \)). IP-10, important in effector T cell recruitment, was secreted by stimulated cord blood cells with the highest levels detected with HRV stimulation (\( p < 0.0001 \)).

**CONCLUSIONS:** Proteomic and flow cytometry assays provide a complementary, detailed characterization of neonatal anti-viral responses and will be used to identify correlates of immune protection against VRIs. These studies will determine the impact of farming exposure on anti-viral responses and clinical correlates.

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**Viral Detection and Cytokine Profile in Early Transient Wheeze and Childhood Asthma**

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**RATIONALE:** Wheeze is a common respiratory symptom in preschool children. Several clinical parameters, including gestational age at birth, parental atopy, and early-life sensitization, are associated with the development of asthma and are used to differentiate between asthma and transient wheeze in early infancy; however, they are only moderately successful. Here, we investigated respiratory viruses and various cytokines/chemokines in transient wheeze cases and established asthma cases.

**METHODS:** We analyzed peripheral eosinophil counts, and 27 cytokines/chemokines in acute exacerbations among 14 transient wheeze and 32 asthma cases, controls (no wheeze) aged from 6 months to 6 years, and in non-symptomatic transient wheeze and asthma cases. Viruses were detected using antigen detection kits and/or RT-PCR, followed by direct DNA sequencing analysis. Serum cytokines/chemokines were measured using a multi-cytokine detection system.

**RESULTS:** The two major viruses detected, rhinovirus and respiratory syncytial (RS) virus, were dominant in acute asthma cases. However, RS virus, rhinovirus, human metapneumovirus, parainfluenza virus, coronavirus, and human bocavirus were detected at almost equal levels in transient wheeze cases. Serum IL-4, IL-6, and IL-9 levels were significantly elevated in acute asthma compared with transient wheeze. Conversely, IL-8 and IL-12 values were significantly higher in transient wheeze than in acute asthma. Elevated IL-5 and IP-10 levels compared with controls were significantly higher in acute asthma than in non-symptomatic asthma cases. On the other hand, only IP-10 was significantly higher in transient wheeze than in non-symptomatic transient wheeze cases.

**CONCLUSIONS:** Cytokine profiles differ between transient wheeze and childhood asthma.
Impaired Tissue Eosinophil Resolution in Obese Asthma May Be Due to Surfactant Protein-A Insufficiency

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RATIONALE: Eosinophils are prominent in individuals with type 2-driven asthma and submucosal eosinophils are elevated in a subgroup of obese asthmatics. Surfactant protein-A (SP-A) is a secreted lipoprotein complex that has recently been shown to mediate several eosinophilic activities. We hypothesized that obese asthmatics may have enhanced tissue eosinophilia due to decreased SP-A in the airway.

METHODS: Bronchoalveolar lavage fluid from 23 lean (13 normal, 10 asthma) and 20 obese (9 normal, 11 asthma) subjects were examined for SP-A. Mouse tracheal epithelial cells (MTECs) grown at an air-liquid interface were used for mechanistic studies. SP-A−/− mice were challenged in allergen models and exogenous SP-A therapy was given after the last challenge. Eosinophils were visualized and quantitated in the lung parenchyma by immunostaining for mouse eosinophil major basic protein.

RESULTS: Significantly less SP-A was detected in samples from obese asthmatics compared to lean asthmatics. SP-A levels negatively correlated with BMI and positively correlated with lung function. Allergic SP-A−/− mice that received SP-A therapy had significantly less tissue eosinophilia compared to mice receiving vehicle. In vitro studies revealed that SP-A deficient epithelial cells have attenuated eotaxin production under basal conditions.

CONCLUSIONS: SP-A functions as an important mediator in resolving tissue eosinophilia. Therefore, significantly decreased levels of SP-A in obese asthmatics could contribute to asthma exacerbations.

Interferon-Related Gene Expression in Respiratory Syncytial Virus (RSV) Infected Pediatric Bronchial Epithelial Cells (BECs) Is Inversely Correlated with Lung Function

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RATIONALE: Respiratory viral infection in early childhood, including that from RSV, has been previously associated with later development of obstructive lung disease. We sought to determine whether in vitro RSV infection of BECs from asthmatic children would induce specific gene expression patterns, and whether this would correlate with lung function measurements obtained from those same subjects.

METHODS: BECs from 26 asthmatic children with varying severity of obstructive lung disease were collected, cultured, and differentiated at an air liquid interface (ALI). Differentiated BECs were grown with RSV or virus free media for 96 hours and RNA was isolated for mRNA sequencing. Differential gene expression was assessed by linear modeling and correlation of differentially expressed genes and lung function measures were assessed by Pearson correlation with multiple testing correction. Findings were validated in an independent cohort of 9 asthmatics.

RESULTS: RSV infection led to increased expression of ~7000 genes in asthmatic BECs compared to uninfected samples. 195 of these genes demonstrated increased expression in asthmatic subjects with fixed obstructive lung disease compared to asthmatic subjects without fixed obstruction and showed significant inverse correlation with FEV1 % predicted. These genes were highly enriched for interferon response genes. The findings were confirmed in an independent cohort.

CONCLUSIONS: These results demonstrate that RSV infection of BECs from asthmatic children with fixed obstructive lung disease demonstrate a greater interferon response to infection than those with normal baseline lung function. This association suggests that an excessive antiviral response by bronchial epithelial cells could influence development of functional lung impairment.

Circulating T cells, natural killer (NK) cells and group 2 innate lymphoid cells (ILC2) of severe asthmatics from the University of California Asthma Network (UCANTM) clinic, express increased levels of both IL-13 and IL-17

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RATIONALE: Neutrophilic inflammation and IL-17 have been implicated in the pathogenesis of severe asthma but the underlying mechanisms remain unclear. We aimed to establish the relationship between inflammatory markers of severe asthma and peripheral blood dendritic cell and lymphocyte populations and their IL-13 and IL-17 expression.

METHODS: Twenty-seven patients with severe asthma all requiring asthma medications and seven non-asthmatic healthy controls were recruited from the UCANTM clinic at the University of California, Davis. Complete blood count, exhaled NO and serum IgE/IgM were investigated. Peripheral blood mononuclear cells were isolated by Ficoll-Paque PLUS and T-cell subsets, dendritic cell subsets, natural killer cells and ILC2 were analyzed by multi-color flow cytometry and compared between the patients and healthy controls.

RESULTS: Severe asthma patients had elevated blood neutrophil counts, exhaled NO, serum IgE and IgM. In comparison with healthy controls, the number of circulating CD1c dendritic cells, CD4 T cells, NK cells and ILC2 were significantly increased (p<0.05). Further, the number of CD141 DC (implicated in activation of Th2 cells) significantly correlated with peripheral blood eosinophils (r=0.70) and CD4 T cells. Intracellular IL-13 and IL-17a expression was significantly elevated in CD4 and CD8 T cells, NK cells and ILC2.

CONCLUSIONS: We showed for the first time the presence of ILC2 producing both IL-13 and IL-17, in the peripheral blood of severe asthma patients. Our data also support that increased IL-17 expression may contribute to the elevated neutrophil count we observed in severe asthma patients.
841 Aryl hydrocarbon receptor in airway epithelium exacerbates cockroach allergen-induced asthma through autophagy

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RATIONALE: Aryl hydrocarbon receptor (AhR), a receptor for common environmental contaminants, is an important regulator of immune responses. Our previous studies have suggested a role of AhR in protecting against cockroach allergen-induced lung inflammation by using AhR−/− mice. Autophagy plays a major role in controlling immune responses and inflammation. We sought to determine whether the activated AhR signaling specifically in airway epithelium by cockroach allergen modulates cockroach allergen-induced lung inflammation through autophagy.

METHODS: The role of AhR expressed in epithelium in cockroach allergen (CRE) induced allergic inflammation was investigated in a mouse model of asthma with AhR epithelial conditional knock out mice (ftpcc-Cre;AhRflox/flox). Cockroach allergen induced the activation of AhR and autophagy signaling in epithelium was determined. The role of autophagy in CRE-induced asthma was also investigated.

RESULTS: CRE-challenged ftpcc-Cre: AhRflox/flox mice displayed decreased lung infiltrates, mucus production, and airway hyper-responsiveness. These mice also showed reduced levels of IL-4, IL-5, IL-13, IL-17, but increased IL-10 and IL-22 in the BAL fluids. Decreased IC3B II in airways was also observed. Moreover, CRE can activate AhR (CYP1A1 and CYP1B1) and autophagy (Beclin-1, Atg5, and p62) signaling in epithelial cells in vitro, and AhR agonist TCDD can potentiate CRE-induced autophagy. Furthermore, CRE-induced lung inflammation was significantly suppressed when autophagy inhibitor was used in the mouse model with decreased lung infiltrates and Th2/Th17 cytokines in BAL fluids.

CONCLUSIONS: Contrast to the protective role previously observed in AhR−/− mice, AhR in airway epithelial may exacerbate CRE-induced inflammation, which may through activating autophagy signaling.

842 Distinct Phenotype of Dendritic Cells Migrating from the Lung to the Lymph Nodes during Allergic Airway Inflammation

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RATIONALE: Dendritic cells are professional APCs which migrate to the draining lymph nodes where they present processed antigens to naïve T-cells. Trafficking to the lymph nodes is dependent upon upregulation of CCR-7. TREM-2, which is expressed on DCs, has been shown to upregulate CCR-7 in vitro. However, a link between the two receptors is yet to be established in the airways. Here, we examined the effect of allergen exposure on TREM-2 and CCR-7 expression on DC subsets in the lung and lymph nodes.

METHODS: Female Balb/c mice were sensitized and challenged with ovalbumin or PBS for a total of 20 days. DCs were isolated from the lungs and lymph nodes and sorted using autoMACS and FACS to determine phenotype and expression of TREM-2, CCR-7 and CD86 on subsets of cells.

RESULTS: Analysis of CD11c+MHC-II+ DCs in the lung and draining lymph nodes revealed that the OVA-sensitized and challenged group had greater density of cells that were CD11b+CD103+ and CD11b+CD103− compared to the control. Further analysis of DC populations revealed that CD86, CCR-7 and TREM-2 were expressed on all subsets in the lungs, with the greatest co-expression on CD11b+CD103+ DCs. TREM-2 and CCR-7, as well as CD86, were markedly upregulated on all three subsets of DCs found in the draining lymph nodes.

CONCLUSIONS: These data suggest that dendritic cells that express high levels of CCR-7, TREM-2 and CD86 could potentially be involved in promoting the immune response associated with allergic airway inflammation.

843 Anti-inflammatory Activity of Jurubeba (Solanum paniculatum L.) Through Reducing the T-bet and GATA3 Gene Expression, In Vitro

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RATIONALE: Solanum paniculatum L. is used in folk medicine for the treatment of gastritis, bronchitis and fever. In previous studies, S. paniculatum possesses antibiotic and antioxidant activity and modulatory effects on gastric acid secretion; however, its anti-inflammatory potential is unexplored. Here, we hypothesize that the S. paniculatum Fruit Hexane Extract (SpE) possesses anti-inflammatory effect, in vitro.

METHODS: SpE was subjected to high-performance liquid chromatography (HPLC) for standardization and quantification of stigmasterol and β-sitosterol. Spleen cells from BALB/c mice were cultivated and stimulated with pokeweed mitogen (PWM) and also exposed to 15, 30, and 60 µg/mL of SpE. Levels of IFN-γ, IL-4, and IL-10 in the culture supernatants were assessed by ELISA. Gene expression of T-bet and GATA3 in spleen was assessed by qPCR.

RESULTS: The phytochemical analysis proved the presence of stigmasterol and β-sitosterol in SpE (2.36 µg/mL and 0.829 µg/200 µg of SpE, respectively). At 60 µg/mL, SpE reduced the amount of PWM-induced IFN-γ on spleen cells (p < 0.001). PWM-stimulated IL-4 levels were reduced in a concentration-dependent manner by treatment with SpE (60, 30, and 15 µg/mL: p < 0.001). IL-10 production was not altered by SpE. Furthermore, SpE at 60 µg/mL reduced the expression of T-bet (p < 0.001), and at 30 and 60 µg/mL had attenuated GATA3 gene expression (p < 0.01) in PWM-stimulated spleen cells.

CONCLUSIONS: Our study provided evidence for the popular use of S. paniculatum in inflammation. More studies are needed to better understand the results observed herein and detailed mechanism of action whereby such effects occur.
**Glycerol Monolaurate (GML) Inhibits Human T Cell Signaling, Metabolism, and Function By Disrupting Lipid Dynamics**

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**RATIONALE:** Glycerol Monolaurate (GML) is a naturally occurring fatty acid with potent antimicrobial properties. Interestingly, GML suppresses lymphocyte proliferation and inositol triphosphate production, suggesting that GML has immunomodulatory functions. In this study, we have mechanistically examined if GML affects the signaling, metabolism, and functional output of human primary T cells.

**METHODS:** Primary human peripheral blood T cells were isolated and expanded from blood cones and treated with GML dissolved in ethanol or ethanol vehicle control. Cytokine production was measured by ELISA. Protein phosphorylation was detected using immunoblotting. Membrane clustering of signaling proteins was imaged using total internal reflection fluorescence microscopy. Flow cytometry assays measuring calcium influx and ordered lipid domains were done by detecting cells stained with the calcium chelator dye, Fluo-4M, and the membrane intercalating dye, Di-4-ANEPPDHQ, respectively. T cell metabolism was assessed using Seahorse XF-96 Extracellular Flux Analyzer.

**RESULTS:** GML potently altered the lipid order and disorder dynamics in the plasma membrane that resulted in reduced membrane localized clustering of the proteins LAT, PLC-γ, and AKT. Altered membrane signaling events induced decreased phosphorylation of PI3K and AKT as well as abrogated calcium influx. In addition to signaling defects, GML treated cells have profoundly altered metabolism profiles characterized by suppressed oxidative phosphorylation and increased glycolysis. Functionally, GML treatment potently reduced TCR-induced production of the cytokines IL-2, IFN-γ, TNF-α, and IL-10.

**CONCLUSIONS:** Our data reveal that the widely used anti-microbial agent GML alters the lipid dynamics of human T cells, leading to their defective signaling, metabolism, and function.

**Mesenchymal Stem Cell Induce Tolerogenic Dendritic cells which Inhibit Proliferation of Autologous T-cells**

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**RATIONALE:** Human olfactory epithelium-derived stem cells (hOE-MSC) inhibit proliferation of T-cells and induce a tolerogenic profile of co-cultured dendritic cells (DC). This study assesses the effects of the hOE-MSC-induced DC on proliferation of autologous T-cells.

**METHODS:** hOE-MSC were generated from 5 patients with non-inflammatory diseases of the nasal cavity. hOE-MSC were CD45-CD90+CD73+CD105+CD31-. Dendritic cells were obtained from blood monocytes. DC were cultured over hOE-MSC monolayer for 3 days. The obtained tolerogenic DC (tDC) were collected and further co-cultured with CFSE-loaded blood T-cells for 3 days with PHA (1ug/mL). The cell proliferation index was assessed.

**RESULTS:** The obtained hOE-MSC-induced tDC, which were assessed for hOE-MSC contamination, were negative for CD90+ cells (<0.1%). tDC expressed high levels of CD273 and CD85k molecules, indicative of tolerogenic properties. hOE-MSC-induced tDC exerted a strong immunosuppressive effect on autologous T-cells, significantly (p<0.02) reducing the proliferation index: T-cells alone – 1.53 (range 1.44-1.56); T-cells and immature DC – 1.44 (range 1.32-1.47); T-cells and mature DC – 1.9 (1.87-2.44); and T-cells and tDC – 1.18 (1.13-1.27).

**CONCLUSIONS:** Generated hOE-MSC-induced tDC have strong immunosuppressive properties making them candidates in treatment of autoimmune diseases.

**Mavs Mediates a Senescence Associated Secretory Phenotype By Inducing Interferon Beta Expression in Human SLE Bone Marrow Stromal Cells**

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**RATIONALE:** Bone marrow mesenchymal stromal cells (MSCs) display robust immunomodulatory properties which are impaired in lupus patients, but the underlying mechanisms are unknown. This study was undertaken to address defects in human SLE BM-MSC and the potential role of these defects in SLE pathogenesis.

**METHODS:** Patients fulfilling SLE classification criteria and healthy controls were recruited under an Institutional Review Board approved protocol (n=6 each). BM-MSCs were isolated with low density Ficoll/Hypaque (1.073 g/mL) and grown in tissue culture. MSC phenotype was verified by flow cytometry. MSCs were studied using immunocytochemistry, real-time PCR, western blotting, comet assay for DNA damage, beta-galactosidase assay, and RNA interference.

**RESULTS:** SLE BM-MSCs displayed significantly reduced proliferation rate, increased production of reactive oxygen species, increased DNA damage and repair, and senescence associate secretory phenotype (SASP) as evidenced by increased cytokine production. The expression of IFNβ was increased 5 folds (p<0.05) and genes specifically induced by IFNβ were elevated in SLE MSCs. The expression of immunomodulatory factors was significantly reduced. Level of MAVs, also known as Interferon Beta Promoter Stimulator Protein 1, was positively correlated with the level of IFNβ (r > 0.9, p < 0.01). Silencing MAVs inhibited IFNβ expression and rescued the SASP in SLE MSCs.

**CONCLUSIONS:** SLE BM-MSCs have a senescent phenotype and display impaired immunomodulatory function. This phenotype is dependent on elevated levels of MAVs, an essential component of innate immune responses to cytoplasmic nucleic acids. Thus, a MAVS-IFNβ positive feedback loop appears to play a key role in the defects seen in human SLE BM-MSC.
847 Enhancing immunogenicity of respiratory syncytial virus vaccine candidates by altering NS1 function

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Rationale: Development of an efficacious live-attenuated vaccine for respiratory syncytial virus (RSV) has been stymied by the difficulty in inducing long-lived immune responses. One potential mechanism of improving the immunogenicity of live-attenuated RSV is decreasing the ability of RSV to block type I interferon (IFN) production from infected cells. The RSV NS1 protein has been shown to be a potent IFN antagonist and recombinant RSV (rRSV) lacking NS1 is immunogenic and attenuated in animal models. However, deletion of NS1 results in a RSV that replicates poorly in vitro even in IFN-deficient Vero cells, indicating that NS1 encodes functions required for efficient viral replication. Our goal was to develop recombinant RSV expressing NS1 mutants that no longer antagonize IFN, but support efficient viral replication.

Methods: We generated a panel of deletion mutant NS1 alleles to identify residues involved in IFN antagonism but not viral replication. These mutants were initially screened for IFN antagonism using a transfection assay then tested in the context of rRSV for IFN antagonism and viral replication.

Results: Initial studies with 10 aa deletions identified sequences in the N- and C-termini of NS1 that are essential for IFN antagonism and viral replication. Through an iterative process using progressively smaller deletions, we identified single residues that affected either NS1’s IFN antagonism or replication activities.

Conclusions: The IFN antagonism and replication effects of RSV NS1 can be segregated by mutagenesis. This should allow for the development of live-attenuated RSV vaccine candidates with enhanced immunogenicity that can replicate efficiently in vitro for vaccine production purposes.

848 Glucagon-like peptide-1 receptor signaling attenuates RSV-induced type 2 responses and immunopathology

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Rationale: Glucagon-like peptide-1 receptor (GLP-1R) agonists are well accepted and safe treatment for Type II diabetes. Although GLP-1R agonists mainly act to potentiate insulin and suppress glucagon secretion, recent evidence suggests that GLP-1R signaling also has anti-inflammatory effects through unclear mechanisms. Severe RSV-associated illness is in part caused by IL-13 production, which mediates the mucus production that directly contributes to airway obstruction and respiratory failure. We hypothesize that GLP-1R signaling inhibits IL-13-mediated immunopathology of RSV 12/12-6, a strain of RSV that was isolated from a hospitalized infant with severe lower respiratory tract infection and bronchiolitis.

Methods: Balb/c WT mice were infected with RSV 12/12-6. GLP-1R agonist or vehicle was administered subcutaneously twice daily beginning 2 days prior to infection. Mice were euthanized and BALs and lungs were collected for cell differentials, histopathology, AHR, ELISA, flow cytometry, or qPCR.

Results: GLP-1R agonist treatment decreased airway inflammation, airway reactivity, and airway mucus production in RSV 12/12-6-infected mice. GLP-1R agonist treatment decreased total lung IL-13 levels, with concurrent decreases in lung IL-13-producing group 2 innate lymphoid cell (ILC2), CD4+ Th2 cell, and basophil numbers. The GLP-1R agonist prevented airway inflammation, and did not impact viral load, anti-viral interferon and antibody production during secondary RSV infection. Relative to the respective mock-infected groups, RSV-infected GLP-1R agonist treated mice did not have increased weight loss compared to vehicle treated mice.

Conclusions: These data suggest that GLP-1R signaling protects against type 2-mediated immunopathology during RSV infection.
850 IL-33 and IL-13 Receptors Are Upregulated in Precision Cut Lung Slices from Donors with Asthma during RV39 Infection

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RATIONALE: IL-25, TSLP, and IL-13 are increased in precision cut lung slices (PCLS) from donors with asthma infected with rhinovirus (RV). However, whether the quantitative increase in cytokine levels correlates to upregulated receptor expression is unknown. We hypothesized receptor expression for IL-25, TSLP, and IL-13 would be enhanced in PCLS from asthma donors infected with RV39 compared to controls.

METHODS: We used precision cut lung slices (PCLS) from donors with a diagnosis of asthma (n = 5) and without asthma (n = 16) and compared rhinovirus infected (RV39) samples from both cohorts at 0, 2, and 48 hours for expression of TSLPR, IL-13Ra, ST2, ST2L, and IL-25R. Expression was normalized to beta-actin and uninfected tissue from the same lung and the same time point. Comparisons were made using Mann-Whitney.

RESULTS: ST2 and IL-13Ra were increased in PCLS from asthma donors after infection at 48 hours compared to control tissue (ST2 median 3.64 asthma: median -0.92 control; p<0.05; IL-13Ra median 5.09 asthma: median -1.040 control; p<0.05). TSLPR and IL-25R trended towards higher expression in tissue from asthma donors (p = 0.08, p = 0.06, respectively). Further, in comparisons of asthma donors infected with RV between 2 and 48 hours, ST2, IL-13Ra, and TSLPR were significantly increased (p<0.05) and were not in controls.

CONCLUSIONS: Innate allergic inflammatory cytokines and their respective receptors are up-regulated during RV39 infection in PCLS from asthma donors, suggesting that these cytokines are active. Infection with RV39 in PCLS from asthma donors leads to increased receptor expression over time, suggesting that the infection plays a role in the regulation of the receptors.

851 Susceptibility of Epidemic and Fermon Enterovirus D68 Strains to RNAi Mediated Targeting of Phylogenetically Conserved Genomic Elements

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RATIONALE: Enterovirus D68 (EV-D68) represents an emerging human pathogen which was noted to disproportionately affect patients with asthma during a large outbreak that began in the fall of 2014. We hypothesized that evolutionary conserved sequences with the EV-D68 genome might serve as ideal targets for short-interfering RNAs (siRNAs).METHODS: Comparative genomic analysis was utilized to identify phylogenetically conserved regions of the EV-D68 genome. Three siRNAs targeting these genomic segments were synthesized. Using an established in vitro, human rhabdomyosarcoma cell based model of EV-D68 infection the impact of siRNA transfection on virus growth was assessed. Absorbance, real-time PCR, plaque assay, endpoint dilution and indirect immunofluorescence were measured to quantify the effects of each siRNA on viral proliferation. Dose escalation and cytotoxicity studies were also performed. ANOVA one-way analysis was used to calculate statistical significance.

RESULTS: An siRNA targeting the viral RNA-dependent RNA polymerase gene showed potent ability to protect cells in vitro from EV-D68 mediated cytopathic effect, while non-coding negative control siRNAs had no impact on viral replication (p<0.0001). This siRNA induced peak antiviral activity at single picomolar concentrations. Viral genome copy number was reduced greater than 10 fold in treated wells (p<.0001) when measured by real time PCR. Indirect immunofluorescence demonstrated absence of detectable viral VP2 capsid protein 48 hours post-infection. No cytotoxic effect of the siRNA was detected in transfected cells.

CONCLUSIONS: The picornavirus EV-68 is susceptible to in vitro, sequence dependent, siRNA mediated targeting of conserved genomic elements within the viral RNA dependent RNA polymerase gene.

852 Study Design, Baseline and Open-Label Results from XTEND-CIU: A Phase IV, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Omalizumab through 48 Weeks in Patients with Chronic Idiopathic Urticaria

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RATIONALE: XTEND-CIU was designed to assess the safety and efficacy of longer-term omalizumab treatment (48 weeks) and enhance understanding of omalizumab discontinuation in patients with chronic idiopathic urticaria (CIU). We summarize XTEND-CIU study design, baseline characteristics and outcomes for the 24-week open-label period.

METHODS: Patients ≥12 years old remaining symptomatic despite standard H1 antihistamine treatment, H2 blockers, and/or leukotriene receptor modifiers were enrolled. XTEND-CIU included 4 phases: 14-day screening, 24-week open-label, 24-week randomized double-blind (omalizumab or placebo), follow-up period (Weeks 48–60). Omalizumab 300 mg was given subcutaneously every 4 weeks. Eligibility for study enrollment required patients to have 7-day urticaria activity score (UAS7) ≥16 within seven days before baseline; eligibility for randomization required UAS7 ≥6 in the final two weeks of the open-label period. Based on data from the pivotal trials, 57% of patients were expected to be randomized. Patients recorded CIU symptoms twice-daily via Urticaria Patient Daily Diary (UPDD).

RESULTS: Of 206 patients enrolled into the study, 175 (85%) completed the open-label period and 134 (65%) were randomized. Mean(SD) age at baseline was 44.7(14.5) years, 74.6% were female, 82.0% were white. At baseline, mean(SD) scores were: UAS7 score, 32.2(7.0), weekly itch score, 15.4(3.6), weekly number of angioedema days, 2.2(2.7). At end of open-label period, average UAS7 and weekly itch scores decreased to 6.2(11.0) and 2.4(4.7), respectively. No new safety signals were detected.

CONCLUSIONS: A higher-than-expected number of patients responded to omalizumab during the 24-week open-label period and were eligible for randomization in the subsequent double-blind period.
All abstracts are strictly embargoed until the date of presentation at the 2017 Annual Meeting.

**AB272 Abstracts**

**853 Autoinflammatory Disease: Presenting As Urticaria**

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**RATIONALE:** Autoinflammatory disease reflects a constellation of new diagnoses, including Cryopyrin Associated Periodic Syndromes (CAPS), marked by related symptoms, genetic and inflammatory markers, and responses to treatment.

**METHODS:** 23 patients presented to an urticaria clinic with rash, periodic fever, arthralgia, and other varying symptoms. Serum amyloid A (SAA) was elevated in 20 patients (87%). 15 patients demonstrated R260W mutations at the NLRP3 gene and were diagnosed with CAPS. Three patients showed M694V mutations at the MEFV gene; two were diagnosed with Familial Mediterranean Fever (FMF). One displayed a R92Q mutation of the TNFRSF1A gene and was diagnosed with tumor necrosis factor-receptor-associated periodic syndrome (TRAPS). Two patients were diagnosed with Schnitzler’s syndrome based on clinical presentation and detection of an MGUS. Three patients presented with undefined autoinflammatory disorders. 15 patients (nine with CAPS, two with Schnitzler’s syndrome, and three undefined) were treated with 150 mg canakinumab subcutaneously every eight weeks. Patients received 1-14 treatments. Drug efficacy was assessed based on SAA levels (pre- and post-treatment), a self-report questionnaire, and physician assessment.

**RESULTS:** 11 out of 15 patients (73%) treated with 150 mg canakinumab experienced remission within one week of treatment, demonstrated by normalized or significantly reduced SAA levels and disappearance of symptoms.

**CONCLUSIONS:** Patients with supposed chronic urticaria and other relevant symptoms should be assessed for autoinflammatory disorders through genetic testing, family history and inflammatory markers. Autoinflammatory disease patients are in need of medical centers offering access to testing and treatment. One treatment for CAPS, the IL-1 inhibitor canakinumab, was associated with rapid symptom improvement.

**854 Serum Periostin Level and Severity and Chronicity of Atopic Dermatitis in Children**

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**RATIONALE:** Recent studies have suggested an important role for periostin in the pathogenesis of atopic dermatitis (AD). We investigated the relationship between periostin and the severity and chronicity of AD in children.

**METHODS:** This population-based study examined 4,076 children from 3 kindergartens and 6 elementary schools who were enrolled in the prospective 2015 Scongnam Atopy Project in Korea between June 2015 and July 2015. Of the 4,076 children, 238 including 185 with a history of AD in the AD group and 53 without allergic diseases history in the healthy control group, were included randomly for the final analysis.

**RESULTS:** Serum levels of periostin were found to be associated with SCORing Atopic Dermatitis (SCORAD) score, pruritus score, and blood eosinophil levels ($r = 0.20, P = 0.008$; $r = 0.20, P = 0.007$; and $r = 0.21, P = 0.004$, respectively) in the AD group, but not with the number of allergens and 25-hydroxyvitamin D₃ level. Children with AD with moderate and severe SCORAD scores had considerably higher levels of periostin than did those with no or a mild score ($P = 0.008$), and those with lichenification exhibited significantly elevated periostin levels than did those without it ($P = 0.027$). Children with severe pruritus scores also had considerably higher levels of periostin than did those with no, mild, and moderate scores in the AD group ($P = 0.024$).

**CONCLUSIONS:** Serum periostin levels significantly correlated with the severity and chronicity of AD in children.

**855 Th2 Cytokines and IL-17 Have Distinct Effects on Sphingolipid Metabolism in Differentiated Primary Human Keratinocytes**

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**RATIONALE:** Atopic dermatitis (AD) and psoriatic skin are characterized by abnormalities in skin lipids required for skin barrier function. The role of IL-4/IL-13 versus IL-17, involved in the pathogenesis of AD and psoriasis, in regulating keratinocyte lipid metabolism has not been studied.

**METHODS:** Lipid profiles were examined by targeted liquid chromatography tandem mass spectrometry in Ca²⁺ differentiated primary human keratinocytes in the presence or absence of IL-4/IL-13 or IL-17a. Cellular expression of selected enzymes of lipid metabolism was examined by real-time PCR.

**RESULTS:** Keratinocyte differentiation resulted in significantly increased levels of long-chain C22-C28 ceramides. However, cells differentiated in the presence of IL-4/IL-13 had a significant decrease in total ceramide levels (Mean±SD: 14,984±731 vs. 36,339±675 pmol/nmol lipid phosphorus in differentiated keratinocytes, p<0.05) and a qualitative decrease in long-chain ceramides. In contrast to IL-4/IL-13, IL-17a significantly increased total ceramide production (107,289±2,599 pmol/nmol lipid phosphorus, p<0.05) and resulted in nonselective increase of all ceramide molecular species. IL-4/IL-13 significantly reduced expression of glusocylceramides in differentiated keratinocytes (1.748±36 vs. 2.825±369 pmol/nmol lipid phosphorus, p<0.05). IL-4/IL-13-treated vs non-treated cells, respectively). IL-4/IL-13 significantly increased expression of fatty acid elongases ELOVL1, ELOVL3 and ELOVL5, ceramide synthases CERS1, CERS4, and glucosylceramide synthase UGCG.

**CONCLUSIONS:** Keratinocyte differentiation in the presence of IL-4/IL-13 in vitro recapitulates changes in ceramide levels and molecular species redistribution in AD skin. These changes are accompanied by altered expression of fatty acid elongases, ceramide synthases and glucosylceramide synthase. These observations reinforce the role of IL-4/IL-13 in driving skin barrier dysfunction in AD.
Minimally Invasive Skin Tape Strip RNA-Seq Identifies Atopic Dermatitis Disease Endotype

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Rationale: Atopic dermatitis (AD) is a heterogeneous disease with varied clinical course, severity, and therapeutic responses. Minimally invasive skin-directed techniques are needed to characterize disease endotypes.

Methods: Non-lesional skin was sampled from AD patients (n=18) and healthy controls (HC, n=13) using tape-stripping methods. Low input, whole transcriptome sequencing was used to generate gene expression profiles of tape strip RNA.

Results: Agnostic gene set analysis of non-lesional skin data revealed upregulation of multiple immune gene ontology (GO) categories among AD subjects including, cytokine receptor interaction, T-cell activation, NF-kappa-B signaling. Unsupervised clustering using these immune GO genes revealed a cluster of AD subjects (n=9) with high expression, and a second cluster composed of the remaining AD and all HC subjects, exhibiting low expression of these genes. Comparing the AD “immune-high” endotype cluster to the “immune-low” cluster we found 337 differentially expressed genes (FDR=0.05). The immune-high subjects had elevated expression of type 2 cytokines (CCL17/CCL22/IL13) and IL4R. Expression levels of macrophage/dendritic (CSF1/CSF1R) and T regulatory (FOXP3) cell markers were also elevated in this group. Increased IL4R expression in non-lesional skin from AD “immune-high” endotype was confirmed by immunostaining (p=0.05) (MFI, Mean±SD 406±100, 260±96 and 311±63 for AD-immune-high, AD-immune-low and HC groups).

Conclusions: We present an accessible approach to assay molecular protective effects in AD skin. Our results suggest an endotype of AD with immune infiltration of superficial non-lesional skin, characterized by type 2 inflammation/activation of immune cells. This group may experience persistent, non-lesional skin inflammation and thus would represent candidates for precision immune inhibition treatments.

Role Of Hormone Signaling In Eosinophilic Esophagitis: 17-Beta Estradiol Attenuation Of IL-13 Induced Barrier Dysfunction In Esophageal Epithelium

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Rationale: Eosinophilic esophagitis (EoE) is a chronic, food-driven, esophageal, inflammatory allergic disease. We have recently found that, in addition to genetic risk loci for allergen sensitization, EoE susceptibility is linked to a tissue-specific genetic factor(s) at 2p23, encoding the CAPN14 gene. In our initial studies we showed that CAPN14 is dynamically upregulated as a function of EoE disease activity and after exposure of epithelial cells to IL-13, a critical regulator of esophageal inflammation in EoE. Patients with EoE and the 2p23 risk haplotype express decreased esophageal CAPN14.

Methods: We performed a replication and fine-mapping study of the 2p23 locus in an additional cohort of subjects with and without EoE. We used DNA affinity precipitation analysis and electromobility shift assays to identify proteins that differentially bound specific variants. Luciferase reporter assays were used to further define the IL-13 and genotype-dependent parts of the CAPN14 promoter.

Results: Using an independent genetic cohort, we replicated the 2p23 EoE-risk locus (rs76562819 Pmeta<1.0E-10, Odds Ratio=1.98) and identified five genetic variants most likely to be causal. We identified the critical promoter elements of CAPN14 using promoter deletion constructs. We demonstrated STAT6 binding to the three putative binding sites in the promoter and first intron. Each of the three STAT6 elements were required for the 10-fold increase in IL-13 induced promoter activity and for the 50% reduction in genotype-dependent expression.

Conclusions: Our work establishes a candidate molecular mechanism for EoE disease etiology in which the risk variant rs76562819 at 2p23 dampens IL-13-induced calpain-14 promoter activity in a STAT6-dependent manner.
859 Outgrowing eosinophilic esophagitis: it is possible

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RATIONALE: Eosinophilic esophagitis, unlike non-IgE mediated food allergy is generally thought to be lifelong with poor prognosis that patients will experience complete resolution of disease.

METHODS: We conducted a retrospective review of 1,812 EoE patients. Inclusion criteria included: initial biopsies on proton pump inhibitor consistent with a diagnosis of eosinophilic esophagitis, if with removal of foods from the diet biopsies normalized and if at a subsequent date their biopsy results were normal on a full open diet unless an additional exclusion was required for IgE-mediated food allergy.

RESULTS: We observe that 8 patients (5 males, 3 females, 75% Caucasian) had outgrown all EoE-related food sensitivities. This comprises 0.44% of our total EoE cohort. In these patients, age of EoE diagnosis was 7.2 ± 3.2 years and age of resolution was 11.9 ± 3.2 years (mean ± st. dev). The duration of time from first diagnostic biopsy to complete food reintroduction was 1.5 to 9 years across this cohort. 7/8 of these patients were managed exclusively with dietary restrictions and during the majority of periods of dietary exclusion had zero eosinophils per high powered field in esophageal biopsies. Only one patient required brief periods of swallowed steroid therapy. These 8 patients were followed for an additional 3.25 ± 2.3 years with no recurrence of symptoms.

CONCLUSIONS: Although this series represents a small portion of eosinophilic esophagitis patients, the confirmation that even a small proportion of patients with food-triggered eosinophilic esophagitis develops tolerance over time is novel and raises new questions about the pathogenesis of this disease.

860 Peripheral blood eosinophil degranulation is inhibited in eosinophilic esophagitis: implications for non-invasive assessment of disease activity

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RATIONALE: Eosinophil peroxidase (EPX) is an eosinophil-specific granule protein responsible for mediating eosinophil effector functions. We have established that tissue EPX correlates with symptoms of eosinophilic esophagitis (EoE). We hypothesized that serum EPX would be elevated in EoE subjects and serve as a potential biomarker.

METHODS: Prospectively collected serum from 19 subjects with incident EoE prior to treatment and 20 non-EoE controls were tested for the eosinophil granule proteins EPX, eosinophil cationic protein (ECP) and eosinophil derived neurotoxin (EDN) using ELISA. Matching esophageal tissue sections were stained and assessed for EPX deposition using a histopathologic scoring algorithm.

RESULTS: Median absolute eosinophil counts (AEC) in the serum were significantly elevated in EoE subjects compared to controls (300 vs 100 cells/ul, p = 0.001). Absolute median serum EPX, ECP and EDN did not differ between groups; however, when normalized for AEC, EoE subjects had significantly lower EPX/AEC (2.56 vs 6.96, p = 0.002, AUC 0.79 (0.64, 0.94 95% CI)) and EDN/AEC ratios (0.07 vs 0.155, AUC 0.74 (0.59, 0.90 95% CI)). Differences in ECP/AEC ratios were not observed. Esophageal biopsies from EoE subjects demonstrated marked EPX deposition compared to controls (median EPX monoclonal antibody score 47 vs 0, p < 0.0001)

CONCLUSIONS: In contrast to increased tissue EPX levels, EoE subjects had significantly lower serum EPX when normalized for AEC. EDN/AEC ratios were also lower in EoE subjects. These findings suggest degranulation is inhibited until eosinophils reach the site of tissue infiltration. Investigation of EPX/AEC and EDN/AEC as peripheral markers of EoE activity should be conducted.

861 Prospective Incidences And The Relationship Between Allergic Proctocolitis And IgE-Mediated Food Allergies In Early Childhood

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RATIONALE: Both IgE and non-IgE mediated forms of food allergy are rising in the United States, but the relationship between rising is poorly described.

METHODS: The Gastrointestinal Microbiome and Allergic Proctocolitis study is a prospective observational cohort study enrolling 1,000 healthy newborn infants, designed to evaluate the development of Allergic Proctocolitis (AP) and IgE-mediated food allergy (FA) in their first 3 years.

RESULTS: Of the 280 infants who have reached 2 years of age, 44 children (16% cumulative incidence) were diagnosed with AP and 18 children (6%) were diagnosed with FA. Two (0.7%) children had both AP and FA. The rate of FA was no higher among those with AP (p=0.75). Milk was implicated in 42 (95%) of the AP cases, but only 1 (5.5%) FA case. Egg (72%), peanut (67%), and tree nuts (32%) were most common for FA. For both children with AP and FA, milk was the trigger for their AP, yet egg and peanut were the triggers for FA, and they tolerated milk at 1 year. Lack of breastfeeding at birth was a risk factor for AP (OR 2.8 [1.1, 7.0], p=0.038), but not FA (p=0.99). Mode of delivery, perinatal antibiotic exposure, and presence of siblings were not associated with either diagnosis.

CONCLUSIONS: The prospective incidences of AP and FA in this suburban US population are high. Yet there is little apparent association between the development of AP and subsequent development of IgE-mediated food allergy. Early breastfeeding is protective against AP, but not FA, highlighting potentially different disease mechanisms.
**862 Predictors of Milk Tolerance Following Baked Milk Challenge**

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**RATIONALE:** Introduction of baked milk (BM) is a mainstay in the management of cow’s milk allergy. We sought to characterize predictors of BM tolerance and progression to baked cheese and direct milk among patients undergoing BM oral food challenges (OFC).

**METHODS:** 126 patients challenged to BM from 2009-2011 were reviewed. OFC success was defined as consumption of ¼ cup BM. Logistic regression was performed utilizing milk-IgE level (log-transformed), age, gender, duration of follow-up, and OFC outcome to determine predictors of subsequent milk intake.

**RESULTS:** 99 patients (4 months-18 years) old were included. Median duration of follow-up was 51 months (range 1.9-85 months). 65% passed the BM OFC. Among those failing, 91% were permitted to introduce specified quantities of BM. Of those passing, 75% progressed to unlimited BM. Of those failing the BM challenge (p=0.004,0.046, and 0.234, respectively).

Milk-IgE was significantly associated with OFC outcome (OR 0.19, p<0.001) and progression to unlimited BM (OR 0.35, p=0.046) or baked cheese (OR 0.38, p=0.05) but not direct milk (OR 0.96, p=0.16). Patients with milk-IgE >10kU/L were less likely to tolerate unlimited BM (10% vs 54%, p=0.015), baked cheese (8% vs 45%, p=0.04), or direct milk (4% vs 29% p=0.06). Gender, duration of follow-up, and age were not significant predictors.

**CONCLUSIONS:** OFC outcome and milk-IgE were the most important predictors of persistent tolerance to BM or more concentrated forms of milk.

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**863 Children With Tolerance Of Baked Egg Demonstrate Higher Eliciting Doses In Challenges To Native Egg**

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**RATIONALE:** It is well recognized that some children with egg and milk allergy tolerate these foods in the heated or baked form. Our study defines differences in median eliciting dose for children undergoing native egg and milk oral food challenges (OFC) by previous tolerance and exposure to baked forms.

**METHODS:** A retrospective chart review of 569 patients, ages 1-18y, who underwent OFC to native egg and milk from 1/2012 through 12/2015. The Mann-Whitney test was used to compare median eliciting doses for each group. Demographics, OFC results (dose, reaction), skin prick test and specific IgE were collected.

**RESULTS:** For native egg, the median eliciting dose in children who previously reacted to baked egg (n=35) was 0.50g (0.13g-9.88g), compared to 3.50g (0.13g-15.80g) in children who tolerated baked egg (n=235) (p=0.0064) and 0.38g (0.13g-3.88g) in those with no exposure to baked egg (n=72)(p<0.0001). For native milk, median eliciting dose in those who had reacted to baked milk (n=40) was 2.32g (0.07g-8.50g), compared to 5.99g (0.15g-12.40g) in those with baked tolerance (n=105) (P=0.318), and 4.49g (0.44g-17.70g) in those with no exposure to the baked form (n=82) (P=0.574). History of no exposure or reaction to baked egg was associated with epinephrine use for 59% and 63% of OFC reactions respectively, but only 42% in those who tolerated baked egg.

**CONCLUSIONS:** Children who tolerate baked egg react at higher eliciting doses and require epinephrine less commonly when challenged

to native forms. There was no significant difference in eliciting dose to native milk based on baked milk exposure history.

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**864 Peanut, tree nuts and sesame seed allergies: Does a single nut allergy necessitate the dietary eviction of all nuts?**

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**RATIONALE:** Although there is a large cross-sensitivity by IgE testing among tree nuts and/or peanut, the clinical relevance remains unknown. In many allergy centres, allergy to either peanut or a tree-nut leads to recommendation for the avoidance of all nuts and often also sesame seed.

**METHODS:** Based on up to 11 sequential nut challenges in each patient, we aimed to identify which nut allergic patients should apply selective or complete dietary avoidance of all nuts. We included children aged from 0 to 16 years with a convincing history of IgE-mediated systemic allergic reaction to ≥1 nut within last 12 months and skin prick tests (SPT) ≥8 mm and/or IgE ≥15kU/L (26kU/L for sesame) or a positive oral food challenge to the nut.

**RESULTS:** Ninety-two children were prospectively recruited in Geneva and London. Fifty-six percent of patients were allergic to more than one nut. We confirmed the strong association between pistachio and cashew nut allergy (84%), as well as between pecan, hazelnut and/or walnut allergy (59%). SPT had a high negative predictive value for the different types of nuts. Regarding hazelnut and peanut, specific IgE to Cor a 14 and Ara h 2, respectively, were the better discriminating factors with larger ROC areas under the curve (84% and 95%, respectively).

**CONCLUSIONS:** Introduction of different nuts may decrease unnecessary dietary avoidance of peanut, tree-nuts and sesame seed. For most nuts, our data showed that SPT and/or specific IgE to recombinant allergens had a high diagnostic value to discriminate between allergic versus tolerant patients.
**865 The Utility of BAT in Diagnosing Treenut Allergy**

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**RATIONALE:** Patients with known allergy to a single tree-nut are often sensitized to other tree-nuts, requiring an oral food challenge (OFC) for definitive diagnosis. Since OFCs are time-consuming and not without risk, we evaluated the utility of the basophil activation test (BAT) to diagnose true clinical allergy.

**METHODS:** Patients with a history of reaction to tree nuts (walnut, hazelnut, cashew, pistachio, almond, and pecan) were evaluated. OFCs were performed to confirm clinical reactivity for all nuts except if they were being currently consumed or clinically contraindicated based on a recent severe reaction. Induced basophil CD63 expression was determined and evaluated against the patients’ clinical allergic status for each nut, respectively.

**RESULTS:** The allergic status of patients was determined (walnut: 23/30 [77%], hazelnut: 7/28 [25%], cashew: 12/28 [43%], pistachio: 6/27 [22%], pecan: 13/28 [46%]). No patients were found allergic to almond (0/29). The performance of BAT for allergy diagnosis was evaluated by Receiver operating characteristic (ROC) curve analysis, yielding an area under the curve (AUC) ± SE of 0.96 ± 0.035, 0.87 ± 0.067, 0.99 ± 0.014, 0.91 ± 0.059, 0.93 ± 0.060 for walnut, hazelnut, cashew, pistachio, and pecan, respectively. Using a critical test value of 5% CD63 induction, we obtained paired sensitivities and specificities of 96%, 86% (walnut); 86%, 76% (hazelnut); 83%, 100% (cashew); 100%, 86% (pistachio); 85%, 100% (pecan). False positive BAT (>5% CD63) were observed for 3/14 (21%) of patients with zero or one nut allergies, and 6/16 (38%) patients with multiple nut allergies.

**CONCLUSIONS:** Depending on the nut tested, BAT may obviate the need for OFC to diagnose or rule out treenut allergy.

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**866 Impact of Microwaving on the Protein Content and Microbial Levels of Whole Wheat Flour for Use in Oral Immunotherapy**

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**RATIONALE:** Food products used in Oral Immunotherapy studies conducted under INDs have to meet specific criteria for allergen content and bioburden. We studied the effect of microwaving on the protein content and bioburden of whole wheat flour proteins (Tri a 19 and Tri a 37).

**METHODS:** SDS-PAGE analysis coupled with densitometric scanning was conducted on whole wheat flour subjected to microwaving at 1000 Watts for increasing lengths of time (0 min, 1 min, 2 min, 4 min, 7 min and 10 min) to determine the effect of microwaving on protein content. Thermally processed and unprocessed whole wheat flour was tested for the presence of Escherichia coli, Salmonella, aerobic bacteria, mold and yeast levels.

**RESULTS:** Microwaving wheat flour for varying times resulted in <10% variance in the content of Tri a 19 and Tri a 37 proteins as revealed by SDS-PAGE and densitometry analysis. Bioburden testing revealed a significant decrease in aerobic plate count (>2500 cfu/g at 0 min to 470 cfu/g at 10 min), yeast (>2500 cfu/g at 0 min to <10 cfu/g at 10 min), mold (150 cfu/g at 0 min to <10 cfu/g at 10 min), Escherichia coli and Salmonella levels (Presumptive/10 g at 0 min to Negative/10 g at 10 min) with microwaving. Importantly, the levels of these microbes after 10 minutes of microwaving met criteria established by USDA for an orally delivered drug product.

**CONCLUSIONS:** Microwaving of whole wheat flour leads to a significant decrease of bioburden levels without significantly altering the protein content. Future studies will determine the effect of microwaving on the allergenicity of wheat proteins using Western blotting, ELISA and basophil activation testing.
867 **Inhibition of Vascular Endothelial Abl1 Signaling Protects Against Food-Induced Anaphylaxis in Mice.**

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**RATIONALE:** The underlying molecular pathways involved in fluid extravasation and cardiovascular collapse in severe food allergy (FA) are not yet fully elucidated.

**METHODS:** We employed BALB/c wild-type (WT), intestinal IL-9Tg and VE-specific Abl1 kinase–deficient (Cdh5Cre Abl1fl/fl) mice and pharmacologic inhibitors (Imatinib) and models of anaphylaxis to determine the requirement of Abl1 kinase in IgE-mediated reactions. Involvement of Abl1 kinase in histamine and IL-4-induced VE dysfunction were examined by electrophysiologic and permeability analyses on a human VE cell line (EA.hy926) following Abl1 kinase shRNA-lentiviral knockdown.

**RESULTS:** *In vitro* genetic ablation of Abl1 activity revealed that histamine induced barrier dysfunction of EA.hy926 cells was dependent on Abl1 (TER (Ωcm²): 90.2 ± 11.0 WT; 114.5 ± 11.8 shRNA-Abl1; p < 0.005). Imatinib pretreatment of ovalbumin (OVA)-sensitized and orally challenged mice protected the mice from anaphylaxis as the level of hypothermia (Temperature loss (°C): -3.1 ± 0.88 vehicle vs. -0.8 ± 0.4 imatinib; p < 0.001); hypovolemic shock (hematocrit %: 65.9 ± 9.6 vehicle; 52.21 ± 2.5 imatinib; p ≤ 0.01); and diarrhea (# mice with diarrhea: 8/8 vehicle vs. 3/8 imatinib; p ≤ 0.05). IgE-MC-activation in IL-9Tg VEΔAbl1 (TiecCre Abl1fl/fl) mice revealed that loss of VE-restricted Abl1 expression attenuated the development of anaphylactic symptoms (maximum temperature loss: -2.6 ± 0.76 °C; IL-9Tg VEWT -4.5 ± 1.64 °C VEΔAbl1; p ≤ 0.05).

**CONCLUSIONS:** These results indicate that the food allergen delivery through IL-13/CD38/cADPR-driven-GAPs plays a critical role in the onset of FIA suggesting that targeting cADPR as an effective therapy in prevention of a FIA reaction.

868 **IL-13-Induced Goblet Cell Antigen Passages (GAP’s) are Required for the Acute Onset of a Food-Induced Anaphylactic Reaction**

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**RATIONALE:** GAPs uptake and transport antigens apical to basolaterally within the small intestine (SI). How food allergens cross the SI epithelium and are delivered to the sub-epithelial immune compartment to initiate the onset of a food-induced anaphylactic (FIA) reaction remains largely unknown. Herein, we examined the food antigen uptake by GAPs and the contribution of this pathway to the onset of a FIA reaction.

**METHODS:** To examine the capability of GAPs to sample SI food antigens *in vivo* and *in vitro* we employed clinically relevant food antigens (MFA: peanut, cows milk and egg), pharmacological inhibitors of GAPs (Tropicamide and 8-bromo-cADPR) and human intestinal organoids derived from pluripotent stem cells and performed two photon (2P) microscopy. To define the requirement of GAPs during the induction of FIA, we examined the onset of FIA in mice following GAP-inhibition.

**RESULTS:** We demonstrate the apical-basolateral translocation of MFA can occur via SI GAPs. We show 1) that murine and human SI GAPs are mediated by cholinergic- and IL-13-induced signals, 2) that food allergic (FA) mice have increased SI GAPs; 3) that SI GAPs in FA mice were dependent on IL-13-induced signals and 4) blockade of IL-13-induced CD38/cADPR-pathway attenuated GAPs in FA mice and that this was associated with reduced food allergen transport, intestinal mast cell activation, and the FIA symptoms.

**CONCLUSIONS:** These results indicate that the food allergen delivery through IL-13/CD38/cADPR-driven-GAPs plays a critical role in the onset of FIA suggesting that targeting cADPR as an effective therapy in prevention of a FIA reaction.

869 **Periostin up-Regulates the Effector Functions of Eosinophils**

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**RATIONALE:** Periostin, an extracellular matrix protein, is up-regulated in asthmatic airways, mainly by T helper (Th) 2 cytokines. Periostin functions as a matricellular protein in cell activation by binding to cell surface receptors. However, the role of periostin in the development of eosinophilic airway inflammation has not been fully clarified. Here, we examined whether periostin could modify eosinophil functions such as superoxide anion (O_2^-) generation, degranulation, and production of cytokines/chemokines.

**METHODS:** Eosinophils were isolated from the blood of healthy volunteers or allergic subjects, and their adhesion to recombinant human periostin was measured using eosinophil peroxidase assays. Eosinophil O_2^- generation was examined based on the superoxide dismutase-inhibitable reduction of cytochrome C. Eosinophil-derived neurotoxin (EDN) concentrations in cell media were measured by ELISA as a marker of degranulation, and concentrations of cytokine/chemokines were also measured.

**RESULTS:** Periostin directly induces eosinophil adhesion, which was enhanced by IL-5. Periostin also activated other functions of eosinophils such as O_2^- generation and EDN release. Anti-αM or anti-β2 integrin monoclonal antibody suppressed the eosinophil adhesion, O_2^- generation, and EDN release induced by periostin. Finally, periostin increased the production of transforming growth factor (TGF-β)1, TGF-β2 and cysteinyl leukotrienes (cysLTs) from eosinophils.

**CONCLUSIONS:** These findings suggested that periostin up-regulates eosinophil functions through αMβ2 integrin. These effects may be involved in the activation of eosinophils and in the development of remodeling in the airway of Th2-dominant asthma, and could possibly aggravate the disease.
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High Microbiome Diversity and IgA Responses in Breast Milk of Old Order Mennonites with a Low Prevalence of Allergic Diseases

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RATIONALE: We have recently shown that the Old Order Mennonites (OOM) residing in Western NY, with farm lifestyle and exposure to unpasteurized milk, have a low prevalence of atopic diseases compared to U.S. population (NHANES). Higher levels of breast milk IgA have been associated with environmental factors related to microbial load and low incidence of atopic diseases. Presence of stable bacterial communities have recently been confirmed in breast milk, related to maternal and infant gut microbiome. We hypothesized that diversity of breast milk microbiome and specific IgA responses would be higher in breast milk from OOM than in Rochester mothers.

METHODS: In this pilot study, breast milk samples were collected from 40 OOM and 21 Rochester city/suburban mothers using a manual breast pump, when infants were 1-2 months old. Specific IgA to 8 fixed whole bacterial species was measured using ELISA. Bacterial DNA was extracted for microbiome analysis by 16S rRNA gene sequencing in 17 samples.

RESULTS: Comparison of Phylogenetic Diversity Whole Tree indices, a measure of alpha diversity, showed a significantly higher microbiome diversity in the milk of OOM than Rochester mothers (p < 0.008). Levels of IgA to Enterococcus faecalis (p = 0.0001), Lactobacillus reuteri (p = 0.0002), and Salmonella typhimurium (p = 0.058) were higher in OOM than in Rochester mothers.

CONCLUSIONS: Our data support the view that breast milk reflects maternal microbial pressure, and that greater microbial diversity is associated with a more robust mucosal immune response in a population with low prevalence of allergy. These breast milk factors may convey protection against atopic diseases amongst OOM children.

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KCNJ2 overexpression induces pro-inflammatory cytokine production, impaired barrier function and acantholysis in esophageal epithelial cells

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RATIONALE: Inward rectifying potassium channel KCNJ2 is upregulated in the epithelium of eosinophilic esophagitis (EoE) patients compared to healthy controls. However, whether KCNJ2 contributes to GI Th2 inflammation and epithelium barrier impairment in EoE is unknown.

METHODS: We employed the EPC2 human esophageal epithelial cell line to determine if KCNJ2 induces EoE-like changes. Chemokine and cytokine productions (at mRNA and protein levels) were examined in empty vector and KCNJ2 overexpressing EPC2 cells following exposure to IL-13, Poly I:C and allergen. Esophageal barrier function was tested by TEER-measuring air-liquid-interface (ALI) culture of EPC2 cells.

RESULTS: Following IL-13 stimulation, KCNJ2 overexpression increases CCL26 (eotaxin-3) production by 3.2 fold compared to empty vector (EV) controls (P < 0.05). Additionally, KCNJ2 overexpression increases the IL-13 induced barrier impairment by 45% compared to EV controls (P < 0.05). With a Poly I:C stimulation, KCNJ2 overexpressing EPC2 cells produce 15-fold more TSLP mRNA and 3.4-fold more protein compared to EV controls (P < 0.001). Likewise, KCNJ2 overexpressing cells produced increased mRNA for IL-8 (6-fold, P < 0.01), GM-CSF (14-fold, P < 0.01) and IFN-β (6-fold, P < 0.01). Finally, KCNJ2 overexpressing cells produced 23-fold higher CCL26 mRNA compared with unstimulated controls following exposure to Aspergillus fumigatus extract (50μg/mL, 24 hours) in contrast to 3-fold increase in EV controls. Moreover, allergen exposure induced acantholysis exclusively in KCNJ2 overexpressing cells.

CONCLUSIONS: KCNJ2 overexpression is sufficient to induce pro-EoE like changes in esophageal epithelial cells including pro-inflammatory cytokine production, impaired barrier function and acantholysis. As such, we propose that over-expression of KCNJ2 has a potential causative role in EoE.