**776** Comparison Efficacy and Safety of Inhaled Magnesium Sulfate to Intravenous Magnesium Sulfate in Childhood Severe Asthma Exacerbation

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**RATIONALE:** Intravenous MgSO4 commonly used in pregnancy-induced eclampsia, is one of the essential drugs for status asthmaticus. Recently, increasing evidence support the valuable of nebulized MgSO4 in adults with severe asthmatic attack. However, the benefit of inhaled MgSO4 in childhood severe acute asthma is controversy and limited.

**METHODS:** A prospective pilot study of MgSO4 treatment was conducted in children admitted with severe acute asthma at Queen Sirikit National Institute of Child Health. Twelve patients were randomized to receive three-intermittent MgSO4 inhaled or intravenously. The wood asthma severity score was measured at the beginning and at 20, 40, 60,120,180 and 240 minutes after the treatment. The primary and secondary outcomes were the asthma severity score at 60 minutes after the treatment and the hospital length of stay.

**RESULTS:** Twelve children (8 males, 4 females), with the mean age of 5.5+/−2.6 years, consented to participate in our study. Eight received nebulized isotonic MgSO4, 4 received intravenous MgSO4. Baseline asthma severity scores were 5.33+/−0.88. There were no statistically significant differences between two groups in asthma severity score at 60 minutes (2.62+/− 1.06 versus 2.54+/−1.29;p=0.92) and the length of stay (3.75+/−1.06 versus 3.25+/−1.5;p=0.53). We also reported no side effect among the two groups.

**CONCLUSIONS:** Our study demonstrated similar safety and clinical benefit of nebulized and intravenous MgSO4 among Thai children with status asthmaticus.

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**777** The Relationship Between Age, Weight and Asthma Severity in Children Admitted to the Hospital with Asthma

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**RATIONALE:** We hypothesized that childhood overweight and obesity impact the severity of asthma for children hospitalized with asthma. Understanding the relationship between age, weight and asthma severity could support inclusion of weight recognition and management in the care of children hospitalized with asthma.

**METHODS:** This study is a retrospective review of medical records of 510 children aged 3 to 17 admitted to a pediatric hospital in the Midwest with a primary diagnosis of asthma in 2012. Age and chronic severity were determined per NHLBI guidelines. Length of stay and intensive care admission were used as measures of severity of acute episode. CDC weight grouping was determined by Body Mass Index percentile. ANOVA, Chi-Square with Fisher’s Exact Test and post-hoc comparison z test with Bonferroni correction were used for analyses.

**RESULTS:** Age was found to differ statistically by weight group (p < 0.001). Healthy weight participants averaged 1.7 years younger than overweight participants (p = 0.008) and 2.3 years younger than obese participants (p < 0.001). When the relationship of chronic asthma severity and weight group was adjusted for age category, obese participants differed statistically from healthy weight participants in the 12-17 year old category (p = 0.033). Age adjusted comparisons of acute severity and weight group did not indicate any statistically significant associations.

**CONCLUSIONS:** Age differed statistically by weight group in children admitted with asthma. Weight and chronic asthma severity were related in older children. The results support the importance of weight recognition and management in the care of children with asthma.

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**778** Asthma Exacerbations and in-Hospital Mortality: Insights from the Nationwide Inpatient Sample

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**RATIONALE:** Asthma accounts for a large proportion of emergency department visits and subsequent hospitalization in the United States. The primary objective of our study was to evaluate the predictors of in-hospital mortality in asthma patients.

**METHODS:** We queried the Healthcare Cost and Utilization Project’s Nationwide Inpatient Sample (NIS) between 2001 and 2010 using the ICD9 procedure code of 493 for asthma (n=7,60,418, weighted n = 3,743,613). The NIS represents 20% of all hospitals in the US. Multivariate survey logistic regression analysis was used to evaluate predictors of in-hospital mortality.

**RESULTS:** The overall in-hospital mortality was 1% and as high as 9.8% in patients requiring mechanical ventilation/intubation. The in-hospital mortality increased from 2001 to 2006 and has been relatively stable since after a slight decrease. Multivariate predictors (OR, 95% CI, p-value) of higher in-hospital mortality included Asian race (1.50; 1.22-1.84, <0.001), increasing age (age ≥ 75 vs age 5-14: 33.65; 24.96-45.35, <0.001) and weekend admissions (1.12; 1.04-1.20, 0.002) as well as hospitalizations during winter months (1.13; 1.04-1.22, 0.003). Private insurance (0.72; 0.66-0.79, <0.001) and elective admissions (0.84; 0.73-0.96, 0.008) were predictive of lower in-hospital mortality.

**CONCLUSIONS:** Asthma continues to account for in-hospital mortality especially in mechanically ventilated patients. Further evaluation of in-hospital mortality predictors shown in our study might be valuable to improve outcomes in hospitalized asthma patients.

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**779** Asthma Exacerbations, Length of Stay and Hospitalization Costs: Insights from the Nationwide Inpatient Sample

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**RATIONALE:** The primary objective of our study was to evaluate the predictors of length of stay (LOS) and cost of hospitalization in asthma patients in United States.

**METHODS:** We queried the Nationwide Inpatient Sample (NIS) between 2001 and 2010 using the ICD9 procedure code 493 for asthma (n=7,60,418, weighted n = 3,743,613). The NIS represents 20% of all hospitals in the US. Multivariate survey linear regression analysis was used to evaluate predictors of LOS and hospitalization costs. Cost to charge ratio files were merged with NIS to calculate cost of care. Cost was adjusted for inflation in reference to 2010.

**RESULTS:** The overall LOS was 3.9 days and as high as 8.3 days in mechanical ventilated/intubated patients. The overall LOS has decreased in recent years though it continues to be higher than in 2001 while the hospitalization costs have steadily increased in the last decade. Multivariate predictors of higher LOS (Increase/Decrease in days; 95% CI, p-value) and hospitalization costs (Increase/Decrease in cost in $, 95% CI, p-value) included white race, increasing age (LOS: 2.56; 2.51-2.61, <0.001; Cost: $4661; 4545-4776, <0.001), and winter month hospitalizations (Cost: $189; 118-260, <0.001). Private insurance (LOS: -0.47; -0.50 - -0.45; <0.001; Cost: -$933; -997 - -868; <0.001) portended shorter LOS and lower costs while elective admissions (Cost: -575; -686 - -465; <0.001) posited lower hospitalization costs.

**CONCLUSIONS:** We reported multiple predictors of LOS and hospitalization costs in asthma patients. Further evaluation of these predictors might be needed to provide better and cost-effective care to asthma patients.
780 Positive Intradermal Mold Skin Testing Correlates with Past and Future Asthma Emergency Room Visits and Hospitalizations
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RATIONALE: Little is known about the effects of allergen testing modalities and outcomes in asthmatics. controversy exists regarding the utility of intradermal testing (IDT) in allergy practice.
METHODS: After informed consent and IRB approval, subjects recruited to the study between 2011 and 2014 underwent clinical evaluation, asthma assessment and allergen skin testing using Greer reagents. Skin testing was interpreted by a board certified allergy physician. IDT was performed if initial mold skin prick testing was negative and was interpreted as positive if 8 millimeters larger than the negative saline control. Past and future asthma emergency room visits, hospitalizations, intubations, and prednisone use was tracked.
RESULTS: IDT positivity to Alternaria alternata was associated with future 12 month room visits and intubations. IDT positivity to Cladosporium/Hormodendrum, Epicoccum nigrum, and Aspergillus fumigatus were associated with asthma hospitalization in the past 12 months. IDT positivity to Stenphylium solani was associated with emergency room visits and hospitalization in the past 12 months.
CONCLUSIONS: In this observational study, IDT positivity to molds, correlated with significant clinical outcomes. Further studies are necessary to confirm the utility of on asthma outcomes.

781 Multiple Hospitalizations for Childhood Asthma: Predictors and Risk Factors
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RATIONALE: Assess the risk factors for multiple hospitalizations for childhood asthma to prevent future admissions with more appropriate interventions.
METHODS: Data for 91 children with asthma, aged 1-18, was collected. We compared characteristics of children with <2 hospital admissions for asthma (Group A, N=54) with children who were hospitalized twice or more for asthma (Group B, N=37).
RESULTS: Group A: Male: Female ratio 70/30. Caucasian 95%, other race 5%. 59% had commercial insurance and 41% had public insurance. 32% had 4 or more ER visits. 24% had 4 or more courses of systemic corticosteroids. 45% had atopic dermatitis. 57% had allergic rhinitis. 24% had food allergies. 84% had family history of asthma. 31% were exposed to secondhand smoke. 45% had gastroesophageal reflux and 9% had enlarged adenoids.
Group B: Male: Female ratio 54/46. Caucasian 77%, other race 23%. 25% had commercial insurance and 75% had public insurance. 60% had 4 or more ER visits. 52% had 4 or more courses of systemic corticosteroids. 57% had atopic dermatitis. 49% had allergic rhinitis. 27% had food allergies. 94% had family history. 66% subjects with history of passive household cigarette smoke exposure. 50% had gastroesophageal reflux and 50% had enlarged adenoids.
CONCLUSIONS: These data suggest that secondhand smoke exposure, minority race, public insurance, systemic corticosteroid use and presence of atopic dermatitis may act as risk factors for multiple hospital admissions for childhood asthma. Early identification and interventions need to address or take these factors into account to reduce asthma morbidity.

782 Asthma and Asthma Exacerbation Exists in Infants (<1 year) and Can be Treated Effectively with Inhaled Corticosteroids
Benjamin Volovitz; Head of Asthma Clinic (ret.), Schneider Children’s Hospital, Tel-Aviv, Israel.
RATIONALE: The study provides prospective evidence that asthma exists in infants (<1 year of age) and can be effectively treated using inhaled corticosteroids.
METHODS: We evaluated 1500 children aged 0-5 years (31% <1 year) with asthma exacerbation who failed to be controlled by conventional drug therapy. The children were treated with inhaled corticosteroids using three protocols according to the severity of their exacerbation: inhalers, inhalation, or inhalation + azithromycin.
RESULTS: The sex ratio, asthma in the family, emergency department visits, hospitalization, duration of asthma symptoms, and usage of beta-agonists or oral corticosteroids were similar in infants and older children. All treated children had a history of prolonged cough and were coughing during their first visit, but only 45% had also wheezing. During the follow-up period there was, for the entire cohort, a 99% reduction in the number of emergency department visits, 93% fewer hospitalizations, and 100% reduction in oral corticosteroid usage. The vast majority of treated children (88%) showed good response to treatment, with similar responses in infants and in older children. No significant differences were found between children with prolonged cough, with or without wheezing.
CONCLUSIONS: The data presented indicates that asthma exists also in infants. Asthmatic infants with or without wheezing, have a similar history, signs and symptoms as older children do, and respond well, similarly to treatment with inhaled corticosteroids.

783 Comparisons of Etiology and Clinical Feature of Wheezing Bronchitis Among Lower Respiratory Tract Infections in Hospitalized Young Children in Southern Taiwan
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RATIONALE: Lower respiratory tract infections (LRTIs) play an important role in pediatric diseases and cause acute wheezing episodes in young children. This study aimed to investigate the clinical and etiology data of wheezing bronchitis in southern Taiwan.
METHODS: Children aged under five years who were hospitalized at a medical center in southern Taiwan with acute LRTIs without recurrent wheezing episodes or asthma from July 2010 to May 2011 were prospectively enrolled. Nasopharyngeal aspirates were obtained and sent for viral cultures, multiplex polymerase chain reactions (PCR) and traditional quick tests. The clinical features, laboratory data and imaging findings were recorded and analyzed.
RESULTS: A total of 90 children were enrolled, 70 of whom had detectable pathogens. Adenovirus and enterovirus were the most common viral etiologies identified (26.5%, respectively) and Streptococcus pneumoniae was the leading bacterial etiology (46.4%). Of 22 patients of wheezing, 19 (86.4%) were associated with identifiable viral infections. Respiratory syncytial virus (RSV) (45%) infections and Influenza A virus (43%) infections show high rate for wheezing. Human metapneumovirus and adenovirus show 25% vs 17% respectively. There were no differences in otitis media, peripheral eosinophile count, and severity of disease or hospital stay among wheezing bronchitis. A similar result was found between non-pneumococcal and pneumococcal infections.
CONCLUSIONS: Viral infections were the main etiologies of LRTIs associated wheezing episodes in young children. Mixed infections do not seem to affect the severity of disease or wheezing episodes. RSV and Influenza A virus show leading etiology for wheezing bronchitis.
784 Observing Medical Insurance Claims Data in a High Risk Asthma Population and Targeting Behavioral Patterns to Improve Controller Medication Compliance and Reduce Emergency Department Visits

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RATIONALE: We hypothesize that patients are more likely to refill a controller medication following an outpatient office visit or hospitalization.

METHODS: Tenncare claims data was analyzed in a high risk asthma population from 2011-2013. An observational study was performed involving 354 patients ages 2-18. Number of controller medication refills in association with outpatient office visits was compared to the number of controller medication refills without clinical outpatient encounters.

RESULTS: Patients were more likely to refill controller medication following an outpatient visit or hospitalization than emergency department visit. Patients who had more frequent asthma outpatient visits were found to have less emergency room visits on average.

CONCLUSIONS: This data suggests that in a high risk asthma population, increasing the number of asthma clinic visits improves compliance of controller medication and decreases emergency room visits.

785 Relationship of S100A9 (S100 Calcium binding Protein A9) with Neutrophilic Inflammation in Murine Asthma Model

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RATIONALE: We previously published elevation of S100A9 protein in sputum of neutrophilic severe uncontrolled asthmatics compared with stable asthmatics. [Annals of allergy, asthma, immunology on 2013 Oct;111(4):268-275] suggesting possible role of S100A9 in neutrophilic severe asthma. The aim of this study was to validate the temporal relationship of S100A9 with neutrophilic airway inflammation and inflammasome activation in CFA/OVA-sensitized/challenged murine asthma model.

METHODS: Expression of S100A9, S100A8 mRNA and protein levels and activated caspase-1 were measured using a RT-PCR, Real-time PCR and western blot. Spatial expression of S100A9 protein was visualized by Immunohistochemical stain and Immunofluorescence stain. To evaluate the potency of S100A9 on neutrophilic inflammation and activation of inflammasome, temporinal changes of neutrophil infiltration and activation of caspase-1 were analyzed in lung tissues of the CFA/OVA model and in those of C57BL/6 mice after intratracheal S100A9 protein.

RESULTS: S100A9 and P20 - activated caspase-1 concomitantly started to increase from day 14 and peaked at day 23 while the number of total cells, macrophage and neutrophils significantly increased with concomitant increase of Penh at day 23. Neutrophil elastase and S100A9 were co-localized in peri-bronchially infiltrating cells and apical portion of bronchial epithelium. Intratracheal instillation of S100A9 (10µg) induced rapid increase of neutrophils in BAL fluid from 2 hr, peaked at 8 hr, then progressively decreased till 80 hr with concomitant activation of caspase-1.

CONCLUSIONS: S100A9 protein and activated caspase-1 begin to express earlier than the appearance of neutrophilics in the airway of neutrophilic inflammation model and S100A9 directly activate inflamma-some in the airway.

786 The Contribution of Peptide-MHC Affinity to the Efficacy of Peptide Immunotherapy in a Murine Model of Allergic Airways Disease

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RATIONALE: In order to be effective at the population level, peptide immunotherapy (PIT) preparations commonly contain several allergen-derived peptides; chosen by their ability to promiscuously bind several Major Histocompatibility Complex (MHC) molecules. Since promiscuous peptides may bind with differing affinity to individual MHC molecules, we sought to understand whether peptide-MHC affinity controls the degree of tolerance elicited, in a humanized murine model of allergic airways disease.

METHODS: Female HLA-DR4 transgenic mice (Tacicoms Farms;6wks, n=5/group, two independent experiments) were sensitized to cat allergens via intraportional injections of Fel d 1 in alum and subsequent intranasal instillations of cat dander extract (CDE). Mice were treated with one of seven peptides, intradermally. Treatment peptides varied in affinity and were assessed individually at several concentrations (ranging from 0.01 to 100 µg). Control mice received sham treatment, or an irrelevant peptide (HAA306-318). Following therapy mice were challenged intranasally with CDE and 48-hours later airway inflammation and responsiveness were assessed by histology and a methacholine challenge, respectively.

RESULTS: Low dose (≥1µg) treatment with high affinity peptides significantly ameliorated airway hyperresponsiveness (AHR), and eosinophilic infiltration (p < 0.05, one-way ANOVA & t-test). Moderate affinity peptides required higher dosing (≥2µg) to suppress eosinophilic accumulation, and were unable to consistently suppress AHR. Sham, irrelevant and low affinity peptide treated mice were not protected from eosinophilia or AHR.

CONCLUSIONS: Both high affinity and moderate affinity peptides elicited antigen-specific tolerance, but at different doses. Clinical response to peptide immunotherapy may vary between individuals as a function of both MHC haplotype and peptide dose.
787 Daily Low-Dose Aspirin Use Leads to a Delay in Diagnosis of Aspirin Exacerbated Respiratory Disease
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RATIONALE: Studies have shown higher rates of depression in asthmatics; however, little is known about the relationship of depression to asthma symptoms and diagnosis, especially in adolescents.

METHODS: Asthma symptoms and depression were assessed as part of Puff City, a randomized controlled trial of a web-based asthma intervention in four rural Georgia high schools. The Lung Health Survey (LHS) was used to classify students as having current diagnosed or undiagnosed asthma. Depression screening was performed in students using the Diagnosis Interview Schedule for Children (DISC) and in parents using Patient Health Questionnaire-9 (PHQ-9). Logistic regression was used to examine the association of various correlates with adolescent depression, including age, gender, race, asthma type (diagnosed or undiagnosed), and parental depression.

RESULTS: Among 2523 adolescents, the prevalence of asthma (n=456, 18.1% diagnosed; n=185, 7.3% undiagnosed) was similar to urban settings. Those with undiagnosed asthma were more likely female (n=106, 73.6%, p<0.001). The overall rate of depression (26.2%) was significantly higher than both national averages and studies specific to adolescents with asthma. Depressed students were more likely to be female (OR=2.50, 95% CI 1.43-4.35) and have undiagnosed asthma (OR=2.56, 95% CI 1.56-4.34). Student age, race, nor parental depression correlated with depression.

CONCLUSIONS: In this rural population, those with undiagnosed asthma and females were at higher risk for depression. Undiagnosed asthma was a more frequent problem than previously reported and females appear to be at highest risk. These findings underscore the need to recognize depression as a barrier to proper diagnosis and asthma self-management.

788 Comparative Serum Hyaluronan Levels in Patients with Aspirin-Exacerbated Respiratory Disease, Asthma, and Healthy Controls
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RATIONALE: Asthma is a chronic inflammatory disease with known clinical and pathological heterogeneity. Aspirin-Exacerbated Respiratory Disease (AERD) represents a subset of asthmatics, often with more difficult to control asthma and concomitant sinus disease. Hyaluronan (HA) is a glycosaminoglycan component of the extracellular matrix that is thought to play a role in inflammation, airway remodeling, and is increased in the asthmatic airways. We hypothesized that the subgroup of patients with AERD would have the highest levels of serum HA compared to non-AERD asthmatics and controls.

METHODS: Adult subjects were recruited in a prospective cohort study in Poland. Serum samples were collected and an HA Elisa-Like analysis was performed. Single tail ANOVA was used for analysis.

RESULTS: A total of 60 samples were included in the study; 23 AERD, 25 with asthma, and 12 controls. The mean age of subjects was 50.5 and 68% were female. Mean HA levels among groups were as follows: 333.30 ng/dL in subjects with AERD, 306.75 ng/dL in subjects with asthma, and 282.35 ng/dL in controls. HA levels were slightly higher in AERD subjects when compared to patients with asthma or controls. However, there was no statistically significant difference when mean HA levels were compared between groups (p = 0.89).

CONCLUSIONS: Though there was no statistically significant difference in HA levels with this small pilot study the trend of higher serum HA levels in patients with AERD deserves further study. Additional samples and correlation of HA with other parameters will be performed in an ongoing analysis.

789 Risk Factors for Depression in Rural Adolescents with Asthma
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RATIONALE: Studies have shown higher rates of depression in asthmatics; however, little is known about the relationship of depression to asthma symptoms and diagnosis, especially in adolescents.

METHODS: Asthma symptoms and depression were assessed as part of Puff City, a randomized controlled trial of a web-based asthma intervention in four rural Georgia high schools. The Lung Health Survey (LHS) was used to classify students as having current diagnosed or undiagnosed asthma. Depression screening was performed in students using the Diagnosis Interview Schedule for Children (DISC) and in parents using Patient Health Questionnaire-9 (PHQ-9). Logistic regression was used to examine the association of various correlates with adolescent depression, including age, gender, race, asthma type (diagnosed or undiagnosed), and parental depression.

RESULTS: Among 2523 adolescents, the prevalence of asthma (n=456, 18.1% diagnosed; n=185, 7.3% undiagnosed) was similar to urban settings. Those with undiagnosed asthma were more likely female (n=106, 73.6%, p<0.001). The overall rate of depression (26.2%) was significantly higher than both national averages and studies specific to adolescents with asthma. Depressed students were more likely to be female (OR=2.50, 95% CI 1.43-4.35) and have undiagnosed asthma (OR=2.56, 95% CI 1.56-4.34). Student age, race, nor parental depression correlated with depression.

CONCLUSIONS: In this rural population, those with undiagnosed asthma and females were at higher risk for depression. Undiagnosed asthma was a more frequent problem than previously reported and females appear to be at highest risk. These findings underscore the need to recognize depression as a barrier to proper diagnosis and asthma self-management.
790 Component-Resolved Diagnostic: Study of Dermatophagoides Pteronyssinus Major Allergen Molecules in a Southern Chinese Cohort
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Rationale: Data on component-resolved diagnosis for allergy to Dermatophagoides pteronyssinus(Der) are available in many western countries. Little is known about this in Chinese population. We presented a study on sensitization to Der p allergen components among patients in southern China.
Methods: 200 Der p-positive and 20 Der p-negative subjects were tested for serum sIgEs against Der p1, Derp2 and Der p10 by using ImmunoCAP 100. 75 poly-sensitized patients were further examined with ImmunoCAP ISAC. Der p10-positive subjects were additionally tested for sIgE to crude extracts of cockroach, moth, and shrimp.
Results: 183 (91.5%) patients were sensitized to Der p1 and/or Der p2. The positive rate and level of sIgE to Der p1 was higher in children than in adults. Der p1 and Der p2 correlated with Der p in sIgE levels. ImmunoCAP ISAC yielded 100% specificity and 84% sensitivity in detecting Der p1. Der p2 and Der p10 compared to ImmunoCAP 100. We found a good correlation between results of the two methods. Sensitization to Der p10 correlated well with sIgE to shrimp, moth cockroach, Pen m 1, Bla g 7, and Ani s3.
Conclusions: Detection of Der p1 and Der p2 well reflect atopy to Der p in a Chinese cohort. Sensitization to Der p10 may result from cross-reactivity to seafood and cockroach in coastal southern China. ImmunoCAP ISAC may offer a useful tool of CRD With comparable performance of ImmunoCAP 100.

791 Use of Wheeze Monitor Device in the Ambulatory Setting
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Rationale: Objective ambulatory measurement of airway obstruction from asthma with peak flow meters are effort-dependent and require coordination. A novel device that measures wheezing by placing sensor over the trachea for 30 seconds is now available (SonoSentrytm, iSonea Ltd.).
Methods: We used the SonoSentrytm to monitor four patients. Patient 1 had chest tightness mainly in his workplace. Patient 2 reported shortness of breath in certain restaurants with negative food skin test. Patient 3 reported chest tightness in the house with a cat but had negative cat skin test. Patient 4 reported recurrent dyspnea with no suspected triggers. All the patients used the SonoSentry twice daily and whenever they had chest symptoms over 4 weeks. Peak flow rate and symptom scores were measured concurrently.
Results: Patient 1 had a significant increase in wheeze only at work. Patient 2 had no wheezing detected despite reported symptoms. Patient 3 showed significant wheeze when at the house with a cat. Patient 4 had significant wheeze with mold exposure. All wheeze measurements correlated well with peak flow rate measurements. Symptom scores correlated well with wheeze measurements in 3 of 4 patients.
Conclusions: These preliminary results indicate that the wheeze monitor is a potential alternative or additive to the peak flow meter for objective measurement of airway obstruction in the ambulatory setting. It is convenient, pocket-size and not dependent on patient effort. Aside from providing physicians with information on a patient’s asthma status, it can clarify suspected allergic triggers, medication effectiveness and occupational asthma.

792 Validity of Asthma Diagnosis in Residency Primary Care Clinics
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Rationale: We noticed that many patients in our internal medicine residency primary care clinics are labeled with a diagnosis of asthma only by history without meeting ATS (American Thoracic Society) criteria for asthma or even having pulmonary function tests (PFTs) done. Our objective was to find out how many patients labeled with a diagnosis of asthma in our internal medicine residency primary care clinics met ATS criteria for asthma.
Methods: We performed a chart review of 117 patients seen in residency primary care clinics at LAC-USC Medical Center from July 2012-June 2013 who were labeled as having asthma to see how many of them actually had PFTs done and how many of those met criteria for the diagnosis of asthma.
Results: Of the 117 patients studied, only 26% (31/117) of the patients had even had PFTs done and of those only 16% (5/31) had PFTs consistent with asthma. Therefore out of the total 117 patients, only 4% (5/117) met ATS criteria for the diagnosis of asthma. Alternative diagnoses noted on PFTs included COPD, Restrictive Lung Disease, obesity related disorders, and overlap syndromes.
Conclusions: Our results showed that 96% of patients labeled with a diagnosis of asthma in our primary care clinic did not meet ATS criteria for asthma. Correctly diagnosing asthma ensures appropriate treatment for patients and decreases morbidity and mortality related to the disease. We plan to perform a quality improvement project to improve understanding regarding diagnosis and management of asthma among residents and increase the number of PFTs performed to correctly diagnose asthma in our patients.

793 Parental Willingness to Participate in Infant Primary Asthma Prevention Trial
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Rationale: Asthma primary prevention trials will target vulnerable populations, such as infants. We studied a diverse group of parents to assess willingness and views about participation in prevention trials to better understand parental perspectives and improve trial design.
Methods: We approached 537 parents in six mid-Tennessee pediatric practices to take a survey regarding a hypothetical blinded randomized controlled trial of RSV immunoprophylaxis during infancy for prevention of childhood asthma. Questionnaires addressed willingness to participate in different hypothetical study designs, reasons for/against enrollment, and demographic characteristics.
Results: Survey participation was 95% (511); 85% were female, 66% identified as Caucasian, and 22% as African American; 23% had self-reported asthma, and 22% had a child with asthma. While 354 (69%) indicated they were willing to participate in the trial, 157 (31%) stated they were not/did not know. Willingness increased when randomization was 2:1 v. 1:1 (62% v. 50%, p < 0.01) and if parents had a child with asthma (26% with v. 14% without, p = 0.027). Most common reasons for participation were asthma prevention (45%), and contributing to the greater good (42%). Concern for safety/risks/reactions was the most common reason for not participating (41%).
Conclusions: Demographic characteristics and trial design were factors differentiating those who were willing/unwilling to allow infant participation in a hypothetical asthma primary prevention trial. Parents’ perspectives can aid in trial design and recruitment to ensure representation of diverse populations.
794 Healthy, Non-Allergic Subjects Do Not Develop Allergic Symptoms When Co-Mingled with Symptomatic Allergic Subjects and Exposed to Airborne Allergen in an Environmental Exposure Chamber (EEC)

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RATIONALE: EEC’s are facilities that provide a predictable level of airborne allergen exposure. These studies challenge allergen-sensitive subjects to a specific concentration of allergen in a closed setting. There is concern regarding some healthy non-allergic subjects (HNS) being influenced by symptoms present in allergic subjects (AS) whilst inside the EEC. (Herd influence).

METHODS: We conducted a study with 15 subjects allergic to ragweed (AS), and 5 HNS. The study was approved by an IRB. AS were confirmed with medical screening and positive skin testing and IgE concentration, absence of allergy confirmed HNS population with skin testing and IgE. All subjects attended the EEC at the same time for 4 hours over 2 consecutive days and recorded their allergic rhinitis symptom scores (ARSS) via electronic patient data acquisition tablets (ePDAT).

RESULTS: The results showed that there was a significant difference in the average symptom scores between AS and HNS (p<0.05). The HNS reported little to no ARSS, whereas the AS developed significant ARSS.

CONCLUSIONS: This study shows that there is no significant influence on symptom generation in HNS related to symptomatic AS in the EEC. The reason for this is likely related to the design of the EEC, the way our ePDAT works and the management of subjects in the EEC at Inflamx. This confirms the validity of our EEC model in causing symptoms in subjects who have a propensity to develop allergic symptoms related to their allergic diathesis compared to HNS.

795 Response to Ragweed Allergen Provocation in the Red Maple Trials Allergen Challenge Theatre

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RATIONALE: Allergen challenge chambers expose allergen-sensitive subjects to predetermined concentrations of allergen in a controlled environment and provide a mechanism to induce clinical symptoms and measure the effect of medication.

METHODS: We evaluated the response of ragweed-allergic subjects to two ragweed challenges in the Red Maple Trials Allergen Challenge Theatre. A provincial Ethics Board approved the study. After signing informed consent, patients with a history of ragweed allergy, not on allergy medications and with positive skin prick tests (>3 mm) were exposed to ragweed pollen in a 3-hour priming session. Total nasal (TNSS), ocular and rhinoconjunctivitis symptom scores (TRSS) were recorded at baseline and every 30 minutes during the challenge. Those with peak TNSS ≥5 were then selected for two further 4-hour challenges.

RESULTS: 48/76 subjects evaluated underwent the priming challenge. Thirty-three subjects achieving a peak TNSS ≥5 underwent two subsequent 4-hour challenges. Baseline TNSS (mean± SD) was 1.70 ±1.34 and 2.53±1.76 in challenges 1 and 2, respectively. Baseline TRSS values were 2.00 ± 1.66 and 3.60±2.60 respectively. Symptom scores reached a plateau by 120 minutes and remained steady for the remainder of the 240-minute exposure. Plateau TNSS was 6.25±0.20 for Challenge 1 and 6.19±0.24 for Challenge 2. Similarly, plateau TRSS values were 9.10±0.20 and 9.11±: 0.33, respectively.

CONCLUSIONS: The Red Maple Trials allergen challenge theatre demonstrated the capacity to induce symptoms of appropriate intensity upon ragweed allergen challenge. The chamber with a 100-person capacity has the ability to evaluate large test groups at one time.

796 Risk Factors for Recurrent Wheezing – International Study of Wheezing in Infants (EISL) Phase 3

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RATIONALE: We aimed to identify factors associated with recurrent wheezing (RW) in infants in the first year of life living in the Southern region of São Paulo city and participating in the “Estudio Internacional de Sibilancias en Lactantes (EISL)” – phase 3 (P3).

METHODS: Parents of infants who were attended in primary care health units in the Southern region of São Paulo city from 2009 to 2010 answered the EISL-P3 written questionnaire. The wheezing group was stratified in accordance to the frequency of wheezing episodes as occasional wheezing (OW, less than three episodes), or RW (three or more episodes). Wheezing-associated factors were evaluated using multivariate analysis and were expressed as odds ratio (OR) and 95% confidence interval (95%CI).

RESULTS: The most relevant factors related to OW were pneumonia (OR=3.10, 95%CI=1.68-5.73), hospitalization due to pneumonia (OR=2.88, 95%CI=1.26-6.56) and recurrent upper respiratory infection (URI, OR=1.87, 95%CI=1.25-2.81). Regarding RW, recurrent URI (OR=5.34, 95%CI=3.83-7.45), pneumonia (OR=4.06, 95%CI=2.87-5.74) and asthmatic siblings (OR=3.02, 95%CI=1.67-5.45) were the most significantly associated factors.

CONCLUSIONS: In the present study, we found that recurrent URI positive history of pneumonia and familiar history of asthma were the most relevant factors associated with RW. The precocious knowledge of these factors can enable the identification of the probable asthmatic infants and can improve both prevention strategies and treatment of these patients.

797 Field Performance of a New Technology with the Potential to Identify Allergy and Asthma Triggers

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RATIONALE: The Compact Ionic Capture Device (cICD) is a consumer friendly device that collects aerosol particles for testing. The aim is to evaluate its performance for a range of analytes and field conditions.

METHODS: Sites were a clean bathroom, a basement with sump drain, and a hay storage room in an equestrian facility. The cICD was run for up to 24 hours at approximately 100 lpm. Reference was 0.2µm polycarbonate filters pumped at 15 lpm. Analytical procedures were MARIA® 9-plex immunoassays for allergens (Indoor Biotechnologies), multiplex qPCR for 23 indoor molds (EMLABs&P&K), and next generation (Illumina) sequencing with Procrustes analysis for V region of bacterial 16S rRNA.

RESULTS: Despite the presence of a unique spectrum of analytes in each environment, there was concordance between cICD and filter for presence or absence of 7 allergens and 21 mold species across all environments. In several instances, significant levels of allergens or spore equivalents were found by the cICD and not by filters. The cICD and filters both showed concordant bacterial community compositions dominated by Actinobacteria, Cyanobacteria, Proteobacteria, and Bacteroidetes. The cICD’s high flow rate permitted faster detection of analytes than the filter.

CONCLUSIONS: There was remarkable consistency between the performance of the cICD and filters over a wide range of environmental types and airborne analytes. Therefore, the cICD may be used to measure and discover new aeroallergens. In clinical practice, it may easily and reliably confirm suspected allergen exposure, direct avoidance recommendations and assist individualization of therapy for allergic patients.
Objective Phenotypes in Gulf War Illness with Chronic Fatigue Syndrome

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RATIONALE: Gulf War Illness (GWI), Chronic Fatigue Syndrome (CFS), fibromyalgia (FM), and allied disorders share subjective complaints such as pain and fatigue. Proposed causes include sarin exposure (GWI), TH2 cytokine deviation and virus infections (CFS), central sensitization of nociceptive pathways (FM), and psychiatric dysfunction. Mechanistically-based objective markers are required to assess these illnesses.

METHODS: Ten Control and 28 GWI subjects who met GWI (Fukuda, 1998) plus CFS (Fukuda, 1994) criteria had submaximal exercise stress tests on DAY 1 and DAY 2. Blood oxygenation level dependent (BOLD) brain imaging during N-back working memory tests were performed before and after stress testing. Two GWI subgroups were identified by exercise-induced autonomic dysfunction. START (Stress Test Activated Reversible Tachycardia; n=10) developed postural tachycardia after exercise that lasted 36 hr, brain stem atrophy, and activation of the cerebellar vermis for cognitive compensation (Rayhan, 2013). STOPP (Stress Test Originated Phantom Pain; n=18) had basal ganglia and insula activation for cognitive compensation. BOLD signals were further analyzed by 2-level general linear modeling and functional connectivity analysis to discriminate between START and STOPP.

RESULTS: BOLD on DAY 2 during the high cognitive load test revealed activated dorsal anterior cingulate cortex (dACC) and left premotor cortex in Controls. STOPP activated dACC, right caudate head, and left superior parietal lobe. START had no regions of significant activation.

CONCLUSIONS: This testing paradigm revealed two objectively defined GWI phenotypes. Studies in progress may reveal distinct phenotypes in CFS, FM, and other functional disorders commonly encountered by allergists in practice.

Positive Oral Peanut Challenge Following Negative Percutaneous Skin Testing, Serum Whole Peanut IgE and Component Testing in Previously Documented Peanut Allergic Child

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RATIONALE: Peanut component testing, particularly Ara h 2, has been shown to increase the accuracy of peanut allergy diagnosis.

METHODS: Peanut IgE and component testing to Ara h 1-3, 8 and 9 were performed by Quest Diagnostics® with subsequent oral food challenge.

RESULTS: A 4-year-old atopic male was diagnosed with peanut allergy at 18 months old based on history of hives, swelling, coughing and choking following ingestion of peanut butter along with a 4+ response to percutaneous peanut skin testing. Serology was not initially performed. Peanuts and tree nuts were subsequently avoided without accidental ingestion. In early 2014, the patient was found to have negative percutaneous skin testing and negative serology to both whole peanut IgE (0.35 kU/L) as well as component testing (Ara h 1-3, 8 &9 by Queen’s University Ethics Committee, in Kingston, Ontario.

RESULTS: Ninety nine patients met the inclusion criteria. Study results showed that 42.4 % of peanut allergic patients were sensitive to birch pollen. Birch pollen sensitive patients experienced the initial reaction to peanut later by 10.5 months (p=0.01). Birch pollen sensitivity was not associated with a higher severity symptomatic score (p=0.22), larger peanut ST size (p=0.63), or higher peanut specific IgE level (p=0.76). Systemic anaphylaxis was more frequent in patients lacking birch pollen sensitivity. Amongst patients who had repeated assessments for peanut allergy, positive skin testing to birch did not predict the direction of change in ST size or RAST level at subsequent visits.

CONCLUSIONS: Peanut allergy demonstrated distinct features in patients with coexistent birch pollen sensitivity in this region, suggesting possible link between both conditions. Further studies are needed to confirm these results.
A Sensitive Immunoassay for Invertebrate Tropomyosin Allergens in Foods, Inhabitants, Ticks and Worms

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RATIONALE: Tropomyosin is a heat stable, major allergen of shellfish and other crustacea. Dust mite and cockroach tropomyosins are also allergenic. Cross-reactivity between tropomyosins may cause allergic symptoms related to allergen exposure. Our aim was to develop a sensitive ELISA that could be used to measure tropomyosin for both exposure and sensitization to both allergens frequently occurs. The aim of this study was to evaluate crop of skin prick test (SPT), specific IgE (sIgE) to shrimp and rPen a 1 in the diagnosis of shrimp allergy in area with high prevalence of HDN sensitization.

METHODS: Fifty-one participants with sensitization to both shrimp and Dermatophagoides pteronyssinus (Der p) were enrolled. Clinical reactions to shrimp were determined. SfGE to Der p, shrimp and rPen a 1 were analyzed.

RESULTS: Patients were divided into 2 groups; shrimp allergy (n=22) and shrimp tolerance (n=29). About half (54%) of shrimp allergic patients had anaphylaxis while 30% had only oral allergy syndrome. Compared to shrimp tolerant subjects, shrimp allergic subjects had a significant larger SPT with size (mm). Cross-reactivity between tropomyosins may cause allergic symptoms related to allergen exposure. Our aim was to develop a sensitive ELISA that could be used to measure tropomyosin for both exposure and allergen standardization.

METHODS: A two-site ELISA was developed using a monoclonal antibody raised against dust mite tropomyosin, with polyclonal anti-shrimp tropomyosin for detection. The assay was calibrated using purified natural shrimp tropomyosin, with protein content determined by amino acid analysis.

RESULTS: The ELISA standard curve ranged from 0.1-50 ng/ml, with a limit of quantification of 0.2 ng/ml. The assay readily detected tropomyosin in allergen extracts from shellfish (shrimp, crab, clam, lobster, crawfish, oyster, n=16) 0.1-297 µg/ml and dust mite species (n=4, 2-72 µg/ml), as well as tick and yellow mealworm extracts. Extracts of fish, mammals and birds did not react in the assay (<0.002 µg/ml).

CONCLUSIONS: A sensitive ELISA with defined specificity for invertebrate tropomyosins has been developed. This assay will allow standardization of tropomyosin levels in diagnostic or therapeutic allergen extracts, as well as providing a method for monitoring tropomyosin exposure in the environment and as a potential source of shellfish contamination in the food industry.
Trends in Soy IgE Levels in Food Allergic Patients
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RATIONALE: Soy allergy is one of the most common food allergies, affecting approximately 0.4% of children. We examined trends in soy serum IgE (sIgE) levels over time.

METHODS: This was a retrospective chart review of all patients at our teaching institution who had soy sIgE drawn on 2 or more occasions and had a diagnosis code of 693.1 (food allergy), or 995 (anaphylaxis), between January 1, 2003, and January 1, 2013.

RESULTS: 315 patients had 2 or more soy sIgE levels performed (median sIgE 7.46 kUA/L, median age 5.9 years). Those with starting values of >5 kUA/L showed greater variability in their levels on subsequent visits (median change -1.04, mean -0.17, range -63.9 to 77.1), than those with starting values of <5 kUA/L (median change 0, mean 0.85, range -28.4 to 32.84). When initial soy sIgE was determined before age 3 years (147 patients), levels tended to rise over the course of 1 year (median sIgE change 0 kUA/L, mean change 4.5 kUA/L, median interval between visits 1 year), whereas levels determined after age 3 years (168 patients) tended to decrease (median sIgE change -0.25, mean change -1.51, median interval between visits 1.2 years).

CONCLUSIONS: Patients with initial soy sIgE >5 kUA/L show greater variability in levels on subsequent visits than those with levels <5 kUA/L. When initial soy sIgE was performed under age 3, subsequent levels tended to increase. When levels were performed above age 3, levels tended to decrease on subsequent visits.

Trends in Repeat Cows Milk Sige Levels
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RATIONALE: Cows milk (CM) allergy is the most common food allergy in children. Approximately 50% of children will outgrow the allergy by age 5 years, with a low initial CM serum IgE (sIgE) being positively correlated with resolution. However, the optimal interval for repeating CM sIgE levels is not well established.

METHODS: This retrospective review included all patients at a teaching institution who had CM sIgE drawn on two or more occasions between January 1, 2003 and January 1, 2013.

RESULTS: 822 patients had two or more CM sIgE levels performed, with a median age of 4.3 years and a median initial sIgE of 10.7 kUA/L. 364 patients (44%) had initial levels ≥5 kUA/L. Of those patients, only 7 individuals (1.9%) had repeat sIgE levels ≤2 kUA/L over a median of 1.7 years (range 0.6-3.9 years) and 15 patients (4.1%) had repeat sIgE levels ≤5 kUA/L over a median of 1.9 years (range 0.6-4.2 years). Additionally, 142 patients (17.3%) had initial milk sIgE levels between 5 and 15 kUA/L. Of these patients 19 (13%) had subsequent levels of ≤2 kUA/L over a median of 1.9 years (range 0.98-3.99 years) while 56 patients (39%) had subsequent levels ≤5 kUA/L over a median of 1.5 years (range 0.03-4.1 years).

CONCLUSIONS: Lower initial CM sIgE levels were correlated with the progression toward a sIgE level at which one could expect a clinical resolution of symptoms. Further analysis is needed to identify the optimal frequency for re-assessing CM sIgE levels.

Analysis of IgE Antibodies in Several Food Allergy Syndromes
By Serial Dilutions of Serum on Immunocap with Whole and Component Allergens
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RATIONALE: IgE ImmunoCAP levels are often above detection limit (>100 IU/mL). Actual IgE levels are determined by re-assay with diluted sera. For most allergens including those specific to food-induced immediate anaphylaxis, consistent, calculated results are obtained across the range of dilutions. By contrast, diluted sera of patients with certain food allergy (FA) syndromes, when assayed, do not yield the predicted results.

METHODS: Sera of adults and children with Peanut Allergy (PA), Milk Allergy (MA), Mammalian Meat Allergy (MMA), or Eosinophilic Esophagitis (EOE) were serially diluted (1:2 to 1:16) and assayed for IgE to whole allergens and correlating component(s) by the ImmunoCAP method (peanut, Ara h 2; milk, Bos d 8, Bos d 4; beef, alpha-gal; wheat; mite; cat).

RESULTS: Dilution assays for allergens showed no change (undiluted vs. calculated titer) in: PA (peanut, Ara h 2), MA (milk, Bos d 8, Bos d 4), and EOE (mite, cat). In contrast, calculated titers up to six times the undiluted titers were noted in EOE (milk, wheat, peanut) and MMA (beef). Assays on MMA sera for alpha-gal IgE showed no change from the undiluted titer.

CONCLUSIONS: Dilution results reveal that assay of undiluted sera is likely adequate for measurement of IgE in food-induced immediate anaphylaxis. However, increasing titers upon dilution, as was found in MMA and EOE, suggest underestimation of specific IgE levels. IgE in MMA is directed against alpha-gal– an established, quantitatively minor component of beef. Increasing titers with dilution assays to whole food allergens in EOE strongly suggest presence of IgE to minor component(s).

Component-Resolved Diagnostics for Diagnosis of Peanut Allergy in Korean Children
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RATIONALE: We intended to evaluate IgE antibodies to peanut allergens for the diagnosis of immediate-type peanut allergy in Korean children and to find the optimal cutoff levels.

METHODS: Forty-eight children with suspected IgE-mediated peanut allergy were enrolled. The total IgE and levels of IgE antibodies to peanut, recombinant (r) Ara h 1, 2, 3, 8, and 9 were measured by immunoCAP. The diagnosis for IgE-mediated peanut allergy was confirmed by an open OFC.

RESULTS: The mean age of subjects was 4.87 ± 2.86 years. 22 participants were male. Twenty-two of the children failed (allergic group), and 26 passed the peanut challenge (tolerant group). The median levels of peanut and rAra h 2–sIgE were statistically significant higher in the allergic group than in the tolerant group (peanut; 5.44 (0.0-101.0) kUA/L vs. 1.14 (0.0-101.0) kUA/L, P<0.0001 and rAra h 2; 0.8 (0.0-101.0) kUA/L vs. 0.0 (0) kUA/L, P<0.0001). The percentage and median levels of rAra h 1, 3, 8, and 9–sIgE were not different between allergic and tolerant group.

The relationship between sensitivity and specificity of peanut and rAra h 2–sIgE antibodies were further explored by ROC curves, yielding acceptable areas under the curve, 0.91, 0.82, respectively. The peanut-sIgE concentration indicating a 100% risk of reaction was 10.3 kUA/L. The rAra h 2–sIgE level indicating a 100% risk of reaction was 4.03 kUA/L.

CONCLUSIONS: The optimal cutoff level for rAra h 2 (4.03 kUA/L) could be considered a useful tool to diagnosis for peanut allergy in Korean children.
810 Is the Allergen-Specific Basophil Activation Test (BAT) Predictive of Oral Food Challenge (OFC) Outcomes?

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Rationale: Although specific IgE (sIgE) is the primary laboratory test for diagnosis of food allergy, some patients with elevated sIgE may only be sensitized. The OFC carries many risks and challenges. This study was undertaken to determine whether an allergen induced BAT is more predictive of food allergy than sIgE/SPT and a potential surrogate for OFC.

Methods: BAT was performed on heparinized blood from patients undergoing OFC. Allergens included egg, milk, peanut, soy, wheat, almond, cashew, hazelnut, Brazil nut, walnut and pistachio. Allergen-specific upregulation of the basophil-specific ectoenzyme E-NPP3 (CD203c) was measured by flow cytometry. The extent of basophil activation, (fold increase of CD203c expression over baseline), was correlated with sIgE, SPT and OFC outcomes.

Results: 9 children underwent testing; 1 was excluded for inadequate response to positive control (anti-IgE). 57% demonstrated basophil reactivity to peanut; 43% egg; 40% pistachio, pecan, hazelnut, Brazil nut, and almond; 33% walnut; 29% milk and soy. Children with negative SPT or sIgE were not BAT positive, indicating good correlation for negative results. Two sensitized patients with negative BAT passed OFCs.

Conclusions: This preliminary data demonstrates the utility of BAT in diagnosing food allergy. In this small cohort, specificity of the BAT appears equal, if not superior to sIgE and SPT in identification of patients with food allergy. The two patients with negative BAT passing OFC suggest that BAT could be used to guide the need for OFC. Recruitment to this study is ongoing. Further studies will focus on the BAT in select patient groups (e.g.; atopic dermatitis, high IgE).

811 The Safety of the Oral Food Challenge Test with the Small Amount of Wheat for the High Risk Patients

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Rationale: To improve the patients’ quality of life (QOL) by avoiding the complete elimination of wheat, we’ve started the oral food challenge test (OFC) with the small amount of wheat (3g noodle: 0.08g wheat protein) for the patients who were expected to elicit symptoms in our center. The two patients with negative reactivity to peanut; 1 was excluded for inadequate response to positive control (anti-IgE). 57% demonstrated basophil reactivity to peanut; 43% egg; 40% pistachio, pecan, hazelnut, Brazil nut, and almond; 33% walnut; 29% milk and soy. Children with negative SPT or sIgE were not BAT positive, indicating good correlation for negative results. Two sensitized patients with negative BAT passed OFCs.

Methods: Compared the patients’ characteristics, the positive reaction rate, the frequency of symptoms which was severer than grade III of Sampson’s classification, and the frequency of adrenalin injections from the patients’ records between the two OFCs with small (group I) and the regular (group II) amount of wheat. Mann Whitney U test or Fisher’s exact test were used for the statistical analysis. Numerical values are the median (minimum - maximum).

Results: There were 32 cases in the group I and 55 cases in the group II. As for the patients’ characteristics, their age (P=0.6), and their elimination reasons (P=0.6) were not different between the two groups. Wheat IgE (41.6(0.15-101) vs. 6.4(0.1-101) UA/ml, P<0.0001), α5 gliadin IgE (5.88(0.15-20.3) vs. 0.96(0.1-9.9) UA/ml, P=0.003) were significantly higher in the group I than the group II. The positive reaction rate (58% vs 41%, P=0.18), the frequency of severe symptoms (4/32vs 2/56 cases, P=0.4), and the frequency of adrenalin injections (2/33 vs 2/56 cases, P=0.6) were not different between the two groups.

Conclusions: OFC with small amount of wheat was as safe as our regular OFC. And patient who takes this OFC might be improved the QOL.
813 Are There Symptoms and Signs Related to a Positive Oral Cow’s Milk Challenge in Brazilian Suspected Children?  
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RATIONALE: Cow’s Milk (CM) is the main cause of food allergy (FA) in children. The aim of this study was searching for main symptoms that could predict a positive CM food challenge (CMFC).  
METHODS: 154 Children with suspected CM allergy (CMA) were undergone to 175 CMFC and comprised 2 groups according to the result: negative test (NG, n=132) and positive test (PG, n=40). Both groups were analyzed regarding to age at first reaction, gender, nutritional status, breastfeeding, familial history of FA, symptoms reported, presence of atopic diseases and results of skin prick test (SPT). PG was analyzed according to required amount of CM to react, symptoms and severity of reaction.  
RESULTS: Comparing groups, PG was significantly associated with patient’s reports of urticaria (77.5% vs 42.4%, OR = 4.7, 95%CI: 2.1-10.6; p<0.0001), pruritus (47.5% vs 7.6%, OR = 11.1, 95%CI: 4.5-27; p<0.0001), vomiting (57.5% vs 31.1%, OR = 3.0, 95%CI: 1.4-6.2; p=0.04) and to have had at least 3 systems affected (47.5% vs 25%, OR = 2.7, 95%CI: 1.3-5.6; p=0.01). Age at 1st reaction was significantly lower on PG (average 3.8±9.5 months; p=0.03). Just 8% of all children were underweight. The median amount of CM to have a positive CMFC was 15mL, boys significantly reacted with less than 15mL (14±5, OR = 3.7, 95%CI: 0.99-14.2; p=0.06) and children who had referred to have diarrhea presented symptoms with more than 16mL (5±10, OR=0.2, 95%CI:0.05-0.77; p=0.02). During CMFC, half of PG patients presented with urticaria and 15%, anaphylaxis.  
CONCLUSIONS: Despite the high number of suspected children, just 1/3 really confirmed the diagnosis. Although there are some suggestive symptoms for CMA, they’re not specific enough to dismiss CMFC.  
814 Accidental Exposures to Known Food Allergens: Lessons from Pediatric Emergency Departments and Urgent Care Centers  
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RATIONALE: Accidental exposures to known food allergens occur frequently and are not always managed appropriately.  
METHODS: We performed a retrospective chart review for food allergic reactions presenting to a pediatric, tertiary care referral center Emergency Department (ED) and affiliated Urgent Care Centers between May 1, 2011 and May 31, 2013.  
RESULTS: Almost one half (270) of the reactions identified were accidental exposures to a known food allergen. Over one fifth of these patients had a previous ED visit for a food allergic reaction. Peanut was the most common trigger (59%), followed by milk, tree nuts, eggs, fish and shellfish. Only 40% of the patients had epinephrine available during the reaction. Children with a diagnosis of asthma (p = 0.05) and with a previous ED visit for a food allergic reaction (p < 0.0001) were less likely to have epinephrine available. Of the patients who had epinephrine available and had reactions consistent with anaphylaxis, 42% did not use epinephrine. Reasons included not knowing it was indicated (33%), discomfort using the device (18%), not knowing how to use correctly (13%), and having an expired device (5%).  
CONCLUSIONS: Epinephrine auto-injectors are frequently not available during accidental reactions, especially for children with asthma (who are already at risk for having a fatal reaction) and children who had a previous ED visit for a food allergic reaction. When present, epinephrine auto-injectors are underutilized. Patients with a history of a prior emergency visit for food allergy and patients with asthma would be groups on which to focus educational efforts.  
815 An Assessment of Knowledge on Identifying Tree Nuts and Tree Nut Products Among Parents and Children in Pediatric Allergy Clinic  
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RATIONALE: To prevent a reaction, identifying and strict avoidance of tree nuts (TN) and TN products are essential to those with a TN allergy. The aim of our study is to determine the knowledge of parents and patients in recognizing TN and TN products.  
METHODS: Subjects were recruited during routine appointments in the Allergy Clinic at the A.I. DuPont Hospital for Children. Subjects included parents and children both with and without a TN allergy to complete a survey. The survey asked participants to identify tree nuts and tree nut products. The IRB at Nemours approved the study and was exempt from further IRB review.  
RESULTS: The majority of participants were able to identify nearly all the tree nuts listed, however participants had a more difficult time choosing which foods commonly contain “hidden” tree nuts, with parents of children with TN averaging only 64% correct, and children with TN allergies averaging 39% correct.  
CONCLUSIONS: There is a need for improved education on identifying tree nut products, especially as label checking is not always an option in a restaurant where accidental exposures commonly occur.  
816 Inflammatory Bowel Disease and Food Allergies  
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RATIONALE: The relationship between food allergy and IBD has not been adequately investigated. We sought to explore the association between IBD and food allergy.  
METHODS: An anonymous survey was sent to email addresses of either parents of patients or patients themselves with IBD followed at the pediatric gastroenterology practice at Mount Sinai. The survey inquired about medical history as well as food allergies, avoidances, and reactions.  
RESULTS: Eighty nine surveys were completed; mean age of the patient was 14.6 years (interquartile range 10.3 to 19.0 years). IBD diagnoses included: 64% Crohn’s, 37% ulcerative colitis, and 5% indeterminate colitis. Fifty percent reported avoiding foods due to concerns that they may worsen IBD symptoms, with most common food avoidances being milk (71%), fruit (67%), corn (65%), seeds (59%), tree nut (54%), peanut (42%), seafood (40%), and wheat (40%). Twenty-five percent reported physician-diagnosed food allergy, with 50% of these reporting anaphylactic reactions to foods, 45% oral allergy syndrome, and 15% food protein induced proctocolitis. Most common reported allergenic foods were: milk (30%), tree nut (25%), peanut (25%), egg (20%), seed (15%), seafood (10%), and wheat (10%). Twenty percent reported a history of being on a hypoallergenic formula.  
CONCLUSIONS: Children with IBD report a high rate of physician diagnosed IgE-mediated food allergy. There is a significant overlap between food avoidance due to exacerbation of IBD and concerns for allergy.
All abstracts are strictly embargoed until the date of presentation at the 2015 Annual Meeting.

AB252 Abstracts

817 Allergy to Galacto-Oligosaccharides in an Atopic Population in Singapore
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RATIONALE: Supplementation of children’s milk formula with galacto-oligosaccharides (GOS) has been accompanied by reports of anaphylaxis in Singapore, all of whom were atopic. We sought to estimate the true prevalence of GOS allergy in the atopic population in Singapore.

METHODS: We aimed to recruit 500 atopic volunteers 5 years old and above with no known history of GOS or cow’s milk allergy. These subjects were administered a questionnaire and underwent skin prick testing with Vivinal® GOS (FrieslandCampina, Netherlands). Subjects with positive skin tests underwent basophil activation tests (BAT) with GOS; adults were invited to undergo an oral challenge to GOS.

RESULTS: Of 472 subjects recruited so far, 30 (6.4%) had positive skin prick tests to GOS. Seventeen of 30 subjects had positive BAT to GOS; the remaining 13 were negative. Thirteen subjects underwent oral GOS challenge; 6 had a positive reaction, and 1 had an equivocal reaction which could not be attributed to anything else. Assuming the subject with equivocal reaction had true GOS allergy, BAT had a sensitivity of 71%, and with a maximum concentration of 100mcg/ml GOS, specificity of 100% for predicting GOS allergy. Extrapolation of these results to our atopic population yields an estimated prevalence of 3.8% of true GOS allergy (95%CI 2.2–6.0%).

CONCLUSIONS: We describe a unique allergy to a pure carbohydrate in our population. This study suggests that 3.8% of our atopic population is allergic to GOS. The relatively few cases reported probably reflects limited exposure as GOS is restricted to certain milk formula.

818 The Relationship Between Eliciting Dose and Reaction Severity to Food Allergens
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RATIONALE: There is wide variability in sensitivity and reaction severity to food allergen exposures. The relationship between the eliciting dose (ED) (a measure of sensitivity) and severity of the clinical symptoms a patient experiences at the ED is still unclear.

METHODS: A three class (mild, moderate, severe) reaction grading system was developed by integrating previously published reaction grading systems. ED and symptom data were collected from published clinical oral food challenge studies for peanut, milk, egg and soy allergic patients and each reaction was graded using the integrated grading system. EDs for the three severity groups of each allergen were modeled by interval censored survival analysis to estimate individual threshold distributions and to assess intergroup differences.

RESULTS: Based on these grading criteria, ED symptoms were judged to be mild/moderate/severe respectively in 81/125/67 peanut challenges (N=273), 75/65/36 milk challenges (N=167), 21/10/14 egg challenges (N=45) and 20/15/10 soy challenges (N=45). Peanut allergic patients who experienced severe reactions had significantly higher thresholds than those who experienced mild and moderate reactions (ED10’s of 0.06 mg of protein for mild, 0.5 mg for moderate and 3.6 mg for severe, respectively using a Weibull distribution model). No significant differences in threshold distributions according to the severity group were found for milk, egg and soy.

CONCLUSIONS: The relationship between sensitivity and severity based on these grading criteria differed between peanut and other allergens. Low EDs were not predictive of mild reactions for milk, egg or soy. More clinical correlation of these observations is needed.

819 Is Peanut Hypersensitivity in Children Related to Household Consumption?
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RATIONALE: Peanut allergy is one of the most common and severe food allergies. The knowledge of risk factors for sensitization is essential to prevent it. The aim of the study was to analyze the sensitization to peanut in children and its association with the household peanut consumption (HPC).

METHODS: Forty-six children ≤18 months with clinical history of food allergy or atopic dermatitis (AD) were included. Prick-tests with whole peanut extract (1000 IC/mL, Alyostal®) were performed. HPC was evaluated by a questionnaire administered by the allergist. Gender, age, AD, breast feeding and first-degree family history of allergic disease were analyzed.

RESULTS: Mean age was 11.6 months (SD 4.1). Male/female ratio, 32/14. Twenty-two children (47.8%) had cow’s milk allergy; 13 (28.3%), egg allergy; 1 fish and 1 fruit allergy (2.2%). Thirty-three (71.7%) suffered from AD. HPC was referred in 30 cases (65.2%). Forty-three (93.5%) were breast feeding and 30 (65.2%) have positive first-degree family history. No children have introduced peanut in his diet. Nine (19.6 %) had positive prick test with peanut. The frequency of sensitization was higher in children with HPC (9/30=30% versus 0/16; p<0.05) and in children with AD (9/33=27% versus 0/13; p<0.05). The Odds ratio was not possible because of the strong association. No relationship was found with the other factors.

CONCLUSIONS: One out of five children in this group was sensitized to peanut. HPC and AD were present in all sensitized children. This suggests that both factors could be involved in peanut hypersensitivity pathophysiology.
Clinical Characteristics of Peanut Allergic Patients in a Midwest, Suburban-Based, Private Allergy Practice

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RATIONALE: Clinical characteristics of peanut allergic patients may vary based on the population studied; they are understood in private, community-based practices.

METHODS: Records of possible peanut allergic patients (clear reaction history or sensitization without a reaction history) undergoing challenges were reviewed.

RESULTS: Of 39 patients (27 male; median age 79 months) undergoing a peanut open oral challenge (pOC), 14 had a prior clinical reaction (11 skin, 2 GI, 1 skin and lower respiratory) while 25 were avoiding peanut based on sensitization alone. The mean peanut skin prick test wheal (pSPT) was 7 mm; the mean peanut IgE (pIgE) was 7.05 kU/L. Eight patients failed the sensitization alone. The mean peanut skin prick test wheal (pSPT) was 7 mm; the mean peanut IgE (pIgE) was 7.05 kU/L. Eight patients failed the challenge alone. The mean peanut skin prick test wheal (pSPT) was 7 mm; the mean peanut IgE (pIgE) was 7.05 kU/L. Eight patients failed the challenge alone. The means of pSPT and pIgE in those patients who passed were 5 mm / 0.72 kU/L versus those who failed 10/16. pSPT > 9 mm was more likely to occur in patients who failed (n=4) versus passed (n=3) pOC (p=0.0099). Logistic regression revealed increasing wheal size was a predictor of oral peanut challenge outcome (p=0.024).

Five patients who passed the pOC had pIgE >5 kU/L but no previous reaction history. Correlation between pSPT and pIgE was 0.087 (p=0.597).

CONCLUSIONS: The predictive values of pSPT and pIgE for clinical peanut allergy in a community based practice likely differ from those published by academic medical centers. pSPT > 9 mm is associated with a failed challenge.

Gastrointestinal Phenotype of Cow’s Milk Food Allergy: Prevalence

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RATIONALE: The phenotypes of IgE-mediated food allergy are heterogeneous. Patients with a phenotype exclusively gastrointestinal (g-i) are increasing but the prevalence is still unknown.

METHODS: We designed a multicenter 1-y retrospective study of pediatric patients with a diagnosis of food reaction to cow’s milk (CM) and gastrointestinal (g-i) symptoms (COLIVAC study) such as discomfort, abdominal cramps, constipation or intermittent diarrhea more than 1 h after intake of a CM glass. A non-matched group with anaphylactic symptoms (<1 h after intake) was taken as control. Skin prick test (SPT) with commercial extracts of CM proteins (CMP) (Stallergenes,France) and in vitro IgE (limit detection of 0.1 kU/L, Phadia, Temse, IL) were determined. Protocol was approved by Regional Ethics Committee (CHUNSC:24/14).

RESULTS: From 1344 pediatric patients seen in 1-y, 306 were seen because of food reactions. Thirty nine out of 306 (12.75%) were complaining exclusively gastrointestinal symptoms. Median age was 5 y-o (n=39: range 2-10 y-o) compared to anaphylaxis group (3 y-o; n=30). SPT were positive in only 20 patients (at least one positive CMP ≥5mm). Median of total IgE was 146 UI/ml compared to 595 UI/ml in anaphylaxis group. Median of specific IgE against whole CM was 0.43 kU/L compared to 38 kU/L in anaphylaxis group.

CONCLUSIONS: Gastrointestinal phenotype of food allergy with cow’s milk has prevalence 12.7% in our region. This specific phenotype has a different profile with less total IgE, less specific IgE to CM and lower SPT diameter compared to anaphylaxis phenotype. Another biomarker would be necessary.

Clinical Descriptions of Polyarthralgia with Alpha-Gal Allergy

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RATIONALE: Southern tick-associated rash illness (STARI) is a disease characterized by erythema migrans and flu-like symptoms that is temporally associated with a bite from Amblyomma americanum (Lone Star tick). Preliminary polymerase chain reaction studies have suggested that STARI is caused by Borrelia lonestari, a spirochete closely related to Borrelia burgdorferi. Delayed anaphylaxis to red meat with an elevated IgE to galactose alpha-1,3-galactose occurring with STARI has not been reported.

METHODS: IgE to Galactose-Alpha-1,3-Galactose was performed at ViraCor-IBT Laboratories Incorporated.

RESULTS: Patient is a 38 year old male with recurrent episodes of anaphylaxis manifested by urticaria, angioedema, shortness of breath, wheezing, diarrhea and hypotension. Episodes occurred 6-8 hours after ingesting red meat. IgE to alpha-gal was elevated at 12.10kU/L. He complained of a rash, polyarthralgia, and fatigue with a recent tick bite. Given his clinical presentation, the fact that Lyme Disease is uncommon in this area, and his elevated IgE to alpha-gal, the patient was suspected of having STARI caused by a bite from the Lone Star tick. He was empirically treated with doxycycline 100mg by mouth twice daily for 10 days and had complete resolution of polyarthralgia and fatigue. He avoided red meat and had no further episodes of anaphylaxis.

CONCLUSIONS: We believe this is the first reported case of STARI in a patient with delayed anaphylaxis to red meat as a result of a Lone Star tick bite. Clinicians should be aware of STARI as a potential diagnosis in patients with alpha-gal allergy who have concurrent flu-like symptoms, polyarthralgia, and a characteristic rash.
Survey on Food Allergy in Elementary School Children: Relationship Between Food Allergy and Other Allergic Diseases

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RATIONALE: This study was performed to evaluate the current status of FA (food allergy), and to analyze the relationship between allergy to individual foods and other allergic diseases in elementary school children.

METHODS: We performed a questionnaire survey for FA, asthma, allergic rhinitis and atopic dermatitis using ISAAC questionnaires. A total of 1929 students in 3 elementary schools were enrolled.

RESULTS: A total of 325 (16.8%) students had ever suffered from FA symptoms more than once, which were caused mostly by hen’s egg (63), fruits (53), crustaceans (50), milk (48), wheat (26), peanut/nuts (22) and soy (16). Only 64 (19.7%) out of 325 students were diagnosed with FA by doctors. Among 325 students, 76(23.4%) had been restricting diet. The foods under restriction were fruits, crustaceans, milk, peanut/nuts, hen’s egg in order. The presence of soy allergy was associated with the increased risk of bronchial asthma (aOR, 5.89; 95% CI, 1.87-18.59). The presence of egg and wheat allergy were associated with the increased prevalence of allergic rhinitis. The allergic symptoms to egg, wheat and crustaceans were associated with the presence of atopic dermatitis. The allergic symptoms to fruits was associated with the increased risk of allergic conjunctivitis symptoms (aOR, 2.97; 95% CI, 1.18-7.47).

CONCLUSIONS: The most common restricting foods were fruits and crustaceans in the elementary school children. A significant positive association between the suspected foods and the allergic diseases other than FA was found. Soy allergy was significantly correlated to having bronchial asthma, and fruit allergy correlated with allergic conjunctivitis.

The Association Between Food Allergy and Habitual Snoring in Young Children

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RATIONALE: Habitual snoring is one of the primary signs of obstructive sleep apnea syndrome which can lead to significant morbidity. There are only few studies about the relationship between habitual snoring and food allergy. We aim to assess this association in young children.

METHODS: Participants who developed habitual snoring before the age of 3 years were recruited. Skin prick test, serum specific IgE to foods and aeroallergens were performed. The participants were instructed to avoid the food suspect to be allergic. Re-challenge was performed to confirm diagnosis of food allergy. Clinical symptoms and questionnaire (OSA-18) were compared before, after food avoidance and after re-challenge.

RESULTS: There were 40 participants, 65% were male. Mean age of patients and mean age at onset of snoring were 23.59 ± 13.36 months and 8.84 ± 7.58 months, respectively. Prevalence of food allergy was 48.4%, which cow’s milk was the main cause identified. There were no significant differences in any factors between patients with and without food allergy. However, in food allergy group, the onset of snoring tended to occur within the first year of life.

CONCLUSIONS: Food allergy should be suspected in young children with habitual snoring, particularly if the onset begins in the first year of life. However, no patient characteristics could predict the presence of food allergy. Food elimination and re-challenge is essential to verify if snoring in early years of life is associated with food allergy.

Allergy to Legumes in Adults: Descriptive Features

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RATIONALE: Legume Allergy incidence is increasing in Spain. The aim of this study was to describe the allergy to Legumes in adults in our area.

METHODS: We studied 455 adults (>14 y.o.) referring allergy to food from our Allergy Unit for 2 years. The allergological evaluation included: Clinical history, skin prick tests and specific IgE antibodies to the most prevalent panoallergens and food allergens.

RESULTS: A total of 31(6.9%) patients (24 females, 7 males, mean age 34 y.o.) reported to have allergy to Legumes. 77% were Spanish. 13% had Atopic Dermatitis and 71% Rhinoconjunctivitis and/or Asthma. Total episodes were 61: 20% Urticaria/Angioedema; 20% Anaphylaxis; 20% EoE; 16% OAS; 3% Rhinitis; 21% Gastrointestinal symptoms. Urticaria/Angioedema: 33% were caused by Lentil or Peanut; 17% by Soy and Bean. Anaphylaxis: 25% were caused by Lentil; 17% by Chickpea, Bean or Green bean, EoE: 25% by Lentil, Chickpea or Bean. OAS: 50% by Soybean; 20% by Chickpea or Peanut. Responsible Legumes were: Lentil 27% of episodes; Bean, 19%; Peanut, 16%; Soybean, 14%; Chickpea, 13%; Pea, 8%; and Greenbean, 3%. Positive Skin prick tests: Peanut: 39% of patients, Greenbean: 32%, Lentil, 19%, Soybean: 6%, Chickpea: 3%. Positive Specific IgE levels: Greenbean: 32% of patients, Soybean: 32%, Chickpea: 29%, Lentil: 26%, Pea: 26%, Bean: 19%, Peanut: 13%.

CONCLUSIONS: In our study, most patients were female, Spanish or atopic. Urticaria/Angioedema, Anaphylaxis and Eosinophilic Esophagitis were the most common clinical entities reported followed by OAS. Lentil was the most frequently involved and responsible for most of the systemic reactions.

Antigens in Glupearl 19S Were Developed By Acid-Heat Treatment

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RATIONALE: Immediate-type wheat allergy caused by a specific hydrolyzed wheat protein (HWP), Glupearl 19S (GP19S), in “Cha no Shizuku” soap has recently received substantial attention in Japan. This study was conducted to identify the mechanism for GP19S to acquire antigenicity.

METHODS: SDS-PAGE and two-dimensional polyacrylamide gel electrophoresis were conducted to analyze protein composition and charge change throughout the manufacturing process of GP19S. Conventional wheat-dependent exercise-induced anaphylaxis (CO-WDEIA) and immediate-type wheat allergy caused by HWP (HWP-IWA) subjects’ IgE antibodies were evaluated for reaction against intermediates throughout the manufacturing process by means of ELISA and Western blotting.

RESULTS: Gluten showed partial change in protein composition after addition of acid. Heating to 95ºC had its molecular weight distribution span widely from low to high molecular weight. Protein composition difference between gluten and Gupearl 19S was prominent in isoelectric point rather than molecular weight. With molecular weight distribution broadened, CO-WDEIA subject’s IgE notably decreased reaction while HWP-IWA subject’s IgE remarkably increased reaction. Proteins HWP-IWA subject’s IgE binded to ranged from 15 to 220 kDa.

CONCLUSIONS: Antigens in GP19S for HWP-IWA were generated through isoelectric point change resulted from adding acid to gluten and heating it to 95ºC.
828 The F3A-App: Interactive Software for Children with Food Allergies

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RATIONALE: Pediatric food allergy (FA) is increasingly common, yet few interventions exist to promote effective management in school-aged children.

METHODS: We utilized focus groups and expert panel input to design a prototype of the Friends, Family, and Food App (F3A-App) a computerized intervention for school-aged children with FA. The F3A-App consists of: a school cafeteria scene where the child interacts with virtual peers and adults; two fast-paced, multi-tiered games to build skills in food avoidance and symptom awareness; and a reward system where the child earns points for making healthy food choices.

RESULTS: The F3A-App was well-received by families (84% would probably/definitely recommend to others). Most children (76%) reported feeling “less nervous” about “what it might be like getting a shot during an allergic reaction”; analyses revealed increased self-efficacy using epinephrine (t = 2.24, p < 0.05), and trends toward increased knowledge of “what would happen” during a reaction (t = 1.98, p = 0.06) and confidence to stay calm during reactions (t = 1.98, p = 0.06). Many parents (62%) reported that the F3A-App prompted family discussions regarding the social pressures of FA, including bullying.

CONCLUSIONS: Computerized interventions may be a useful channel to enhance children’s confidence regarding FA management and facilitate family communication regarding the stresses of FA management around peers.

829 Allergy to Cereals in an Area Population of Madrid -Spain: Clinical Features

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RATIONALE: Allergy to cereals has been less investigated compared to other food allergies, and the prevalence unknown. Our objective was to determine the clinical features in patients with cereals allergy.

METHODS: A retrospective study was done evaluating 1.330 patients (adults and infants) referred to our Allergy Unit from February 2011 to August 2014. Clinical data were registered and the allergic evaluation included a symptoms questionnaire, skin prick test (SPT), prick by prick (p-p) test and determination of specific IgE.

RESULTS: A total of 55 patients(4.2%) were diagnosed as allergic to cereals. All these had a positive result in SPT or p-p test with the implicated cereals. More than 112 episodes were registered: 26.3% with corn: 15% Anaphylaxis, 50% Urticaria/Angioedema (U/AE), 20% Oral allergy syndrome (OAS), 5% Rhinoconjunctivitis (Ashtma/RC/A), 5% Gastrointestinal Symptoms (GI) and 5% Eosinophilic Esophagitis (EoE). 26.3% with wheat: 20% Anaphylaxis, 20% U/AE, 20% GI, 15% EoE, 10% RCA, and 10% OAS, 15.7% with rice: 25% EoE, 16.6% Anaphylaxis, 16.6% U/AE, 16.6%, 16.6% OAS, 16.6% GI and 8.3% RCA, 14.4% with barley: 36% U/AE, 18% EoE, 18% GI, 9% Anaphylaxis and 9% OAS, 10.5% with oat meal: 25% EoE, 25% OAS, 25% GI, 12.5% RCA, 12.5% U/AE and 12.5% Anaphylaxis, 6.5% with Rye : 40% U/AE, 40% EoE and 20% Anaphylaxis.

CONCLUSIONS: The local Institutional Review Board approved this study. Pediatric outpatient clinic data from 2004-2014 was obtained through our hospital’s electronic medical record. Patients with ICD-9 codes 995.3, 995.60-995.69, 995.7, 693.1, 708, V15.01-V15.05, and V15.09 were selected. Multiple encounters by the same patient were consolidated. Using Geographic Information System software, patients’ home addresses were mapped and located within the greater Kansas City area by ZIP code. A food desert map was then overlaid. Using location and attribute value, we tested for individual clustering using the Local Moran’sI test for spatial autocorrelation.

RESULTS: Home addresses of 9010 distinct food allergic children were mapped, revealing a mean of 23.8 food allergic patients per food desert ZIP code (SD 24.8) and 15.3 per non-food desert ZIP code (SD 30.6). Visual inspection indicated a spatial relationship between food allergy diagnoses and residence within food deserts. The Local Moran’sI test was significant (p = .05) for non-random spatial clustering.

CONCLUSIONS: Our exploratory spatial analyses indicate an association between residence within ZIP codes containing food deserts and a diagnosis of food allergy. This may suggest a correlation between dietary habits and development of food allergy.

830 An Association Between Pediatric Food Allergy and Food Deserts

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RATIONALE: A food desert is defined as a low income area that has low access to healthful food retailers. We hypothesize that living within or near a food desert is associated with the diagnosis of food allergy due to potential reliance upon highly processed, nutrient poor foods.

METHODS: The local Institutional Review Board approved this study. Pediatric outpatient clinic data from 2004-2014 was obtained through our hospital’s electronic medical record. Patients with ICD-9 codes 995.3, 995.60-995.69, 995.7, 693.1, 708, V15.01-V15.05, and V15.09 were selected. Multiple encounters by the same patient were consolidated. Using Geographic Information System software, patients’ home addresses were mapped and located within the greater Kansas City area by ZIP code. A food desert map was then overlaid. Using location and attribute value, we tested for individual clustering using the Local Moran’sI test for spatial autocorrelation.

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CONCLUSIONS: Our exploratory spatial analyses indicate an association between residence within ZIP codes containing food deserts and a diagnosis of food allergy. This may suggest a correlation between dietary habits and development of food allergy.

831 Parental Perceptions of Causes of Food Allergy

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RATIONALE: Many theories as to causes of food allergies circulate the Internet on parenting message boards, blogs, and social media sites. The aim of this study was to determine perceptions of cause from parents of children with food allergy.

METHODS: Parents of children with physician-documented food allergies were recruited from local allergy clinics to take an anonymous survey regarding perceptions of causes of their own child’s food allergies. Questions about cause of food allergy were open-ended so as not to lead the respondent. The surveys also assessed demographic data, child’s other atopic conditions, and parental perceptions of food allergies in the general population. Descriptive data including means and percentages were analyzed.

RESULTS: A total of 48 surveys have been analyzed to date. The most commonly reported presumed cause for a child’s food allergy was genetics/heredity (21%) followed by the mother eating allergenic foods during pregnancy (17%). Yet, the most common belief as to the cause of food allergy in the general population was processed food (46%). Parents overestimate the prevalence of food allergy, with 65% believing that at least 50% of the general population is afflicted. A majority (92%) felt that the incidence of food allergies in children is increasing.

CONCLUSIONS: Parents’ beliefs about the causes of their own child’s food allergies do not coincide with their beliefs about the cause of other children’s food allergies, and what is causing the increase in food allergies today. Perceptions about the prevalence of food allergies is greatly exaggerated in parents of these children as well.
Persisting Food Allergen Sensitization after Allogeneic Hematopoietic Stem Cell Transplantation for DOCK8 Deficiency

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RATIONALE: DOCK8 deficiency is a combined primary immunodeficiency commonly associated with eczema and clinical food allergy. Previous reports of hematopoietic stem cell transplantation for DOCK8 deficiency have described mixed clinical food allergy outcomes. The leading hypothesis explaining mixed outcomes is that mixed donor chimerism allows for food allergy persistence.

METHODS: Among a cohort of 6 patients receiving hematopoietic stem cell transplantation with a reduced intensity myeloablative regimen at the National Institutes of Health, allergy-specific history revealed 2 patients with food allergy-induced anaphylaxis prior to transplantation. Skin prick testing was performed after transplant for relevant food allergens for these 2 patients. Food challenges were not performed.

RESULTS: Skin prick testing performed 2 years after transplant for a 27-year-old male with history of DOCK8 deficiency and peanut allergy was positive for peanut. Similarly, skin prick testing performed 6 months after transplant for a 10-year-old female with history of DOCK8 deficiency and egg, milk, wheat, and tree nut allergies was positive for milk, egg, wheat, and cashew. Peripheral donor chimerism was 100% in myeloid and lymphoid cells for both patients.

CONCLUSIONS: These cases are the first demonstrating food allergen sensitization by skin prick testing in DOCK8 patients after hematopoietic stem cell transplantation, despite 100% donor chimerism in peripheral blood. Food allergy may not be cured by hematopoietic stem cell transplantation, even when full donor chimerism in peripheral blood is achieved.

Transient Peanut Allergy Following Solid Organ Transplant

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RATIONALE: Food allergy acquisition following solid organ transplant is poorly understood; prior management of post-transplant reactions to foods has focused on avoidance. Here, we present a case report of transient peanut allergy in a patient who experienced anaphylaxis to peanut after liver transplant from a peanut allergic donor.

METHODS: IgE directed against peanut and peanut components were quantified in both liver donor and recipient serum prior to transplant, at two weeks post-transplant following anaphylaxis and 3 months after liver transplantation. Skin prick tests were used to monitor sensitivity prior to food challenge.

RESULTS: Total IgE and peanut-specific IgE were measured in the donor prior to transplant and in the recipient pre and post-transplant. Donor peanut IgE was 387 kUA/L. Recipient pre-transplant IgE was 648 kUA/L with a peanut IgE of <0.35 kUA/L. Anaphylaxis occurred at two weeks post-transplant, when total IgE was 146 kUA/L and peanut specific IgE was 4.93 kUA/L. At that time, previously negative (<0.1 kUA/L) IgE to Ara h 1, h 2 and h 3 were noted to be positive with the values of 1.20, 1.43 and 0.39 kUA/L, respectively. Repeat serum testing for peanut performed prior to food challenge was negative at 3 months with negative SPT within 6 months.

CONCLUSIONS: Here we demonstrate the passive transfer of specific peanut component IgE from a deceased donor liver to a previously peanut tolerant recipient who presented with de novo peanut anaphylaxis. We proved the transient nature of this allergy by following serial SPT and IgE over 6 months followed by a successful negative food challenge.

Stratification of Health Risk Posed By Allergic Responses at Peanut Threshold Doses: A Pilot Study

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RATIONALE: Stratifying the health risk posed by allergic responses at threshold doses has important value in food allergy risk assessment.

METHODS: Peanut challenge data with both eliciting dose (ED) and symptom information were collected from published challenge studies and unpublished Consortium of Food Allergy Research (CoFAR) data. Symptoms were independently graded by a panel of 12 health professionals according to risk score [yes (Y) or no (N) to whether symptoms posed risk to human health] and severity score (1 to 5). Threshold distributions of cumulative EDs for health risk consensus groups (defined as ≥ 7/12 reviewers reporting either a Y or N risk score) were modeled by interval censored analysis to assess intergroup differences.

RESULTS: 302 ED symptom data points from 18 different studies were identified and scored. Although lack of scoring consistency was noted between reviewers, symptoms associated with consensus Y risk (N=104; 34% of total) had mean severity score, 3.37 +/- 0.57, significantly higher than consensus N risk (N=167) score, 1.74 +/- 0.43, p < 0.001, 31 data points with no consensus (6 Y/N) were excluded from analysis. Applying this consensus grading approach to threshold data, ED01/ED05/ED50 values for consensus Y risk (.0003/.02/22 mg) were significantly lower than those for consensus Y risk (.01/86 mg; Weibull model; p < .0001).

CONCLUSIONS: Based on health professional consensus, Y grading of ED symptoms posing risk to human health had significantly higher mean severity scores and was associated with higher peanut threshold doses. Refinement of this grading mechanism is ongoing as a tool to stratify threshold health risk.

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835 Assessing the Risk Reduction Achieved By Lowering the Regulatory Threshold for Sulfite Labeling in Foods to Asthmatics
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RATIONALE: There is need to understand if reducing the regulatory limit of 10 ppm for declaring sulfites in food products benefits sulfite-sensitive asthmatics.

METHODS: We evaluated the risk to sulfite-sensitive asthmatics presented by 12 foods/drinks suspected to contain sulfites at concentrations below 10 ppm. The risk to this group was assessed because they are more likely to suffer an allergic-type reaction to sulfiting agents. Sulfite concentrations in foods were obtained from data generated by FDA field laboratories using the Optimized Monier-Williams method. Exposure to sulfites from consuming each of these foods was estimated using consumption data extracted from the 2007-2010 NHANES database. Data from published oral sulfite challenge studies in asthmatics were fit to a Weibull distribution ($\kappa=0.95; \lambda=38.71$) to generate a dose-response model, and quantitative risk assessment methods were used to assess comparative risk reduction if the sulfite threshold for labeling exemption was reduced to 5 ppm.

RESULTS: At the current threshold (10 ppm), we found, with 88% and 75% confidence respectively, that estimated reaction rates to fruit juices and cola drinks, would be 1 in 10,000 exposures or less. This confidence increased for fruit juice and cola drinks (93% and 82% respectively) if the threshold were reduced to 5ppm. Ten other foods did not show increases in confidence indicating no benefit in decreasing the threshold for these foods.

CONCLUSIONS: The current risk assessment suggests that reducing the threshold limits for sulfites to 5 ppm will result in minimal reductions in reaction risk to sulfite-sensitive asthmatics for a few select foods.

836 (1) Childhood Food Allergy and the Hygiene Hypothesis
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RATIONALE: Childhood food allergy and related atopic diseases are increasing. Although the exact mechanism of this increase is not known, it has been hypothesized that changes in overall hygiene and infection risk play an important role. The hygiene hypothesis suggests that early exposure to infections decreases the risk for atopic disease by altering Th-2 immune response to a more balanced response.

METHODS: 1,359 children from families with at least one food-allergic child, aged 0-21, were included from a family-based cohort. Parents were asked questions about various measures of microbial exposure. Multiple logistic regression models were constructed to identify characteristics significantly associated with the development of food allergy or asthma.

RESULTS: No significant associations were identified between food allergy status and hygiene exposures including: c-section birth, early infections, antibiotic use, pet ownership, childcare, and breastfeeding for children with food allergy. Children had higher odds of developing asthma if they had a cold (OR 1.38; 1.86 – 3.85) or RSV (OR 2.68; 1.86 – 3.85) during their first year; or if they spent time in a childcare center (OR 1.23; 0.90 – 1.68). Children with cats had lower odds of developing asthma than children without cats (OR 0.53; 0.36-0.79).

CONCLUSIONS: There are differential associations between early microbial exposures and food allergy versus asthma. For food allergy, no hygiene measures were significant. Further research is needed to better understand the common versus specific mechanism underlying the development of food allergy and asthma.

837 The Effect of Pediatric Food Allergy on Caregiver Quality of Life: A Study in Asian Population
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RATIONALE: Food allergy is associated with decreased caregiver quality of life (QoL). While incidence of food allergy has been increasing worldwide, studies of caregiver QoL are limited in Asian population. We aimed to evaluate the effect of pediatric food allergy on caregiver QoL in a population treated in a tertiary care center in Thailand.

METHODS: Fifty caregivers of children with food allergy were enrolled. The Food Allergy Quality of Life –Parental Burden (FAQL-PB) form was used to measure the effect of pediatric food allergy on caregiver QoL.

RESULTS: Over all mean QoL score in the population was 3.56. The mean question score for families whose children had 3 or more food allergies compared with those with 2 or fewer was 4.18 vs 3.21; P< 0.05. The factors which were significantly associated with the QoL were parental highest education level ($p<0.01$), allergic to more than 3 foods ($p<0.05$), and soy allergy ($p<0.05$).

CONCLUSIONS: Caregivers of food-allergic children had significantly impaired QoL. Type of food allergens, having multiple food allergies and level of parental education can significantly affect caregiver QoL. In our population, soy allergy was associated with worse caregiver QoL. Type of food allergens that affect QoL may vary among populations with different dietary tradition.

838 Oral Cow's Milk Immunotherapy: Relevant Cofactors during Long-Term Follow-up
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RATIONALE: Oral food immunotherapy is a novel therapeutic approach in patients with persistent cow’s milk allergy (CMA). Several clinical and individual factors have been considered critical to achieve a successful and long-lasting CMA desensitization.

METHODS: We select patients with persistent CMA and severe uncontrolled anaphylactic symptoms under food immunotherapy for at least two years. Desensitization procedure was performed in the Pediatric Critical Care Unit in the initial phase. The second phase was weekly scheduled in the Outpatient clinic to reach a final cumulative dose of 250 ml of undiluted milk. Clinical and serological date were collected every six month in long-term follow-up.

RESULTS: Twenty-seven children (2-17 y.o.) were included. All children reached the final dose of 250 ml of undiluted milk in less than ten weeks. Clinical follow-up every 6 months remained during 3-5 years to register all adverse reactions and possible factors involved. Serological changes were obtained every six months during the subsequent five years. Clinical, physical and psychological factors were recorded.

CONCLUSIONS: Anaphylactic CMA patients may benefit from rush oral Cow’s Milk immunotherapy. Clinical and serological changes have been found both at early and long-term follow-up. We record several factors involved in reactions that induce temporary loss of tolerance.
Sensitization to Food and Spt Wheal Magnitud Among Children Attending to an Allergy Service in a Major Mexican City Near the United States

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RATIONALE: Up to 60% of the children may have sensitization to a food, several authors have proposed that a SPT greater than 6 mm has a positive predictive value of 95% for food allergy, sensitization can change form one region to another. In this study we wanted to analyze how different is the sensitization in children attending to and allergy service in an major Mexican city close to the United States in comparison to the sensitization reported in US children.

METHODS: Food SPT reports done to children under 16 years of age, from January 2012 to April 2014 were analyze, a panel of 54 commercial food extracts was use. The frequency of sensitization was evaluated as the size of the wheal ≥6 mm or ≥4 mm.

RESULTS: SPT reports form 120 patients were analyzed. Sixty seven children had at least one positive SPT to a food. Only 13% had at least one SPT with a wheal > 6 mm. Food sensitization was more common in children younger than 6 years of age. However, wheals greater than 6 mm were more frequently seen in children under 3 years of age. Vegetables and fruits were the most common foods sensitisation, while egg, dairy, fish and beans had a wheal greater than 6 mm.

CONCLUSIONS: Sensitization is frequent but SPT with wheal ≥6 mm are not, as it is seen in US children peanut is not a among the main cause of allergy in children in Monterrey Mexico.

Specific IgE Value and Skin Prick Test of Sesame Allergy in Children: Role of Peanut and Tree Nut Cross-Reactivity

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RATIONALE: To describe specific IgE and skin prick test (SPT) of children with sesame allergy and cross-reactivity with peanuts and tree nuts.

METHODS: Chart review of patients with sesame IgE seen in Texas Children’s Hospital Allergy/Immunology clinic from January 1, 2010- March 31, 2014, was performed. Diagnosis of sesame, peanut and tree nut allergy was based on a convincing clinical history with elevated specific IgE and/or +SPT. Mann–Whitney U test was used for analysis.

RESULTS: Of 1645 patients, 126 had sesame IgE and 13 had documented sesame sensitization (mean 16.3 (1.01-64.1) kU/L). Nine had sesame allergy with symptoms after ingestion (urticaria/respiratory symptoms) and elevated sesame IgE (mean 12.0 (1.01-26.4) kU/L). Five of 7 had +Sesame SPT (mean 17.2 mm wheal). Of 13 patients with sensitization, 69% (n=9) had peanut allergy [mean peanut IgE 63.7 (13.3–100.0) kU/L] and 77% (n=10) had tree nut allergy/sensitization (walnut, cashew, pistachio, hazelnut, pecan almond and Brazil nut). The 9 patients with peanut/tree nut allergy had higher sesame IgE compared to those without nut allergy but this was not significant (sesame IgE mean, 19.8 kU/L vs. 9.4 kIU/L; p=0.28). Three sesame allergic patients’ sesame IgE decreased over time [mean difference, 11.78(4.4-24.5) kU/L; mean duration, 40(30-49) months], with one passing oral food challenge (OFC). One passed sesame/peanut OFC 48 months from diagnosis after -SPT to sesame/peanut. Six peanut allergic patients had elevated sesame IgE [mean 1.75(0.52-5.52) kU/L] but tolerated sesame.

CONCLUSIONS: True sesame allergy occurred in 0.5% of this population. Three-fourths of sesame allergic children have peanut/tree nut allergy. Sesame IgE in children may decrease over time with development of tolerance.

Oral Immunotherapy for Fish Allergy Using a Hypoallergenic Decomposed Fish Meat

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RATIONALE: Patients with allergy to one fish species tend to be allergic to others because a parvalbumin which is a fish major allergen has cross-reactivity. The only strategy to patients with multiple fish allergies is to avoid all fish. We start oral immunotherapy for fish allergy using a hypoallergenic decomposed fish meat.

METHODS: We decomposed salmon meat with a protease which has already used for food processing. Patients with multi-fish-allergy diagnosed by oral food challenge (OFC) tests consume 1 gram of the decomposed salmon meat every day. We confirmed threshold amount for salmon by OFC test every four months. We measured fish IgEs during this study.

RESULTS: Five patients enrolled in this pilot study. Four patients who got hives when they ate a small amount of salmon meat (less than 2 gram) could eat 20 gram salmon meat after five to eleven months. Three patients of them became able to eat not only salmon but also horse mackerel. One patient could eat ten times of salmon meat after two months. There is no adverse reaction throughout this study. The specific fish IgEs tended to decrease by this treatment.

CONCLUSIONS: Oral immunotherapy for fish allergy using a hypoallergenic decomposed fish meat is effective and safe. And this method might be also effective to other fish species.
Successful Specific Oral Tolerance Induction with Hake in an Allergic Child Detecting Fish in Cooking Steam

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Rationale: To describe a specific oral tolerance induction (SOTI) protocol with hake in a child suffering urticaria/angioedema upon fish cooking steam exposure.

Methods: A 6-year old girl who presented at 9 months of age acute urticaria after eating different types of fish (i.e. hake, sole). Skin prick test rendered positive results and since then she avoided fish. Subsequently she suffered several acute urticaria episodes after accidental intakes and even when exposed to tuna fish cooking steam. Comorbidities: mild and controlled atopic dermatitis, no bronchial asthma. A SOTI protocol was decided to apply. Sensitization was evaluated by Prick-to-prick (T1), specific IgE (sIgE) and IgG4 (sIgG4) to hake during the induction phase (T2) and when finalized (T3). SOTI to hake was performed using frozen hake loin, starting with lyophilized hake and when 20gr were tolerated, we used cooked hake until reaching 40gr.

Results: The induction phase of the SOTI lasted 11 months until 40gr of hake were reached suffering one anaphylaxis, related to an infectious process and 5 episodes of abdominal pain requiring antihistamines in only 2 of them. After one month in maintenance-phase, eating 40gr of hake daily without reactions, she tolerated 50gr of bass, 50gr. of tuna, 50gr. of monkfish uneventfully. No atopic dermatitis exacerbation was observed. sIgE against hake (T1: 3.31kUA/L; T2: 3.98kUA/L; T3: 2.02kUA/L) and wheal size for hake prick-to-prick (T1: 13x11mm; T2: 10x6mm; T3: 7x5mm) decreased during induction phase whereas hake sIgG4 levels increased (T2: 12.7kU/L; T3: 39.2kU/L).

Conclusions: In our case, SOTI with hake induces tolerance to bass, tuna and monkfish.

Severe Food Allergy to Cow’s Milk Treated with Oral Immunotherapy Along with Omalizumab

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Rationale: Given the rise in prevalence of food allergy in developed countries, oral immunotherapy (OIT), has given many patients hope for a widely available form of treatment. However some patients are included in the pattern of non-responders because of failure of active therapy.

Methods: Since 2006 we have treated 51children suffering from IgE mediated cow’s milk allergy (CMA) with OIT. Among them three (6%) patients had severe or life-threatening events during up-dosing protocol with cow’s milk (CM). Therefore, we used for these patients an anti-IgE monoclonal antibody(omalizumab) as an adjunct to OIT, in order to enhance both the safety and efficacy of oral immunotherapy. The allergic children with severe food allergy caused by milk were 9,11,and 12 years old respectively. Median CM specific IgE levels 48 (+–21) kU/L. Median total IgE 650 (+–125) kU/L. The dose of omalizumab was of 0.016 mg/Kg/IgEU/mL (75-to300mg) every two weeks for 10weeks. Afterwards, specific desensitization phase was started along with omalizumab.

Results: The patient n. 1 (male- 9y) after two months of treatment reached the dose of 50ml of CM (1.60g. of proteins): the patient n. 2 male (male-11y.) reached the dose of 80ml of CM (2.50g of proteins) ; the third patient (female-12y) reached 40ml of milk (1.20g of proteins). No moderate to severe side effects were observed at this phase of desensitization.

Conclusions: The treatment of severe food allergy with omalizumab and oral desensitization combination therapy in significant IgE mediated CMA could be an effective treatment in selected patients with severe food allergy non-responders to OIT.
Clinical Features of Patients with Filaggrin Gene Mutations in Childhood Atopic Dermatitis
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RATIONALE: Filaggrin (FLG) gene mutation carriers have increased risk of atopic dermatitis (AD). Herein we describe the clinical features of Japanese children with AD with and without FLG-null mutations.

METHODS: Children with moderate-to-severe AD whose parents consented to filaggrin gene mutation analysis during February 2009 to July 2014 were enrolled. Each child was genotyped for the eight most prevalent FLG-null mutations in the Japanese population (R501X, 3321delA, S1695X, S1701X, S2554X, S2889X, S3296X, and K4022X). We retrospectively investigated total IgE, specific IgE (house dust mite, cedar pollen, egg white, milk, and wheat), eosinophil count, serum TARC, SCORAD, and eczema onset age on first examination.

RESULTS: Of the 95 children (2 months–13 years, median 11 months), 25 had FLG-null mutations (positive ratio 35.7%, 22 heterozygotes, three compound heterozygotes). Eczema onset age was earlier in children with FLG-null mutations than in wild type. In children >1 year old at initial examination, the egg, milk, and wheat-specific IgEs in patients with FLG-null mutation were significantly higher than in wild type (P=0.004, P=0.044, P=0.040, Mann–Whitney U test). Among only the cases with FLG-null mutations, egg white, house dust mite, and pollen-specific IgEs at 2 years were significantly lower in the AD patients treated before 1 year of age, compared with those who had been treated between 1 and 2 years (P=0.059, P=0.015, P=0.014, Mann–Whitney U test).

CONCLUSIONS: Our study indicates that eczema onset was earlier in children with FLG-null mutations and specific IgEs were higher on delayed treatment. Even with FLG-null mutation, sensitization to allergens might be preventable by treating AD early.

Duration of Breastfeeding Modulates the Effect of Filaggrin Variants on the Risk of Eczema Early in Life: Results from the Isle of Wight Birth Cohort
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RATIONALE: Filaggrin gene (FLG) variants are common risk factors for eczema development; whereas, breastfeeding has been suggested as a possible protective factor. We hypothesized that breastfeeding will be protective in those with FLG variants. Thus, with increasing duration of breastfeeding the risk of eczema early in life will become similar among those with and without FLG variants.

METHODS: In the Isle of Wight birth cohort (n = 1,456), information regarding eczema was collected at ages 1, 2, 4, 10, and 18 years. Information on duration of breastfeeding was obtained at 1 and/or 2 years follow-ups. FLG variants (R501X, 2282del4, and S3247X) were genotyped in 1,150 participants. Using log-binomial regression models, the interaction effect between FLG variants and duration of breastfeeding on the risk of eczema at 1 and 2 years was evaluated controlling for potential confounders.

RESULTS: FLG variants increased the risk of eczema by 1.64-fold (P-value = 0.009) during the first 2-years of life. Duration of breastfeeding did not show an independent association with eczema. However, a possible interaction effect was observed (RRInteraction = 0.97, PInteraction = 0.062). The effect of FLG variants on the risk of eczema decreased as the duration of breastfeeding increased (in the absence of breastfeeding: RR = 2.27, P-value = 0.002; at 6-months of breastfeeding: RR = 1.27, P-value = 0.323).
Evaluation of Gene Expression Using a Skin Tape Stripping Method
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RATIONALE: Skin tape stripping is a non-invasive method used to evaluate epidermal protein expression. However, this technique has not been verified whether this skill is reliable to evaluate gene expression.

METHODS: Skin tape stripping samples and skin punch biopsies were collected from 10 normal subjects and 10 patients with atopic dermatitis (AD). Total RNA was isolated from the same donors for skin tape stripping samples and skin biopsies, and then real time RT-PCR was performed for filaggrin (FLG), thymic stromal lymphopoietin (TSLP) and loricin (LOR).

RESULTS: FLG gene expression was significantly decreased in lesional AD skin compared with skin from normal subjects in both tape stripping samples (P<0.05) and skin biopsies (P<0.05). LOR gene expression was also significantly decreased in lesional AD skin compared with skin from normal subjects in skin tape stripping samples (P<0.01) and skin biopsies (P<0.05). Additionally, LOR gene expression was significantly decreased (P<0.05) in nonlesional AD skin compared with normal subjects in tape stripping samples. TSLP gene expression from tape stripped samples was significantly increased in lesional AD skin compared with skin from normal subjects (P<0.05) and nonlesional AD (P<0.05).

CONCLUSIONS: Using PCR data from both tape stripping samples and skin biopsies, we have found reduced filaggrin and loricrin, but increased TSLP, gene expression in AD. Skin tape stripping method may be used to examine gene expression in the skin since it is a non-invasive, and can be used for serial evaluation of the skin and protein expression. However, further study is required to validate this method.

Short-Term Effect of Airborne Formaldehyde on Skin Barrier Function in Atopic Dermatitis
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RATIONALE: It is necessary to prove causality between air pollutants and aggravation of atopic dermatitis (AD). This study aimed to evaluate the effect of airborne formaldehyde on skin barrier function in children with AD.

METHODS: We enrolled 41 patients with AD and 34 normal healthy children. Provocation test was performed by stimulating 2 different areas of normal-appearing skin on the forearm with airborne formaldehyde at 500 mg/m3 or placebo for 2 hours. We measured transepidermal water loss (TEWL) and skin pH at baseline, 1 and 2 hours of exposure, and calculated the percent change from baseline.

RESULTS: In both groups, exposure to formaldehyde increased TEWL and skin pH, when compared to the change by placebo (all P < .001). This increase was dependent on the duration of exposure. The level of TEWL after 2 hours of formaldehyde exposure was higher than that measured after exposure to placebo in AD patients and normal controls (P < .001 and P = .008). The extent of the increase in median TEWL from baseline after 2 hours of formaldehyde exposure in the AD group was significantly higher than the control group (21.3% vs 11.2%; P < .001), whereas exposure to placebo showed no change. The AD group demonstrated a higher % increase in skin pH after exposure to formaldehyde compared to the control group (P = .003).

CONCLUSIONS: Short-term exposure to formaldehyde causes skin barrier dysfunction in both healthy children and AD patients, and this effect is more prominent in AD.

Dominant Proportion of Staphylococcus Aureus in the Skin of Atopic Dermatitis Patients through Metagenomic Analysis
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RATIONALE: Staphylococcus aureus is known to be the most common bacterium colonizing in the skin of atopic dermatitis patients. Here, we performed metagenomic analysis to determine the proportion of colonizing bacteria in the skin of atopic dermatitis patients.

METHODS: Children diagnosed with atopic dermatitis in a tertiary hospital were included. Skin washing fluids were obtained from the skin lesion of atopic dermatitis patients. After genomic DNA was extracted from the skin washing fluid, 16s ribosomal DNA was amplified, sequenced through next generation sequencer, and then the sequenced data was analyzed using bioinformatics.

RESULTS: Skin washing fluids from total 17 atopic dermatitis patients were analyzed. Boys were 11 (64.7%). The mean age was 83.3 ± 64.6 months. Seven (41.2%) patients showed positive specific IgE antibody to house dust mite. S. aureus was cultured in the skin washing fluid of 14 patients. S. aureus was also dominant from the metagenomics of 14 patients, mean proportion of S. aureus in the total bacterial DNA was 62.8%. S. epidermidis occupied 0.26% in other Staphylococcal subspecies. Following frequent bacterial species were Pseudomonas (10.7%), Streptococcus (9.6%), Acinetobacter (0.07%), Enterococcus (0.03%) in order.

CONCLUSIONS: In this study, through the metagenomics of bacterial DNA in the skin washing fluid of atopic dermatitis patients, we confirmed that S. aureus is a main skin colonizer of atopic dermatitis. We can also suggest that metagenomics of bacterial DNA could be a good alternative test of bacterial culture test that is time consuming and shows limited bacterial data.

Higher Plasma Adiponectin Levels in Patients with Atopic Dermatitis
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RATIONALE: Adiponectin is the most prevalent adipokine in humans and has multiple metabolic and inflammatory actions by autocrine, paracrine and endocrine modes. We wanted to study the association of its plasma level with the presence of Atopic Dermatitis.

METHODS: 170 patients (88 males, 82 females) diagnosed with AD and 141 age matched controls (75 males, 66 females) were enrolled from 2 hospitals in northern Jordan. Clinical data was collected for each individual and venous blood sample drawn and plasma separated. Adiponectin level was measured by ELISA kit (R&D System, USA). Statistical analysis was done by Chi-squared test.

RESULTS: Mean plasma Adiponectin level was 1.909 ± 0.02 µg/ml in AD patients compared to 1.093 ± 0.038 µg/ml in controls (p<0.0001).

CONCLUSIONS: - In a Jordanian cohort Adiponectin plasma level was much higher in patients with AD than controls. It could represent a link between environmental / metabolic factors and the Immune system. This inflammatory mediator from adipose tissues could be an etiological factor for TH2 shift and atopy. Further studies are needed explore the association of hyper-adiponectinemia and other allergic diseases and its mechanisms.
Activity of Natural Moisturizing Factor Forming Enzyme Bleomycin Hydrolase in Atopic Dermatitis Affected By Disease Control Status and Seasonal Change

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RATIONALE: Bleomycin hydrolase (BH) is thought to have an important physiological role by localizing at the stratum corneum (SC) in mammalian skin, and generating free amino acids from citrullinated peptides in the last step of filaggrin degradation pathway. In this study, we investigated whether disease activity and seasonal change affected BH activity.

METHODS: We recruited 11 poorly controlled AD children (SCORAD>25), 51 well-controlled AD children (SCORAD<10) and 27 healthy volunteer children aged 15 or younger. SC samples were collected from the forearms in summer and winter using the tape-stripping technique. BH activity was measured using a fluorescent substrate, citrullinated aminomethylcoumarine as a substrate.

RESULTS: BH activity was low in summer across all three groups. In winter, the activity elevated significantly in both the well-controlled AD and healthy groups, but not in the poorly controlled AD group. (summer vs. winter: well-controlled, 29±20.3 pmol/mg/min vs. 174.2±156.8 pmol/mg/min, p<0.0001; poorly controlled, 24.02±5.24 pmol/mg/min vs. 51±10.4 pmol/mg/min, p=0.252). In winter, BH activity of poorly controlled AD was significantly lower than that of well-controlled AD and healthy controls. (healthy vs. poorly controlled in winter: mean (SD), 76±75.0 pmol/mg/min vs. 28±10.9 pmol/mg/min, p=0.013).

CONCLUSIONS: BH activity is affected by seasonal change and disease control status. Regardless of the baseline severity of AD, the skin barrier can be recovered with improved BH activity as a result of appropriated treatment of AD.

Serum microRNA Expression in Maternal Blood or in Cord Blood As Biomarkers of Atopic Dermatitis at One Year of Age

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RATIONALE: It has been shown that serum microRNA expression profiles are altered in a variety of diseases. However, it is unclear whether serum microRNAs in maternal bloods or cord bloods are associated with atopic dermatitis (AD) in infancy.

METHODS: A prospective birth cohort study of 268 newborn infants with family history of allergies was set up in Seikei-kai Chiba medical center and Chiba University Hospital in Japan from January 2010 to January 2012. We collected maternal sera (MS) at 36 weeks pregnant and cord blood sera (CS). AD at one year of age was diagnosed based on a physical examination and visual inspection of the skin by an allergist. We selected the nested case-control population (AD: 18 mother-infant pairs, non-AD: 18 mother-infant pairs) defined by propensity score matching. The baseline characteristics of the infants and their mothers in the nested case-control population were similar to those in the cohort population. Expressions of 179 microRNAs in the MS and in the CS of the nested case-control population were quantified using real-time PCR.

RESULTS: We did not find any significant correlation of each microRNA expression between MS and CS. The orthogonal projections to latent structures-discriminant analysis identified 24 microRNAs in MS and 23 microRNAs in CS, which were significantly associated with AD at one year of age. Multiple regression analysis identified 3 microRNAs in MS and a microRNA in CS as independent biomarkers of AD at one year of age.

CONCLUSIONS: Serum microRNAs in maternal blood or in cord blood may be a useful biomarker to predict atopic dermatitis at one year of age.

Vitamin D Deficiency As a Risk Factor of Atopic Dermatitis in Korean Female Adolescents

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RATIONALE: Vitamin D deficiency be widely known that is associated with the prevalence of atopic dermatitis (AD). However, little is known the association between atopic dermatitis and vitamin D level in Korean adolescents. We evaluated whether the occurrence of atopic dermatitis is related to serum vitamin D levels in the general Korean adolescents.

METHODS: We obtained data of 2,748 adolescents (from 12 to 18 years old) from the fourth and fifth Korean National Health and Nutrition Examination Survey (2008 to 2012). We divided 3 groups according to level of Vitamin D (<15 ng/ml, 15-<25 ng/ml; ≥25 ng/ml). Multivariate regression analysis was performed to find which Vitamin D deficiency could be risk factors for AD.

RESULTS: Adolescents with diagnosed AD were 10.2% in all participants answered to questionnaires. Vitamin D level of total, male and female adolescents was 16.2 ng/ml, 16.65 ng/ml and 15.65 ng/ml, respectively. After adjusting for obesity, age, income quartile, exercise, parental allergic history, drinking, and smoking, lower serum vitamin D level didn’t associated with AD of total and male adolescents, but significantly related to AD in female adolescents (adjusted odd ratio (aOR) = 5.91, p=0.02 in group of <15 ng/ml; aOR = 8.37, p=0.01 in group of 15-<25 ng/ml).

CONCLUSIONS: This study suggested vitamin D deficiency is a risk factor of AD in Korean female adolescents. Further studies are required to find the reason why vitamin D level in females is lower than in males and a policy needs to prevent vitamin D deficiency.
855 Phenotypes of Atopic Dermatitis in School Children
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RATIONALE: Atopic dermatitis (AD) develops from a complex interplay between environmental and immunologic factors, incomplete understanding of its pathophysiology. AD is characterized by heterogeneous features in its onset and severity. The aim was to define the distinct phenotypes of AD children aged 6 to 13 years.

METHODS: 242 children diagnosed with AD ever and AD symptoms during the last 12 months were included from the first survey of Children's Health and Environmental Research survey (n=2941). Variables such as personal characteristics, age at onset of AD, treatment during the last 12 months, number of positive skin prick tests (SPTs), total serum IgE levels and eosinophil were included. After 4 years, lung function tests, methacholine provocation tests, and blood test including IgE and eosinophil were performed.

RESULTS: We identified 4 AD phenotypes. Class types were characterized as "early onset with low atopy" (26.4% of sample, Group 1), "early onset with high atopy" (48.3%, Group 2), "late onset with low atopy" (9.9%, Group 3), or "intermediate onset with high atopy" (15.3%, Group 4). At 4 years follow-up, although group 2 and 4 showed persistently elevated IgE levels, only group 2 showed persistently elevated eosinophil level, increased prevalence of new onset of bronchial hyperresponsiveness (BHR) (13.5%) and new diagnosis of asthma (8.5%), and higher positive SPTs, compared to group 4.

CONCLUSIONS: The LCA revealed four distinct AD phenotypes in school children. Cluster analysis of AD may lead to a better understanding of the pathophysiology of AD, a better prediction of the prognosis, and furthermore, an ideal application of personalized therapy in future.

856 Effect of Prenatal Maternal Trait Anxiety on Atopic Dermatitis and Immunoglobulin E Level: Cocoa Study
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RATIONALE: The present study aimed to elucidate the effect of prenatal maternal anxiety on occurrence of atopic dermatitis (AD) and serum immunoglobulin E (IgE) level in offspring and examine whether this effect was modified by nuclear factor-like 2 (Nrf2) gene polymorphisms.

METHODS: From August 2007 to November 2013, 1060 pregnant women were recruited. Prenatal maternal anxiety was self-reported at 36th week of pregnancy using State-Trait Anxiety Inventory. AD was ascertained by physician diagnosis at 6 months, 1, 2 and 3 year of age. IgE level was measured from cord blood and serum at 1st and 3rd year of age. Polymorphism in Nrf2 (rs6726395) was genotyped by using the TaqMan assay.

RESULTS: Prenatal maternal anxiety increased the risk of AD at 1 and 3 year of age (aOR 1.35; 95% CI 1.06-1.90 and aOR 2.72; 95% CI 1.15-5.47, respectively). Serum IgE at 1 year of age was significantly increased in offspring of anxious mothers (aOR 1.57; 95% CI 1.10-2.24). When stratified for Nrf2 (rs6726395) polymorphism and prenatal maternal anxiety, Nrf2 (rs6726395) GG genotype and prenatal maternal anxiety synergistically increased the risk of AD at 1 and 3year of age (aOR 2.43; 95% CI 1.24-4.77; p for interaction 0.018 and aOR 15.97; 95% CI 2.80-89.13; p for interaction 0.012, respectively).

CONCLUSIONS: Prenatal maternal anxiety increased the susceptibility to AD in offspring. This AD promoting effect of prenatal maternal anxiety was modified by Nrf2 (rs6726395) polymorphism. Interventions to reduce maternal anxiety during pregnancy may be helpful in preventing AD during infancy especially in genetically susceptible infants.

857 Relationship Between Breast-Feeding and Atopic Dermatitis in Early Childhood in Korean Children: Based on the Fourth and Fifth Korea National Health and Nutrition Examination Survey 2007–2012
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RATIONALE: There is widely known that breast-feeding has protective effect to atopic dermatitis in childhood, particularly less than 2 years old. But, epidemiological evidence for a role of breast-feeding on risk of atopic dermatitis is inconclusive in Korea. The objective of this study was to investigate the associations between breast feeding and risk of atopic dermatitis in early childhood in Korea.

METHODS: We combined the fourth and fifth Korea National Health and Nutrition Examination Survey data collected from 2007 to 2012 and analyzed 2,015 children who had been surveyed in regards to breast-feeding. Multivariate regression analysis was used to identify association among the following variables: presence of atopic dermatitis by diagnosed doctors, feeding types and duration of breast-feeding, previous history of parents’ allergic diseases.

RESULTS: The peak prevalence of exclusive breast-feeding and atopic dermatitis was 35.5% in 2009 and 17.7% in 2008, respectively. Since then, the prevalence of exclusive breast-feeding and atopic dermatitis annually decreased to 26.2% and 8.9% in 2012, respectively. No measurable statistically significant relationship was observed among breast-feeding, formula-feeding, duration of breast-feeding and risk of atopic dermatitis in the multivariate analysis except previous history of parents’ allergic diseases.

CONCLUSIONS: The present study showed no statistically significant relationship between breast-feeding and the risk of atopic dermatitis in early childhood in Korean children. National prospective study is needed to clarify the role of breast-feeding in development of atopic dermatitis.
858 Natural History of Children with Food Triggered Atopic Dermatitis and Development of Immediate Reactions

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RATIONALE: Case reports suggest that children with food allergy triggered atopic dermatitis (AD) on elimination diets may develop immediate reactions upon accidental ingestion or reintroduction of the food. The incidence and risk factors associated with these immediate reactions have not been systematically described.

METHODS: A retrospective chart review of 298 patients presenting to a tertiary-care allergy-immunology clinic with concern for food triggered AD. Data regarding triggering foods, laboratory testing and clinical reactions were collected prospectively from the initial visit. Food triggered AD was diagnosed by supportive history and laboratory testing. Immediate reactions were defined by timely typical signs and symptoms upon reingestion with evidence of sIgE. Differences between children with and without new immediate reaction were determined by Mann-Whitney, Chi-square, or Fisher’s exact test as appropriate.

RESULTS: Cow’s milk, egg, and peanut were the most common food allergens causing delayed and immediate-type reactions. Nineteen percent of patients with food-triggered eczema and no previous history of immediate reactions developed new immediate reactions after initiation of elimination diet. Sixty-four percent of reactions were cutaneous but 36% were anaphylactic; this did not differ between foods. Children with allergic rhinitis were more likely to develop immediate reactions (50% vs. 28%, p<0.01). Avoidance of a food was associated with increased risk of developing immediate reaction to that food (p<0.01). Risk was not related to specific IgE level.

CONCLUSIONS: A significant number of patients with food triggered atopic dermatitis may develop immediate type reactions. Elimination diets need to be thoughtfully prescribed as they may lead to decreased oral tolerance.

859 Assessment of Bronchial Hyperresponsiveness to Methacholine in Children with Atopic Dermatitis

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RATIONALE: The methacholine challenge test (MCT) is commonly used to assess a bronchial hyperresponsiveness (BHR). Many studies have shown the importance for BHR in children with bronchial asthma, but BHR in children with atopic dermatitis (AD) is poorly defined. The aim of this study is to identify the BHR in children with AD and investigate the correlation between the degree of BHR and the severity of AD.

METHODS: We performed the MCT in 105 children with AD and without the history of bronchial asthma. For each subjects, sex, age, parental allergic history, SCORAD score, blood eosinophil and neutrophil count, serum total IgE, serum eosinophil cationic protein (ECP), and skin prick test were assessed. Positive MCT is defined as PC20 ≤ 16mg/mL.

RESULTS: Positive MCT was noted in 41 children (39%). Blood eosinophil count was significantly higher in the group with a positive MCT compared with the group with a negative MCT (0.62±0.055 vs. 0.459±0.032 K/μL, P=0.008). The sensitization to house dust mite was more observed in the group with a positive MCT (82.9%, P=0.037). SCORAD score, serum total IgE, serum ECP were not significantly different. Significant negative correlation was found between the PC20 level and blood neutrophil count (r=-0.413, P=0.007). But, the PC20 level was not significantly correlated with SCORAD score.

CONCLUSIONS: The BHR to methacholine was detected in children with AD. The degree of BHR to methacholine is not significantly correlated with the severity of AD.
861 Efficacy and Safety of Chitosan Coated Garments on Atopic Dermatitis Management: A Randomized Controlled Trial
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RATIONALE: Patients with atopic dermatitis (AD) may benefit from using textiles coated with antiseptic and skin repairing compounds. Chitosan, a natural biopolymer with inhibitory activity against Staphylococcus aureus and immunomodulatory properties has been considered potentially useful in AD management.

METHODS: Patients with AD (were randomly assigned in a 1:1 ratio to receive either chitosan coated or placebo cotton long sleeved pyjamas for 8 weeks. Primary efficacy outcome was the change in severity scoring for atopic dermatitis index (SCORAD). Secondary outcomes were the number of patients with minimal clinically detected difference, change in quality of life, daily score of pruritus and sleep loss, need of rescue medication, number of exacerbations, of totally and well-controlled weeks and of adverse events. Microbiological outcomes from five skin regions included changes in number of colony forming units of total staphylococci, Staphylococcus aureus and respective ratio. Analyses were done on an intention-to-treat basis.

RESULTS: Of the 102 patients screened, 78 were included aged 30±13 years (mean ±SD), 61% female, 77% atopic, with AD for 16±10 years. After intervention, patients in chitosan group had a mean relative reduction of 24.59%. In the IIG, in which PASIT was applied, a high percentage of infectious complications overlay was recorded what influenced the QOL of Ch with AD. In the IG receiving IM, the therapeutic effect was the lowest.

CONCLUSIONS: Including CIT in the AD treatment Ps makes it possible to monitor the disease better, a percentage of side effects being low; moreover, it reduces expenses for BT and provides a high level of QOL.

862 Combination Immunotherapeutic Therapy of Atopic Dermatitis in Children: Cost-Benefit Analysis
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RATIONALE: The study was aimed at a cost-benefit analysis (CBA) of various immunotherapy (IT) programmes (Ps) for children (Ch) with AD.

METHODS: 94 Ch 3-18 ages with AD having lasted for 1-15 years were examined. All the patients received routine clinical and immuno-allergological examinations. The treatment was conducted in 2 stages: background therapy (BT) and IT. Ch were divided into 3 groups (G): IG (n=30) received immunomodulator (IM) on a step-by-step basis in the course dose of 20 mg; IIG (n=31) received an accelerated course of parenteral allergen-specific IT (PASIT); IIIG (n=33) - a combination IT (CIT) - IM+PASIT at an accelerated pace was applied. The quality of life (QOL) of Ch with AD was assessed using the Dermatology Specific Quality of Life (DSQI) questionnaire. The CBA was conducted with due regard to specific characteristics of the disease, the age composition of the G examined during a current year.

RESULTS: The best ratio of high therapeutic effect was recorded in the III G, in which CIT was applied - 88.0±4.59%. In the IIG, in which PASIT was applied, a high percentage of infectious complications overlay was
Skin Histopathology in Patients with Dermatologic Manifestations of Hypereosinophilic Syndrome

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AB266 Assessments of TNF-α, IFN-γ and IL-4 Levels in Patients with Oral Mucosal Lichen Planus

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RATIONALE: Oral lichen planus is a chronic inflammatory disease whose erosive form tends to progress, frequently relapses, and can lead to malignancy. This study assesses the role of IL-4, TNF-α, and IFN-γ in patients with frequent relapses of erosive oral lichen planus.

METHODS: 97 patients aged 18 to 60 years were studied including 35 with erosive oral lichen planus, 32 with non-erosive oral lichen planus and 30 healthy control subjects of similar age. In vitro serum cytokine assessment (TNF-α, IFN-γ, IL-4) used an enzyme-linked immunosorbent assay (“Invitrogen”; USA).

RESULTS: During relapse of erosive oral lichen planus, spontaneous and induced cytokines versus healthy controls show: TNF-α is 1.2 fold reduced (18.4±9.2 and 30.1±7.1 pg/ml versus 21.2±6.1 and 33.4±4.2 pg/ml); IFN-γ is 1.4 fold reduced (12.1±5.1 and 32.2±8.1 pg/ml versus 17.7±0.2 and 44.3±7.2 pg/ml); and IL-4 is 1.4 fold increased (74.3±3.2 and 140.4±16.1 pg/ml versus 41.2±9.1 and 80.4±9.1 pg/ml). In remission versus healthy controls TNF-α increases 2.4 fold (36.5±5.6 and 80.4±7.3 pg/ml versus 21.4±6.1 and 33.4±4.2 pg/ml); IFN-γ increases 1.8 fold (35.2±7.2 and 80.7±7.1 pg/ml versus 17.7±0.2 and 44.3±7.2 pg/ml); and IL-4 increases 1.1 fold (61.4±4.1 and 78.3±8.2 pg/ml versus 41.2±9.1 and 80.4±9.1 pg/ml) (P<0.05).

CONCLUSIONS: Acute relapse of oral lichen planus is characterized by reduced TNF-α and IFN-γ and increased IL-4 while in remission each cytokine increases. These cytokines appear to influence the process of chronic disease progression.

Adverse Vaccine Reactions in Children with Pediatric Mastocytosis

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RATIONALE: Children with cutaneous or systemic mastocytosis may demonstrate severe manifestations of mast cell mediator release such as anaphylaxis which may place them at risk for severe adverse reactions to vaccines.

METHODS: Using the NIH Biomedical Translational Research Information System, we conducted a retrospective chart review of 115 children, evaluated at NIH with the diagnosis mastocytosis between 1996-2014. We queried for the search terms, “immunizations” and “vaccines,” which identified 75 children. Based on the CDC childhood immunization schedule, we estimated that these 75 patients should have received approximately 431 immunizations during the routine immunization period from age 2 months to 16 yrs. The number, severity and type of adverse reactions reported in their medical record were determined.

RESULTS: Adverse reactions were reported after administration of a vaccine in 8 instances out of an estimated 431 administered (1.8%) which occurred in 6 of 75 patients (8%). These reactions included 2 large local cutaneous reactions in 2 patients (pertussis and undetermined multiple vaccines), generalized rash with MMR, and fever for >24 hrs post-vaccine with irritability in two patients after DPT. One patient was treated for anaphylaxis 2 hours post-varicella vaccine after onset of flushing, wheezing, and shortness of breath. Adverse reactions occurred with both live and attenuated vaccines.

CONCLUSIONS: Amongst children with mastocytosis receiving routine vaccinations, we estimated the vaccine adverse reactions to occur in 8%. In patients with adverse reactions and no specific vaccine identified, an altered schedule may be helpful to identify the inciting antigen as demonstrated in one patient with an adverse reaction to pertussis.

Safety of a Sublingual Tablet of House Dust Mite Allergen Extracts in an Environmental Exposure Chamber Study

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RATIONALE: The efficacy of house dust mite (HDM) sublingual tablets was demonstrated in an environmental exposure chamber (EEC) study of patients with allergic rhinitis upon exposure to HDM allergens. Here we report the safety results.

METHODS: Adults (18–55 years) with medically confirmed HDM-associated allergic rhinitis were randomized in this DBPC study to receive 500IR, 300IR or 100IR HDM tablet or placebo daily for 6 months. Patients with intermittent asthma were eligible. Participants were exposed to five 4-hour allergen challenges in the EEC (baseline, treatment months 1, 2, 4, 6). Adverse events (AE) were monitored throughout the study and analyzed descriptively. All patients receiving at least one dose of the investigational product were included in the safety set.

RESULTS: 355 patients (safety set: 500IR=93, 300IR=86, 100IR=89 and Placebo=87) were randomized. 94% (500IR), 91% (300IR), 97% (100IR) and 83% (Placebo) reported at least one AE on treatment. Application site reactions were the most commonly reported AEs (500IR=74%, 300IR=70%, 100IR=69%, and Placebo=37%). The incidence of asthma and related symptoms was higher during the peri-EEC challenge periods (i.e., the day of and the day after challenge: range: 37%-45%) than outside these periods (16%-21%) but was similar across treatment groups. No anaphylaxis or serious drug-related AEs were reported. 20 patients withdrew due to a TEAE, mostly due to application site reactions.

CONCLUSIONS: Treatment with HDM sublingual tablets was generally well tolerated regardless of dose. While asthma and related symptoms were more common during the peri-EEC challenge periods, rates did not differ between active and placebo treatment.
Safety of the 300 IR and 500 IR Doses of a House Dust Mite Allergen Extracts Sublingual Tablet in Adults with Allergic Rhinitis

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RATIONALE: The efficacy of two doses (300IR and 500IR) of house dust mite (HDM) sublingual tablets was demonstrated in a randomized, DBPC study in patients with HDM-associated allergic rhinitis. Here we present the safety of this treatment.

METHODS: Adults (18-50 years) with medically confirmed HDM-associated allergic rhinitis for at least one year were randomized to receive 300IR or 500IR HDM tablet or placebo once daily for one year and were followed for the subsequent year. Adverse events (AE) were monitored throughout the study and analyzed descriptively. All patients who received at least one dose of the investigational product were included in the safety set.

RESULTS: 509 patients (300IR = 170, 500IR = 169, Placebo = 170) were randomized and received at least one dose. 88% (300IR), 85% (500IR) and 80% (Placebo) reported at least one AE on treatment (TEAE). The most common adverse reactions reported in the active groups were mild or moderate application site reactions i.e., oral pruritus (25-30% of patients), throat irritation (21-24%) and mouth edema (12-17%), which mostly occurred within the first month of treatment. Nine participants experienced serious TEAEs of which 4 were considered drug-related: pharyngeal edema (300IR), eczema (300IR), moderate respiratory distress related to a sublingual edema (500IR), and urticaria (Placebo); all recovered. Forty-two patients (300IR = 17, 500IR = 20, and Placebo = 5) withdrew from the study due to a TEAE, most commonly pharyngeal edema, dyspnea, nausea and mouth edema.

CONCLUSIONS: Treatment with HDM sublingual tablets at doses of 300IR and 500IR was associated with a favorable safety profile. There was no appreciable difference in tolerability between the tested doses.

Clinical Outcome and Tolerability of a 2-Year Sublingual Allergen Immunotherapy (AIT) with a 5-Grass Pollen Tablet in Polyallergic Patients – Real-Life Medical Practice Data

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RATIONALE: Patients with respiratory allergies are often polyallergic, i.e. allergic to more than one allergen. Clinical trials have shown that these patients can effectively and safely be treated with AIT, however data from real-life medical practice remain scarce.

METHODS: We performed a prospective, open, non-controlled, multicenter, observational study of 1482 patients with grass pollen-induced allergic rhinoconjunctivitis (RC) in Germany to assess the clinical outcome, safety and tolerability of a pre-/coseasonal AIT with a 5-grass pollen tablet over 2 treatment seasons. Here we report the results in polyallergic patients with or without concomitant AIT (either SLIT or SCIT).

RESULTS: 1011 polyallergic patients participated. 76.8% received only the 5-grass pollen AIT (=w/o AIT). 23.2% were treated concomitantly with another AIT (=with AIT). For the “with AIT” patients, the RC score (scale 0-6; severity rhinitis [0-3] + conjunctivitis [0-3]) was reduced by 62% (from 4.19 in the grass pollen season preceding AIT (Y0) to 2.02 (1st study year (Y1)) and 1.60 (2nd study year (Y2))). The RC score reduction in “w/o AIT” patients was 63% (from 4.18 (Y0) to 2.15 (Y1) and 1.55 (Y2)). Treatment was well tolerated. 18.0% of “with AIT” and 17.5% of “w/o AIT” patients experienced adverse drug reactions (ADRs). The most frequent ADRs were throat irritation and oral paraesthesia in both subgroups. Serious ADRs occurred in 4 of the “w/o AIT” and none of the “with AIT” patients.

CONCLUSIONS: In real-life practice, grass pollen polyallergic patients treated with 5-grass pollen AIT reported similar tolerability and symptom reduction regardless of concomitant use of AIT.

Sustained Efficacy Assessed By Number Needed to Treat for Timothy Grass Immunotherapy Tablets in the Treatment of Allergic Rhinitis with/without Conjunctivitis up to 2 Years after 3 Years of Treatment

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RATIONALE: Number needed to treat (NNT) is a quantitative measure to assess relative treatment efficacy; lower NNT indicates greater efficacy. Using NNT, we explored efficacy for up to 2 years after 3-years of Timothy grass sublingual immunotherapy tablet (SLIT-tablet) treatment for allergic rhinitis with/without conjunctivitis (AR/C).

METHODS: Yearly NNT was calculated for grass SLIT-tablet 2800 BAU/75,000 SQ·T (Merck/ALK-Abelló [MK-7243]) using data from a randomized, double-blind, placebo-controlled trial (n=634; 3-year treatment+2-year follow-up; NCT00227279). In addition, overall NNT was calculated from pooled single-season data (n=3094) from grass SLIT-tablet pivotal trials. In the absence of an established responder definition, NNT was based on 2 exploratory post-hoc responder definitions. Definition-1 was achievement of ≥50% well-days (symptom score of none or mild for each of the 6 symptoms measured, and no rescue medication use) during pollen season. Missing data were considered non-well-days. Definition-2 was achievement of average total combined symptom+medication score (TCS) ≤3 during pollen season (~10% of observed range as cutoff). Subjects were included in Definition-2 analysis for a given year when average TCS was non-missing.

RESULTS: Using the ≥50% well-days definition, NNT was 5.9, 5.2, 6.9, 6.0, and 6.4 for years 1, 2, 3, 4, and 5, respectively. Using the TCS ≤3 definition, NNT was 6.4, 4.8, 5.3, 7.3, and 7.3 for years 1, 2, 3, 4, and 5, respectively. Overall NNT was 7.9 using the ≥50% well-days definition and 9.4 using the TCS ≤3 threshold.

CONCLUSIONS: NNT confirms favorable and sustained efficacy of grass SLIT-tablet for AR/C up to 2 years after a 3-year treatment period.
871 Treatment Effect of House Dust Mite Sublingual Immunotherapy Tablet for Allergic Rhinitis with/without Conjunctivitis

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RATIONALE: Overall treatment effect of a house dust mite (HDM) sublingual immunotherapy tablet (SLIT-tablet) evaluated in an environmental exposure chamber trial was explored by measuring rhinoconjunctivitis symptoms and quality-of-life outside the controlled exposure challenges (pre-challenge).

METHODS: In this double-blind, 24-week trial, adults (n=124) with HDM-induced allergic rhinitis with/without conjunctivitis (AR/C) received daily HDM SLIT-tablet (Mercer/ALK-Abelló (MK-8237)) 12-DU, 6-DU, or placebo. At randomization (baseline) and pre-challenge (weeks 8, 16, and 24), subjects evaluated severity of rhinoconjunctivitis symptoms experienced in their natural environment over the previous week on a visual analog scale (VAS; range 0–100), and completed Rhinoconjunctivitis Quality-of-Life Questionnaires With Standardized Activities (RQLQ[S]; range 0–6). Pre-specified immunologic parameters were assessed at screening, week 8, and post-hoc at week 24.

RESULTS: VAS with placebo and 6-DU worsened 31% and 3%, respectively, from baseline to week 24, and improved 28% with 12-DU. At week 24, VAS improved 49% with 12-DU versus placebo (mean difference: −18.41 points; P=0.001). RQLQ(S) with placebo worsened 9% from baseline to week 24, and improved 8% and 11% with 6- and 12-DU, respectively. At week 24, RQLQ(S) improved 26% with 12-DU versus placebo (mean difference: −0.64; P=0.007). No significant difference for VAS or RQLQ(S) was observed with 6-DU versus placebo at any timepoint. Specific IgE and IgG4 increased with 6- and 12-DU treatment versus placebo at week 8 (P<0.001); post-hoc analyses indicated sustained increments at week 24.

CONCLUSIONS: Outside controlled exposure challenges, HDM SLIT-tablet 12-DU exhibited an overall treatment effect for AR/C based on rhinoconjunctivitis symptoms and quality-of-life, suggesting a meaningful clinical effect.

872 The HDM SLIT-Tablet Reduces Symptoms of House Dust Mite Allergic Rhinitis Independently of Asthma Status and Allergen Sensitisation Type; A Subgroup Analysis of Results from a Dbpc Phase III Trial (MERIT)

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RATIONALE: The house dust mite (HDM) SLIT-tablet (ALK, Denmark) has been shown to significantly reduce HDM allergic rhinitis (AR) symptoms in the MERIT trial, which met its primary endpoint (EAACI 2014, Abstr 415,417). To investigate the effect in AR in different subpopulations, we present a subgroup analysis that compares the efficacy of the HDM SLIT-tablet on rhinitis symptoms and medication use in subjects with asthma versus no asthma and mono- versus polysensitised subjects.

METHODS: MERIT (EudraCT no.2011-002277-38) was a double-blind, placebo-controlled, multi-centre phase III trial including 992 adults with moderate to severe HDM AR despite having received symptomatic treatment. Subjects were randomised 1:1:1 to 1 year of daily treatment with placebo, 6 SQ-HDM or 12 SQ-HDM. The primary endpoint was the total combined rhinitis score (TCRS, sum of rhinitis symptom and medication score) during the last 8 weeks of the treatment. A subgroup analysis was pre-specified in the protocol with respect to differences in average TCRS from placebo depending on asthma status and allergen sensitisation type (not adjusted for multiplicity).

RESULTS: The analysis showed that differences in average TCRS between active treatment (6 SQ-HDM, 12 SQ-HDM) and placebo were not statistically significant between any of the subgroups (asthma/no asthma, p=0.81, mono-/polysensitised, p=0.74). Treatment was well-tolerated in all subgroups.

CONCLUSIONS: The subgroup analysis showed that there was no statistically significant difference between the effect of the active treatment in reducing HDM AR symptoms in subjects with asthma versus no asthma and mono- versus polysensitised subjects, supporting the use of the HDM SLIT-tablet in these subpopulations.
Ten-Year Experience with Sublingual Immunotherapy for Juniper Pollenosis

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RATIONALE: Juniper species are major spring allergens in the southwestern USA. We previously reported a study of sublingual immunotherapy (SLIT) for Juniper (J. Asheii) pollenosis in 2005. Over the last ten years, we have gradually expanded the use of SLIT for this allergen. This study summarizes our results.

METHODS: Pollen counts for J. Asheii and J. Scropulorum typically start to rise in mid-March in our area of southwest Colorado. Patients are contacted in early January to begin the SLIT program. Patients receive 2 vials of J. Scropulorum (Rocky Mountain Juniper, Greer Labs) extract containing a total of 150-200 micrograms of protein. Maintenance dose is one dropper (6 micrograms) every 3 or 4 days until late May. Patients are instructed to place the drops under the tongue for at least one to two minutes, and then expectorate the remainder. Pollen counts are observed during the season using a Rotorod sampler. Patients are then contacted by phone or office visit in May for assessment of efficacy.

RESULTS: For the 2014 season, 165 patients were treated with Juniper SLIT. 77 of these patients were monosensitized. 149 (90%) patients reported positive results. Side effects were mostly local oral discomfort. There were no systemic reactions. In the 2013 season, there were 53 patients reporting 79% positive results.

CONCLUSIONS: Juniper SLIT may be an effective form of immunotherapy when given pre-co-seasonally at the doses studied.
AB270 Abstracts

876 Clinical Usefulness of Visual Analogue Scale to Monitor Symptoms of Allergic Rhinitis in Children
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RATIONALE: Visual analog scale (VAS) is shown to be one of the simple quantitative measures to assess the severity of allergic rhinitis (AR). However, there is still few reports evaluating the VAS as a tool to monitor AR symptoms in children.

METHODS: A total of 69 children (6-18 years old) with AR were enrolled in this cross-sectional study. The severity of AR was categorized according to the allergic rhinitis and its impact on asthma (ARIA) criteria. The discomfort due to AR symptoms was evaluated by VAS. The degree of AR symptoms (sneezing, rhinorrhea, and nasal blockage) were assessed using the scoring system of Practical Guideline for the Management of Allergic Rhinitis in Japan (PG-MARJ). These parameters were assessed at the consultation day and 1-2 months later.

RESULTS: Among AR children, 30 children (43.5%) and 39 children (56.5%) were categorized as mild and moderate/severe, respectively. The mean of VAS value of children with moderate/severe AR was significantly higher than that of children with mild AR. There was a clear relationship between the VAS value and the sum of three AR symptom scores (r=0.69, p<0.001). As to each symptom, the VAS value was significantly related with the scores for rhinorrhea and nasal blockage, but not with the score for sneezing. Among 57 children who visited 1-2 months later, the changes in VAS values were significantly related to the changes in the sum of symptom scores (r=0.63, p<0.001).

CONCLUSIONS: The VAS could be a useful tool not only to assess the severity of AR, but also to monitor symptoms of AR in children.

877 Specific Nasal Provocation Test with Dermatophagoides Pteronyssinus Monitored By Acoustic Rhinometry in Children and Adolescents with Allergic Rhinitis and Controls
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RATIONALE: Specific nasal provocation tests (NPTs) are indicated in confirming clinically relevant allergy and in the diagnosis of allergic rhinitis. Our objective was to evaluate a Dermatophagoides pteronyssinus (Dp) NPT protocol monitored by Acoustic Rhinometry (AR) and nasal symptom score in children and adolescents.

METHODS: Seventeen patients with allergic rhinitis sensitized to Dermatophagoides pteronyssinus and 15 controls were submitted to NPT with Dp. Acoustic Rhinometry was performed after bilateral instillation of 0.15ml of nasal saline and Dp, 5.000 UBE/ml (1:10000; 1:1000; 1:100; 1:10) until 20% fall in nasal volume in the segment between 0 and Scm (V5) or nasal symptom score >3 (0 to 11).

RESULTS: Median age was 122 months (108 to 143 months) in controls and 142 months (117 to 156 months) in allergic rhinitis group. At the end of the NPT, the mean V5 fall was 5.7% (-8.7% to 4%) in controls and 22.8% (-24% to -20%) in allergic rhinitis group. None of the 15 controls and 88% (15 of 17 patients) of the allergic rhinitis group had a positive Dp NPT. Considering positive NPTs, 23.5% (4/15) were positive at 1:10000, 23.5% (4/15) at 1:100 and 6% (1/15) at 1:10 concentration.

CONCLUSIONS: This protocol has showed to have good specificity and sensitivity to discriminate patients with allergic rhinitis from controls. A simplified protocol with two Dp concentrations (1:1000 and 1:100) seems to be less expensive and less time consuming NPT protocol to be applied in the clinical practice.

878 Correlation Between Serum 25-Hydroxyvitamin D Levels and Allergic Rhinitis in Children and Adolescents in Korea
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RATIONALE: Vitamin D is known to play a role in the regulation of the immune system and in preventing allergic diseases. The aim of this study was to examine the association between vitamin D and allergic rhinitis (AR) in children and adolescents.

METHODS: In total, 100 AR subjects aged 1 to 18 years were enrolled at Severance Children’s Hospital. Serum 25-hydroxyvitamin D (25(OH)D) levels were measured in all the subjects, which were compared with the results of controls, and between the symptom severity group of AR patients. We used the data from 550 subjects of the Korea National Health and Nutrition Examination Survey (KNHANES) with similar ages as a control group. Allergic rhinitis symptom severity was classified by the Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 guidelines. Multivariate logistic regression analysis was used to evaluate the effects of gender, age, and body mass index.

RESULTS: The mean serum 25(OH)D level was significantly higher in AR patients than in controls (20.68 ± 6.96 vs. 16.23 ± 4.87, p < 0.001). The serum 25(OH) concentration associated with increased odds of AR (odds ratio 1.06, 95% CI (1.00 to 1.12), p = 0.039). There was no difference in the 25(OH)D level between the mild and moderate/severe AR patients (21.03 ± 7.08 vs. 20.01 ± 6.78, p = 0.49).

CONCLUSIONS: Elevated serum vitamin D levels may be associated with increased risk of AR in Korean children and adolescents.

879 Calcium Glycerophosphate Nasal Spray Reduces Rhinitis Symptoms
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RATIONALE: Many patients with rhinitis remain symptomatic and/or intolerant of treatment. Recently, Baines et al. (2014) reported that alkaline phosphatase is elevated in neuropathic asthma, leading us to hypothesize that a topical spray of calcium glycerophosphate (CGP), an alkaline phosphatase inhibitor, might be useful in treating rhinitis.

METHODS: This study was approved by the IRB of Drexel University College of Medicine. Seven subjects (42 ±7 YOA, 2M, 5 F) with target composite run-in scores ≥5 (0=no symptoms to 3=severe symptoms) for rhinorrhea, itching, congestion, and sneezing were treated with intranasal CGP (30 mg per nostril, b.i.d., as a spray) over 3 weeks. Subjects scored AM and PM pre and post treatment rhinorrhea, itching, congestion and sneezing for the three week period of the study. Results, including PFTs, were assessed weekly and data analyzed by analysis of variance for repeated measures.

RESULTS: The mean pre-treatment composite score was 6.929 ± 4.2. The score declined significantly (p<0.0001) over the period of the study, to 2.80±0.635 (AM, pre), 2.03±0.617 (AM, post), 3.17±0.757 (PM pre) and 2.30±0.605 (PM, post). There were no changes in pulmonary function or blood chemistry over the study period.

CONCLUSIONS: These data demonstrate that intranasal CGP effectively reduces the symptoms of rhinitis. The molecule is classified as “generally recognized as safe” by the FDA. As a normal metabolic intermediate, it is unlikely to have significant abuse liability, even when used over a long period of time. These properties make it an attractive candidate for rhinitis treatment.
880 A Randomized Controlled Trial of a Phytotherapeutic Compound Containing Boswellia Serrata and Bromelaine for Seasonal Allergic Rhinitis Complicated By Upper Airways Recurrent Respiratory Infections
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RATIONALE: phytotherapeutic compound containing boswellia serrata and bromelaine (Bifloxen) has natural antilergic properties with pronounced action on 5-lipoxigenase and thromboxane synthetase. Its clinical effect in seasonal allergic rhinitis (SAR) complicated by recurrent upper respiratory infections (RRI) was assessed.
METHODS: this randomized open controlled trial recruited 150 patients (5-59 years-old) allergic to birch or grass pollen with upper RRI. During a first pollen season of antiallergic treatment wash-out (only on demand nasal steroids admitted), the monthly average 7 allergy symptoms, symptoms of upper airways infections, days of antibiotic therapy, days of work/school absence, use of nasal steroids, nasal eosinophils (at the end of season) were calculated and compared to those of the subsequent season under daily treatment with phytotherapeutic compound or cetirizine. The analyses of intra-group and between-group differences were carried out on four balanced blocks stratified on allergen sensitization and treatment.
RESULTS: the study was concluded by 132 patients (n.68 phytotherapy, n.64 controls). All groups improved in all outcomes from baseline to the second season (p<0.05). Phytotherapy reduced allergy symptoms -73.37% (cetirizine -44.08%; p<0.01), infections -70.55% (cetirizine -33.36%; p<0.01), antibiotic therapy -79.50% (cetirizine -29.03%; p<0.01), absences -85.35% (cetirizine -40.53%; p<0.01), nasal steroids use -69.13% (cetirizine -28.52%; p<0.01), nasal eosinophils -69.97% (cetirizine -35.28%; p<0.01). The same comparisons stratified on the kind of allergen sensitization found similar changes in favor of phytotherapy (p<0.01). No serious adverse events occurred.
CONCLUSIONS: this is the first controlled trial showing a large benefit of a boswellia serrata and bromelaine compound in SAR complicated by RRI.

881 Inhibitory Effect of Phlai Capsule on the Histamine and Allergen-Induced Wheal and Flare Response on Skin Test Response Among Allergic Rhinitis Patients
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RATIONALE: The Zingeriber cassumunar Roxb. (Phlai) has been used for treatment of chronic airway diseases including mucin production. The purpose of this study was to assess the antihistamine effect of Phlai.
METHODS: This was a randomized two-way cross-over study with a wash out of 1 week between periods. 20 AR patients were enrolled per group. Skin prick test for 5 common allergen (mite, cockroach, grass, dog, cat) were performed. One group of patients received Phlai capsules (8 mg), and the other group received 10 mg loratadine. Inhibition of wheal and flare response to skin prick test to histamine and aeroallergen were measured at 1, 2, 3, 4, 6, 8, 12 and 24 hours after doses. After a washout period of 1 week, the treatments were reversed. The effect of Phlai and loratadine on wheal size was analyzed by the Friedman test for non-parametric analysis of repeated measures.
RESULTS: Phlai inhibited the wheal induced by histamine with peak effect at 6 hours from 4.58+/-0.89 to 3.65+/-0.69 (p<0.0001). Loratadine showed stronger histamine inhibition with peak effect at 3 hours from 4.83+/-1.08 to 3.23+/-0.87 (p<0.0001). Phlai inhibited the mite-induced wheal with peak effect at 4 hours from 5.98+/-2.9 to 4.98+/-2.97 (p=0.0024), whereas loratadine more strongly inhibited the mite-induced wheal from 5.73+/-3.52 to 3.80+/-2.12 (p<0.0001). Both medicines were well-tolerated with no adverse events.
CONCLUSIONS: Phlai capsule inhibits histamine and allergen-induced skin test wheal responses in AR patients, although these inhibitory effects are less potent than those of loratadine.

882 The Chinese Herbal Formula Seasonal Tea Alleviated Rhinitis and Conjunctivitis Symptoms in a Murine Ragweed Allergy Model
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RATIONALE: Allergic rhinitis and conjunctivitis are becoming increasingly prevalent. They are a significant health burden. This study was to determine the effects of Seasonal Tea on a murine model of these conditions.
METHODS: BALB/c mice were sensitized by 2 weekly intraperitoneal (i.p.) injections of 200µg ragweed and 2mg of alum followed by intranasal (i.n.) challenges with 500 µg ragweed and ocular challenges (o.c.) with 5µg ragweed weekly for 3 weeks. They then received four daily ragweed challenges to induce symptoms of allergic rhinitis and conjunctivitis. Beginning one day following the first i.n. and o.c. challenges, mice received Seasonal Tea (10.3mg/mouse/day) or water (sham) treatment twice daily for 3 weeks. Frequency of sneezing and numbers of eosinophils in nasal lavage fluids (NFL) as well as eye puffiness were evaluated following the last challenge. The nasal airway mucosa stained with H&E may be a valuable option for treating these conditions.
RESULTS: Repeated antigen challenges induced sneezing, and infiltration of eosinophils into the nasal airways in sham treated mice. Seasonal Tea treatment significantly reduced sneezing frequency (P<0.05) and number of eosinophils in the NFL (P<0.01) compared to samples from sham treated mice. Histological analysis showed that Seasonal Tea reduced the number of nasal mucosa eosinophils. Seasonal tea also reduced eye puffiness scores as compared the sham treated mice (p<0.05).
CONCLUSIONS: Seasonal Tea treatment had a beneficial effect in a murine model of ragweed induced allergic rhinitis and conjunctivitis, and may be a valuable option for treating these conditions.

883 Efficacy of Fluticasone Propionate Nasal Spray on Ocular Symptoms Relief in Seasonal Allergic Rhinitis
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RATIONALE: Attempt to demonstrate nasal fluticasone propionate 200 µg daily (FP200QD) for 14 days is superior to placebo in relieving ocular symptoms.
METHODS: This was a randomized, double-blind, parallel group, multicenter study comparing FP200QD with placebo in patients (n = 626, age 12 to 79 years) with seasonal allergic rhinitis. The primary endpoint was change from baseline in patient-rated reflective Total Ocular Symptoms Score (rTOSS). Secondary endpoints included change from baseline in the am and pm rTOSS, end-of-treatment assessment of response, and daily activities impact. Primary analysis was analysis of covariance (linear fixed-effects mode).
RESULTS: FP200QD was more efficacious in ocular symptoms relief than placebo utilizing primary endpoint (difference = -0.36, p = 0.0024). It improved am and pm rTOSS vs placebo (AM: difference = -0.33, p = 0.0057; PM: difference = -0.41, p = 0.0009). More patients on FP200QD reported overall improvement at end of treatment (177 vs 146 in placebo, p = 0.0118). FP200QD significantly improved daily activities as measured by MiniRQLQ (p<0.0001) and was well tolerated.
CONCLUSIONS: The study results support that FP200QD relieves ocular symptoms in AR.
**Ocular Allergy Treatment Practical Impact Treatment (OAT-PIT) Trial**

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**RATIONALE:** Ocular allergy contributes to the burden of allergic rhinitis (AR) and lowers the quality of life. In order to study the impact of alcaftadine in patients treated with other ophthalmic ocular agents in an allergy outpatient setting.

**METHODS:** In an IRB approved study, AR patients > age 12 years with ocular symptoms (>7 days), positive skin test to seasonal allergens with a baseline Total Ocular Symptom Score > 4 treated with ocular examina agents (> 1 week) (+Tx) or no treatment (-Tx) were then switched to alcaftadine for 7 days. Patients with an active infection, recent eye surgery, pregnancy of hypersensitivity to alcaftadine were excluded. The 35 question Eye Allergy Patient Impact Questionnaire (EAPIQ) was the primary outcome measure with sections for symptoms (sx), daily life impact (dli), psychosocial impact (psi) and treatment satisfaction (tx).

**RESULTS:** A total of 51 (age x 41; 34%M; 66%F) skin test positive patients (47/51 to trees; 31/51 to grasses and 25/51 to ragweed) were enrolled over a course of 6 months. (+Tx) patients had improvement in 3 domains (symptoms < 0.0001, dli < 0.0001, and psi <0.0006)(paired T-Test SAS V9.3). (+Tx) patients (olopadatine, bepotastine, azelastine) prior enrollment had improvement in all 4 domains (sxs = 0.0206; dli = 0.0003; psi = 0.0542 and tx < 0.0001).

**CONCLUSIONS:** Alcaftadine demonstrated statistical improvement for those on no prior medications as well as those that had been on prior prescription and OTC treatments.

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**Increased Airways Hyperresponsiveness and Inflammation in Influenza-Induced Murine Model of Asthma**

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**RATIONALE:** The Influenza virus is one of the most common causes of acute asthma exacerbations in adults and children. The aim of this study was to examine the different mechanisms of airway inflammation after influenza virus infection in a murine model of asthma in relation to allergen sensitization.

**METHODS:** Using house dust mite-sensitized mouse model of asthma, we grouped six mice into 4 groups: phosphate-buffered saline (PBS) group, house dust mite (HDM)-sensitized group, influenza-induced group, and HDM/influenza group. We evaluated the airway hyperresponsiveness (AH) by Penh value, pulmonary histopathological changes, and broncho-alveolar lavage fluid (BALF) analysis including cells and cytokines by ELISA of each groups.

**RESULTS:** HDM/Influenza group showed the most increase in airway hyperresponsiveness to inhaled methacholine (P < 0.05). In the lung tissue pathology and BALF analysis, both neutrophils and eosinophils showed a statistically significant increase in the influenza virus-induced group compared to other groups, including more prominent increase in neutrophils. These changes correlated with the cytokines by increasing CXCL1, RANTES, MIP-1α, INF-γ, IL-1β, TNF-α in the BALF (P < 0.05). Also, the levels of IL-4, IL-5, and IL-10 in the BALF increased in the influenza virus-induced murine model but less than HDM and HDM/influenza groups.

**CONCLUSIONS:** These findings suggest that the mechanism of the influenza-induced exacerbation is associated with simultaneous activations of neutrophilic, eosinophilic, and Th2 inflammation.
Human Rhinovirus Species Induce Differential Antiviral and Inflammatory Responses in Peripheral Blood Mononuclear Cells

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RATIONALE: Human rhinoviruses (RV) are a common cause of asthma exacerbations in children. RV-C causes more severe respiratory illnesses than RV-A or RV-B. However, the mechanism(s) underlying this observation remain unclear. Prior studies have shown that children with allergic asthma have impaired antiviral responses in peripheral blood mononuclear cells (PBMCs). We hypothesize that RV-C would induce differential antiviral responses in PBMCs when compared to RV-A and RV-B.

METHODS: PBMCs were isolated from peripheral blood samples of 40 children ages 13-14 years enrolled in the Childhood Origins of Asthma (COAST study). PBMCs were incubated with RV-A36, RV-B52, RV-C15 or medium alone for 22 hours. Supernatants were frozen at -80 and assayed for interferons (IFN-alpha2, IFN-gamma, IFN-lambda1) using an in-house multiplex ELISA. Interferon levels induced by the different RV species were compared.

RESULTS: Stimulation with RV-A led to significantly greater production of IFN-alpha2 and IFN-lambda1 compared to RV-B, RV-C, or control [(median IFN-alpha2: RV-A 1000 pg/ml, RV-B 4 pg/ml, RV-C 3.2 pg/ml, control <3.2 pg/ml), p<0.0001; (median IFN-lambda1: RV-A 142 pg/ml, RV-B <12.2 pg/ml, RV-C <12.2 pg/ml, control <12.2 pg/ml, p<0.0001)]. All RV species increased production of IFN-gamma compared to control, with RV-C leading to the least IFN-gamma [(median IFN-gamma: RV-A 55 pg/ml, RV-B 15 pg/ml, RV-C 6 pg/ml, control <3.2 pg/ml, p<0.0001)].

CONCLUSIONS: PBMCs stimulated with RV-C15 secreted significantly less interferon compared to cells stimulated with other RV species. RV-C may evade the antiviral response of mononuclear cells in the airway, which could contribute to greater illness severity.

Association of the Infant Gastrointestinal Microbiome with Nocturnal Symptoms in Children with Asthma

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RATIONALE: Nocturnal asthma is common among asthmatics and is associated with higher disease morbidity and mortality. While current studies support an association between the microbiome and asthma, whether the early life gastrointestinal microbiome is associated with nocturnal symptoms among asthmatic children has not been studied.

METHODS: Gastrointestinal 16S rRNA bacterial microbiome data were available from a sub-cohort of 298 infants participating in a racially diverse population-based birth cohort (WHEALS) from metropolitan Detroit, MI. Stool samples from 1 and 6 months visits were analyzed using the Illumina MiSeq platform. Nocturnal symptoms were defined as parental report of any nighttime waking as the result of coughing not due to a cold. Compositional differences in the microbiome were evaluated using permutational multivariate analysis of variance, and individual bacterial taxa associations with nocturnal symptoms were tested using a zero-inflated negative binomial model, accounting for multiple tests using false discovery rate q-values.

RESULTS: Among the 39 children with a doctor diagnosis of asthma at age 4-7 years, 20 (51%) reported nocturnal symptoms. Compositional differences in the 6-month visit specimens were significantly associated with nocturnal symptoms (p-value=0.004), with nocturnal symptomatic children having more rich, even, and diverse gastrointestinal microbiomes than non-symptomatic asthmatics (all p<0.015). Among the 6-month specimens, 515 taxa were differentially abundant. The taxa enriched in those with nocturnal cough were most commonly from the families Lachnospiraceae(57%), Ruminococcaceae(15%), Bacteroidaceae(9%), and Veillonellaceae(5%).

CONCLUSIONS: The early life gastrointestinal microbiome distinguishes between asthmatic children with and without nocturnal symptoms, suggesting distinct bacterial taxa associated with the pathogenesis of this asthma sub-phenotype.

Infant Gut Microbial Composition Alters IgE Response to Tetanus Toxoid Immunization

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RATIONALE: The gut microbiome is thought to impact immune development and response to allergens, but studying the effects of risk factors on IgE sensitization in early life is difficult because of the varying routes, times and intensities of allergen exposure. In contrast, immunizations to tetanus toxoid are given in consistent immunogenic doses close to pre-specified times.

METHODS: Microbiomes of infant stools from 1 and 6 month visits from the Detroit WHEALS birth cohort were characterized by MiSeq sequencing of the 16S rRNA gene. Indices of stool microbial community composition (sMCC): richness, evenness and diversity were calculated, as were measures between-sample microbiome composition similarity. Anti-tetanus toxoid (anti-TT) was measured at 6, 12 and 24 months using Phadia UniCAP and anti-TT trajectories were modeled over time using mixed models.

RESULTS: Among 298 children, anti-TT was significantly correlated with total IgE (r=0.70) and with IgE to egg, milk and peanut (r=0.41, 0.49, 0.31, respectively). SMCC evenness in 1 and 6 month visit samples was significantly inversely associated with anti-TT at 24 months and with a lower anti-TT trajectory over the first two years of life. Children who responded to anti-TT at 24 months (>0.35 IU/ml) had different sMCCs at 6 months, compared to children who did not respond to anti-TT at 24 months (p=0.024).

CONCLUSIONS: Our results show that sMCCs at 1 and 6 months of age are associated with IgE response to TT immunizations during infancy. These findings suggest that the infant gut microbiome impacts IgE responsiveness to allergens during early life.
Decrease in Diversity of Nasal Microbiota during Wheezing Episodes in Preschool Children

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RATIONALE: Wheezing episodes are responsible for significant morbidity in children and are closely associated with respiratory tract infections (RTIs). We hypothesized that the composition of airway bacteria would be altered during these illnesses.

METHODS: Using DNA from nasal lavage samples prospectively collected in the Maintenance and Intermittent Inhaled Corticosteroids in Wheezing Toddlers (MIST) clinical trial, we sequenced the 16S rRNA gene sequence reads per sample were subsampled at random and classified using Mothur (RDP database) in order to generate standard ecologic metrics and identify the abundance of specific bacteria.

RESULTS: Among the 18 males and 15 females (mean age 36 months), a majority had allergic sensitization (51.5%) or a parent with asthma (57.6%). Microbial diversity was significantly decreased during RTIs (Shannon Index 1.17 vs. 0.71, P < 0.01). There was a non-significant trend toward elevated Proteobacteria during RTIs. There were no differences in the nasal microbiome of children randomized to daily versus intermittent inhaled steroids, either at baseline prior to any treatment or during RTIs (Bonferroni P > 0.01).

CONCLUSIONS: Severe RTIs are associated with decreased bacterial diversity in the upper airway, indicating that the composition of nasal microbiota may influence wheezing episodes. Future studies should define the role of specific bacterial populations in these episodes. The nose is an accessible site to assess these relationships.

Cytokines Production, Expression of CD40/CD40L and Correlation with Immunoglobulins in Patients with Ataxia-Telangiectasia

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RATIONALE: Ataxia-telangiectasia (AT) is a complex disease with abnormal production of antibodies. We propose to analyze the interaction between B and T lymphocytes through the expression of CD40 and CD40 ligand (CD40L) and cytokines production in patients with AT, correlating that with immunoglobulin levels.

METHODS: Blood samples were obtained from 18 AT patients (from the Federal University of Sao Paulo) and 8 age-sex-matched controls (C). Peripheral blood mononuclear cells (PBMC) and plasma were separated and cryopreserved. PBMC were thawed and divided onto two plates, one of them with Phorbol myristate acetate (PMA) and Ionomycin to stimulate cells in vitro. After 3 hours cells were stained with conjugated monoclonal antibodies. Plasma was thawed and cytokines involved with IgA production (IL-6, IFN-gamma and TGF-beta) were measured using CBA method (Cytometric Bead Array). Events were analyzed by flow cytometer (BD LSRFortessa), using FlowJo Software. Linear association between IgM level and CD40 was measured via Pearson correlation, and Spearman correlation for TGF-b and IgA. Statistical analysis was performed with SPSS 20.0 and STATA 12.

RESULTS: AT expression of CD40 was reduced compared with controls (AT = 69.9%; range: 48.6–94; C = 87.4%; range: 83.1–91; p=0.001). No significant statistical difference in CD40L expression or cytokines between patients and controls was found. There was no association between CD40 expression and IgM levels (r=0.423; p=0.091) or between TGF-b and IgA (r= 0.073, p=0.77).

CONCLUSIONS: Patients with AT showed a lower expression of CD40 on the surface of B lymphocytes, which could induce abnormal production of antibodies.

Multispecialty Prioritization of Evidence-Based Indications for Intravenous Immunoglobulin

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RATIONALE: Comprehensive consideration of IVIG application is critical owing to limited donor pools and complex production/distribution. A 3-axis prioritization algorithm has been proposed and was evaluated in a US multi-specialist pilot to obtain diverse perspective towards best practices for IVIG use.

METHODS: The published 3-axis algorithm depends upon the traditional first axis of evidence to support use of IVIG (AAAAI classification). The second axis is disease severity and the third axis is efficacy of therapeutic alternatives. These concepts were introduced to a multi-specialist panel whose level of agreement with the AAAAI “Axis 1” evidence ratings for 50 diseases was surveyed. Respondents also rated their perceptions of Axis 2 and Axis 3. Conditions determined “definitely” or “probably beneficial” on Axis 1, but with low consensus on Axes 2/3, were identified for group discussion. A 2nd survey was conducted for these conditions, which were re-ranked on Axes 2/3 to assess for changes. RESULTS: There was generally high agreement with the AAAAI ratings. Eight conditions with strong supporting evidence, but low consensus on the Axes 2/3 were identified. In the 2nd survey, 4 conditions increased in consensus; 4 remained unchanged or decreased. The majority of consensus-building occurred in disease severity; the consensus declined in efficacy of therapeutic alternatives. Only 1 condition (SCID) increased in its overall priority ranking; 7 decreased or remained unchanged.

CONCLUSIONS: Multi-specialty input on evidence-based IVIG uses augmented with disease severity and efficacy of therapeutic alternatives will enable balanced perspective on IVIG prioritization while subsequent multi-specialty dialogue will improve consensus amongst clinical stakeholders.
893 Use of Enteral Immunoglobulin in NEMO Syndrome for Eradication of Persistent Symptomatic Norovirus Enteritis

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RATIONALE: Norovirus enteritis is usually a self-limiting infectious disease, but serious complications can occur in immunocompromised hosts. Norovirus-associated pneumatosis intestinalis to our knowledge has not been reported in primary immunodeficiency disease (PIDD) patients. No treatment for Norovirus infection is available. We describe a 12 year old male with norovirus-associated pneumatosis enteritis, NEMO syndrome, persistent symptomatic Norovirus shedding and the results of enteral immunoglobulin (Ig) therapy.

METHODS: Retrospective case and literature review.

RESULTS: Our patient with NEMO syndrome caused by 2 mutations (D113N and 348X in NEMO gene) and hypogammaglobulinemia (on intravenous Ig replacement therapy) developed large bowel pneumatosis. His past history included multi-organ impairment with pulmonary bronchiectasis, renal insufficiency, gastroapresis, and feeding intolerance (TPN-dependent). Norovirus was persistently isolated in his stool and he was continuously symptomatic with abdominal pain and diarrhea. Enteral Ig was delivered at 300 mg/kg/dose weekly for 10 consecutive doses. Abdominal pain markedly improved after his first dose. Weekly stool evaluation showed viral clearance after the 6th dose. He remains asymptomatic and norovirus free 3 months after enteral Ig discontinuation.

CONCLUSIONS: Successful clearance of chronic norovirus pneumatis enteritis has not previously been described in NEMO syndrome. Enteral Ig has been postulated to diminish viral adherence to the intestinal epithelium thus inhibiting replication by viral neutralization. Our case documents viral clearance in a child with profound immunodeficiency and active bowel disease. Enteral Ig should be considered as trial therapy in PIDD patients with virus associated pneumatosis enteritis.

894 Undetectable Serum IgE Is a Sensitive and Specific Marker of Common Variable Immunodeficiency (CVID)

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RATIONALE: Common variable immunodeficiency (CVID) is characterized by antibody deficiency and recurrent infections as well as autoimmunity, lymphoproliferation, and hematologic malignancy. The current diagnostic criteria for CVID include reduction in serum immunoglobulin (IgG) and either IgA or IgM and failure of antibody production. Serum IgE level is not currently considered in establishing the diagnosis of CVID.

METHODS: A cohort of 123 subjects from the University of Virginia Health Systems, Medical College of Wisconsin and Mount Sinai School of Medicine were diagnosed with CVID by an experienced immunologist on the basis of currently accepted diagnostic criteria, including clinical history, serum IgG, IgA and IgM, and antibody response to vaccinations. Serum IgE was measured in all of these subjects using the Phadia ImmunoCap system. Serum IgE was also measured in an unbiased control cohort of 963 healthy 17-18 year olds from northern Sweden.

RESULTS: The prevalence of undetectable (<2 IU/ml) total serum IgE in our cohort of 123 subjects with CVID was 84.6% and the prevalence of IgE <10 IU/ml was 97.6%. In comparison, IgE <2 IU/ml was found in only 3.8% of controls, in agreement with other published population estimates.

CONCLUSIONS: The finding of an undetectable (<2 IU/ml) serum IgE has both a high sensitivity of 84.6% and a high specificity of 96.2% for the diagnosis of CVID. Based on this observation, measurement of serum IgE should be included as a part of the routine laboratory work-up for CVID, and an undetectable serum IgE included as a component of the diagnostic criteria.

895 Thirteen Cases of Sustained Post-Rituximab Hypogammaglobulinemia

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RATIONALE: Long-lasting hypogammaglobulinemia following rituximab use has been demonstrated in case reports. Whether rituximab causes hypogammaglobulinemia or whether this represents progression of a pre-existing disease is unknown. We discuss 13 cases of hypogammaglobulinemia noted after rituximab use.

METHODS: A retrospective chart review was performed of 13 patients aged 8 to 58 with hypogammaglobulinemia noted >6 months following rituximab use. Indication for rituximab use, time elapsed since rituximab use, pre- and post-rituximab immunoglobulin levels, vaccine titers, and symptoms associated with hypogammaglobulinemia were examined.

RESULTS: Rituximab was used to treat idiopathic thrombocytopenic purpura (8), autoimmune hemolytic anemia (2), eosinophilic-myoclonus syndrome (1), granulomatosis with polyangiitis (1), and post-transplant lymphoproliferative disorder (1). Of the 5 patients with recorded pre-rituximab IgG levels, one had pre-existing hypogammaglobulinemia (IgG < 319mg/dL). The others were in the normal range. Post-rituximab immunoglobulin levels were IgG: <10 to 471mg/dL (mean: 219mg/dL), IgA: <1 to 67mg/dL (mean: 18mg/dL), IgM: <4 to 324mg/dL (mean: 62mg/dL). 8 patients noted increased frequency of infections post-rituximab. Pre-rituximab, 2 individuals had protective pneumococcal vaccine titers (no levels recorded for 12 patients). Post-rituximab, 4 individuals had non-protective titers and 1 had protective titers. Average duration of hypogammaglobulinemia has been 5.4 years to date.

CONCLUSIONS: 13 subjects had sustained post-rituximab hypogammaglobulinemia, with increased infections in 8. For 8 subjects, pre-treatment IgG levels had not been determined; of the 5 for whom levels were tested, 4 had normal IgG levels before treatment. As rituximab may accelerate or trigger B cell failure in certain patients, testing serum immunoglobulin levels before use is warranted.
Wheeze, Recurrent Wheeze, Nd Rhinovirus and Respiratory Syncytial Virus Infections during the First 5 Years of Life; Observations from a Birth Cohort in Rural Ecuador

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Rationale: There are limited data from the rural tropics on the association between respiratory viral infections and wheezing in early childhood. We investigated the association between wheeze and rhinovirus (RV) and respiratory syncytial virus (RSV) infections during the first 6 years of life in a rural birth cohort in Ecuador.

Methods: We did passive surveillance for influenza-like illnesses and wheeze in a birth cohort of 2,404 children in a rural tropical Ecuador from birth to 6 years. Nasopharyngeal swabs were collected from symptomatic children and routinely from asymptomatic children and analysed for the presence of RSV and RV RNA by real-time PCR.

Results: We analysed 400 swabs from a sample of 50 asymptomatic children, 48 children with influenza-like illness and no wheeze (ILI/noW), and 214 children presenting with 302 episodes of wheeze. Wheeze was more strongly associated with RV infection (adj. OR 6.2, 95% CI 2.3-16.8, P < 0.001) than ILI/noW alone (adj. OR 2.7, 95% CI 0.9-8.4, P = 0.091) compared to controls. Children with wheeze and ILI/noW had a higher risk of RSV infection compared to controls. Children with wheeze and ILI/noW had a higher risk of RSV infection compared to controls. Children with wheeze and ILI/noW had a higher risk of RSV infection compared to controls.

Conclusions: Our data indicate that RV infection in our population is strongly associated with wheeze and the later development of asthma.

Diesel Exhaust Particles Exacerbate Allergic Rhinitis in Mice By Disrupting the Nasal Epithelial Barrier

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Rationale: A traffic-related air pollutant, diesel exhaust particles (DEP), is considered an environmental factor that adversely affects allergic diseases. However, the direct effect of DEP on allergic rhinitis (AR) and the underlying molecular mechanisms are poorly understood.

Methods: Mice were sensitized by intraperitoneal injection of ragweed pollen, followed by nasal challenge with ragweed pollen in the presence or absence of DEP. The frequency of sneezing was evaluated immediately after each nasal challenge. Immunological parameters and nasal histology were examined 24 hours after the final challenge.

Results: Mice challenged with ragweed pollen plus DEP showed increased frequency of sneezing compared with mice challenged with pollen alone, while Th2-type immune responses against the allergen were comparably induced in both groups. Interestingly, intranasal DEP pretreatment before ragweed pollen challenge increased ragweed-pollen-induced sneezing to levels comparable with the co-administration group. In vitro examination revealed that DEP reduced the expression of a tight junction (TJ) protein, zonula occludens-1, and increased paracellular permeability of cultured nasal epithelial cells. Additionally, intranasal administration of DEP, but not ragweed pollen, disrupted nasal mucosal TJs in vivo.

Conclusions: Our results demonstrate that DEP disrupts TJs, leading to an increased permeability of nasal epithelial cells. This may result in the promotion of allergen delivery into subepithelial tissues contributing to the exacerbation of antigen-specific IgE bearing mast-cell-mediated immediate allergic responses.

Inhalational Exposure to House Dust Conditions Pulmonary Conventional Dendritic Cells to Induce T Helper 2 Responses Against Innocuous Antigens

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Rationale: House dust, which contains a complex mixture of allergens and microbial products, can promote allergic sensitization to innocuous antigens. Our objective was to identify the pulmonary dendritic cell (DC) subsets responsible for inducing T helper 2 (Th2) responses following airway exposure to house dust extract (HDE).

Methods: The airways of C57BL/6 mice were exposed to ovalbumin (OVA) alone or in combination with either HDE or the viral mimetic poly(I:C). After 16 hours, pulmonary DC subsets were isolated by flow activated cell sorting and cultured with naïve OVA-specific CD4(+) T cells. T helper differentiation was determined by measurement of IL-4, IL-13 and IFN-gamma.

Results: Airway exposure to HDE resulted in the accumulation and activation of conventional (c) DCs and monocyte-derived (mo) DCs. However, only cDCs induced Th2 differentiation following HDE exposure. HDE specifically conditioned lung DCs to stimulate Th2 responses, as cDCs exposed to poly(I:C) failed to induce Th2 differentiation. HDE and poly(I:C)-exposed cDCs expressed comparable costimulatory molecules and stimulated equivalent T cell proliferation, indicating that Th2 induction was not the consequence of suboptimal DC maturation by HDE. HDE exposure suppressed IL-12p40 expression in lung cDCs, suggesting a possible mechanism for Th2 induction.

Conclusions: HDE conditions pulmonary cDCs to preferentially induce Th2 responses against innocuous inhaled antigens. Transcriptional analysis of HDE-conditioned cDCs may reveal previously unknown factors involved with Th2 differentiation, and thus identify novel therapeutic targets for allergic asthma.
The Impact of Age in the Airway Inflammatory Response to Organic Dust Exposure in Mice
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RATIONALE: Agricultural-related organic dust exposures induce airway inflammation leading to asthma, chronic bronchitis, and obstructive lung disease. Workers over 65 years represent the fastest growing age group of farmers; older farmers have more respiratory symptoms than their peers. Models of inflammatory lung injury have previously focused on young mice, and in this study we utilized older mice to provide insights into the normal aging airway response to organic dust exposures for future therapeutic applications.

METHODS: Using an established intranasal inhalation exposure animal model, young (7-9 weeks) and older (12-14 months) C57BL/6 mice were exposed to swine facility organic dust extract (ODE) or saline once or daily for 3 weeks. Bronchoalveolar lavage fluid and lung tissue were collected to determine differences in inflammatory cellular influx, cytokine responses, and histopathology.

RESULTS: Following single exposure, there were significant reductions in ODE-induced influx of total cells (66% reduction) and neutrophils (71% reduction) in older mice as compared to younger animals. ODE-stimulated TNF-α, IL-6, and CXCL1 responses were also significantly reduced in older mice as compared to younger animals. Following repeated exposures for 3 weeks, ODE-induced inflammatory cellular and cytokine responses were similar between young/old animals, except older mice demonstrated significant increase in lymphocyte influx. In the older mice, a CD8 as opposed to CD4 response predominated. ODE-induced histopathologic changes were increased in older mice.

CONCLUSIONS: Aging impacted organic dust-induced airway responses. Older mice demonstrated an impaired response to acute exposure, but with repeated exposures, there were trends toward increased inflammation marked by an enhanced lymphocytic response.

Characterization of the T Cell Response Targeting Timothy Grass Antigens in Allergic, Healthy and Specific Immunotherapy-Treated Patients
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RATIONALE: T cells play an important role in mediating the pathogenesis of allergic disease. Previously, we identified and characterized T cell epitopes from the 10 known Timothy grass allergens as well as 93 additional, previously un-described antigens. Here, we aim to further analyze the phenotype of allergic, healthy and allergen-specific immunotherapy-treated patient’s T cell responses targeting dominant peptides from the known allergens and the additional antigens.

METHODS: T cell responses against dominant peptides derived from Timothy grass antigens from allergic, healthy and specific immunotherapy-treated patients were studied. Antigen-specific T cells were identified by detection of upregulation of activation marker CD40L (CD154) and cytokine production (IL-4, IL-5, IFNg, IL-10, IL-17). Peptide-reactive T cell populations were phenotypically analyzed based on expression of chemokine receptors and other surface markers associated with different T helper cell subsets.

RESULTS: Antigen-specific T cell responses are associated with a central memory Th2 phenotype. A high enrichment in central memory cells was observed after peptide pool stimulation in the activated (CD40L positive cells) CD4 T cell subset compared to total CD4 T cells. In addition, activated cells also expressed higher levels of CCR4 and CRTh2 compared to total CD4 T cells.

CONCLUSIONS: Investigating the T cell repertoire associated with Timothy grass specific T cell responses in allergic, healthy and allergen specific immunotherapy-treated patients will provide more insights into the role of T cell pathogenesis in type I hypersensitivity and how the allergic immune response is modulated throughout the course of allergen specific immunotherapy.

Pathogenesis of Hereditary Angioedema with Normal C1 Inhibitor: Evidence for Abnormalities in Plasminogen Activator Inhibitors
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RATIONALE: Hereditary angioedema (HAE) with normal C1 inhibitor (C1-INH), or type 3 HAE, is associated with a factor XII mutation in 30% of subjects. We sought evidence for abnormalities in the pathways of bradykinin formation and degradation in plasma of patients.

METHODS: Bradykinin was added to plasma and its rate of degradation measured by ELISA. Plasminogen activator inhibitors (PAI) 1 & 2 were also measured by ELISA. Plasma autoactivation was assessed by chromogenic assay of kallikrein.

RESULTS: PAI-1 levels varied from 0.9-4.5 units in controls (mean 2.6±1.2), from 0.2-2 units in type 3 with a factor XII mutation (mean 1.3±0.6) and from 0.0-3.7 units in type 3 HAE without a factor XII mutation (mean 1.3±1.2). PAI-2 levels varied from 100-250 units in controls, had values of 0 in 4/9 patients with the factor XII mutation and was 0 in 7/8 patients without the mutation; individual values were 70, 75, 20, 10 and 10 in patients with the mutation and 25 in one patient without the mutation. Autoactivation characteristic of type 3 HAE was abnormally high in 8 subjects (4 in each sub-category) and was corrected by additional C1-INH in 4 of them. Bradykinin degradation was abnormal in one of 17 type 3 HAE patients.

CONCLUSIONS: Since plasmin can activate factor XII (Kaplan and Austen, J Exp Med 1971, 133: 696-712), abnormalities of fibrinolysis can lead to abnormal bradykinin formation. Our results indicate a marked abnormality in PAI-2 and diminished levels of PAI-1 in patients with type 3 HAE. One patient may have a kininase abnormality.
The effect of BCX4161 on disease activity and quality of life was assessed in OPU-S-1 using the disease-specific Angioedema Activity Score (AAS), the Angioedema Quality of Life Questionnaire (AE-QoL) as well as the assessment of attack characteristics.

METHODS: Twenty-four subjects with HAE and frequent angioedema attacks received 4 weeks of treatment with BCX4161 400 mg TID and placebo in a randomized sequence in OPU-S-1, a double-blind, placebo-controlled, 2-period crossover study. Subjects recorded attack details and an AAS for each attack, and completed the 17-item, 4-domain AE-QoL at baseline and at the end of each treatment period. Four-week activity scores (AAS28) and AE-QoL total and domain scores were calculated and the results from each treatment were compared using a mixed-effects model.

RESULTS: Overall disease activity assessed by the AAS28 was markedly reduced with BCX4161 versus placebo (total score 21.4 vs 28.8, p = 0.022). Quality of life was improved during BCX4161, with a mean AE-QoL score difference of 7.9 points versus placebo (p = 0.004). An improvement in the functioning domain was seen with BCX4161 (-18.9 vs -5.5, p = 0.016); trends in other domains were observed. Fewer subjects reported stomach/gut (58% vs 87%, p = 0.049) and hand attacks (25% vs 71%, p = 0.003) during BCX4161 versus placebo treatment.

CONCLUSIONS: Four weeks of BCX4161 treatment in HAE subjects with frequent attacks reduced disease burden with improved quality of life and decreased disease activity.
905 The IcGabrant Outcome Survey: Observational Data in Patients with Angioedema Due to Acquired C1 Inhibitor (C1-INH) Deficiency

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RATIONALE: The IcGabrant Outcome Survey (IOS; NCT01034969) monitors icGabrant safety and effectiveness in a real-world setting. While icGabrant is licensed in numerous countries for hereditary angioedema (HAE) attacks in adults with C1-INH deficiency, we report IOS data for off-label use in angioedema due to acquired C1-INH deficiency. This condition shares a mechanism and clinical profile with HAE, but is less prevalent.

METHODS: Data were collected at clinic visits (July 2009–July 2014). Statistical analyses used a mixed model for repeated measures.

RESULTS: Thirteen patients across Europe (female, 38.5%; mean age, 60.9 years) experienced 254 icGabrant-treated attacks of angioedema due to acquired C1-INH deficiency. Of 249 attacks with anatomical location data, most affected the abdomen and/or skin (224/249, 90.0%; vs 1667/1682, 99.1%, for HAE type I/II attacks). Of 218 attacks with severity data, most were moderate (116/218, 53.2%), or severe/very severe (84/218, 38.5%; vs 95/1545, 61.8%, severe/very severe for HAE type I/II attacks). Median time to injection was 0.5 hours (N=72 attacks; vs 1.0 hour for HAE type I/II attacks [N=794]; p=0.072). Median time to symptom resolution was 1.3 hours (N=77 attacks; vs 4.9 hours for HAE type I/II attacks [N=860]; p=0.0001). Median attack duration was 3.3 hours (N=58 attacks; vs 7.0 hours for HAE type I/II attacks [N=692]; p=0.004). For comparison, median duration of untreated abdominal or skin attacks was 48.0 hours (N=22 attacks; also 48.0 hours for equivalent HAE type I/II attacks [N=377]).

CONCLUSIONS: In IOS, icGabrant-treated attacks of angioedema due to acquired C1-INH deficiency were shorter than HAE type I/II attacks.

906 International Consensus Guidelines for Diagnosis and Management of Food Protein-Induced Enterocolitis Syndrome

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RATIONALE: Food Protein-Induced Enterocolitis Syndrome (FPies) is a cell- mediated food allergy that can be severe and lead to shock. FPies prevalence and pathophysiology are poorly understood. There are no biomarkers and best-practice strategies. As a result, FPies is frequently under-recognized and mismanaged.

METHODS: AAAAI work group has been convened to establish evidence-based consensus guidelines on diagnosis and management of FPies. A comprehensive literature search of Pubmed / Medline and Embase identified 879 potentially relevant articles, of which 110 met inclusion criteria.

RESULTS: An international work group was assembled to provide robust input, inclusive of board-certified allergists, gastroenterologists, emergency medicine and intensive care physicians as well as social workers and representatives of lay patient organizations. Member of this group included individuals representing the US, Europe, Israel, Australia, Japan, Korea, and Brazil, providing diverse international consensus. The available evidence has been graded according to established criteria used in AAAAI guidelines and Joint Taskforce Practice Parameters. The complete document addresses manifestations and definition, diagnosis, management, epidemiology, natural history, pathophysiology, gastrointestinal and nutritional aspects. Treatment recommendations address both acute as well as chronic FPies. Additionally, unmet needs and future directions have been identified to help bridge gaps in knowledge and clinical practices.

CONCLUSIONS: Evidence-based consensus guidelines will assist medical providers in diagnosing and managing FPies and improve care for patients with FPies.
908 A New Valid and Reliable Parent Proxy Questionnaire to Measure the Impact of Food Protein Enterocolitis Syndrome on Children: The Fpies Quality of Life Questionnaire, Parent Form
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RATIONALE: No tool currently exists to measure health related quality of life (HRQL) in Food Protein Enterocolitis Syndrome (FPIES). We investigated the ability of the Parent Form of Food Allergy Quality of Life Questionnaire (FAQ-LQ-PF) to accurately assess the impact of FPIES on the HRQL of children, aged 0-12 years.

METHODS: 148 European caregivers of children with FPIES completed on-line versions of the FAQ-LQ-PF and the Food Allergy Independent Measure (FAIM). FAQ-LQ-PF items were rated for relevance and importance. Participants were asked if any other questions should be included and/or if any of the questions should be reworded. The questions underwent further psychometric analysis including factor analysis and clinical impact methods to modify the items, and scale and item analysis to assess reliability and construct validity.

RESULTS: Caregivers of 148 children (62% male) aged between 6 months and 9 years completed the questionnaires. 19 of the 30 items were identified as relevant (Overall Importance Mean = 2.0). An additional 5 rated as Somewhat Relevant to Relevant (Overall Importance Mean > 1.5). These were reworded as suggested by participants. Analyses demonstrated high reliability (α = .92). Bartlett’s test of sphericity, χ²(45) = 257.3, p < .001, showed good correlation between items. Three components had eigenvalues over the KMO criterion of 1 and explained 64% of the variance in the impact of FPIES on HRQL, demonstrating construct validity.

CONCLUSIONS: The new questionnaire allows for a disease specific analysis of HRQL in FPIES. Further reliability and validity testing of this index is on-going.

909 Assessment of Self-Efficacy in Food Protein Induced Enterocolitis Syndrome
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RATIONALE: Improved self-efficacy (SE) improves health related quality of life (QoL), lessens uncertainty and anxiety, and strengthens self-determination and health care in chronic diseases. We sought to investigate the relationship between SE and QoL in children with food protein induced enterocolitis syndrome (FPIES).

METHODS: 180 European caregivers completed the Food Protein Enterocolitis Syndrome quality of life questionnaire (FPIES-QLQ-PF), modified from the Food Allergy Quality of Life, Parent Form (FAQ-LQ-PF), and a new Food Allergy Self-Efficacy Questionnaire (FASEQ). We used principle component analyses and Pearson’s correlational analyses to investigate the relationship. Similar analysis was conducted between the FASEQ and the Food Allergy Quality of Life Parental Burden (FAQL-PB) in a US caregiver cohort (n=68).

RESULTS: In the European cohort, index reliability was high for all measures (α = .94). Bartlett’s test of sphericity, χ²= 274.5 < χ².001, showed good correlation between items. PCI of the FASEQ revealed two components (‘self ’and ‘environmental’ control) explaining 72% of the variance in self-efficacy. Correlations between subscales of the FAQ-LQ-PF (emotional impact, food anxiety, and social and dietary restrictions) and the FASEQ-PF ranged from 0.4 to 0.7 (p<0.05). FASEQ had high reliability in the US cohort (α = .88), good correlation with the FAQL-PB (r=0.4, p <0.001), and has a single component explaining 58% of the variance in self-efficacy.

CONCLUSIONS: The use of a measure of SE may help clinicians and researchers to investigate the correlates of QoL in FPIES which in turn will help to fine tune interventions to improve both self-management and well-being.

910 Caregiver Quality of Life in Food Protein Enterocolitis Syndrome
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RATIONALE: Food Protein Enterocolitis Syndrome (FPIES) is a non-IgE mediated gastrointestinal food allergy. Caregiver quality of life (QoL) in FPIES is unknown, as no FPIES QoL measure exists.

METHODS: The Food Allergy Quality of Life-Parental Burden (FAQ-LPB) index, the PedsQL, and the Food Allergy Independence Measure (FAIM) were co-administered to 68 caregivers attending an FPIES advocacy conference. FAQ-LPB responses were compared to an academic cohort of caregivers of children with IgE-mediated food allergy (FA) (n=305).

RESULTS: Among FPIES caregivers, 77%(n=52) reported children with multiple food FPIES. 50% reported income>$100,000, and 70.6% graduated college. The index had a Cronbach’s-α of 0.91. Mean FAQ-LPB score was 3.2 (95% CI 2.88-3.44) and mean PedsQL score was 1.9 (95% CI 1.67-2.05). FAQ-LPB had good construct validity with strong correlation to both the PedsQL (r=0.73, p<0.001) as well as to the FAIM (r=0.39, p=0.001). Individual FAQ-LPB domains were strongly correlated with PedsQL score (0.49), and mildly correlated with FAIM score (0.25). Caregivers of children with FPIES had significantly worse (higher) mean and individual domain QoL scores than caregivers of children with FA (3.1 vs. 1.9, difference 1.29, p<0.001). Factor analysis of the FAQ-LPB revealed 3 domains in the FPIES population, versus 2 in the FA population.

CONCLUSIONS: The FAQ-LPB is a valid measure to assess caregiver QoL in FPIES. Caregiver QoL in FPIES is significantly worse than in caregivers of children with FA, indicating this population is at particular high risk.
**911 Pre-Treatment Level of Specific Grass IgE Is Associated with Efficacy and Safety of a Timothy Grass Sublingual Immunotherapy Tablet**

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**RATIONALE:** Post-hoc efficacy and safety of Timothy grass (TG) sublingual immunotherapy tablet (SLIT-tablet) was evaluated in subjects with varying pre-treatment levels of specific TG IgE.

**METHODS:** Pre-treatment IgE levels against TG and its allergen components (Phl p) were determined by ImmunoCAP-ISAC for a subset of 1140 randomized North American subjects in a double-blind, placebo-controlled grass SLIT-tablet (2800 BAU/Merck/ALK-Abelló [MK-7243]) trial (NCT01385371). Subjects were TG skin-prick-test–positive and IgE-positive. Total combined symptom+medication score (TCS) and 23.3%. TRAE incidence with grass SLIT-tablet in subjects with undetectable pre-treatment Phl p-IgE was 48.2% and 49.7%, respectively.

**RESULTS:** TCS improvements versus placebo by Phl p1-IgE groups 1–3 were 3.2%, 32.1%, and 30.6%, respectively, and by Phl p5-IgE groups 1–3 were 7.7%, 23.9%, and 35.4%. TCS improvements for subjects with undetectable Phl p1- and Phl p5-IgE were 35.4% and 18.7%, respectively, indicating different Phl p sensitization profiles impact efficacy. TRAE incidence with grass SLIT-tablet by Phl p1-IgE groups 1–3 was 54.7%, 55.7%, and 74.3%, respectively, and by Phl p5-IgE groups 1–3 was 56.1%, 66.6%, and 74.5%. Corresponding placebo values were 27.6%, 21.9%, and 21.3%, respectively, and 23.7%, 23.3%, and 23.3%. TRAE incidence with grass SLIT-tablet in subjects with undetectable Phl p1- and Phl p5-IgE was 48.2% and 49.7%, respectively. Corresponding placebo values were 20.4% and 23.2%. Other major Phl p demonstrated similar trends but with greater population diversity.

**CONCLUSIONS:** Subjects with detectable and higher pre-treatment Phl p-IgE trended toward higher efficacy and increased incidence of having at least one TRAE.

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**912 Epinephrine Use in Clinical Trials of Sublingual Immunotherapy Tablets for Treatment of Allergic Rhinitis with/without Conjunctivitis**

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**RATIONALE:** We describe epinephrine use in the clinical trial development programs of 3 rapidly-dissolving sublingual immunotherapy tablets (SLIT-tablets; Merck/ALK-Abelló).

**METHODS:** Data on epinephrine use was collected from 8 Timothy grass SLIT-tablet trials (MK-7243; 2800 BAU; Merck/ALK-Abelló; n=2079), 4 short-ragweed SLIT-tablet trials (MK-3641; 1.5, 6, and 12 Amb A-1 U, n=1707; placebo, n=757), and 4 house dust mite (HDM) SLIT-tablet trials (MK-8237; 6-DU and 12-DU, n=1424; placebo, n=721).

**RESULTS:** In grass SLIT-tablet trials, epinephrine was used 13 times (grass SLIT-tablet, n=10; placebo, n=3). Eight administrations were for SLIT-tablet-related adverse events (AEs): 4 for systemic reactions and 4 for local events of pruritus and/or swelling in the mouth and/or throat. The remaining 5 administrations were unrelated to grass SLIT-tablet (SLIT-tablet: bed-bug reaction, viral infection; placebo: anxiety, wheezing, vasculitis). Three of the 13 administrations were self-administered. In ragweed SLIT-tablet trials, epinephrine was used 9 times in 8 subjects (ragweed SLIT-tablet, n=7; placebo, n=1 [2 administrations]). Four administrations were for SLIT-tablet-related AEs: 1 for systemic reaction and 3 for swelling in the mouth and/or pharynx/throat. The remaining 5 administrations were unrelated to ragweed SLIT-tablet (SLIT-tablet: food allergy, n=2; vomiting/diarrhea: placebo: anaphylaxis, n=2). Five of the 9 administrations were self-administered. In HDM SLIT-tablet trials, epinephrine was administered once for a SLIT-tablet–related event of mouth/throat pruritus and dysphonia.

**CONCLUSIONS:** Of 8804 subjects in 16 trials for 3 SLIT-tablets, epinephrine administrations were uncommon (event rate=0.1% and 4%) and were for events assessed by the investigator as unrelated to SLIT-tablets.

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**913 Allergen Sensitivity Profile of Subjects with Allergic Rhinitis with/without Conjunctivitis Participating in Clinical Trials of Timothy Grass and Short Ragweed Sublingual Immunotherapy Tablets**

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**METHODS:** Serum specific IgE data against a panel of ≥16 aero-allergens selected based on regional importance were collected from skin-prick-test–positive subjects in 3 grass SLIT-tablet (MK-7243; n=2278) trials and 2 ragweed SLIT-tablet (MK-3641; n=1342) trials. Sensitivity was defined as specific IgE >0.35 kU/L to any allergen tested including: 6 grasses, cat dander, dog epithelium, house dust mites (HDM), 13 trees, short ragweed, and 6 molds.

**RESULTS:** For grass SLIT-tablet trials, 85.6% of subjects were polysensitized. The proportion of subjects with sensitivities in addition to grass were: +1 sensitivity=15.8%; +2 sensitivities=19.9%; +3 sensitivities=18.0%; +4 sensitivities=14.8%; +≥5 sensitivities=17.1%. Overall, 59.8% were sensitized to grass+ragweed, 59.6% to grass+tree, and 35.3% to grass+HDM. A total of 47.7% were sensitized to grass+ragweed+tree, and 21.3% were sensitized to grass+ragweed+tree+HDM. For ragweed SLIT-tablet trials, 80.8% of subjects were polysensitized. The proportion of subjects with sensitivities in addition to ragweed were: +1 sensitivity=13.6%; +2 sensitivities=20.6%; +3 sensitivities=16.5%; +4 sensitivities=13.6%; +≥5 sensitivities=16.5%. Overall, 58.7% were sensitized to ragweed+grass, 57.0% to ragweed+tree, and 36.9% to ragweed+HDM. A total of 47.3% were sensitized to ragweed+grass+tree, and 22.7% were sensitized to ragweed+grass+tree+HDM.

**CONCLUSIONS:** In these North American trials, ~70% of grass- or ragweed-allergic subjects were sensitized to 2 or more other aero-allergens, with tree and HDM being the most frequent additional sensitivities.
914 The Prevalence and Clinical Characteristics of Local Allergic Rhinitis in Thai Children
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RATIONALE: Local allergic rhinitis (LAR) is characterized by local specific IgE (sIgE) production, a nasal Th2 pattern during natural exposure to aeroallergen and a positive response to nasal allergen provocation test (NAPT). This entity affects >47% of adults with nonallergic rhinitis (NAR). In children, the prevalence and characteristics of LAR have not been reported.

METHODS: Children 8-18 years with NAR were recruited. A NAPT with Der p 1 solutions (NAPT-DP) at 200 AU/mL, 600 AU/mL and 2000 AU/mL at 15-minute interval was performed, respectively. The immediate responses to NAPT-DP were assessed using symptoms score, peak nasal inspiratory flow (PNIF) and acoustic rhinometry (ARM). The nasal tryptase and sIgE-DP were measured at baseline, 15 min and 1 h after positive NAPT-DP. Two allergic rhinitis (AR) patients were used as positive control.

RESULTS: Twenty-five NAR subjects (72% boys) had the mean±SD age of 11.1±2.1 years. The mean±SD duration of disease was 6.5±2.5 years. The most frequent comorbidity was asthma (40%). Eighty percent of patients had mild persistent severity. NAPT-DP was negative in all NAR children. There were no significant changes of symptoms score, PNIF and ARM compared to baseline. In contrast, 2 AR patients had positive NAPT-DP and the nasal tryptase showed a peak at 15 min without the change of sIgE-DP after positive challenge. There was no serious adverse event.

CONCLUSIONS: LAR is rare in children. The further investigation in large population of children with NAR is needed.

915 Predicting Acquisition of Sustained Unresponsiveness Following Peanut Oral Immunotherapy Using Skin Prick Test Size and Serum Levels of Immunoglobulins Specific to Peanut
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RATIONALE: Oral challenge is currently being used to assess outcome of peanut oral immunotherapy (OIT) in research trials. We investigated whether peanut specific immune parameters could provide markers of sustained unresponsiveness (SU) as a sub-study within a DBPC randomized trial.

METHODS: The Probiotic and Peanut Oral Immunotherapy (PPOIT) RCT randomised 62 children with peanut allergy aged 1-10 years to receive PPOIT or placebo for 18 months. SU was assessed by DBPC food challenge (FC) 2-5 weeks after stopping treatment. Peanut skin prick test (SPT) and serum sIgE and sIgG4 to peanut and Ara h 1, 2,3,8,9 were determined at baseline (T0), end of intervention (T1) and 12 weeks after T1(T2). Longitudinal changes in immune markers were compared in SU and allergic subjects using Ranksum test. Prediction of SU was assessed by ROC analysis.

RESULTS: There was a significant longitudinal reduction in median peanut SPT and Ara h 2 sIgE along with an increase in median sIgG4 to peanut and Ara h 1,2,3 in children who achieved SU. ROC analysis suggested SPT size of ≥8 mm (positive likelihood ratio (+LR) 9.47, 95% confidence interval (CI)3.2-27.9 at T1, +LR 10.22, 95% CI 3.47-30.12 at T2) and peanut sIgG4 levels of ≥6.01 mg/A/L at T1 (+LR 8.9, 95% CI 1.97-32.45) and ≥3.54 mg/A/L at T2 (+LR 8.35, 95% CI 2.06-33.78) were most useful markers.

CONCLUSIONS: SU was associated with a reduction in peanut SPT weal size and an increase in peanut and Ara h 1,2,3-sIgG4. SPT size and peanut sIgG4 were significant predictors of sustained unresponsiveness in PPOIT trial.

916 Acute Systemic Reduction in Regulatory T Cells Is Associated with Atopic Airway Disease
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RATIONALE: Regulatory T cells (Tregs) control immune responses. We hypothesized that reduction in Tregs would drive atopic disease development. To test this, we utilized Foxp3DTR mice where Tregs are selectively depleted by administration of diphtheria toxin (DTx). The effect of an acute drop in Treg cell numbers on T cell skewing and mucous cell metaplasia was determined.

METHODS: DTx (50 μg/kg) or vehicle was administered i.p. to C57BL6 Foxp3DTR mice. Four and 12 days post DTx, spleen CD4 T cell skewing was determined by intracellular staining after culture with PMA and ionomycin. Serum total IgE was measured by ELISA. Whole lung IL-4-, IL-5-, IL-13-, IFNγ, Muc5ac, and Gapdh message was determined by qPCR.

RESULTS: DTx significantly increased IL-5-, IL-13-, IL-17-, and IFNγ-producing T cell frequencies at day 4 and 12 (p<0.05 versus vehicle, n=5). The fold increase over vehicle was greatest for IL-5 and IL-13 (day 4: 100.9, 39.9, 12.2, and 6.9, respectively; day 12: 91.2, 35.6, 5.4, and 4.1). Serum IgE also significantly increased (1.7±1.0 ng/ml baseline; 42.5±18.4 ng/ml day 4; 45.3±7.5 ng/ml day 12; p<0.05; n=4). Similarly, whole lung IL-4-, IL-5-, IL-13, and IFNγ were elevated on day 4 and 12; Muc5ac was elevated at day 12 (0.12±0.03 versus 3.6±1.6 Muc5ac/Gapdh copies, n=4, p=0.004).

CONCLUSIONS: Acute systemic disruption of Tregs dysregulates the immune system, characterized by both Th1 and Th2 skewing. Over time, Th2 disease appears to drive airway atopic disease. Whether this effect is long-lasting is being investigated, as are the effects of less severe disruption in Tregs.
Pre-pregnancy Exposure to Diesel Exhaust Particles Predisposes Offspring to Asthma
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RATIONALE: We and others have shown that exposure to diesel exhaust particles (DEP) during pregnancy predisposes offspring to asthma. It is unknown whether pre-pregnancy exposure has a similar effect.
METHODS: To address this we developed a mouse model. C57BL/6 female mice repeatedly received intranasal applications of DEP or phosphate-buffered saline (PBS). Two weeks after final application, females were mated with unexposed males. Offspring underwent immunization and challenge with ovalbumin or received PBS. Offspring were then examined for features of asthma and levels of pulmonary transcripts for IL-1β, IL-5, IL-6, IL-13, IL-17A, IL-17F, IL-25 and IL-33.
RESULTS: Pre-pregnancy exposure to DEP predisposed offspring to asthma. Compared to ovalbumin-treated pups of PBS-exposed females (PBS-OVA), ovalbumin-treated pups of DEP-exposed females (DEP-OVA) had increased airway inflammation and hyperresponsiveness. We then searched for mechanisms through examination of pulmonary cytokine profiles. DEP alone (without ovalbumin) induced transcripts for IL-1β, IL-5, IL-6, IL-13, IL-17A and IL-25. Ovalbumin synergized with DEP in transcription of IL-1β. For other cytokines, the synergistic/additive effect was not observed. Levels of IL-5, IL-6, IL-13 and IL-17F mRNA were equally elevated in PBS-OVA and DEP-OVA pups. Compared to PBS-OVA pups, DEP-OVA pups had higher levels of IL-1β and IL-17A mRNA.
CONCLUSIONS: Our mouse model links pre-pregnancy exposure to DEP with asthma susceptibility in offspring. “Pre-pregnancy” DEP induces a wide selection of cytokines (Th2, Th17, pro-inflammatory, IL-5). In the context of allergen-induced inflammation, the susceptibility effect of “pre-pregnancy” DEP may predominantly rely on induction of IL-1β and IL-17A.

The Adapter Protein Sprouty 2 (Spy 2) Differentially Regulates Lymphoid and Myeloid Cell Function and is Important for Allergic Asthma
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RATIONALE: Sprouty 2 is an adapter protein that is known to negatively regulate MAPK signaling in most cell types. Its function in hematopoietic cells is largely known.
METHODS: We have developed a tamoxifen inducible Spy2 knockout mouse line (Spy2f/f;ERTCre). Hematopoietic cells were studied by flow cytometry, western blotting and functional assays. The development of asthma was analyzed by measuring airway hyperreactivity to methacholine (Flexivent) and airway inflammation.
RESULTS: Tamoxifen induced deletion of the spy2 gene in adult mice caused a significant reduction in proportion and absolute cell numbers of lymphoid cells—splenic T cells (p<0.05), B cells (p<0.05) and NK cells (p<0.01) in comparison to their wild type (WT) counterparts (spy2f/f). In contrast, the percentage and number of myeloid cells—macrophages (p<0.05) and neutrophils (p<0.01) were increased. Spy2 KO CD4 T cells displayed defective proliferation in response to TCR but not PMA+ionomycin. CD8 proliferation was normal. CD4+ T cells from Spy2 KO produced decreased levels of IL-2 in vitro (p<0.05). T cells, B cells and neutrophils exhibited defective activation of Src family kinases and multiple downstream pathways including ERK1/2 and Akt. Deletion of spy2 after immunization with Aspergillus was associated with reduced BAL eosinophils but increased neutrophils. Airway hyperreactivity to methacholine was significantly reduced.
CONCLUSIONS: Spy2 exerts a dichotomous effect on hematopoietic cell signaling and activation. Spy2 is a positive regulator of lymphoid cell lineages and eosinophils but is a negative regulator of neutrophils and macrophages. Spy2 signaling is critical for development asthma.

Proteolytic Activity of per a 10 Cleaves Tight Junction Proteins and Increases TSLP Secretion
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RATIONALE: Serine protease activity of Per a 10, a major allergen from Periplaneta americana augments airway inflammation in mouse model. The present study is aimed to assess the role of protease activity of Per a 10 on junctional proteins.
METHODS: Calu-3 cells were exposed to proteolytically active native nPer a 10 or heat inactivated ∆Per a 10 to check the effect of its activity on epithelial permeability and tight junctions. nPer a 10 or ∆Per a 10 was administered i.n. to Balb/c mice three days a week for two weeks and mice were sacrificed on 15th day. Immunoglobulin levels were assessed in sera, cytokines in BALF and TSLP in lung homogenate. Tight junction cleavage was assessed by immunohistochemical analysis of lung sections.
RESULTS: Per a 10 increases the transepithelial permeability of Calu-3 cells in time and activity dependent manner by disrupting tight junction proteins ZO-1 and claudin-1. There was significant increase in permeability from one hour of exposure and increased gradually till 16 hours. nPer a 10 exposed mice has significantly higher IgE levels in sera, IL4, IL33 levels in BALF and TSLP levels in lung homogenate. Immunohistochemical analysis of lung sections shows disruption of ZO-1 and claudin-1 in nPer a 10 exposed mice. There was no significant change in IgE and cytokine levels in mice exposed to inactive Per a 10 as compared to control group of mice.
CONCLUSIONS: Proteolytic activity of Per a 10 causes airway inflammation in mouse model by tight junction protein cleavage and elevation of TSLP and IL33 levels.

Association Between IL-13 -1112 C/T Promoter Polymorphism and Patterns of Allergen-Induced Asthmatic Response in House Dust Mite Allergic Patients
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RATIONALE: Interleukin-13 (IL-13) plays a crucial role in allergic asthma. The aim of this study was to evaluate a possible association between IL-13-1112 C/T promoter polymorphism and patterns of allergen-induced asthmatic response in house dust mite (HDM) allergic patients.
METHODS: 150 HDM-allergic asthma (AA), 142 HDM allergic rhinitis (AR) and 150 nonatopic healthy controls (HCs) were studied. Bronchial reactivity to histamine and allergen were evaluated in all HDM-AAs. The presence of individual polymorphisms was assessed using allele specific polymerase chain reaction. In 30 HDM-AAs in vitro IL-13 expression by allergen-stimulated peripheral blood mononuclear cells (PBMCs) was evaluated using ELISA and real-time polymerase chain reaction methods.
RESULTS: The frequency of the T allele in HDM-AA patients (0.46) was significantly greater than in HDM-AR patients (0.28, p<0.05) and in HCs (0.19, p<0.01). The greatest baseline bronchial reactivity to histamine was demonstrated in HDM-AAs carrying two T alleles. After intrabronchial allergen challenge the late asthmatic response developed in 84.6%, 54.1% and 30% of HDM-AAs with the TT, CT and CC genotype respectively (p<0.05). In vitro, allergen-stimulated PBMCs from HDM-AAs with TT genotype released more IL-13 than those from the patients with CT or CC genotypes. This was accompanied by elevated expression of IL-13 on RNA level.
CONCLUSIONS: Altered IL-13 expression due to IL-13-1112 C/T promoter polymorphism may predispose to asthma via augmented inflammatory response after allergen exposure of sensitized individuals.