792  The Effect of Aerobic Exercise on Asthma-related Responses in Adults  
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RATIONALE: Increasing evidence indicates that decreased physical activity may play a role in asthma development (Lucas & Platt-Mills, 2005). In light of this evidence, this study has examined the effect of moderate intensity aerobic exercise on asthma responses in adult patients.  
METHODS: We have completed a randomized, parallel group proof of concept study in which sixteen adults (33 - 78yrs) with mild to moderate persistent asthma were assigned randomly to either: i) a 12-week protocol of moderate intensity aerobic exercise plus usual care or ii) a 12-week protocol of usual care only. All participants had evidence of reversibility via spirometry as performed by the ATS guidelines. Exercise participants completed a walking program at a frequency of 3x/wk, 60 - 75% of age-predicted HRmax.  
RESULTS: Before and after protocol completion, participants were monitored for differences in asthma control, lung function, and pro-inflammatory targets in peripheral blood and nasal lavage. Results suggest that participants in the exercise group exhibited a trend toward improved fitness levels, including increased VO2 peak and total treadmill time. Subjects in both groups exhibited improved asthma control; no changes were observed in lung function or pro-inflammatory mediator levels. As indicated by heart rate monitors and exercise logs, adherence in the exercise group was satisfactory.  
CONCLUSIONS: This study has demonstrated the feasibility of the protocol and measurements, established proof of concept, and generated preliminary data for a larger, clinical efficacy trial that will test the efficacy of exercise as an adjunct therapy for the treatment of asthma.

793  The Effects Of Asthma On REM-related Sleep-disordered Breathing In Children With Obstructive Sleep Apnea (OSA)  
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RATIONALE: Sleep-disordered breathing (SDB) occurs in up to 50% of children with asthma. The literature suggests that children with asthma have an increase in sleep apnea and hypopnea index (SAHI) during REM sleep. The association of asthma and SDB in children is not clear. This study evaluated the relationship of REM sleep apnea and hypopnea index (SAHI) and obstructive sleep apnea-hypopnea index (AHI) during sleep cycles in asthmatic children with OSA.  
METHODS: 100 children were divided into three groups: 20 children with only asthma (A), 20 children with both asthma and OSA (AO), and 60 children with OSA alone (OA). The severity of asthma was assessed using the asthma control test (ACT).  
RESULTS: Subjects with OSA had significantly higher AHI (34.6/hr; 95%CI 22.8 - 56.7/hr) and SAHI (11.4/hr; 95%CI 6.3 - 18.4/hr) in both the AO and OA groups compared to A group (AHI: 10.2/hr; 95%CI 7.7 - 13.8/hr; SAHI: 4.6/hr; 95%CI 2.8 - 6.1/hr). Ogilvie index was also significantly greater in the OA group (Ogilvie index: 29.6% vs. 16.2% in A and AO groups, respectively). No significant difference was found in TST. No significant correlation was found between the AHI and the ACT scores.  
CONCLUSIONS: These results demonstrate that in the setting of OSA, the nocturnal respiratory disturbances associated with pediatric asthma are determined by sleep cycle biology as they occur predominantly during REM sleep. Thus, our data support the novel notion that sleep neurobiological mechanisms modulate the phenotypical expression of the asthmatic condition in children.

794  Positive Bronchial Responses To D. pteronyssinus In Subjects With Confirmed Local Allergic Rhinitis  
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RATIONALE: Local allergic rhinitis (LAR) is characterized by positive responses to nasal challenge with allergens in absence of systemic atopy. Subjects with LAR frequently show other co-morbidities including asthma. The possible role of allergens in the bronchial symptoms of subjects with LAR has not been addressed.  
METHODS: Twenty subjects with confirmed LAR with D. pteronyssinus (DP) and asthmatic symptoms (LARA), 20 subjects with allergic rhinitis with DP and asthmatic symptoms (ARA) and 10 healthy subjects as control group (CG) were recruited. Bronchial challenge was performed with DP extract at 4 μg/ml. Metacholine challenge and induced sputum were performed prior to and 24 hours after challenge. Cell populations and Th1/Th2 cytokines in sputum were evaluated by flow cytometry, and ECP and triptase in sputum by CAP method.  
RESULTS: Forty percent of LARA and all ARA subjects had positive responses to bronchial challenge with DP. DPc20 values decreased in both groups 24 hours after challenge (p <0.05). Sputum ECP values also increased after challenge in both LARA and ARA groups (16.8±14.5 vs. 20.1±21 and 52±69 vs. 95±298, respectively). Also, an increase in sputum eosinophils was observed (LARA: 6.9±11 vs. 14.2±7.3, ARA: 3.7±3 vs. 7.2±6). LARA subjects had higher values of IL5,IL8, IL10, IL12 and IFN-gamma at baseline compared to ARA and controls, but no significant variations after challenge.  
CONCLUSIONS: Positive responses to D. pteronyssinus were observed in the lower airways of subjects with clear history of asthmatic symptoms. Similar methacholine responses and increases in ECP and eosinophil levels were observed in both LARA and ARA groups.

795  Relationships Between Airway Hyperresponsiveness to Methacholine, Blood Eosinophil Markers and FeNO in Asthmatic Children  
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RATIONALE: Airway inflammation, airflow limitation, and airway hyperresponsiveness (AHR) are distinctive features of asthma. Eosinophilic inflammations in the airways are correlated with baseline lung function and AHR. Fractional concentration of exhaled nitric oxide (FeNO) is one of the useful markers of eosinophilic airway inflammation in asthmatic patients.  
METHODS: Measurements of baseline pulmonary function and methacholine challenge tests were performed in 55 children with mild persistent to moderate asthma. They were followed up at the Allergy Clinic of Korea University Anam Hospital. Each subject was evaluated by serum total IgE, blood eosinophil counts and serum eosinophil cationic protein (ECP). FeNO levels were evaluated in two occasions, i.e., ‘at baseline’ and the ‘just after challenge’.  
RESULTS: The mean (range of 1 SD) post-methacholine challenge FeNO level (25.7 ppb [13.8-47.9]) was significantly lower than the baseline level (36.3 ppb [20.9-63.1]; p=0.001). FeNO levels significantly correlated with the methacholine PC20 (r= -0.527, p=0.0001), blood eosinophil counts (r=0.296, p=0.028), but not with the serum ECP levels (r=0.174, p=0.203).  
CONCLUSIONS: FeNO, one of the surrogate markers in airway inflammation in asthmatics may be decreased after repeated spirometry. The levels of FeNO were correlated with methacholine airway hyperresponsiveness and blood eosinophil counts in asthmatic children.
Comparison of Respiratory Impedance Data Measured by the MostGraph and Master Screen IOS in Adults with Bronchial Asthma

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RATIONALE: An impulse oscillometry systems (IOS) is a type of respiratory resistance meter that uses the forced oscillation technique to analyze respiratory impedance. An IOS can assess the function of central and peripheral airways separately. The MostGraph is another oscillation-based system. We assessed the correlation of respiratory impedance measurements between the MostGraph-01 (Chest M.I., Tokyo, Japan) and the Master Screen IOS-J (Jaeger/Toennies Höchberg, Wurzburg, Germany).

METHODS: The population consisted of 66 adults with bronchial asthma. Concurrently with acquisition of measurements from the MostGraph and IOS, measurements of flow volume, closing volume, fractional exhaled nitric oxide (FeNO) and an acetylcholine inhalation test (PC20) were also performed, to further analyze the correlation between these parameters.

RESULTS: A comparison of measurements by the MostGraph and IOS revealed significant correlation (p < 0.001) in both the resistance components (R5 [r = 0.86], R20 [r = 0.82], and R5-R20 [r = 0.72]) and the reactance components (X5 [r = 0.80], AX [r = 0.86], and Fres [r = 0.82]). These parameters (R5, R20, R5-R20, X5, AX, and Fres) measured by the MostGraph and IOS were significantly correlated with ∆N2, FEV1, V50, V25, and PC20 (r = 0.3 to 0.4, p < 0.01) in non-smokers but not in smokers. No significant correlation with FeNO was found in any parameter measured by the MostGraph or IOS (r < 0.2, p > 0.2).

CONCLUSIONS: Our study of adults with bronchial asthma demonstrated significant correlation between all parameters measured by the MostGraph and Master Screen IOS. These parameters were also correlated with respiratory function and airway hyperresponsiveness, but would not serve as a marker of airway inflammation.

Maternal Diet during Pregnancy and Wheeze and Eczema in Infants; the Japanese Birth Cohort (T-CHILD) Study

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RATIONALE: This prospective birth cohort study examined the effect of maternal diet during pregnancy on the emergence of wheeze and eczema in infants.

METHODS: A total of 1,344 Japanese mother-infant pairs from a prospective birth cohort (Tokyo-Children’s Health, ILlness and development; T-CHILD) study, who responded to a diet history questionnaires in the second trimester and health event questionnaires at 6-8 months, 12 months, 18 months, 2 and 3 years of age were investigated. Health event questionnaires include items of the International Study of Asthma and Allergies in Childhood (ISAAC).

RESULTS: Cumulative incidence of wheeze and eczema at 6-8 months was 12.6% and 62.1%, respectively. Maternal intake volume of calcium was positively associated with eczema up to 6-8 months (Odds ratio (OR) between extreme quartiles was 0.632, 95% confidence interval (CI) 0.429-0.932), but with wheeze. The prevalence of current wheeze was 16.2% at 12 months, 16.6% at 18 months, and 5.2% at 2 years, 15.3% at 3 years of age, respectively. Point prevalence of current eczema was reported 60.1% at 12 months, 45.3% at 18 months, and 34.7% at 2 years, 31.0% at 3 years of age respectively. There were no evident relationships between maternal consumption of dairy food, fish, vitamin D, n-3 and n-6 polyunsaturated fatty acids during pregnancy and the risk of wheeze and eczema in the infants up to 3 years of age.

CONCLUSIONS: Maternal consumption of calcium during pregnancy may have the protective effect on eczema in early infancy.

The Elevation Of Th2 cytokines In Airway In Infants With RSV Infection Is High Risk For Recurrent Wheeze In Young Children

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RATIONALE: The correlation between RSV infection in infants and recurrent wheeze has been long discussed. Recently, epidemiologic study proved that newborn who develops childhood asthma shows high possibility of detecting bacterial colonization in his airway, suggesting congenital immunological difference between asthmatics and non-asthmatics. However, there is not enough information in airway cytokines and with or without post-RSV recurrent wheeze. Here, we examine the levels of airway mediator in infant of RSV infection between with or without recurrent wheeze.

METHODS: 28 RSV positive children between the age under 6month old were participated in the study. 8 children showed recurrent wheeze (Wheezer) and 20 were transient symptoms (Control). 6 kinds of cytokines, IL-4, IL-10, LTE4, ECP, IFN-g and RANTES in nasal aspiration were measured by using ELISA Kit (R&D systems, Mineapolis, MN) according to the manufacturer’s protocol. Unpaired-t test were used for statistic analysis. We followed the prognosis of patients by reference to patient records 1 year from the date on which the initial diagnosis had been made.

RESULTS: The levels of IL-4, IL-10 and RANTES of recurrent wheezers (n = 8) were significantly higher than those of controls (n = 20). (p = 0.02, 0.02, 0.03 respectively) However, LTE4, ECP, and IFN-g did not show any difference. (p = 0.15, 0.94, 0.0526 respectively).

CONCLUSIONS: The infant who is likely to develop recurrent wheeze releases significant amount of Th2 cytokines when infected with RSV. Our study suggest there might be an immunological difference in their early childhood before infected in RSV.

Unmet Awareness of Allergic Asthma

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RATIONALE: Atopy with increased production of IgE has been demonstrated to be the underlying cause of most cases of asthma (Sanderstrom T, J Asthma Allergy 2009; 2:49-62). Many asthma sufferers and primary care providers are still not well aware of this significant relationship. A survey conducted by the Asthma and Allergy Foundation of America revealed that 81% of the general population and 63% of asthma sufferers were not aware that the most frequent form of asthma is allergic asthma. The goal of our study was to further investigate the association of asthma and atopy by means of a clinical history of allergies and skin testing to environmental allergens.

METHODS: We evaluated 122 patients (n = 122; mean age 42 years) with the diagnosis of asthma according to the American Thoracic Society criteria. All patients underwent allergy skin testing and spirometry.

RESULTS: Of the 122 patients with asthma, 93 patients (76%) had a positive allergy skin test to environmental allergens that correlated clinically with a history of asthma symptoms.

CONCLUSIONS: Primary care providers and asthmatic patients should be aware of the correlation between allergy and asthma, and that allergen exposure in sensitized subjects is a major inducer of airway inflammation and obstruction. Thus, both physician specialists treating asthmatic patients and asthma support groups should continue to expand their campaign to educate the public of this association in order to better achieve asthma control. Consequently, asthma management should include an allergy evaluation for potential allergen avoidance to further help decrease morbidity and mortality from bronchial asthma.
All abstracts are strictly embargoed until the date of presentation at the 2012 Annual Meeting

**800** Specific Expression of Cytokine Receptor-like Factor-1 and IL-27p28 in Fibroblast-Like Synoviocytes: Potential Feedback Loops to Modulate the Inflammatory Axis in Arthritis

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**RATIONALE:** Both the cytokine receptor-like receptor factor-1 (CRLF1)-cardiotrophin-like cytokine (CLC) complex and heterodimeric IL-27 (EBI-3/p28) share receptor signaling subunits (gp130). In addition, an alternative secreted complex, formed by CRLF1 and IL-27p28, can drive Th17 differentiation in vitro (Journal of Immunology, 2009, 183:7692-7702). Given the known pleiotropic effects of these cytokines on the inflammatory response, we analyzed for their expression in fibroblast-like synoviocytes (FLS).

**METHODS:** FLS and dermal fibroblasts (DF) were derived from rheumatoid arthritis (RA), OA, and post-trauma patients. Specific mRNA expression of CRLF1, IL-27p28 and EBI-3 was quantitated by real-time PCR after stimulation with 10 ng/ml of TNFα, IL-1β, IL-17 and lipopolysaccharide, both alone and in combination treatments.

**RESULTS:** Expression of CRLF1, which encodes the gene responsible for Crispom syndrome, was greater than 20-fold in FLS compared to DF. Its increased expression in RA-FLS. Its potential heterodimeric partner, CLC, was constitutively and equally expressed in DF and FLS. No increased expression in CRLF1 or CLC was noted after stimulation. In contrast, TNFα significantly increased mRNA expression of the EBI-3 subunit of IL-27 in DF and FLS (p<0.012 and p<0.009, respectively). Furthermore, a specific increase in the second subunit of IL-27, the p28 subunit, was noted in FLS but not DF, after TNFα stimulation (n=17, p<0.03).

**CONCLUSIONS:** CRLF1 and IL-27p28 are specifically expressed in FLS. Identification of the composition of their potential heterodimeric partners may provide clues to important feedback loops in the inflammatory arthritis.

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**802** Suppression of Delayed Type Hypersensitivity by Fullerene Derivatives

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**RATIONALE:** Water-soluble fullerene derivative (FD) C60 which modulate IgE immune responses may also impact delayed type hypersensitivity (DTH). **METHODS:** Water-soluble of FDs containing e-aminoacproic acid (C60-Acp), L-arginine (C60-Arg), L-lysine (C60-Lys) and cyclic diamine aziridine (C60-Pip6) were synthesized. DTH was induced by s.c. immunization of BALB/c mice with 100 μg of keyhole limpet hemocyanin (KLH) emulsified with Freund’s complete adjuvant (FCA). Two weeks later pre-sensitized mice were challenged by i.d. right rear footpad injections with 20 μg of KLH in 50 μl of PBS and left rear footpad injection of 50 μl PBS only. 24 h before immunization FD treated groups were administered i.v. 200 μl of 10 μg/ml: Group1- C60-Acp; Group 2- C60-Acp; Group 3- C60-Lys; Group 4- C60-Pip6; Group 5 control- 200 μl PBS; Group 6- non-sensitized but challenged with KLH. DTH was determined by measuring footpad thickness prior to and at 24, 48, 72 and 144 hours post challenge expressed as thickness change area under the curve (AUC).

**RESULTS:** KLH challenge in sensitized mice gave maximal footpad swelling at 24-48 h post-challenge. No footpad edema was observed in non-sensitized animals. Treatment of mice with FD C60-Acp or C60-Lys (Groups 1 and 2) did not lead to footpad swelling in comparison to control (Group 5). Treatment of mice before the sensitization with C60-Lys (Group 3) slightly decreased DTH; treatment with C60-Pip6 (Group 4) significantly suppressed DTH compared to Group 5.

**CONCLUSIONS:** DTH can be suppressed by treatment with FD C60-Pip6 suggesting possible therapeutic value for FDs in treatment of DTH inflammatory conditions.

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**803** Immunologic Phenotype Of GRK3-null Mice At Baseline And In Inflammatory Disease

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**RATIONALE:** Chemokine receptors are G-protein coupled receptors (GPCRs) phosphorylated by G-protein receptor kinases (GRKs), which turn off GPCR signaling. Recently, the GRK3 isoform was shown to uniquely regulate CXCL12/CXCR4 signaling in WHIM (Warts, Hypogammaglobulinemia, Infections, Myelokathexis). Therefore, we chose to examine the immunologic phenotype of the GRK3-null (GRK3--/--) mouse at baseline and in inflammation.

**METHODS:** After CXCL12 stimulation of leukocytes, CXCR4 internalization was measured by flow cytometry, and Erk1/2 activation was assessed by Western blot. Chemotaxis to CXCL12 was measured by flow cytometry as % migrated granulocytes from baseline input through endothelial-coated Transwells. Quantitative serum immunoglobulins were measured by ELISA. Blood leukocytes were enumerated in BD TruCount tubes by flow cytometry. Inflammatory arthritis models (serum transfer K/BxN, Collagen Antibody Induced Arthritis or CIA, and type II Collagen Induced Arthritis or CIA) were performed using standard published techniques.

**RESULTS:** GRK3--/-- mice share some immunologic similarities to WHIM patients (delayed internalization of the CXCR4 receptor on leukocytes, enhanced chemotaxis of leukocytes to CXCL12, and myelokathexis). Immunologic differences from WHIM include a peripheral blood leukocytosis with lymphocyte expansion and mild antibody defects (IgG1, IgA, and IgE decreased). GRK3--/-- mice are protected in all three inflammatory arthritis models and have fewer circulating granulocytes in the peripheral blood and decreased relative mRNA expression of granulocyte markers (elastase and myeloperoxidase) in the joints during active inflammatory arthritis.

**CONCLUSIONS:** We conclude that the GRK3--/-- mouse has partial immunologic features of WHIM and may protect mice from inflammatory arthritis through negative regulation of CXCR4/CXCL12 mediated signaling and altered trafficking of granulocytes.
804 Cytokine Status In Patients With Systemic Lupus Erythematosus
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RATIONALE: The production of cytokines involved in the inflammation is crucial for the development of system lupus erythematosus (SLE) as well as SLE complications, such as lupus nephritis (LN). Establishment of predictive tests for SLE complications is important. This study evaluates serum, urine and intracellular cytokines in SLE and SLE+LN.

METHODS: Blood samples from patients with SLE (n=14), SLE+LN (n=15) and healthy controls (C) (n=16) were assayed for intracellular IL4, IFN-γ and TNF-α. Serum and urine samples assayed for IFN-γ, IL17, IL6, IL1β and IL8 by ELIZA.

RESULTS: The number of IL17+ Th17-cells and IFN-γ + Th1-cells was significantly increased in SLE and SLE+LN patients in comparison with the C. However no differences between SLE and SLE+LN patients were observed. No correlation between intracellular cytokine levels was also found supposing highly variable individual cytokine spectra. Correlation between intracellular IL17 and serum IL1β, IL8 was shown consistent with their proinflammatory activity and chemotactic role for neutrophils. Serum IL6 levels were correlated with urine IL17, and levels of urine IL8 excretion with IL1β in urine. INF-γ levels were undetectable in the vast majority of patients’ serum.

CONCLUSIONS: Increase of Th1 and Th17 polarized T-cells was established in SLE and SLE+LN patients while no differences between groups was found. Some correlations between intracellular, serum and urine cytokines support the role of these cytokines in the inflammation, but don’t help to predict LN. The future prospect is to study mRNA expression of genes involved in the immune system functioning using DNA-microarray.

805 Exhaled nitric oxide a biomarker for activity of Systemic Lupus Erythematosus in children
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RATIONALE: Several studies have shown increased levels of serum NO in lupus correlates with activity of the disease. Our objective was to determine if exhaled NO (eNO) levels correlates with SLE disease activity scores.

METHODS: Patients diagnosed with Systemic Lupus Erythematosus (SLE) according to 1997 revised criteria for classification of SLE (n=24) and healthy aged matched controls (n=10) were recruited at SUNY Downstate Pediatric Lupus clinic. Both groups underwent measurement of eNO (Aerocline). Lupus activity index (LAI) was assessed before the measurement along with the evaluation of laboratory values by a physician for the group diagnosed with SLE. Spearman correlation and Mann-Whitney test were used for statistical analysis.

RESULTS: The eNO measurements showed a statistically significant correlation between the presence of lupus nephritis and increased eNO (p-value=0.007). With in the SLE group the spearman correlation between LAI and eNO was 0.299, which indicates a weak association between increased activity scores and eNO, however it is not statistically significant (p-value=0.156).

CONCLUSIONS: In the SLE cohort there was a statistically significant correlation between the elevated eNO and the presence of lupus nephritis. Association between increases in both LAI and eNO remained weak. This study shows measurement of eNO may be applied as a marker for the development and progression of nephritis in children with SLE.

806 Periodic Fever, Aphthous Stomatitis, Pharyngitis and Adenitis (PFAPA) Syndrome: Evaluation of Patients in San Diego, California
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RATIONALE: Periodic Fever, Aphthous stomatitis, Pharyngitis and Adenitis (PFAPA) syndrome is an inflammatory disorder of childhood. Little is known about the true incidence, natural course, pathogenesis, and most appropriate therapy.

METHODS: Patient data was collected for over 150 children with recurrent fevers including 70 patients with PFAPA to create a prospective cohort to delineate the natural history of recurrent fever syndromes, with a specific focus on patients with PFAPA, over a 4-year period.

RESULTS: In our cohort, the average age of onset is 2.9 years, but diagnosis delayed until 4.9 years. Febrile episodes last 3-4.5 days and occur every 23-38 days, with 66% experiencing stomatitis, 84% pharyngitis, and 69% adenitis. The diverse ethnic background of San Diego was reflected in this group, without predilection more common to the hereditary fever syndromes. Family histories revealed 33% of patients with a first degree relative with recurrent fevers or tonsillitis and 50% with a history of tonsillactomy in childhood.

For a subset of patients electing to undergo tonsillectomy, symptoms are equivalent to those of entire cohort. Post-operatively, tonsils from patients with PFAPA are notably smaller and grossly friable, although no granulomas or abscesses are noted on histological examination. With an average of 18 months of follow-up, 90% of the patients have not experienced any additional fever episodes.

CONCLUSIONS: Our cohort demonstrates clinical characteristics consistent with PFAPA. The presence of atopic diseases and family history of fevers, recurrent tonsillitis and tonsillectomy suggests that patients with recurrent fever syndromes including PFAPA may have a general propensity toward immunodysregulation.

807 Clinical Features And Prognostic Factors Of Churg-Strauss Syndrome
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RATIONALE: Churg-Strauss syndrome (CSS) is a rare systemic necrotizing small-vessel vasculitis, with accompanying bronchial asthma, eosinophilia, and tissue eosinophilia. Aims of this study were to characterize clinical features of CSS and to evaluate the factors associated with prognosis in Koreans.

METHODS: Medical records were retrospectively reviewed for all physician-diagnosed CSS cases in the Seoul National University Hospital between January 1990 and March 2011. Data was analyzed according to the presence of ANCA or achievement of clinical remission.

RESULTS: A total 52 patients were analyzed. Respiratory tract was the most commonly involved organ (90.4%). All patients received systemic steroids, and 34.6% received additional immunosuppressants such as cyclophosphamide or azathioprine. Renal involvement was less frequent in ANCA (-) patients than ANCA (+) patients (8.6% vs. 42.9%, P=0.048). Clinical remission was attained in 95.3% of patients but 16.3% of them had subsequent relapse. At the time of diagnosis, patients who maintained remission for more than 6 months were relatively older (51 vs. 26 years, P=0.004) and were diagnosed in the earlier stages (P=0.027), showed more frequent respiratory involvement (97.1% vs. 66.7%, P=0.024), less frequent cutaneous involvement (35.7% vs. 77.8%, P=0.030) and generalized symptom (38.2% vs. 0%, P=0.039), and higher initial CRP values (0.54 mg/dL vs. 0.13 mg/dL, P=0.031) compared with those who had relapse within 6 months.

CONCLUSIONS: ANCA (-) patients showed less frequent renal involvement. Factors related with longer remission were relatively older age, earlier stages, less cutaneous involvement, more respiratory involvement, and high CRP levels at the time of diagnosis.
808 B Cell Reconstitution Following Rituximab in Autoimmune Disorders
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RATIONALE: B cell depletion via rituximab, an anti-CD20 monoclonal antibody, has successfully and extensively been used by us and others in lymphomas, autoimmune disorders, and autoimmune complications of common variable immunodeficiency (CVID). The kinetics of B cell reconstitution has, however, not been well documented in immune deficiencies.
METHODS: A retrospective chart review was conducted comparing CD19+ and CD20+ reconstitution in one patient with lymphoma, two patients with autoimmune disorder, and in two patients with CVID and an autoimmune disorder.
RESULTS: In the CVID group, the reconstitution of both CD19+ and CD20+ B cells lasted over 149 months in one patient. Switch memory B cells were nearly absent in one of the CVID patients pre-rituximab treatment. In the non-CVID patients B cell depletion involved mainly the CD20+ population and resolved after 6-16 months.
CONCLUSION: B cell reconstitution in CVID post rituximab treatment may be markedly delayed and involves both the CD19+ and CD20+ B cells. The delayed or absent recovery may be due to the initially abnormal B cell population in some patients with CVID, especially in those with abnormal switch memory B cells.

809 Effects Of Short-chain Galacto- And Long-chain Fructo-oligosaccharides On Systemic And Local Immune Status During Pregnancy
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RATIONALE: Non-digestible carbohydrates can positively influence health via various mechanisms, but little is known about their effects on the immune system during pregnancy. In this study, immune responses at the feto-maternal interface as well as systemic immune parameters were investigated in mice supplemented with a specific oligosaccharide mixture.
METHODS: Pregnant and non-pregnant mice were fed either a control diet or a diet supplemented with short-chain galacto- and long-chain fructo-oligosaccharides (scGOS/lcFOS; ratio 9:1). 7 days after mating mice were vaccinated with Influvac. Delayed-type hypersensitivity responses (DTH) were induced on day 17 and measured on day 18. Afterwards, mice were sacrificed and systemic and local immune parameters were analysed.
RESULTS: scGOS/lcFOS supplementation improved the DTH in non-pregnant mice, but this effect was not observed in pregnant mice. In contrast, scGOS/lcFOS supplementation did not affect cytokine production by Influvac-stimulated whole blood cells from non-pregnant mice, whereas whole blood cells from pregnantscGOS/lcFOS supplemented mice produced more IL-4 and IL-2 compared to pregnant control mice. Flow-cytometric analysis of maternal splenocytes showed no differences in (activated) T-cell populations. However, in the placentas of scGOS/lcFOS supplemented mice the number of alternatively activated macrophages was increased compared to controls. Furthermore, an increase in splenic IL-10 expression was found in foetuses of scGOS/lcFOS fed mice, as compared to foetuses from control mice.
CONCLUSIONS: In non-pregnant mice the DTH, as a readout for Th1-dependent cellular immunity, is increased after scGOS/lcFOS supplementation. In contrast, scGOS/lcFOS supplementation appears to elicit a more tolerogenic immune reaction in pregnant mice.

810 Eosinophil And Interleukin-5 In Urine Of Patients With Systemic Lupus Erythematosus
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RATIONALE: Lupus nephritis (LN) is an organ-specific autoimmune disease characterized by intra-renal activation of inflammatory cells and the formation of glomerular, tubular, and interstitial lesions. To investigate eosinophils and IL-5 corrected by creatinine (uIL-5/Cr) ratio in urine in patients with systemic lupus erythematosus (SLE), with or without LN, as possible urinary markers of renal inflammation in SLE.
METHODS: Seventy-four patients with SLE, 20 with clinical and laboratory evidence of lupus nephritis (LN group) and 54 without evidence of renal involvement (non-LN group), were analyzed for eosinophilia observed by Hansel’s stain and IL-5 by quantitative sandwich enzyme immunoassay. Eosinophilia and uIL-5/Cr ratios were compared with glomerular erythrocyturia, protein/creatinine ratio (Pr/Cr ratio), serum creatinine, estimated glomerular filtration rate (eGFR), anti-double-stranded DNA (anti-dsDNA), and SLE disease activity index. A p value < 0.05 was considered as significant.
RESULTS: Patients of the LN group had higher eosinophilia and uIL-5/Cr ratios than patients of the non-LN group (p<0.01 for both parameters). These variables showed a significant correlation with numbers of erythrocytes in urine, glomerular dysmorphic erythrocytes and casts; Pr/Cr ratios; serum creatinine levels; eGFRs, anti-dsDNA titers; and SLE disease activity indexes (p<0.05 for all parameters). The ROC curve results demonstrated the performance of eosinophilia (area under curve, AUC = 0.697) and of uIL-5/Cr ratio (AUC = 0.789), using the Pr/Cr ratio as state variable (p<0.01).
CONCLUSIONS: These findings indicated that eosinophilia and uIL-5/Cr ratio showed positive correlations with tests that evaluate renal function and with index of disease activity in SLE patients.

811 Immunologic and Rheumatologic Diseases Temporally Associated With Mycoplasma pneumoniae Infection In Children
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RATIONALE: Although pneumonia has been considered the hallmark of Mycoplasma pneumoniae infection, multiple extrapolmonary manifestations have been reported in the literature. Molecular mimicry between mycoplasmal and mammalian proteins has been postulated as a potential trigger of immune-mediated human diseases. The objective of the present study was to describe immunologic and rheumatologic diseases temporally associated with Mycoplasma pneumoniae infection.
METHODS: We performed a retrospective chart review of pediatric patients with immunologic or rheumatologic diseases and a positive Mycoplasma pneumoniae IgM, who were evaluated at the immunology clinics of the Pontificia Universidad Catolica de Chile health network between 2007 and September of 2011.
RESULTS: Thirty-eight patients were included in the study. Median age was 7.8 years and 55% were female. Respiratory symptoms were present before or during the onset of the immunologic disease in 45%. Maculopapular manifestations were present in 68% of patients (n = 26): acute urticaria (12/26), urticaria multiforme (5/26), Steven Johnson syndrome/toxic epidermal necrolysis (3/26), erythema nodosum (2/26), linear IgA dermatosis (1/26), genital ulcers (1/26), oral stomatitis (1/26) and erythema multiforme (1/26). Nine patients had joint disease: arthritis (n = 6), and arthralgias (n = 3). Vasculitis was observed in 8 patients: Henoch-Schonlein purpura (n = 5), retinal vasculitis (n = 1), cutaneous vasculitis (n = 1), and Kawasaki disease (n = 1). Neurologic diseases were observed in 3 patients: cerebellitis, autoimmune encephalitis and neuroretinitis (n = 1 each).
CONCLUSIONS: The onset of multiple immunologic and rheumatologic diseases may be temporally associated with Mycoplasma pneumoniae infection. Further studies are required to clarify the role this pathogen plays in the etiology and pathogenesis of these immune diseases.
812 Varied Manifestations and Treatment of Pediatric Wegener’s Granulomatosis
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RATIONALE: Wegener’s Granulomatosis (WG) is an autoimmune inflammatory small-vessel vasculitis. Due to disease rarity, less awareness of pediatric manifestations exists compared to adults. As symptoms are often vague or unique, children typically remain undiagnosed until deteriorating clinically. Additionally, little is known about the effectiveness of adjuvant therapies in acute pediatric WG.

METHODS: Three pediatric Wegener’s patients were identified through routine clinical contact in an Allergy/Immunology program. Their medical histories were reviewed and symptoms and clinical progression monitored. Standard treatment protocols of intravenous steroids and cyclophosphamide were initiated. Two required additional agents - plasmapheresis and Rituximab to achieve induction of remission. After the acute phase of illness resolved, patients were followed in clinic to optimize their medication regimens.

RESULTS: These young patients presented with complaints of refractory sinusitis or wheeze. Despite varied presentations, all had pulmonary pathology with pertinent findings on imaging. Each achieved remission with the immunomodulatory agents used. Two required the use of plasmapheresis and one required Rituximab in addition to standard protocols of intravenous steroids and cyclophosphamide.

CONCLUSIONS: Given the heterogeneity of clinical appearance in these patients, it is important to keep WG in the differential diagnosis of pediatric allergic disease, especially if not responding to routine therapy. Each patient successfully achieved remission; one with steroids and cyclophosphamide alone while two also required Rituximab and/or plasmapheresis, demonstrating the clinical effectiveness of these agents in the pediatric population. Education of physicians regarding pediatric Wegener’s may help improve timing from symptom onset to initiation of treatment and decrease disease-associated morbidity.

813 Chronic Urticaria as Possible Manifestation of Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy (APECED)
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RATIONALE: APECED is an autosomal recessive disorder due to mutation of autoimmune regulator (AIRE), a transcriptional regulator of autoantigen expression by medullary thymic epithelial cells. APECED is characterized by autoimmune polyendocrinopathy and chronic candidiasis. Ectodermal abnormalities such as keratoconjunctivitis or vitiligo are common. Furthermore, transient rash with fever has been reported. An association with chronic urticaria, however, has not yet been described.

METHODS: A female patient with chronic urticaria and APECED underwent serial clinical evaluations, genetic testing, serology, and functional histamine release assays.

RESULTS: APECED was diagnosed at age 3 presenting with blepharo-spasms, keratoconjunctivitis and severe hypocalcemia in the setting of intermittent chronic diarrhea. Genetic testing revealed a 13bp deletion in exon 8 of AIRE. Patient’s clinical course entailed alopecia, vitiligo, tooth enamel hypoplasia, hypothryoidism with positive anti-thyroid antibodies, positive 21-hydroxylase antibodies and premature ovarian insufficiency. At age 12 she developed chronic corticosteroid dependent urticaria. FcRI serology and serum histamine release assay results supported the presence of anti-FcRI autoantibodies. Steroid sparing treatment with omalizumab led to resolution of symptoms.

CONCLUSIONS: We present the first case report of APECED with autoimmune chronic urticaria. Further study is warranted to determine if autoimmune urticaria and anti-FcRI autoantibodies are associated with the APECED spectrum of disease, as well as exon 8 specific mutations.

814 Therapeutic Effects Of Recombinant Salmonella Typhimurium Expressing Ccl22 Mirna On Atopic Dermatitis
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RATIONALE: Th-2 biased immune responses are known to play a key role in the pathogenesis of atopic dermatitis. In particular, the macrophage-derived chemokine CCL22 is directly implicated in Th-2 associated skin inflammatory reactions and its levels are significantly elevated in serum and are correlated with disease severity in atopic dermatitis. In this study, we hypothesized the immune suppression using bacteria expressing CCL22 miRNA would be induced therapeutic effects on atopic diseases.

METHODS: The recombinant strain of Salmonella typhimurium expressing CCL22 miRNA (ST-miRCCCL22) was prepared for in vivo knockdown of CCL22. The Ig-E, Interleukin-4 (IL-4), CCL22 and interferon-γ (IFN-γ) were examined after treatments with ST-miRCCCL22 in murine atopic model. In addition, atopic patient’s blood samples were collected and examined for CCL22 expression.

RESULTS: We constructed a recombinant strain of Salmonella typhimurium expressing CCL22 miRNA (ST-miRCCCL22) for the in vivo knockdown of CCL22. The CCL22 gene was downregulated with CCL22 miRNA in activated lymphocytes. In mice with a cutaneous disease similar to atopic dermatitis, Interleukin-4 was inhibited and interferon-g was induced after treatments with ST-miRCCCL22. Furthermore, CCL22 levels were suppressed in the atopic patients.

CONCLUSIONS: ST-miRCCCL22 suppressed Th1 immune responses and induced therapeutic effects in atopic mouse model.

815 Development of an Airway Epithelium In Vitro Model System
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RATIONALE: Airway epithelial cells (AECs) are among the first cells to encounter inhaled antigens and play an integral part in immune homeostasis. To define the airway epithelium role in allergy an in vitro model system with airway epithelial cell lines and dendritic cells (DCs) was used. In order to obtain reproducible effects of AEC-DC co-culture several key steps in the culture procedure needed refinement and optimization.

METHODS: In the original model, 16HBE14o epithelial cells polarize and form a monolayer on culture inserts. Polarization is verified by confocal microscopy analysis and Trans-Epithelial-Electrical-Resistance (TEER) measurements before monocyte derived DCs were added to the basolateral side of the AEC and stimulated with LPS. In the optimized model both AECs and DCs were cultured in the same media on opposite sides of culture inserts compared to the original model.

RESULTS: Allowing the AECs and DCs to be cultured in the same media even before they are co-cultured removes the risk of DCs maturing due to change of media. In the optimized model system, DCs can be added to the system without damaging the epithelial cells. Initial testing with monocyte derived DCs showed an increased expression of ILT3, PD-L1 and CD80 when DCs have been in direct contact with AECs compared to controls, with increased expression of CD23 and ILT3 compared to controls after LPS addition.

CONCLUSIONS: Consistent changes in DC phenotype were observed after AEC-DC co-culture and endotoxin exposure, suggesting that the optimized model can be used to investigate the airway epithelium role in immune responses to allergens.
**816 Interleukin-4 Induces Bronchial Epithelial Cells Barrier Dysfunction**

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**RATIONALE:** Airway epithelia actively participate in lung defense against respiratory pathogens and allergens. The integrity of airway epithelial cells is essential for the maintenance of barrier function and paracellular permeability. Emerging evidence indicates that epithelial barrier function is compromised in asthma, a Th2-dominant disease, but the mechanisms involved are not well understood. The purpose of this study was to investigate the role of Th2-type cytokines on airway epithelial barrier function.

**METHODS:** 16HBE14o- human bronchial epithelial cells monolayers were grown on collagen coated Transwell inserts. The basolateral or apical surfaces of airway epithelia were exposed to human interleukin-4 (hIL-4), TSLP, IL-25, or IL-33 alone or in combination at various concentrations and time points. We analyzed epithelial apical junctional complex (AIC) function by measuring transepithelial electrical resistance (TEER) and permeability to sodium fluorescein (NaF) over time.

**RESULTS:** Transepithelial resistance was significantly decreased after basolateral (but not apical) exposure to IL-4 at 48 and 72 hours, with optimal IL-4 concentrations between 5-50 ng/ml. IL-4 also induced increased epithelial permeability as shown by increased apical-to-basal flux of NaF. None of the other cytokines examined significantly affected TEER. Wortmannin, an inhibitor of PI3 kinase signaling pathway, did not block IL-4 mediated TEER reduction.

**CONCLUSIONS:** Our study indicates that IL-4 has a disruptive effect on airway epithelial barrier function. IL-4 induced epithelial barrier dysfunction may contribute to airway inflammation in allergic asthma. The molecular mechanisms by which IL-4 increased bronchial epithelial cell permeability require further investigation.

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**817 Mutants of the Major Cockroach Allergen, Bla g 2, Modulate T Cell Responses in Cockroach-Allergic Subjects**

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**RATIONALE:** The majority of cockroach (CR) allergic subjects have IgE antibodies to Bla g 2. Our objective was to test whether variants of Bla g 2 that contain mutations in conformational epitopes have the potential to modulate T cell responses and provide candidates for immunotherapy.

**METHODS:** PBMCs from CR-allergic subjects (± anti-Bla g 2 IgE antibodies) were stimulated with 12 Bla g 2 mutants (containing up to 3 point mutations), most of which showed reduced monoclonal antibody and IgE antibody binding. Cytokine responses were assessed by intracellular staining with flow cytometry, and by analysis of culture supernatants by cytometric bead assay. T cell proliferation was assessed by [3H] thymidine incorporation.

**RESULTS:** Both wildtype Bla g 2 and mutants induced IFN-γ/CD4+ T cells, with few IL-4+ or IL-10+ cells, regardless of sensitivity to Bla g 2. In cultures from Bla g 2-sensitized subjects, the deglycosylated variant N268Q enhanced secretion of IFN-γ, IL-5, and IL-13. This mutant also increased TNF-α secretion, and the proportion of IFN-γ+ T cells co-expressing TNF-α. These effects were generally diminished when additional mutations were introduced. In contrast to other cytokines, the variable profile of IL-10 secretion induced by different mutants (likely APC-derived) was remarkably consistent among subjects. Mutants inducing the highest proliferation contained substitutions that mapped to discrete molecular regions, but did not always induce the highest cytokine release, indicating the capacity to uncouple T-cell proliferation and cytokine pathways.

**CONCLUSIONS:** Bla g 2 mutants modulate a Th1-dominated response and have the potential to enhance immunogenicity with or without inducing pro-inflammatory cytokines.

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**818 IgG Fc Receptor Activity in vivo is Under Complement Control**

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**RATIONALE:** Immunoglobulin G (IgG) receptors (FcγR) possess a critical role in the pathogenesis of immune-complex (IC) diseases. Previous reports suggest complement does not affect IC interaction with FcγR, but we assert the classical complement pathway down-regulates IC binding to FcγR. The Arthus reaction is a model of IC-mediated vasculitis, and we performed reverse passive Arthus reactions (RPAR) in normal and C1q-deficient (C1q-/-) C57BL/6 mice. We hypothesized the absence of C1q would enhance IC-mediated tissue damage.

**METHODS:** Sedated and shaved mice (9 normal, 10 C1q-/-) were injected intradermally with 20 μl containing PBS alone on one side and affinity purified rabbit anti-BSA IgG 5 μg on the opposing side. Immediately after, purified BSA 100 μg and 125Iodine-labeled BSA 1.25 μg in PBS containing 1% Evans blue was injected intravenously. After 4 hours, skin sections were weighed and radioactivity was measured in cpm/gm of tissue. An Arthus index (AI) for each mouse was calculated by dividing cpm/gm of treated skin by cpm/gm of control skin. The Mann-Whitney U test was used to evaluate for significant difference between the median AI of the two mice groups.

**RESULTS:** C1q-/- mice exhibited more vigorous RPAR (mean AI 3.6±0.8) than normal mice (mean AI 2.5±1.3). The median AI for C1q-/- mice was significantly higher than normal mice (3.8 vs 2.3, two-tail P<0.05).

**CONCLUSIONS:** Our results provide physiologic evidence that the classical complement pathway down-regulates in vivo IC and FcγR mediated inflammation. They may also further understanding of why individuals with classical pathway defects are susceptible to developing autoimmune disease.

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**819 Effects of Vitamin D Deficiency on Inner City Children and Adolescents with HIV**

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**RATIONALE:** We previously reported high incidence of vitamin D deficiency in our HIV patients (primarily African American and living in low sunlight environment). We sought to identify any correlation with HIV disease markers and medications.

**METHODS:** Serum 25 hydroxyvitamin D (25 OHD) was obtained from 160 HIV infected youth (25 OHD < 20 ng/ml classified as vitamin D deficiency; 20-35 ng/mL classified as vitamin D insufficiency). 25 OHD levels were correlated to HIV RNA (VL) and CD4+ T-cells.

**RESULTS:** 152/160 (95%) youth had 25 OHD insufficiency. Out of these, 110/160 (68.8%) had deficiency. 24/110 (21.8%) of 25 OHD deficiency patients had undetectable VL as opposed to 15/50 (30%) with 25 OHD < 20 (p-value = 0.15). CD4+ T-cell count was not significantly different between youth with insufficiency vs deficiency. Treatment with tenofovir or efavirenz significantly increased probability of vitamin D deficiency (48/66; 72.7% vs 27/49; 55.1%; p-value = 0.074). We did not have sufficient youth with HIV and normal vitamin D levels to make any comparisons.

**CONCLUSIONS:** Very high prevalence of vitamin D deficiency was confirmed. Higher 25 OHD tended to predict higher viral loads. No effect on CD4+ T-cell count was observed. Treatment with tenofovir or efavirenz significantly increased the chance of vitamin D deficiency, as previously reported. HIV infection in African American youth in low sunlight areas are at significant risk for low vitamin D. Vitamin D supplementation should be routine in this population.
Efficacy of Icatibant in Non-Laryngeal Attacks of Type I and II Hereditary Angioedema: Integrated Results from Three Phase III Trials

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RATIONALE: Integrated analyses were performed to further explore icatibant efficacy in patients with non-laryngeal attacks of type I or II hereditary angioedema (HAE) in three Phase III studies, FAST-1, -2 and -3 (ClinicalTrials.gov identifiers: NCT00097695, NCT00500656 and NCT00912093, respectively).

METHODS: Adult patients with moderate-to-severe non-laryngeal attacks were randomized to receive a single 30 mg icatibant injection or comparator (placebo or tranexamic acid [data excluded for the tranexamic acid arm]). Symptom severity over time was evaluated using a patient-assessed Visual Analog Scale (VAS) of individual attack symptoms (skin swelling, skin pain and abdominal pain).

RESULTS: 104 patients (median age 36.0 years, 62.5% female, 95.2% Caucasian) received icatibant and 74 patients (median age 35.5 years, 67.6% female, 90.5% Caucasian) received placebo. Pretreatment mean composite VAS scores (mm) were 36.90 (icatibant) and 39.23 (placebo). At 2, 4 and 12 h, mean changes were -17.85, -24.41 and -27.12 (icatibant) and -8.40, -9.28 and -18.23 (placebo; p<0.0001 except at 12 h where p=0.0191). Individual VAS score differences for skin swelling and skin pain favored icatibant between 1.5-8 h (p=0.0101 versus placebo). Individual VAS score differences for abdominal pain favored icatibant between 1.5-8 h, but fluctuated over time with p-values ranging between 0.0329 and 0.2994. Times to onset of symptom relief (composite VAS) were 2.0 h (icatibant) and 8.2 h (placebo; p<0.0001). Times to almost complete symptom resolution were 9.3 h (icatibant) and 33.9 h (placebo; p=0.0001).

CONCLUSIONS: Icatibant demonstrated significant benefits over time compared with comparator in patients with non-laryngeal attacks.

Efficacy of Icatibant in Laryngeal Attacks of Type I and II Hereditary Angioedema (HAE): A Pooled Analysis of Three Phase III Trials

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RATIONALE: A pooled analysis of first laryngeal attacks treated with icatibant in patients with type I and II HAE in three Phase III studies (FAST-1, FAST-2 and FAST-3; ClinicalTrials.gov identifiers: NCT00097695, NCT00500656 and NCT00912093, respectively) is presented.

METHODS: Sixty patients presenting with their first laryngeal/hypopharyngeal attacks (mild, moderate, severe and a subpopulation of very severe) were treated with subcutaneous icatibant (30 mg) in the controlled and open-label phases of FAST-1, -2 and 3. Patients’ efficacy analyses included patient-assessed individual symptom scores of difficulty swallowing and voice change using a five-point scale (0-absent; 4-very severe) and open-label phases of FAST-1, -2 and 3. Physicians’ Global Assessments were also reported.

RESULTS: Patients’ median age was 38.5 years, with the majority being female (63.3%) and Caucasian (85.0%). Pooled patient-assessed individual symptom scores at pretreatment for difficulty swallowing and voice change were assessed as severe/very severe by 28.6% and 29.1% patients, respectively. At 2 h and 4 h post-treatment they were 10.6% and 1.9% for difficulty swallowing, and 7.1% and 0.0% for voice change, respectively. By 12 h post-treatment, difficulty swallowing and voice change symptoms were absent in all patients. Pooled patient-assessed median time to initial symptom improvement was 0.6 h (95% CI: 0.5 h-0.9 h) and was consistent across FAST-1, -2 and 3 (0.6 h, 0.8 h and 0.8 h, respectively). No patient required intubation.

CONCLUSIONS: Icatibant treatment consistently reduced symptom score measures and resolved laryngeal edema in this pooled database of patients with laryngeal attacks of type I and II HAE.

Efficacy of Icatibant is Consistent by Attack Frequency and Baseline Severity in the Treatment of Type I and II Hereditary Angioedema (HAE) Attacks

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RATIONALE: To analyze the effects of baseline attack severity and frequency on icatibant efficacy in type I and II HAE attacks across three Phase III, controlled, randomized studies, FAST-1, FAST-2 and FAST-3 (ClinicalTrials.gov identifiers: NCT00097695, NCT00500656 and NCT00912093, respectively).

METHODS: Adults with moderate-to-severe non-laryngeal HAE attacks were randomized to receive 30 mg icatibant (subcutaneous) or comparator (tranexamic acid or placebo). Efficacy evaluations included a patient-assessed, 3-symptom composite score for skin swelling, skin pain and abdominal pain using a Visual Analog Scale (VAS).

RESULTS: Median times to onset of relief (using 3-symptom composite VAS score for skin pain, skin swelling and abdominal pain) were 1.8 h (FAST-1; n=26), 3.5 h (FAST-2; n=35) and 2.0 h (FAST-3; n=43) for moderate attacks and 2.5 h, 2.0 h and 2.0 h, respectively for severe attacks. Median times to onset of primary (worst) symptom relief were 2.0 h, 3.5 h and 1.5 h for moderate attacks and 2.5 h, 2.0 h and 1.8 h for severe attacks across FAST-1, -2 and -3, respectively. Median times to onset of symptom relief by historical attack frequency (6 months prior to first on-study attack) across FAST-1, -2 and -3 respectively were 6.5 h, 1.5 h and 2.0 h for <4 attacks; 2.0 h, 2.5 h and 2.0 h for 4 to <18 attacks and 1.1 h, 4.3 h and 3.0 h for >18 attacks.

CONCLUSIONS: These analyses suggest that icatibant efficacy was relatively consistent across the three studies irrespective of baseline HAE attack severity and frequency of previous attacks.

Efficacy of Icatibant for Cutaneous and Abdominal Attacks of Type I and II Hereditary Angioedema: A Pooled Analysis of Three Phase III trials

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RATIONALE: A pooled analysis of data from three Phase III randomized controlled studies, FAST-1, FAST-2 and FAST-3 (ClinicalTrials.gov identifiers: NCT00097695, NCT00500656 and NCT00912093, respectively) was performed to evaluate the efficacy of icatibant treatment vs placebo (FAST-1 and -3) or tranexamic acid (FAST-2) in patients with type I or II hereditary angioedema (HAE).

METHODS: Adult patients with moderate-to-severe non-laryngeal HAE attacks received a single 30 mg icatibant injection (n=104), tranexamic acid (n=38 [excluded from this pooled analysis]) or placebo (n=74). Efficacy evaluations included patient-assessed Visual Analog Scale (VAS) of the primary (worst) symptom and individual attack symptoms. Physicians’ Global Assessments were also reported.

RESULTS: Median times to onset of primary (worst) symptom relief were 2.5 h (icatibant [95% CI: 2.0-3.5 h]) and 18.5 h (placebo [95% CI: 8.0-25.0 h]; p<0.0001) for cutaneous attacks, and 1.1 h (icatibant [95% CI: 1.0-2.0 h]) and 3.5 h (placebo [95% CI: 2.0-6.1 h]; p=0.0002) for abdominal attacks. Median times to onset of symptom relief based on skin swelling were 3.5 h and 19.9 h (p=0.0002), for skin pain were 2.0 h and 7.0 h (p=0.0039) and for abdominal pain were 2.0 h and 4.0 h (p=0.0045), for icatibant and placebo respectively. Physicians’ Global Assessments at 4 h indicated improvements in attack severity in favor of icatibant (p<0.0001) for both cutaneous and abdominal attacks, irrespective of pre-treatment attack severity.

CONCLUSIONS: Icatibant provided effective symptom relief across FAST-1, -2 and -3 for patients with cutaneous and abdominal attacks, irrespective of attack location and baseline severity.
824 Icatibant in Patients with Acquired Angioedema Who Did Not Respond to pdC1INH
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RATIONALE: Icatibant is an effective and generally well-tolerated treatment for acute attacks of hereditary angioedema (HAE) in adults. Our experience with icatibant in 8 acquired angioedema (AAE) patients is reported. Icatibant is currently not approved for the treatment of acquired angioedema (AAE).

METHODS: Patients with AAE who were non-responsive to plasma-derived C1-INH concentrate were treated with subcutaneous icatibant 30 mg for acute angioedema attacks. Outcome measures included patient-reported times to first improvement and complete symptom resolution, recorded in patients’ diaries.

RESULTS: Eight adult patients with AAE (median age 73.5 yrs, 87.5% male, all with C1-INH levels 50% below normal) recorded 50 angioedema attacks: 48 (1 cutaneous, 4 oro-pharyngeal-laryngeal, 18 facial, 25 abdominal) were moderate-to-severe and treated with icatibant; 2 were moderate and resolved without treatment. For treated attacks, the median (range) duration from attack onset to complete resolution was 9.33 (1.67-39) h; the duration of 2 untreated attacks was respectively 72 and 96 h. After icatibant administration, time to first symptom improvement was 0.5 (0.25-2.1) h and time to complete symptom resolution was 6.75 (0.5-39.75) h. Adverse events of transient, self-resolving burning sensation and erythema at the injection site were reported by 5 patients for a total of 24 attacks. A single icatibant injection achieved complete symptom resolution for all but one of the 48 treated attacks, including in 3 patients treated for more than 5 attacks each.

CONCLUSION: In the opinion of the authors, icatibant was an effective and generally well-tolerated treatment in these AAE patients.

826 Ecallantide Reverses Laryngeal Hereditary Angioedema Attacks: Experience from the EDEMA Clinical Development Program
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RATIONALE: Hereditary angioedema (HAE) is a rare disorder characterized by well-demarcated angioedema affecting subcutaneous and submucosal areas. Upper respiratory obstruction due to laryngeal edema may cause asphyxiation. Ecallantide is a plasma kallikrein inhibitor indicated for treatment of HAE attacks. We present an analysis of laryngeal attacks treated with 30 mg subcutaneous ecallantide.

METHODS: Data were pooled from four clinical studies (EDEMA2, EDEMA3, EDEMA4, and DX-88/19 [Continuation]) of 30 mg subcutaneous ecallantide for treatment of acute HAE attacks. Efficacy was assessed with 2 validated, HAE-specific, patient-reported outcomes: Mean Symptom Complex Severity (MSCS) score (negative change from baseline indicates improvement, minimally important difference [MID] equals -0.5) and Treatment Outcome Score (positive score indicates improvement, MID equals 30). Time to onset of sustained improvement was also calculated.

RESULTS: A total of 98 patients were treated for 220 laryngeal attacks, of which 13% were mild in severity, 62% moderate, and 25% severe. Approximately 57% of these patients were treated for 1 laryngeal attack; 9% were treated for ≥5 laryngeal attacks. Symptoms at additional sites accompanied 85% of laryngeal attacks. Mean change in MSCS score was -1.1 at 4 hours and -1.6 at 24 hours, while mean TOS was 73.5 at 4 hours and 85.5 at 24 hours. Onset of sustained improvement was reached within 4 hours by 80% of patients (median time: 113 minutes). Four serious adverse events were reported: 2 unrelated hospitalizations for HAE, 1 anaphylactic reaction, and 1 hypersensitivity reaction.

CONCLUSIONS: Ecallantide demonstrated clinically meaningful efficacy for potentially life-threatening laryngeal edema due to HAE.
Hypersensitivity Reactions to Ecallantide: an Update of the Clinical Trial Experience and Post-Market Surveillance for Treatment of Attacks of Hereditary Angioedema

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RATIONALE: Ecallantide is a plasma kallikrein inhibitor indicated for treatment of hereditary angioedema (HAE) attacks. We present an update of potential hypersensitivity cases reported in ecallantide clinical trials and following commercial use of ecallantide.

METHODS: Data from 4 studies utilizing a 30 mg subcutaneous dose of ecallantide (EDEMA2, EDEMA3, EDEMA4, and DX-88/19) and post-marketing surveillance were evaluated for possible hypersensitivity reactions. Reported events suggestive of potential hypersensitivity were assessed using the World Allergy Organization (WAO) Subcutaneous Immunotherapy Systemic Reaction Grading System (grade 1: single organ system involved; grade 2: >1 organ system/mild respiratory distress/gastrointestinal symptoms; grade 3: moderate respiratory distress; grade 4: respiratory failure/hypotension; grade 5: death). Reactions were also classified as “likely” or “unlikely” hypersensitivity based on the temporal sequence of events and presence of confounding factors including patient history, underlying disease, concomitant medications, and outcomes following ecallantide re-exposure.

RESULTS: In clinical studies, 230 patients received 1045 doses of 30 mg subcutaneous ecallantide. Fourteen patients experienced potential hypersensitivity. Eight were classified as likely (seven WAO grade 2; one grade 1) and 6 as unlikely (three grade 2; three grade 1). Symptoms included pruritus, urticaria, erythema, flushing, dyspnea, chest discomfort, dizziness, nausea, laryngeal edema, and blood pressure changes. All events resolved without sequelae. Frequency of post-marketing cases appear similar, with 9 potential cases reported among those in clinical trials.

CONCLUSIONS: Potential hypersensitivity reactions are a risk of ecallantide treatment, but patient monitoring and appropriate treatment can mitigate this risk.

Prompt Reversal of Airway Obstruction Secondary to Angiotensin Converting Enzyme Inhibitor (ACEI) Induced Angioedema by Ecallantide: A Case Report

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RATIONALE: Fatal airway obstruction from ACEI angioedema has been described but effective therapy has not been established. Intubation is sometimes required for progressive airway compromise. Ecallantide is a kallikrein pathway blocker and may offer benefit in reversing ACEI induced angioedema.

METHODS: A 54 year old African-American male with a history of hypertension treated with lisinopril daily, remote cocaine abuse associated myocardial infarction, seizures and prostate cancer, presented with a 2 day history of facial and throat swelling along with dysphagia. He was treated in the emergency department with intravenous methylprednisolone, epinephrine and diphenhydramine. He was admitted, but angioedema progressed overnight, confirmed by laryngoscopy. ICU transfer and intubation was undertaken the next morning for airway protection. Tryptase level was 2 ng/ml. C3 and C4 and routine chemistries were normal. Ecallantide 30mg was administered subcutaneously at 1014 hours.

RESULTS: Patient improved over the day and self-extricated prior to 1800 hours. He had no dysphagia or difficulty with respiration and was discharged the next morning.

CONCLUSION: ACEI angioedema is a recognized complication of ACEI treatment that can occur months to years after starting therapy. The incidence is thought to be 0.1-0.5% (Warner. Ann Pharmacother 2000; 34: 526). Fatalities from airway obstruction are described (Dean. J Forensic Sci 2001; 46: 1239). Angiotensin converting enzyme is an important enzyme for degradation of bradykinin. Ecallantide selectively and reversibly inhibits plasma kallikrein, preventing bradykinin generation. This case suggests that ecallantide may indeed be effective in reversing ACEI induced angioedema, even in patients requiring intubation for airway protection.

Efficacy and Safety of Ecallantide Treatment for HAE Attacks in Patients Treated with Both Ecallantide and Placebo

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RATIONALE: Hereditary angioedema (HAE) is an autosomal dominant disorder characterized by recurring and unpredictable attacks of angioedema. Ecallantide, a plasma-kallikrein inhibitor, is approved for treatment of acute attacks of HAE. Patients could enroll in multiple ecallantide trials including EDEMA3 and EDEMA4 (both placebo-controlled) and Continuation (open-label). This post hoc study assesses the efficacy and safety of ecallantide in patients who were treated, for comparable HAE attacks, with placebo in one study and ecallantide in another.

METHODS: Patient episodes treated with placebo in EDEMA3 or EDEMA4 were matched with episodes (same patient, same primary attack location, similar severity level) treated with ecallantide in Continuation. Efficacy comparisons included Treatment Outcome Score (TOS), Mean Symptom Complex Severity (MSCS) score, and time to complete or near-complete symptom resolution. Safety was assessed by treatment emergent adverse events.

RESULTS: The analysis includes 36 patients, each with 1 placebo-treated and 1 matched ecallantide-treated attack. At 4 hours, the ecallantide-treated episodes had greater improvement compared to placebo based on TOS (P <0.001) and change in MSCS score (P<0.001). By 4 hours, complete or near-complete symptom resolution was reached in 24 (66.7%) episodes treated with ecallantide compared to 8 (22.2%) episodes treated with placebo (P<0.001). The majority of patients showed greater improvement in their ecallantide-treated attack compared to their placebo-treated attack; 24 (67%) based on TOS, 25 (69%) based on MSCS score. Safety profiles appeared similar across the 2 groups of episodes.

CONCLUSIONS: In this longitudinal analysis, patients showed significantly better improvement and comparable safety following treatment with ecallantide versus placebo.
830 Absence of Inhibitory Anti-C1 Esterase-Inhibitor Antibody Formation in Subjects Treated With C1 Esterase-Inhibitor Concentrate (Berinert®) for Successive Hereditary Angioedema Attacks

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RATIONALE: Limited data are available on the occurrence of autoantibodies to C1 esterase-inhibitor (C1-INH) in patients with hereditary angioedema (HAE) after treatment with C1-INH concentrate. In the I.M.P.A.C.T studies, we assessed the development of anti-C1-INH antibodies.

METHODS: During treatment with C1-INH concentrate (Berinert®, CSL Behring, Marburg) for successive HAE attacks, anti-C1-INH antibodies were evaluated every 3 months after a baseline assessment, using a modified binding enzyme-linked immunosorbent assay (screening assay, confirmatory assay for determination of isotypes, and antibody inhibition assay based on the VIII-Bethesda assay).

RESULTS: No inhibitory anti-C1-INH antibodies were detected in the 57 antibody inhibition assay based on the VIII-Bethesda assay. Nineteen subjects (33%) had ≥1 antibody-positive result (titre ≥1:50); 8 of these subjects already had antibody-positive results before enrollment. For 3 subjects with antibody-positive results, anti-C1-INH antibody tests returned to antibody-negative at later measurements, suggesting fluctuations in this variable. The majority of positive samples (63%) were confirmed by isotyping. Between subjects with ≥1 antibody-positive result (n=19) and subjects without antibodies (n=38), there were no clinically relevant differences in the efficacy of C1-INH concentrate (medians of individual average values: 32 and 24 min for time to onset of symptom relief; 15.5 and 15.4 hours for time to complete resolution of HAE symptoms) or the proportion of subjects experiencing adverse events (47.4% and 42.1%).

CONCLUSIONS: There is no indication for the development of inhibitory anti-C1-INH antibodies in subjects treated with C1-INH concentrate for HAE attacks, and the presence of non-inhibitory antibodies does not seem to be of clinical relevance.

831 Effect of Time to Treatment on Treatment Response With C1 Esterase-Inhibitor Concentrate (Berinert®) for Acute Hereditary Angioedema Attacks

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RATIONALE: Treatment with C1 esterase-inhibitor (C1-INH) concentrate (Berinert®, CSL Behring, Marburg) is well established for hereditary angioedema (HAE) attacks; treatment as early as possible is recommended. To investigate the relationship between time to treatment and treatment response, we conducted a post-hoc analysis of data from the I.M.P.A.C.T studies.

METHODS: The relationship between time to treatment (<6 or ≥6 hours) and efficacy (times to onset of symptom relief and complete resolution) was evaluated by Cox-regression for I.M.P.A.C.T.1, including hazard ratios (HRs; 10 or 20 U/kg C1-INH or placebo), and by linear regression for I.M.P.A.C.T.2 (20 U/kg C1-INH). HRs >1 indicate higher probabilities for faster relief or resolution with C1-INH vs. placebo.

RESULTS: With 20 U/kg C1-INH in I.M.P.A.C.T.1 and I.M.P.A.C.T.2 (per-attack analysis), median times to onset of symptom relief were similar after treatment within 6 hours (30 and 25 min) and ≥6 hours (31 and 16 min). Median times to complete resolution were shorter after treatment within 6 hours (2.8 and 12.6 hours) compared with ≥6 hours (7.9 and 14.4 hours). After treatment within 6 hours, times to onset of symptom relief and complete resolution were considerably faster with 20 U/kg C1-INH vs. placebo (HRs: 3.36 and 4.30). When treated after ≥6 hours, HRs for 20 U/kg C1-INH vs. placebo were substantially reduced for time to onset of symptom relief and complete resolution (1.18 and 1.61). Linear regression also indicated longer times to complete resolution with later treatment.

CONCLUSIONS: Early treatment of HAE attacks (<6 hours) with C1-INH provides better treatment response than later treatment.
**833 Efficacy of Recombinant Human C1 Inhibitor Treatment for Abdominal Attacks of Hereditary Angioedema**

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**RATIONALE:** Recombinant human C1-inhibitor (rhC1INH) has been developed for the treatment of angioedema attacks in patients with hereditary angioedema (HAE). Abdominal attacks are extremely painful and disabling, and can mimic an acute abdomen, leading to unnecessary medical interventions and operations. The efficacy of rhC1INH for the treatment of abdominal angioedema attacks in patients with HAE has been assessed.

**METHODS:** Four studies involving rhC1INH for the treatment of angioedema attacks were conducted in N. America, Argentina, Europe and Israel. In these studies, HAE patients completed visual analogue scales (VAS) to record the severity of symptoms at all affected anatomical locations. As a subset of these analyses, the efficacy of rhC1INH administration for the treatment of abdominal attacks has been assessed separately.

**RESULTS:** Ninety-eight patients were treated with rhC1INH for 207 acute abdominal attacks. 12/207 (6%) of the attacks were treated with 100 U/kg rhC1INH, 85/207 (41%) with 50 U/kg and 110/207 (53%) with 2100 U (18-40 U/kg) rhC1INH. The median time to beginning of relief was 50 minutes (1st-3rd quartile: 30-106), 36 minutes (1st-3rd quartile: 22-64) and 60 (1st-3rd quartile: 30-62) minutes for doses of: 100, 50 and 18-40 U/kg respectively. No treatment failures were reported and none of the rhC1INH treated attacks relapsed. Treatment efficacy for patients treated for their first attack was similar to patients treated for multiple attacks.

**CONCLUSIONS:** rhC1INH is effective for the treatment of abdominal attacks in HAE patients.

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**834 Angioedema Hospitalization Trends and Characteristics in the US: 2000-2009**

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**RATIONALE:** The data on angioedema (AE) epidemiology is sparse. In this study we sought to profile AE hospitalizations and characteristics in the new millennium.

**METHODS:** A national hospitalization database in the US was queried for admissions due to AE and other allergic disorders (anaphylaxis, urticaria, and allergy unspecified) 2000-2009. AE hospitalization trends and clinical/demographic associations were determined.

**RESULTS:** The AE hospitalization rate rose from 2.7/105 in 2000 to 4.2/105 in 2009, while the rate of all other allergic disorders was stable at ~1.5/105. The increase in AE was higher for African Americans (AA) who constituted 32% of AE admissions in 2000 and 41% in 2009. Adverse drug effects (ADEs) due to hypertension/cardiovascular agents were most strongly associated with AE, and were coded in 29% of patients, increasing from 22% in 2000 to 36% in 2009. ADEs were found in 38% of AA AE patients and 25% of other races. ADEs (17.1, 15.8-18.6), hypertension (1.9, 1.8-1.9), increasing decade of life (1.3, 1.2-1.4), and significant multivariate associations with AE hospitalizations compared to the other allergic admissions. Asthma and ischemic heart disease had significant negative associations with AE relative to other allergic disorders. Seven percent of patients with AE had endotracheal intubation/mechanical ventilation while hospitalized.

**CONCLUSIONS:** AE hospitalization rates have continued to rise from 2000 to 2009, in the US especially in the AA population. Hospitalization rates of AE continue to exceed hospitalization rates of other acute allergic reactions.
Association of C1 Esterase-Inhibitor Functional Activity and Treatment Response With C1 Esterase-Inhibitor Concentrate (Berinert®) for Acute Attacks of Hereditary Angioedema

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RATIONALE: Diagnosis of hereditary angioedema (HAE) is based on functional C1 esterase-inhibitor (C1-INH) levels. We studied the association between C1-INH functional activity (C1-INHf) and efficacy endpoints in a post-hoc analysis of data obtained from the double-blind, placebo-controlled study I.M.P.A.C.T.

METHODS: C1-INHf was determined at screening, baseline (prior to administration of 10 or 20 U/kg of C1-INH concentrate [Berinert®], CSL Behring, Marburg) or placebo for an acute HAE attack), and 1 and 4 hours after administration. The relationship between C1-INHf (at 1 hour) and efficacy endpoints (times to onset of symptom relief and complete resolution of HAE symptoms) was evaluated by Cox-regression for subjects treated with 10 or 20 U/kg of C1-INH concentrate (38 and 42 subjects); hazard ratios (HRs) were calculated.

RESULTS: Dose-dependent changes in C1-INHf from baseline were observed (median change at 1 hour after study drug administration: 0% with placebo; 23.4% and 43.5% with 10 or 20 U/kg C1-INH concentrate). With 20 U/kg of C1-INH concentrate, there was no relevant association between C1-INHf at 1 hour after treatment and time to onset of symptom relief, while higher C1-INHf at 1 hour after treatment tended to be associated with faster time to complete resolution of HAE symptoms (p=0.053; HR for C1-INHf of <30% vs. >30% to <60%: 0.64; HR for C1-INHf of >60% vs. <30% to >60%: 2.06).

CONCLUSIONS: Increase in C1-INHf after administration of C1-INH concentrate was dose-dependent. With 20 U/kg of C1-INH concentrate, higher C1-INHf after treatment appears to be associated with shorter time to complete resolution of HAE symptoms.

High Doses of C1 Esterase Inhibitor as Treatment for a Patient with Exacerbating Hereditary Angioedema During Pregnancy

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RATIONALE: Hereditary Angioedema (HAE) results in swelling of the subcutaneous and submucous tissues of the skin, gastrointestinal and respiratory tracts and can be life threatening when the larynx is involved. We report on management of a pregnant patient with frequent HAE episodes.

METHODS: A pregnant mother (G2P1) presenting with a case of severe HAE episodes. Hypereosinophilia from other causes is associated with hydorxyurea added as a steroid sparing agent.

RESULTS: Occurred over a few days and lasted for 2-3 months, initially occurring biannually. Recent episodes have occurred more frequently. Initial workup showed 16.31K/mm3 WBC with 60% vs. <30% to >60%: 2.06).

CONCLUSIONS: Increase in C1-INHf after administration of C1-INH concentrate was dose-dependent. With 20 U/kg of C1-INH concentrate, higher C1-INHf after treatment appears to be associated with shorter time to complete resolution of HAE symptoms.

Self Intravenous (IV) Administration of C1-INH Concentrate for Hereditary Angioedema: A Retrospective Analysis of Patient Outcomes

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RATIONALE: Hereditary angioedema (HAE) is a rare and difficult to manage disorder. The availability of C1 inhibitor (C1-INH) concentrate is encouraging the development of improved management strategies based upon patient self IV administration.

METHODS: We conducted a retrospective, case-cohort review of longitudinal data gathered in the routine follow-up of 10 HAE patients (mean age, 35.4 yrs [range, 17-54]; 60% female) trained to self-administer IV C1-INH concentrate (Berinert®/CSL Behring or Cinryze®/ViroPharma) on-demand for acute attacks or ongoing prophylaxis.

RESULTS: Patients were taught self IV administration. Four patients were placed on C1-INH prophylaxis (1000U given once weekly, twice weekly, Q3 days or Q4 days) and six used C1-INH on-demand (1000-1500U/attack). Over an average of 16 months, 4 patients on prophylaxis experienced a mean of 0.33 attacks/patient/month. Six patients treated on-demand had a mean of 0.22 attacks/patient/month over an average of 10 months. Thirty-three reported attacks were treated with self IV-administered C1-INH. Administration was in home/school/camp settings in all but 2 attacks: in one, the location of swelling interfered with IV placement and the other was patient preference. Thirty-two of the 33 attacks resolved without further medical intervention; one laryngeal attack was followed by 24-hour hospital observation. Three patients switched C1-INH product during the study, but all remained on home-based treatment. Side effects were infrequent and not serious and there were no reported complications from self-administration of C1-INH.

CONCLUSIONS: Self-administration of intravenous C1-INH concentrate as prophylaxis or on-demand therapy can be a good option for patients with HAE.

Gaining Weight And Loosing Appetite!: A Case Of Recurrent Diffuse Angioedema, Weight Gain and Peripheral Eosinophilia Without Visceral Organ Damage

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RATIONALE: Gleich’s syndrome is a variant of Hypereosinophilic syndrome (HES) presenting with episodic angioedema, urticaria, fever, anorexia and significant weight gain but lacking visceral involvement seen in classic HES.

METHODS: History, clinical exam, appropriate laboratory tests.

RESULTS: Patient presented with five years of episodic generalized facial, extremities and trunk swelling accompanied by weight gain, fever, urticaria and anorexia. Each episode developed over a few days and lasted for 2-3 months, initially occurring biannually. Recent episodes have occurred more frequently. Initial workup showed 16.31K/mm3 WBC with 8,644 normal appearing eosinophils. Strongyloides titer was negative. FIP1L1/PDGFR fusion by FISH was negative. C3, C4, C1 Inhibitor functional assay, metabolic profile and TSH were all normal. IgE was 804 IU/mL but other immunoglobulins were normal. ANA and ANCA were negative. CT showed esophageal, supraglottic and glottic edema. Esophageal mucosal biopsy with biopsies showed no pathology. In absence of findings for other cause of eosinophilia and no organ involvement, a diagnosis of Gleich’s syndrome was made. Patient responded to prednisone with hydroxyurea added as a steroid sparing agent.

CONCLUSIONS: Gleich’s syndrome should be considered in patients with episodic angioedema. Hypereosinophilia from other causes is associated with angioedema and should be ruled out. Lack of visceral involvement is the key to diagnosing this variant of HES.
Auto-antibodies in Chronic Idiopathic Urticaria (CIU) and Non-urticarial Systemic Autoimmune Disorders

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**Rationale:** 30-50% of patients with CIU have “functional” auto-antibodies to FcεRI or IgE as measured by basophil histamine release assay or basophil activation markers. It is unknown if patients with systemic autoimmune diseases have a similar prevalence of these auto-antibodies.

**Methods:** Adult patients, 26 with CIU, 27 with Rheumatoid Arthritis (RA), and 26 with Systemic Lupus Erythematosus (SLE), were recruited from an allergy clinic and a rheumatology clinic. 20 healthy controls were compared. The patients with RA and SLE did not have chronic urticaria. Atopy history and disease activity were obtained. The CU Index Panel (basophil histamine release assay), anti-IgE, and anti-thyroid antibodies were performed by Viracor-IBT laboratories.

**Results:** CU Index values were significantly higher in the CIU group (mean 15.6) as compared to the RA group (mean 2.3), p=0.007). In contrast to patients in the RA and control groups, 11% of SLE and 7.6% of CIU patients had elevated anti-IgE antibody values (>188 ng/mL). Elevated anti-thyroid peroxidase (TPO) levels did not correlate with a positive CU Index. Elevated CU Index and anti-IgE values in the RA and SLE groups were not associated with disease severity.

**Conclusions:** The CU Index values differentiated CIU patients from RA patients, but not from SLE patients. Interestingly, SLE patients were found to have “functional” auto-antibodies without associated urticaria. The presence of auto-antibodies did not correlate with disease activity or having thyroid antibodies. Functional auto-antibodies may not be useful in distinguishing autoimmune chronic urticaria from non-urticarial autoimmune disorders.

Autoimmune Profiling in Chronic Idiopathic Urticaria – Is there Utility or Futility?

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**Rationale:** Chronic idiopathic urticaria (CIU) is increasingly recognized to have an autoimmune mechanism. We present characterization of the prevalence of autoimmune markers in CIU, their patterns of expression, and implications for disease course.

**Methods:** We retrospectively evaluated 195 patients with a diagnosis of CIU over a 2-yr span for the presence of autoimmunity including antinuclear antibody (ANA), anti-microsomal antibody (ATPO), anti-thyroglobulin antibody (ATG), and chronic urticaria (CU) index. The patients were categorized into controlled and refractory subgroups based on their response to the use of antihistamines with or without the use of a leukotriene receptor antagonist.

**Results:** Among those tested for the respective autoimmune markers in our CIU cohort, the prevalence of a positive test for ANA (title>1:160), ATPO, ATG, and CU Index were 29%, 6%, 26%, and 38% respectively. In comparing controlled and refractory subgroups, the percent of ANA positive (22.6 vs 40.4; p=0.04) and CU index positive (15.0 vs 52.0; p=0.01) patients differed significantly; however, a similar relationship was not observed for ATPO or ATG antibodies. Furthermore, in those patients with positive CU indices or ANA, the percent of patients categorized as refractory was higher. Logistic regression analysis of individual autoimmune markers and combination of markers in CIU suggests that the CU index independently offers the best characteristics to help predict clinical course.

**Conclusion:** Our data indicates the CU index independently is a better predictor of disease severity than any combination of additional autoimmune markers (ANA, ATG, or ATPO).
**845 Metabolic Syndrome In Patients With Chronic Urticaria**

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**Rationale:** An association between some inflammatory diseases and the metabolic syndrome has been reported. Chronic urticaria (CU) is a chronic inflammatory skin disease characterized by infiltrating T cells, eosinophils and neutrophils. This study was aimed to investigate the prevalence and clinical characteristics of metabolic syndrome in patients with CU.

**Methods:** A hospital-based cross-sectional study on 131 CU patients (49 males and 82 females, mean age 40.5 years) was performed. Metabolic syndrome was diagnosed in the presence of three or more criteria of the NCEP ATP III (2001). The disease activity of CU was assessed by the UAS, a total score of 0-15. Serum CRP and TNF-α concentrations were measured by ELISA assay using commercially available reagents.

**Results:** Thirty-two (27.1%) patients had a metabolic syndrome. CU patients with metabolic syndrome were older and had higher levels of complement 3 and 4 and serum ECP and TNF-α and showed higher mean UAS compared with CU patients without metabolic syndrome. No significant correlations were found between the metabolic syndrome, and presence of auto-antibodies, disease duration, serum total IgE levels in CU patients. The proportion of patients in uncontrolled status for 3 months of treatment was significantly higher in those with metabolic syndrome.

**Conclusions:** CU patients have a higher prevalence of metabolic syndrome. TNF-α-associated systemic inflammation could be a common pathogenic mechanism of CU and metabolic syndrome. We suggest patients with severe and uncontrolled CU should be evaluated for metabolic syndrome to correct cardiovascular risk factors as well as to improve CU outcomes.

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**846 The Urticaria Severity Score May Serve As An Early Clinical Indicator In Monitoring Patients With Chronic Urticaria**

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**Rationale:** The Urticaria Severity Score (USS) is a valid instrument for chronic urticaria (CU) severity. Vascular endothelial growth factor (VEGF) and matrix metalloproteinase-9 (MMP-9) levels are elevated in CU and may parallel disease severity. Chronic urticaria (CU) index greater than 10 suggests chronic autoimmune urticaria. This project aims to correlate these inflammatory biomarkers with the USS for CU patients.

**Methods:** The study was conducted following IRB approval at Montefiore Medical Center. Selection criteria: hives >6 weeks, no urticaria-specific treatment, age >18. The USS, plasma and serum VEGF, MMP-9 and CU index were evaluated before urticaria-specific treatment initiation and every two weeks thereafter.

**Results:** Thus far, seven patients (5 females and 2 males; 4 with atopy, 2 with thyroid autoimmunity) have been enrolled. The USS significantly decreased in 6 of 7 patients from baseline to 2 weeks (<p<0.05). 4 patients with USS <20 at 2 weeks had unremarkable baseline serum levels of MMP-9 and VEGF. 2 patients with USS >20 at 2 weeks had elevated baseline serum levels of MMP-9 and 1 patient had elevated baseline serum levels of VEGF. Baseline plasma levels of MMP-9 and VEGF were elevated in most patients with no correlation to USS. Baseline CU index was <10 in 6 patients.

**Conclusions:** The USS may represent an early indicator of CU clinical improvement after starting urticaria-specific treatment. Serum MMP-9 and VEGF levels were unremarkable in most patients with USS <20. No relation was found between plasma MMP9, VEGF levels and the USS.

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**847 Omalizumab (Xolair) in the Treatment of Severe Refractory Chronic Urticaria (SRCU)**

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**Rationale:** We report the treatment with omalizumab (Xolair) in 13 patients with SRCU.

**Methods:** Thirteen patients were followed prospectively at an average of 7 months follow-up (range of 2 - 74 weeks). We studied the effective omalizumab dosage and the treatment course of these patients.

**Results:** Patients treated with omalizumab all previously required high dose prednisone for control. Omalizumab was administered subcutaneous at 150mg dosage for 12 patients and at 225mg for 1 patient. Seven patients (54%) had complete remission within 1 week of their 1st injection. Two patients (15%) had complete remission within 2 weeks of their 2nd and 3rd injection. Seven patients (54%) remain in complete remission (mean 32 weeks, range 2-74 weeks). Two patients (15%) are in partial clinical remission. Urticaria recurrence was seen in 5 patients (38%) at an average of 2 months after their 4th injection (range 1-10 injections). One patient had a total of 9 injections and was refractory to treatment. One patient has not responded after a total of 2 injections but requires further treatment. One patient (8%) had 2 injections and remitted a month after the 2nd injection.

**Conclusions:** Omalizumab is effective in treating and inducing remission in SRCU patients (54% of patients). This response was seen with a 150mg dose (46% of patients). This clinical response is independent of serum IgE levels. There was a 38% recurrence and 23% of these patients responded to additional omalizumab injections. This may be a more cost-effective treatment schedule. Further study is required to determine the optimal dose schedule.

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**848 Treating Chronic Urticaria With Omalizumab - Our Experience in An Immunology Allergy Department**

A. C. Costa, P. M. Silva, J. G. Dias, A. Mendes, E. Pedro, M. P. Barbosa; Hospital de Santa Maria EPE, CHLN, Lisboa, PORTUGAL.

**Rationale:** Omalizumab has been included as 4th line treatment for severe chronic spontaneous urticaria(CSU). Its success has been reported in the management of CSU with underlying autoimmune disorder but recommendations for the treatment’s duration are lacking. Goal is to share our Department’s experience treating severe CSU with omalizumab.

**Methods:** Seven patients(41 year-old average[27-49]) with cortico-dependent CSU and positive autologous serum test were selected for treatment. Disease’s duration was on average 6 years[1-18]. Five patients had elevated total serum IgE(mean:184kUA/L). Two had anti-thyroid autoantibodies. Patients were evaluated for Urticaria Activity Score(UAS) and daily/rescue medication before and during treatment. Dose was chosen according to patients’ weight and IgE levels.

**Results:** Before omalizumab, all patients were medicated with anti-H1antihistamine(maximum established dose), montelukast and oral corticoid(average dose:13mg/day[5-40], average duration:3 years[10months-5years]). Three patients were previously medicated with cyclosporine, stopping due to lack of response/presence of side effects. Five were previously medicated with intravenous immunoglobulin G(400-1000mg/kg/month) with no response.

All patients improved after 2 administrations of omalizumab(4 patients with UAS=0 after 1st dose). Five patients are presently without other medication for CSU(average treatment duration: 13months[2-27]). In 2 patients with total clinical response, treatment was suspended after 12 and 18 months. In both cases, a relapse of urticaria occurred after 3 months, requiring reintroduction of corticotherapy and subsequently omalizumab with good response.

Pre-treatment UAS=5.3[4-6], post-treatment UAS=0.7[0-2]. No adverse reactions were reported.

**Conclusions:** Omalizumab seems to be effective and safe in the treatment of severe autoimmune-associated CSU. However patients seem to need continuous treatment to benefit from its effects.
849 Neutrophil Predominant Urticaria: A Systematic Review of Patients Undergoing Skin Biopsy in an Allergy Practice
S. H. Axelrod1, M. Punsoni1, B. Arendash1, B. Kim1, M. Feuerman1, M. Jacobson2, L. Fonacier1; 1Winthrop University Hospital, Mineola, NY, 2DermPath Diagnostics, Port Chester, NY.

Rationale: Just as neutrophils are associated with severe asthma, neutrophilic urticaria (NU) is difficult to treat. Our study aims to show that NU requires more intensive systemic therapy to achieve adequate symptom control, and to investigate if histological findings on biopsy can guide the treatment of chronic urticaria (CU).

Methods: A retrospective chart review of 65 CU patients (56 F, 9 M) who underwent skin biopsy from 1999-2011 at Winthrop University Hospital Allergy and Immunology. All patients failed antihistamine monotherapy. Biopsies were reviewed by 2 independent pathologists. The therapeutic regimens were evaluated to determine which medications were given to achieve clinical remission.

Results: The age range of patients was 11-85 years (mean: 50 years). 54/65 (83%) of biopsies were NU vs. 11/65 (16.9%) lymphocytic predominant urticaria. Of the 53 patients with NU, 44 (83%) were more likely to be on immunomodulating agents compared to 5/10 (50%) without neutrophils (p = 0.0354). Patients who achieved remission were less likely to have neutrophils on biopsy compared to patients who did not achieve remission (p = 0.056). Quantity of neutrophils did not affect the treatment required or resolution status, rather, the mere presence of neutrophils achieved significance. After biopsy, 64.6% of patients had a change in therapy with either the addition of, or change in immunomodulator.

Conclusions: The presence of neutrophils (rather than quantity) on biopsy is associated with difficult to treat urticaria and requires more intensive therapy often including immunomodulating medications; these patients are less likely to achieve complete resolution of symptoms. Skin biopsy can guide in the treatment of difficult to control CU.

850 Mutations in the Factor XII Gene in Solitary Cases of Recurrent Angioedema with Normal C1 Inhibitor Induced or Worsened by Oral Contraceptives or Hormonal Replacement Therapy
C. Stanger1, K. Wulf2, J. Hardt3, G. Witzke1, K. Bork1; 1Department of Dermatology, University of Mainz, Mainz, GERMANY, 2Institute of Human Genetics, University of Greifswald, Greifswald, GERMANY, 3Department of Medical Psychology and Medical Sociology, University of Mainz, Mainz, GERMANY.

Rationale: To determine the influence of oral contraceptives or hormonal replacement therapy on solitary cases of recurrent angioedema with normal C1-INH and to investigate whether women with such a constellation have a mutation in the FXII gene indicating a subtype of hereditary angioedema type III.

Methods: The influence of estrogens was recorded in 124 women with recurrent angioedema who fulfilled the following criteria: no urticaria, family history negative for angioedema, normal C1-INH activity in plasma, no response to antihistaminics, and angioedema that was not a reaction to drugs, infections, or allergens. Mutations in the FXII gene were determined by sequencing the coding regions of the gene.

Results: 62 of the 124 women had taken oral contraceptives or hormonal replacement therapy. 28/62 women did not recognize any influence on the frequency of angioedema attacks while 34 patients reported a marked change in attack frequency: 17/34 women reported that the angioedema attacks started after the beginning of oral contraceptive intake, with an average latency of 5.4 months (SD 9.6 months; range 0.1 to 36 months). Six patients had their first angioedema following the onset of hormonal replacement therapy. 11 patients had a marked worsening of a preexisting angioedema following the onset of estrogen intake. Search for mutations in the FXII gene in the 34 women revealed a missense mutation p.Thr328Lys only in one patient, a 16-year-old woman.

Conclusions: In solitary cases of recurrent angioedema with normal C1-INH exogenous estrogens may induce or worsen angioedema. Mutations in the FXII gene are found only as an exception.

851 Effect of Topical Minocycline on Immediate and Late Phase Allergic Skin Responses
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Rationale: Minocycline has known anti-inflammatory and anti-allergy effects. This study determined the effects of topical minocycline on cutaneous allergic immediate and late phase responses before and after application of a 2% minocycline ointment.

Methods: Adult subjects (n = 8) with known respiratory allergy to pollen, molds, or dander enrolled in the study. Skin prick test (Dermapik) to four Aeroallergens was performed on the upper back, and wheal size was measured at 15 minutes, 1 hour, and 24 hours. Minocycline ointment was placed on the opposite side of the upper back and covered with adherent dressing for a total of 48 hours. Repeat skin testing was performed over the minocycline treated area at 24 hrs. Mean diameters were calculated for the results of the pre- and post-minocycline skin tests. Skin responses were evaluated with respect to current QOL (Juniper) scores. For statistical analysis, a mixed linear model was constructed, with dependent variable mean wheal diameter (square-root transformed, to preserve symmetry and homogeneity of variance).

Results: A significant time-by-minocycline interaction was detected (F[2,82] = 5.87, p = 0.004). Simple effects analysis showed significant differences between minocycline conditions at 24 hr (F[1,166] = 8.88, p = 0.004), but not at 15 min (F[1,143] = 3.95, p = 0.053) or at 1 hr (F[1,154] = 0.20, p = 0.654). No significant 3-way interactions involving allergen, RQLQ or AQLQ were detected.

Conclusions: The presence of minocycline significantly reduced late phase mean wheal diameter 24 hours after allergen administration. No significant differential effects of minocycline were found across allergens, although this test lacked power. No significant differential effects of minocycline were found depending on subject RQLQ or AQLQ scores.

852 Vaccination-induced Severe Bullous Eruption in a Child with Diffuse Cutaneous Mastocytosis
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Rationale: To investigate if histological findings on biopsy can guide the treatment of chronic urticaria (CU).

Methods: A retrospective chart review of 65 CU patients (56 F, 9 M) who underwent skin biopsy from 1999-2011 at Winthrop University Hospital Allergy and Immunology. All patients failed antihistamine monotherapy. Biopsies were reviewed by 2 independent pathologists. The therapeutic regimens were evaluated to determine which medications were given to achieve clinical remission.

Results: The age range of patients was 11-85 years (mean: 50 years). 54/65 (83%) of biopsies were NU vs. 11/65 (16.9%) lymphocytic predominant urticaria. Of the 53 patients with NU, 44 (83%) were more likely to be on immunomodulating agents compared to 5/10 (50%) without neutrophils (p = 0.0354). Patients who achieved remission were less likely to have neutrophils on biopsy compared to patients who did not achieve remission (p = 0.056). Quantity of neutrophils did not affect the treatment required or resolution status, rather, the mere presence of neutrophils achieved significance. After biopsy, 64.6% of patients had a change in therapy with either the addition of, or change in immunomodulator.

Conclusions: The presence of neutrophils (rather than quantity) on biopsy is associated with difficult to treat urticaria and requires more intensive therapy often including immunomodulating medications; these patients are less likely to achieve complete resolution of symptoms. Skin biopsy can guide in the treatment of difficult to control CU.
853 Drug Rash Eosinophilia and Systemic Symptoms (DRESS) Syndrome in Association with Vancomycin

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RATIONALE: DRESS is a rare drug reaction usually associated with aromatic anticonvulsants (phenytoin, phenobarbital, and carbamazepine) or sulfonamides. Vancomycin-induced DRESS syndrome has been reported only in 1 pediatric and 7 adult cases.

METHODS: Review of 2 cases of DRESS syndrome associated with Vancomycin.

RESULTS: Patient 1 was a 15-year-old boy with Kartagener syndrome presented with fever and erythematous eruption on his upper extremities and trunk within three days of finishing a 4-week course of Ceftriaxone and Vancomycin. Physical exam was notable for fever, periorbital and perioral edema, generalized lymphadenopathy, diffuse pulmonary crackles, hepato-splenomegaly, and maculopapular eruption on the face, torso, palms and soles, and purpuric lesions on the legs. Patient 2 was a 40-year-old man who presented with fever, pruritic rash, and facial edema after finishing a 4-week course of Vancomycin and Flagyl for osteomyelitis. Physical examination revealed fever, enlarged cervical and axillary lymph nodes, and bright erythematous maculopapular eruption over entire body. Laboratory evaluation of both patients revealed eosinophilia, atypical lymphocytes, and elevated liver enzymes. Treatment with methylprednisolone and antihistamines were initiated, and symptoms improved significantly within 24 hours in both patients. Fever, liver enzymes, and eosinophilia improved markedly within days. Patient 1 had one episode of recurrence of rash while tapering the steroid that resolved with increased dose. T-cell stimulation index (T cell Rs, Vibrococ-IBT) was performed on Patient 1 and was strongly positive to Vancomycin.

CONCLUSIONS: Vancomycin-induced DRESS syndrome may be seen more common than previously thought as long-term treatment is commonly used in both pediatric and adult populations.

854 Is It Contact Dermatitis Or Something More Serious?

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RATIONALE: Contact dermatitis is one of the most common inflammatory skin diseases diagnosed by allergists, dermatologists, and primary care providers. This condition is an eczematous disease that can range from red clustered vesicles and bullae with both scaling and pruritus, and bright erythematous maculopapular eruption over entire body. Physical examination revealed fever, enlarged cervical and axillary lymph nodes, and bright erythematous maculopapular eruption over entire body. Laboratory evaluation of both patients revealed eosinophilia, atypical lymphocytes, and elevated liver enzymes. Treatment with methylprednisolone and antihistamines were initiated, and symptoms improved significantly within 24 hours in both patients. Fever, liver enzymes, and eosinophilia improved markedly within days. Patient 1 had one episode of recurrence of rash while tapering the steroid that resolved with increased dose. T-cell stimulation index (T cell Rs, Vibrococ-IBT) was performed on Patient 1 and was strongly positive to Vancomycin.

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CONCLUSIONS: Vancomycin-induced DRESS syndrome may be seen more common than previously thought as long-term treatment is commonly used in both pediatric and adult populations.

855 Gabapentin for the Treatment of Neurogenic Pruritis

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RATIONALE: Peripheral neurogenic pruritis is defined as localized itching in the absence of a rash and other known systemic or central nervous system diseases that cause pruritis. Effective treatment of this non-histamine-mediated pruritis is challenging. Here we present a case of neurogenic pruritis that responded to Gabapentin.

METHODS: Gabapentin 300-1200 mg daily was used to treat a patient with peripheral neurogenic pruritis.

RESULTS: A 38 year-old white male was referred to the allergy/immunology clinic at Virginia Commonwealth University for chronic pruritis without rash not relieved by antihistamine therapy. A prior dermatology work-up included negative ANA, anti-thyroglobulin and anti-TPO titers, normal skin biopsy, normal ESR and normal CT exams of the chest, abdomen and pelvis. Prick skin testing was positive for environmental allergens. Patient was started on immunotherapy for environmental allergens; and on cyclosporine-A (150 mg daily) with only modest relief of pruritis. Permethrin and Ivermectin for presumed scabies also provided no relief. A short course of systemic steroids minimally reduced symptoms.

In the allergy clinic, prior medications for pruritis were discontinued. Gabapentin was initiated at 300 mg daily, and increased to 900 mg daily. This dose was well tolerated and pruritis substantially improved. In a follow up visit 1 month later, patient’s dose was escalated to 1200 mg PO daily which was well tolerated, resulting in only minimal residual pruritis.

CONCLUSIONS: We believe this is the first reported case of spontaneous peripheral neurogenic pruritis that responded to Gabapentin. Further studies of Gabapentin for this condition as well as other forms of pruritis are warranted.

856 Ability of Medical Students and Allergists to Correctly Identify Flying Hymenoptera Species

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RATIONALE: Hymenoptera stings are a common cause of anaphylaxis. Immunotherapy with the appropriate venom has been very successful in preventing future anaphylaxis; however, the ability of allergists to identify appropriate Hymenoptera species either via visual recognition or patient description has not been evaluated.

METHODS: 34 allergists were compared with 81 first year medical students in their ability to correctly identify Hymenoptera species on both Visual and Descriptive Identification Questionnaires. In the visual section, each Hymenoptera image was projected for three seconds to mimic the approximate time a victim might have to visualize the stinging insect. The descriptive section consisted of six written questions that would be helpful in obtaining a patient history regarding a recent insect sting. For each question in both sections, the participants were asked to choose the correct species among 5 multiple choice selections.

RESULTS: Although allergists scored significantly higher than students on each section, both groups scored significantly below 100% overall (Student mean-52.56%; Allergist mean-70.85%, p<0.0001).

CONCLUSIONS: Both medical students and allergists failed to reliably identify Hymenoptera. In order to reduce the risk of future life threatening anaphylaxis, all patients should receive allergy testing and be given prophylaxis against all venoms to which they demonstrate sensitivity rather than relying on the likely flawed ability of either allergists or stinging victims to correctly identify the stinging insect.
857 Use To The Recombinant Species-Specific In The Diagnosis Of Hymenoptera Venom Allergy
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RATIONALE: Diagnosis of hymenoptera venom allergy (HVA) based on a clinical history and skin tests or specific IgE with whole venom may result in some misdiagnosis due to cross-reactivity phenomena. Molecular diagnosis may help to choose a more accurate immunotherapy.

METHODS: 15 patients with history HVA were included in the study. We performed skin tests (ST prick and intradermal) for yellow jacket, polistes and honeybee venom extracts (ALK-Abelló, Spain). Specific IgE to these venom and to rPolD5, rVesV5 and rApiP1 (ImmunoCAP®, Phadia, Uppsala, Sweden) were also performed.

RESULTS: Eight patients had large local reactions, 5 systemic reactions and 2 anaphylactic reactions. ST were positive to wasp and yellow jacket in 5, all with positive specific IgE to both venom, but 3 had positive rPolD5 and rVesV5 and 2 positive to rPolD5 only. ST to polistes was positive in 3 cases, one with all specific IgEs negative, 1 with positive specific IgE to whole venom but negative rPolD5, and 1 with positive specific IgE positive to polistes and vespula but positive to rPolD5 only. 3 had positive ST and specific IgE to vespula venom, but rVesV5 was positive in 2. In 2 ST were positive to wasp and honey bee, but only one with positive specific IgE to bee venom and rApi m1. One had all tests positive for honey bee. In 1 patient ST and all specific IgEs to wasps and honey bee were negative.

CONCLUSIONS: Molecular Diagnosis may help to discriminate single or double sensitization to hymenoptera venom.

858 Possible Association Between Elevated Basal Serum Tryptase Levels and Systemic Reactions To Stings From Blood-Feeding Insects
W. Hemmer1, B. Zahel2, R. Jarisch1; 1Floridsdorf Allergy Center, Vienna, AUSTRIA, 2Dept. of Dermatology, General Hospital Linz, Linz, AUSTRIA.

RATIONALE: Systemic reactions after stings from blood-feeding insects are rare. Relevant risk factors have not yet been identified.

METHODS: Prompted by two own cases and a recent paper describing a mastocytosis patient with anaphylaxis from deer ked stings, we retrospectively assessed tryptase levels in serum samples collected in previous years from patients with a history of anaphylaxis from blood-feeding insects.

RESULTS: In all, 11 patients were included in the study (6 male/5 female, mean age 42.5 ± 14.1 yrs). The culprit insects were mosquitoes (Culicidae, n=6), horse flies (Tabanidae, n=4), or black flies (Simuliidae, n=1). Symptoms reported by patients included generalized itch, urticaria, dizziness, angioedema, breathing difficulties, diarrhea and vomiting as well as hypotension and syncop. 6/11 patients had positive in vitro test results for the incriminated insect, and 4/11 had a concomitant history of Hymenoptera venom allergy. Assessment of serum tryptase levels revealed normal values (<11.4 μg/l) in six patients, and elevated levels (11.7-46.0 μg/l) in five patients (45.5%). At least two patients had confirmed mastocytosis.

CONCLUSIONS: This retrospective study in a limited number of patients indicates the possibility that underlying mast cell disorders may represent a relevant risk factor for anaphylactic reactions after stings from blood-feeding insects.
Venom Allergy In Systemic Mastocytosis
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Rationale: To analyze venom allergy in patients with systemic mastocytosis (SM).

Methods: A retrospective chart review of 168 patients with a diagnosis of SM between 1997 and 2009 was performed after institutional IRB approval.

Results: The rate of venom allergy in our SM population was found to be 12.5% (21/168). Male: female ratio was 3:4. The insects were identified in 12 cases, and honey bee (4) and yellow jacket (4) predominated. Baseline tryptase was elevated in all but 2 patients and unavailable in 3 others. Baseline urine n-methyl histamine excretion was elevated in 7 out of 10 patients measured and urine beta protaglandin (PG) alpha excretion was elevated in 11 out of 11 patients. 6/21 patients had other atopic diseases. 15/21 patients were found to have allergies to medications and 7/15 had intra procedural/intraoperative reactions. Out of 21 patients, 7 were not seen by an allergist and none of the 7 was carrying an Epinephrine Autoinjector. Immunotherapy data was available on 11 patients. Of 4 patients receiving immunotherapy, 2 required dosage adjustments during build up and 1 had a severe reaction requiring ER visit and subsequent pretreatment to build up to maintenance.

Conclusion: This study confirms the high rate of venom allergy in SM (12.5%) compared to the general population (0.5-3%). 24 hour urine mediators were elevated in a majority of patients tested and can add to the diagnostic value. Our experience suggests that the frequency of vespid allergy in SM is increased, and that a substantial number of these patients remain sub-optimally treated.

Food Allergy Impact and Quality of Life in Children with Food Allergy; Evolution of a New Tool for Outcome Measurements
K. Robbins, C. A. Keet, R. A. Wood; Johns Hopkins School of Medicine, Baltimore, MD.

Rationale: Food allergy (FA) can cause significant distress to families and can impact quality of life (QoL) of affected children. It is important to have standardized tools to evaluate FA impact, especially for quality of life (QoL). The Food Allergy Adaptation and Management Scale (FAMAS) is a tool that measures QoL in FA families.

Methods: A semi-structured family interview was developed and rating scales were constructed on 7 dimensions of FA management and children’s adaptation. Preliminary analyses of the FAMAS strongly support its validity and reliability.

Conclusion: The validated FAMAS will facilitate assessment of family integration. The validated FAMAS will facilitate assessment of family adaptation.

Food Allergy Adaptation and Management Scale (FAMAS)
K. Robbins, C. A. Keet, E. LoPresti, J. O. Hourihane, S. Cohen, H. Fransen; National Jewish Health, Denver, CO, University of Colorado School of Medicine, Aurora, CO, Brown School of Medicine, Providence, RI, University College, Cork, IRELAND.

Rationale: Families of children with FA are challenged to maintain a positive quality of life. Existing measures of families’ adaptation to FA fail to assess coping strategies that families use in balanced adaptation.

Methods: A semi-structured family interview was developed and rating scales were constructed on 7 dimensions of FA management (FAMComposite), child anxiety (CAnx), mother anxiety (MAnx), and overall balanced integration (BI). Interviews conducted with 40 parents and children, ages 6-12, with physician-documented food allergies were video-recorded. Psychosocial researchers viewed and rated interviews for FAMComposite, C&MAnx, and BI. Validation measures included: global ratings by physicians for families’ food avoidance (P-FFA) and reaction response management (P-RRM), parent demonstrations of self-injectable epinephrine (Epi-Demo), parent and child anxiety questionnaires (STAI), food allergy impact (FAIS), and Food Allergy QoL Parent Burden (FAQLPB).

Results: Children were 8.6 (SD = 1.7) years old, 73% male, 83% Caucasian, and allergic to 3.3 (SD = 1.8) foods. Inter-rater reliability was excellent for FAMComposite scales (ICC range 0.91-0.98) and physician ratings (ICC = 0.98). FAMComposite correlated with P-FFA (r = 0.88, p < 0.0001) and P-RRM (r = 0.85, p < 0.0001). Mean FAMComposite was higher for parents passing Epi-Demo (t(38) = 2.18, p < 0.04). CAnx correlated with child anxiety (r = 0.48, p < 0.002); MAnx did not correlate with mothers’ self-reported anxiety. BI correlated at trend levels with FAIS stress subset (r = 0.33, p = 0.06) and FAQLPB (r = 0.29, p = 0.07).

Conclusions: Preliminary analyses of the FAMAS strongly support validity of the FAMComposite and largely substantiate the negative influence of family anxiety and the positive influence of balanced integration. The validated FAMAS will facilitate assessment of family adaptation to children’s food allergies.
865 Relationship of Asthma and Food Allergy In An Urban Pediatric Population
H. Mehta; The Mount Sinai School of Medicine, New York, NY.

RATIONALE: Food allergy and asthma often co-exist and some studies demonstrate that having food allergy increases the risk for asthma morbidity. We investigated the relationship between food allergy and asthma in an urban minority pediatric population.

METHODS: A retrospective chart review of 455 urban, predominately Hispanic and African American, pediatric patients from the Mount Sinai Allergy & Immunology clinic was performed to examine the association between food allergy and severity of asthma (defined by inhaled corticosteroid use and healthcare utilization).

RESULTS: 38% of asthmatic children (61% male, 39% female, mean age of 6.8 years old, ranging from 9 months to 19 years old), seen at the clinic had evidence of food allergy to at least one food (convincing reaction history and positive food specific IgE and/or skin prick test). There was no significant difference in inhaled corticosteroid use, hospitalizations, or PICU admissions between asthmatics who had food allergy as compared to asthmatics without comorbid food allergy.

CONCLUSIONS: In this urban minority pediatric population, there is no significant association between food allergy and severity of asthma. Environmental allergens and irritants (e.g. dust mite, cockroach, and environmental tobacco smoke) or socioeconomic factors (e.g. fragmented healthcare and poor compliance) may be the predominating determinants in asthma morbidity in these children.

866 Food Allergy is an Independent Risk Factor for Decreased Lung Function in Children
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RATIONALE: Food allergy (FA) is an early expression of the atopic march, a progression that may lead to the development of asthma. However, the effect of FA on pulmonary function (PF) is not known.

METHODS: 1,066 children were enrolled as a part of a family-based food allergy cohort. Children were categorized as having FA by physician diagnosis with evidence of specific IgE and typical symptoms within 2 hours of food ingestion. Asthma was diagnosed by parent report of physician diagnosis. Spirometry was measured in accordance with ATS criteria. Multivariate linear regression controlling for confounding variables (male sex, socioeconomic status, RSV hospitalization, parental asthma, household smoke exposure and total IgE) was performed to evaluate the association between food allergy and lung function.

RESULTS: Of the 1,066 children enrolled, 402 (38%) had FA and 417 (39%) had asthma. After adjusting for relevant factors, children with asthma had decreased FEF25-75%predicted compared to children without asthma (-6.77±1.71%, p<0.001), but no difference in FEV1%predicted. Univariate analysis of multiple food allergies on PF also demonstrated lower FEF25-75%predicted (-5.68±2.3%, p=0.01), while food sensitization alone had no effect. Interestingly, multiple food allergies with asthma had a combined effect with a decrease of -10.22±2.64% FEF25-75%predicted (p=0.0001). There was no effect in children with asthma and one food allergy or in children without asthma and multiple food allergies.

CONCLUSION: Having multiple food allergies is an independent risk factor for decreased PF among children with asthma, highlighting the need for close clinical follow-up and improved intervention strategies for these patients.
869 Increase In Prevalence Of Food Allergy On The National And State Level In The National Survey Of Children’s Health
K. A. DeMuth, C. McCracken; Emory University, Atlanta, GA.

RATIONALE: Although the prevalence of food allergy has increased, there is little information regarding regional differences in the disorder.

METHODS: The prevalence of food allergy at the national and state level was estimated from the National Survey of Children’s Health conducted in 2003 \( (n = 102,353) \) and 2007 \( (n = 91,642) \). Food allergy was defined by parental report of physician diagnosis of food allergy. The weighted prevalence of food allergy was calculated for each time period. Socioeconomic data were evaluated for possible associations.

RESULTS: The prevalence of food allergy increased nationally from 3,566 cases/100,000 in 2003 to 4,848 cases/100,000 in 2007 \( (p < 0.001) \), with a significant increase in 16/51 (31%) states. The prevalence of food allergy from 2003 to 2007 was otherwise stable. Factors associated with increased food allergy prevalence included: having insurance (insured vs. uninsured; OR = 1.49, 95% CI (1.19, 1.87), \( p = 0.0005 \)), age (0-5 years vs. 12-17 years; OR = 1.35, 95% CI (1.19, 1.54), \( p < 0.0001 \)) and parental report of atopic dermatitis (yes vs. no; 4.56 95% CI (4.07, 5.10), \( p < 0.0001 \)).

CONCLUSIONS: While the prevalence of food allergy increased from 2003 to 2007, there are regional differences. Age, insurance status, and atopic dermatitis were associated with the increase in food allergy prevalence. Future prospective studies of food allergy are warranted, particularly in younger insured children with atopic dermatitis.

870 Prevalence Of Food Allergy In Urban Children
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RATIONALE: Although it has been well documented that urban children have high rates of asthma and allergic rhinitis, little is known about food allergy in this population.

METHODS: A retrospective review of electronic medical records from July 1, 2008 to July 1, 2010 was performed of children from the Mount Sinai Pediatric clinic which serves East Harlem, NY. Charts for review were selected based on ICD-9 codes for food allergy and/or epinephrine auto injector prescriptions. The majority of the patients (89%) were insured with Medicaid/Medicaid managed care.

RESULTS: Of 9314 children seen in this predominantly minority clinic (Hispanic 52%, Black 31%), 3.6% had physician-diagnosed food allergy, with 1.5% having peanut allergy. Among children with food allergy, the mean age was 8.5 years (range 14 mo to 21 yrs), and 59% were male. Three percent of Hispanic and 5.6% of Black children were diagnosed with food allergy. The most common food allergies were peanut (40.1%), shellfish (30.1%), egg (22.6%), tree nuts (18.4%) and milk (13.2%). Nine percent of food allergic children had a documented episode of anaphylaxis; triggers were most commonly peanut (15.2%), milk (13.6%) and shellfish (6%). Among food allergic children, asthma (48.8%), eczema (50.3%), and allergic rhinitis (47.6%) were common.

CONCLUSIONS: The prevalence of food allergy in this urban minority population is consistent with the reported prevalence in the general population. Peanut and shellfish food allergies were most common, and anaphylactic reactions most frequently affected children with peanut and milk allergies. Concomitant allergic disease was also prevalent.

871 The Development of Atopic Dermatitis according to Age of Onset and the Association with Prenatal and Early Life Exposures
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RATIONALE: To determine prospectively whether prenatal and early postnatal exposures, such as nutrition, are associated with atopic dermatitis according to different age of onset, to avoid reverse causality.

METHODS: 1041 children who participated in a birth cohort study (PASTURE/EFRAIM) were included in this study. Atopic dermatitis was defined by doctor diagnosis reported by the parents up to 4 years of age and with positive Scord score from 1 year of age. Atopic dermatitis with early onset was defined when the disease was present in the 1st year of life and with late onset, when occurring after the 1st year. Feeding practices of the 1st year of life were reported by parents in monthly diaries.

RESULTS: Prenatal contact to farm animals, previously described as having a protective effect on atopic dermatitis, was associated with a decreased risk of developing atopic dermatitis only with early onset and not with late onset. Introduction of complementary food in the 1st year of life was associated with a reduced risk of having late onset atopic dermatitis, especially the introduction of yogurt (adjusted OR and 95% CI for late onset atopic dermatitis: 0.41, 0.23 to 0.73) and the increasing number of different major food items introduced (adjusted OR and 95% CI for each additional food introduced: 0.76, 0.65 to 0.88).

CONCLUSIONS: Prenatal exposures to animals have a protective effect only on atopic dermatitis with early onset. The introduction of yogurt and diversity of food introduced in the 1st year of life might have a protective effect on atopic dermatitis.

872 Do Factors Known to Alter Infant Microbial Exposures Alter the Risk of Food Allergy and Eczema in a Population-based Infant Study?
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RATIONALE: To determine whether factors known to alter infant microbial exposures affect the risk of developing food allergy or eczema in the first year of life.

METHODS: In a population-based study of 5,302 one-year-old infants (HealthNuts), all infants were skin prick tested to egg, peanut and sesame, and if positive underwent oral food challenges. Challenge-confirmed egg, peanut and sesame allergy was diagnosed in 460, 148 and 36 infants respectively while 1325 infants had a history of diagnosed eczema. Multiple logistic regression was used to investigate associations between risk factors and allergic disease, adjusted for confounding factors including family history of allergy and socioeconomic status.

RESULTS: Infants with older siblings, those who attended childcare by 6 months of age and those with dogs at home were less likely to develop food allergy (adjusted OR [aOR] 0.7, 95% CI 0.5, 0.8, aOR 0.5, 95% CI 0.3, 0.8 and aOR 0.6, 95% CI 0.5, 0.8, respectively). Caesarean section delivery, antibiotic exposure in infancy and maternal probiotic use during pregnancy were not associated with food allergy risk. Eczema was less common in infants with older siblings or dogs (aOR 0.8, 95% CI 0.7, 0.9 and aOR 0.8, 95% CI 0.7, 0.9 respectively). Maternal use of probiotics appeared to be positively associated with risk of infantile eczema however this association was no longer present after adjustment for maternal history of allergy (aOR 1.1, 95% CI 0.9, 1.4).

CONCLUSIONS: Factors known to increase infant microbial exposures in infancy may decrease the risk of subsequent food allergy and eczema.
873 Goji Berries, a Novel Potent Allergenic Source with High Cross-Reactivity with Other Fruits
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RATIONALE: Goji berry (GB) is a Solanaceae fruit recently introduced in the Western countries diet. The objectives of the study were to analyze their allergen capacity and the cross-reactivity with other fruits.

METHODS: 566 individuals were recruited in five different hospitals from the Mediterranean coast of Spain. They were skin prick tested (SPT) with GB extract. The protein profile was analyzed by SDS-PAGE and 2D electrophoresis. Specific IgE to GB, peach, tomato peel and a mix of nuts were measured in SPT positive individuals. Allergenic profile and cross-reactivity were performed by immunoblot.

RESULTS: Only 85 subjects (15%) had tried GB. Thirty-three individuals (5.8%) had positive SPT to the GB extract (9.4% of those having tried them). Most positive individuals were sensitized to aeroallergens and/or food. Proteins in a MW of 7 to 100 kDa were visualized by SDS-PAGE and 2D electrophoresis. Sera was obtained from 24 SPT positive individuals, 13 of them (54.2%) had positive specific IgE to GB. Among them, 12 were positive to peach (92.3%), 8 to tomato (61.5%) and 9 to nuts (69.2%). In immunoblot, 7 individuals recognized 8 bands, specially one of 7 kDa (6 patients, 86%). Tomato, tobacco, nuts and Artemisia polina pollen inhibited almost completely the Goji berry extract. The 7 kDa band was inhibited by purified Lyc e 3 and Pru p 3.

CONCLUSIONS: Goji berries have a strong allergenic potential and high cross-reactivity with tomato, tobacco, nuts and Artemisia. LTP is an important allergen implicated in the cross-reactivity with other allergens.

874 State Health Departments’ Misinformation on Shellfish Allergy and use of KI in the Aftermath of Fukushima
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RATIONALE: In the wake of the nuclear disaster in Japan in March 2011, the California Department of Public Health disseminated information that use of KI was not indicated and could cause significant side effects in people with allergies to iodine or shellfish. The Department was given the AAAAI Practice Paper on "Risk of severe allergic reactions from the use of potassium iodide for radiation emergencies" (Sicherer SH, JACI 2004;114:1395-7), and information was corrected on the website. This prompted interest in whether other states had posted incorrect information.


RESULTS: Thirteen (26%) of 50 states’ health department websites advised that KI should not be taken by shellfish allergic individuals due to risk of allergic reactions (California included). Eleven additional states had a primary link to the US Center for Disease Control statement that is somewhat ambiguous, i.e., "...a seafood or shellfish allergy does not necessarily mean that you are allergic to iodine" (www.bt.cdc.gov/radiation.ki.asp). Next, the 31 states with active nuclear reactors for power generation were considered: eight (26%, California included) contained statements warning against use of KI in people with shellfish allergies.

CONCLUSIONS: One quarter of state health departments are perpetuating the myth that shellfish allergy is linked to iodine (here, KI) allergy. The AAAAI issued a Practice Paper in 2004 with a strong statement that KI-mediated allergy to shellfish is not related to iodine that can be used to educate government health officials.

875 In-silico Assessment of Potential Allergenicity of Transgenes Used For The Development of Genetically Modified Food Crops
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RATIONALE: Genetically modified (GM) food crops require allergenicity and toxicity assessment of the foreign protein(s) to ensure complete safety to the consumers. In the present study, an in-silico approach is employed to evaluate the allergenic potential of five transgenes routinely used for the development of GM food crops.

METHODS: Sequence homology studies were carried out using-Structural database of allergenic proteins (SDAP), Allermatch and Allergen online (Farrp) databases. Transgene(s) evaluated for potential allergenicity are - manganese superoxide dismutase (Mn-SOD) from Nicotiana plumbaginifolia, Orzya sativa chinatan, β-1, 3 glucanase from Medicago sativa and Triticum aestivum, and glycine betaine aldehyde dehydrogenase (gbsA) from Bacillus subtilis.

RESULTS: Mn-SOD shares greater than 90% identity with latex allergen (Hev b 10) and 60% with Aspergillus fumigatus Mn-SOD (Asp f 6), while chinatan shares greater than 70% identity with reported allergens namely avocado endochitinase and latex class 1 chinatan (Hev b 11). Glucanases (M. sativa, T. aestivum) and gbsA gene shares 50% homology with allergens like olive, β-1, 3 glucanase (Ole e 9), Cladosporium herbarum aldehyde dehydrogenase (Cla h 10) and Alternaria alternata allergen (Alt a 10). As per Codex, 2003 guidelines, an alignement of >35% identity over 80 amino acid sliding window depicts that the query sequence may be a potential allergen since it shares high degree of identity with known allergen(s).

CONCLUSION: The present study elucidates the allergenic potential of five trangenes and these genes should be avoided for development of GM crops.

876 Similar IgE Binding to Soybean Proteins from a Genetically Modified Soybean Line, a Near-Isogenic Line and Three Other Non-GM Soybean Lines Using 10 Sera from Soybean Allergic Subjects
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RATIONALE: Food safety guidelines from the Codex Alimentarius Commission and the European Food Safety Authority recommend evaluating new GM plants for potential changes in endogenous allergenicity if the plant is considered a common source of food allergy. This study compared IgE binding from soybean allergic subjects to extracts of a glufosinate ammonium herbicide tolerant GM soybean, non-GM near-isoline and three commercial lines to evaluate potential risks for soybean allergic consumers.

METHODS: Extracts of soybean lines were compared by IgE binding to 1D- and 2D-PAGE immunoblots using 10 individual soybean allergic sera and non-soybean allergic control sera. Bound IgE was detected with a horseradish peroxidase-conjugated monoclonal anti-IgE and chemiluminescent substrate and compared for qualitative differences.

RESULTS: The only difference noted between the GM soybean and the near-isoline was an additional low intensity spot in the GM soybean by 2D-PAGE immunoblot by sera from one soybean allergic subject. With 6 sera, an obvious IgE binding band/spot was noticed in 1D/2D blots of one of the non-GM commercial lines, which correlated with IgE binding to phytohemagglutinin in navy bean, suggesting the presence of a cross-reactive carbohydrate determinant. Comparison of all 2D-immunoblots demonstrated minor differences between all extracts for at least one subject.

CONCLUSIONS: There was no evidence that LibertyLink soybean presents an increased risk for soybean allergic subjects especially since those with soybean allergy should avoid all soybeans. Furthermore, based on the observed variation among commercial lines, it is not clear that similar tests are useful to evaluate food safety for typical GM varieties.
ABSTRACTS

877 Identification And Analysis Of The IgE Binding By Parvalbumin And Other Potential Allergens In Different Fish And Frog Species

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RATIONALE: Serological cross-reactivity to different fish and frog species is common among fish-allergic individuals. We examined the intra- and inter-individual diversity in IgE responses of fish-allergic subjects to various fish and frog species and identified novel allergens besides parvalbumin.

METHODS: Sera from 38 subjects with a clinical history of fish allergy were analyzed for IgE-binding profiles to crude extracts of 26 raw fish and frog species, and purified cod and carp parvalbumin using IgE-immunoblotting. Sera of 7 subjects showing similar IgE-binding profiles in the IgE-immunoblotting were pooled to identify potential allergens in pilchard, herring, cod, cusk, and rainbow trout using two-dimensional electrophoresis (2D) combined with IgE-immunoblotting and liquid chromatography-tandem mass spectrometry.

RESULTS: IgE-immunoblotting demonstrated great diversity among the fish-allergic individuals with respect to the IgE-binding to the parvalbumins and non-parvalbumin proteins in fish and frog species. Of the 38 individuals, 26 (68%) and 21 (55%) reacted to cod and carp parvalbumin, respectively. However, low IgE reactivity to parvalbumin from frog, mahi-mahi, and swordfish was observed. The pooled sera showed IgE-binding to parvalbumin and its corresponding isoforms separated by 2D in all 5 species. The IgE from pooled sera also recognized several novel fish allergens, including alpha actin, enolase, creatine kinase, glyceraldehyde 3-phosphate dehydrogenase, and fast myosin light chain proteins.

CONCLUSIONS: The variation in IgE-binding depended on the individual and fish species analyzed. The results suggested parvalbumin as the major cross-reactive allergens among fish species. Further characterization of the novel fish allergens is warranted at the molecular level using sera from additional fish-allergic subjects.

878 Monoclonal Antibodies for Defining Conformational Epitopes in Ara h 2 and Ara h 6

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RATIONALE: In addition to linear B-cell epitopes, strong evidence of the presence of conformational epitopes on peanut allergens exists. The goal was to obtain monoclonal antibodies (mAb) against Ara h 2 and Ara h 6 for defining conformational epitopes by X-ray crystallography.

METHODS: Natural Ara h 2 and Ara h 6 were purified from peanut extracts. A panel of mAb (n=110) was raised against both allergens. A recombinant fusion protein of maltose-binding protein (MBP) attached to Ara h 2 was expressed in E. coli. ELISA was used to test recognition of the three allergen molecules by mAbs. IgE inhibition assays were performed using mAb or the allergens as inhibitors.

RESULTS: The antibodies showed four main epitope specificities by direct binding to the three allergens: 1) 43% were cross-reactive, 2) 23% bound only the two Ara h 2 forms, 3) 8% bound only natural Ara h 2, recognizing an epitope covered by MBP, and 4) 1% bound only Ara h 6. Selected anti-Ara h 2 mAb1C3 and IC4 recognizing only natural Ara h 2, inhibited 40-50% IgE antibody binding to natural Ara h 2. The strongest inhibition (80%) was observed for mAb2B6, which recognizes a cross-reactive epitope, not masked by MBP. The MBP-construct allowed to distinguish if mAb bound an epitope masked by MBP or not, and assess the relevance of the allergen N-terminus for IgE antibody binding.

CONCLUSIONS: A panel of mAb interfering with IgE antibody binding was raised against peanut allergens and is a valuable tool for defining allergen-specific and cross-reactive conformational epitopes.

879 Similar Repeated Sequences May account for Cross-Reactions Caused By Many Different Nuts

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RATIONALE: Many peanut allergic individuals also have allergies to tree nuts. Our previous work has shown that the PD scale in SDAP can identify similar IgE binding areas that may be important for cross-reactivity between allergens.

METHODS: A cluster of repeat sequences in the N-terminal pro-sequence of the walnut allergen Jug r 2 was identified and a consensus sequence prepared from the repeats. A peptide from the consensus was used to generate antibodies in chickens. Western blotting was used to identify allergens in extracts from nuts recognized by the chicken antibodies, and by serum IgE from patients allergic to peanuts, walnuts, almonds, and or almonds. Proteins in the reactive bands were identified by mass spectroscopy.

RESULTS: Searching the Structural Database of Allergenic Proteins (SDAP) using the property distance (PD) tool with the consensus peptide sequence revealed many potential IgE epitopes with similar physicochemical properties in nut allergens, including several 7S, 2S and 11S albumins. The antibodies to the consensus peptide recognized proteins of the appropriate size to these proteins in various nut extracts. Many of the proteins that bound the consensus peptide antibodies were identified by mass spectroscopy and recognized by IgE in the sera of patients with documented clinical cross-reactivity.

CONCLUSIONS: A repeated sequence motif, summarized by our consensus peptide, is common to many different allergenic proteins from nuts and seeds. The repeat may be a relic of a very ancient storage protein that has been conserved in various forms in nut proteins, perhaps because of antifungal properties.

880 Effect of High Pressure on Peanut Allergens in Presence of Polyphenol Oxidase and Caffeic Acid

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RATIONALE: High pressure (HP) enhances enzymatic reactions. Because polyphenol oxidase (PPO) is an enzyme and reduces IgE binding of peanut allergens in presence of caffeic acid (CA), we postulated that a further reduction in IgE binding can be achieved, using HP and PPO/CA.

METHODS: Peanut extracts containing CA were treated with PPO, followed by treatments with and without HP. The conditions for HP treatment were: 300 and 500 MPa, each for 3 and 10 min. Treatments without PPO but HP were also performed. After treatment, SDS-PAGE was performed and IgE binding was determined colorimetrically in competitive ELISA.

RESULTS: SDS-PAGE data showed that in the absence of PPO, HP had no effect on major peanut allergens. In the presence of PPO, HP at 500 MPa (3 and 10 min) induced a higher reduction of allergens than PPO alone. IgE binding was reduced in both PPO and PPO/HP-300 min treatments, as compared to the control (no PPO). However, a higher reduction in IgE binding was seen with PPO/HP-500 at 10 min.

CONCLUSIONS: PPO together with CA reduced the levels of major peanut allergens and IgE binding. Applying HP at 300 MPa (3-10 min) to the PPO treatment did not enhance the reducing effect. By contrast, HP at 500 MPa (3-10 min) enhanced the reduction of allergens, but only HP-500 at 10 min appeared to lower the IgE binding further, compared to PPO treatment alone. In the absence of PPO, HP had no effect on major peanut allergens under the conditions tested.
881 A Combination of Boiling and Frying, but not Pressure or Temperature, Decreases Soluble Peanut Allergens but Does not Generate Hypoallergenic Peanuts
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RATIONALE: Peanut allergy continues to be a problem in most developed countries of the world. We sought a processing method which would render peanuts safer for consumption by some peanut-allergic individuals.
METHODS: Peanuts were untreated (raw), or treated by a boiling and frying process (boiled/fried) and then subjected to various pressure/temperature/time treatments prior to pulverizing into a peanut butter. Using immunoblot and immunoblot inhibition experiments, we characterized the IgE binding capabilities of the peanut protein extracts.
RESULTS: The combination treatment of boiling and frying decreased recovery of Ara h 1 and Ara h 2 at their expected MWs (recovered from peanut extracts, boiling fluid not assayed). Pressure and temperature treatments had no significant effects on protein profiles for either raw or boiled/fried samples. Upon dot blotting, serum from a broadly-reactive peanut individual bound all extracts. Immunoblotting showed that IgE from peanut allergic individuals bound fewer proteins in the boiled/fried samples than the raw samples. Pre-incubation of serum from peanut allergic individuals with boiled/fried extract, removed the majority of raw peanut-reactive IgE from solution.
CONCLUSIONS: It is likely Ara h 1 and Ara h 2 epitopes remain in extracts of boiled/fried samples since serum IgE from some peanut-allergic individuals bound proteins in both raw and boiled/fried samples. Thus, this method of processing is unlikely to generate a hypoallergenic peanut.

882 Milk Is The Predominant Undeclared Allergen In Us Food Product Recalls
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RATIONALE: Hazardous exposure to undeclared allergens in packaged food products is an unfortunate reality for food allergic consumers. Data on food product recalls involving allergens were analysed to provide information on risk of allergen exposure and reactions posed by this scenario.
METHODS: The US FDA generates a health hazard evaluation (HHE) for every recall involving food products. This HHE database was queried for incidents involving undeclared major food allergens (allergen recalls) between 2005 and 2008. Information was collected on allergen type(s), food products and specifics of allergen recalls associated with consumer reactions.
RESULTS: Allergen recalls occurred at a frequency of 64-87/yr and comprised 302 total recalls (31% of food recalls) with 551 different products. Milk represented the most common undeclared allergen (43%) followed by egg (21%), tree nuts (18%) and wheat (17%). 51 recalls (16% of total) were associated with 70 total consumer reactions (25% of these recalls involved ≥ 2 reactions). Milk was involved in 59% of reactions, followed by egg (27%) and tree nuts (10%). Eight reactions (11%) were reported as anaphylaxis (5 milk, 2 egg, 1 wheat). The most frequently implicated products in reactions were baked goods (22%) and chips/snacks (16%). In 16 recalls associated with reactions, allergen concentrations in products reported to FDA ranged from 25 to > 5000 ppm.
CONCLUSIONS: These data show that undeclared milk is the most frequently reported cause of recalls as well as adverse reactions in allergen recall scenarios. About 1 in 6 product recalls associated with undeclared allergen result in adverse health consequences.

883 Life-threatening Allergic Reactions To Foods In Adult Patients From Spain
RATIONALE: Peanuts and tree nuts have been reported as the most common cause of severe anaphylactic reactions in several countries. However, the frequency of specific foods eliciting allergic reactions varies depending on different factors, such as age, staple diet, and geographic location. Therefore, we sought to analyze the characteristics of severe anaphylaxis induced by foods in a group of adult patients from a central area of Spain.
METHODS: Clinical records of adult patients from the Allergy Clinic of the Hospital Universitario 12 de Octubre (Madrid, Spain) who fulfilled the NIAID/FAAN criteria for the diagnosis of anaphylaxis.
RESULTS: Of 176 subjects diagnosed with food-induced anaphylaxis, 41 (16 men and 25 women) had a total of 46 severe reactions with reduced blood pressure or symptoms of end-organ dysfunction. Median age at presentation was 29 yr (IQR = 15.25). The implicated foods were apple, 9 patients; kiwi, 5; banana, 4; shrimp; 4; melon; 3; chestnut, 3; walnut, 2; peach, 2; and almond, lupine, hazelnut, peanut, plum, avocado, barley, sunflower seed, octopus, lentil, honey, shellfish, fish, and bean, 1 each. Besides the hypotension/associated symptoms, urticaria/angioedema occurred in 44 cases (95%), gastrointestinal anaphylaxis in 12 (26%), and bronchospasm in 29 (63%). Interestingly, a rapid onset of oropharyngeal symptoms associated with the ingestion was reported in 29 of 46 reactions.
CONCLUSIONS: We report a group of 41 adult subjects who experienced severe food-induced allergic reactions, including hypotension/end-organ dysfunction symptoms. Fresh fruits were the culprit food for over half of the reactions.

884 Overall Prevalence Of Self-reported Food Allergy In Canada
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RATIONALE: Food allergy prevalence estimates vary considerably across studies. Although our research team recently published prevalence estimates for peanut, tree nut, fish, shellfish, and sesame allergy in Canada, the overall prevalence of self-reported food allergy has never been reported.
METHODS: A randomized telephone survey of Canadian households was performed to assess the prevalence of food allergy. Respondents were asked to self-report any food allergies in the household.
RESULTS: Of 10,596 households surveyed, 3,666 responded (35% response rate), of which 3,613 provided data on food allergies, representing 9,667 individuals. Of these, 8.0% (95% CI, 7.5, 8.6) self-reported at least one food allergy. Given that milk, egg, wheat, and soy allergies often resolve by adulthood, adults reporting only one of these were excluded to generate a conservative estimate of 6.6% (95% CI, 6.1, 7.1). A greater proportion of individuals residing in households where the primary respondent was Canadian-born reported an allergy than households where the respondent was not Canadian-born [8.3 versus 6.6%, difference, 1.7% (95%CI, 0.3, 3.2)]; a greater proportion of individuals residing in households where the primary respondent was a post-secondary graduate reported an allergy than households where the respondent was not a post-secondary graduate [8.7% versus 7.1%, difference, 1.5% (95%CI, 0.4, 2.7)].
CONCLUSIONS: Although 8% of Canadians self-report a food allergy, fewer are likely to have true food allergy. Despite not being diagnosed, those who believe they are allergic follow the same dietary restrictions and experience the same anxiety. Hence, it is critical to encourage all suspecting they have a food allergy to seek medical care.
Prevalence of Common Food Allergies in Canada: Targeting Specific Demographic Groups across Canada

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RATIONALE: To compare the prevalence of food allergies in specific demographic groups in Canada: those of lower income versus higher income, immigrants versus Canadian-born and Aboriginals versus non-Aboriginal.

METHODS: Postal codes with a high proportion of the targeted vulnerable populations were identified. Households were randomly selected from these postal codes and asked to participate in a telephone survey. Food allergy was based on self-report.

RESULTS: Of 8508 households surveyed, 4169 responded (representing 13233 individuals, 49.00% response rate). The prevalence of peanut, tree-nut, fish, shellfish, milk, egg, soy, wheat and sesame allergy were: 0.98% (95%CI, 0.82%,1.17%), 0.94% (95%CI, 0.78%,1.12%), 0.63% (95%CI, 0.51%,0.79%), 1.49% (95%CI, 1.29%,1.71%), 0.63% (95%CI, 0.51%,0.79%), 0.49% (95%CI, 0.38%,0.63%), 0.25% (95%CI, 0.17%,0.35%), 0.15% (95%CI, 0.09%,0.23%) and 0.12% (95%CI, 0.07%,0.20%) respectively. Our preliminary results show that individuals residing in households at or below the low income cut-off had lower prevalence of tree-nut, shellfish, and wheat allergy (-0.78% (95%CI, -1.16%,-0.4%), -0.66% (95%CI, -1.2%, -0.12%) and -0.22% (95%CI, -0.37%, -0.07%) respectively. Households in which the primary respondent had no post-secondary education had lower prevalence of tree-nut and shellfish allergy (-0.41% (95%CI, -0.80%, -0.04%) and -0.68% (95%CI, -1.00%,0.20%) respectively. Those not born in Canada had less peanut and tree-nut allergy (-0.78% (95%CI, -1.09%, -0.47%), -0.68% (95%CI, -1.69%, -0.43%)) and Aboriginals had less shellfish and wheat allergy (-0.72% (95%CI, -1.19%, -0.25%), -0.18% (95%CI, -0.35%, -0.01%) respectively.

CONCLUSIONS: We hypothesize that dietary habits (e.g. age of introduction and preparation of food) associated with specific demographic characteristics might contribute to a lower food allergy prevalence.

Low Level Specific IgE Sensitization in Parents of Food Allergic Children

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RATIONALE: Allergen specific IgE (sIgE) is often measured in the assessment of food allergy. We sought to assess the utility of a 0.1kUA/L cutoff compared to the standard 0.35kUA/L used in practice in relation to physician diagnosed food allergy (FA) in adults. We also evaluated the association of low level sensitization (sIgE level 0.1-0.35kUA/L) with FA.

METHODS: 1953 parents enrolled as part of a family-based food allergy cohort in Chicago, were evaluated. Standardized questionnaires assessed for reported physician diagnosed FA to common allergens (peanut, milk, egg, soy, wheat, shrimp, codfish and sesame seed). Fisher’s exact tests were used to evaluate the association of a physician diagnosis of FA with level of sIgE (Phadia Immunocap, Uppsala Sweden) in the following categories (>0.1, 0.1-0.35 and >0.35 kUA/L).

RESULTS: 20.2% of mothers and 17.9% of fathers reported physician diagnosed FA. FA was associated with sIgE>0.1kUA/L for 6 of the 8 foods in both mothers and fathers. In comparison, FA was associated with the presence of sIgE >0.35 kUA/L for only 4 of 8 foods for each parent. For sIgE between 0.1-0.35kUA/L, only 2 of 8 foods assessed for mothers and 4 of 8 foods assessed for fathers were associated with FA.

CONCLUSIONS: Although the lower cutoff of 0.1kUA/L may be associated with physician diagnosis for a greater number foods compared to the standard cutoff of 0.35, there appears to be little discriminative power for subjects who have low level sensitization (0.1-0.35).

Increasing The Accuracy Of Peanut Allergy Diagnosis Using Ara H2

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RATIONALE: Measurement of whole peanut-specific IgE (sIgE) is often used to confirm sensitization but does not reliably predict allergy. As Ara h2 is the dominant peanut allergen detected in 90-100% of peanut allergies, we hypothesize that Ara h2 testing might improve the accuracy of diagnosing peanut allergy and therefore circumvent the need for an oral food challenge (OFC).

METHODS: Infants from the population-based HealthNuts study were skin prick tested to determine peanut sensitization and subsequently underwent a peanut OFC to confirm allergy status. In a stratified random sample of 200 infants (100 peanut allergic and 100 peanut tolerant), whole peanut sIgE and Ara h2 sIgE were quantified by fluorescence enzyme immunoassay.

RESULTS: To provide a specificity of 95%, the diagnostic cutoff level for Ara h2 sIgE is 0.46 kUA/L (sensitivity 73% [95% CI: 66%-84%]), and for whole peanut sIgE 6.2 kUA/L (sensitivity 44% [95% CI:34%-54%]). If the 15kUA/L threshold (95% PPV for positive food challenge) is adopted, the sensitivity of the whole peanut sIgE test reduces to only 26% [95% CI: 18%-36%]. At the same specificity of 98%, Ara h2 sIgE testing correctly identifies 60% [95% CI: 50%-70%] of true peanut allergics.

CONCLUSIONS: Ara h2 sIgE testing provides higher diagnostic accuracy than whole peanut sIgE and could be considered as a new diagnostic tool to distinguish peanut allergy from peanut tolerance and may reduce the need for an OFC.
888 Peanut Allergen (Ara h 2) in Settled Dust Samples of Inner-City Schools and Homes of Children with Asthma

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RATIONALE: The management of peanut allergy includes strict avoidance; however, children may be cutaneously exposed to small amounts of peanut protein in the environment.

METHODS: Settled dust samples from classrooms and cafeterias of 12 inner-city schools were analyzed for peanut protein, Ara h 2, by ELISA. Dust samples were linked to students with asthma enrolled in the School Inner-City Asthma Study. For comparison, settled dust samples were also collected from the students’ homes (bedrooms) and analyzed for the presence of peanut protein in the same manner.

RESULTS: A total of 236 school and home settled dust samples were collected and 13.6% (n=32) had detectable levels of Ara h 2 (>0.4 mcg per gram dust). In the school samples, 8.8% (14 of 159) of samples had detectable levels of Ara h 2 with the detectable samples having a median level of 0.76 mcg/g (range 0.47-6.59 mcg/g). Peanut protein was detectable in 18.2% of cafeteria samples and 7.3% of classroom samples. Two schools, in particular, had detectable peanut protein in 21.4% and 18.8% of dust samples. By comparison, 23.4% (18 of 77) of home samples had detectable levels of Ara h 2 with the detectable samples having a median level of 1.13 mcg/g (range 0.40-9.79 mcg/g).

CONCLUSIONS: Peanut protein, Ara h 2, was detectable in settled dust samples from classrooms and cafeteria samples from 12 inner-city schools were analyzed for peanut protein, Ara h 2, by ELISA. Dust samples were linked to students with asthma enrolled in the School Inner-City Asthma Study. For comparison, settled dust samples were also collected from the students’ homes (bedrooms) and analyzed for the presence of peanut protein in the same manner.

889 Peanut Protein Contamination in Peanut Hulls/Shells Used in Compost and Other Lawn Service Applications

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RATIONALE: Peanut hulls are increasingly used as a composted soil additive, especially in Southeastern USA. We sought to quantitate the levels of peanut protein contamination in peanut hulls and assess any potential allergenic risk associated with soil compost applications.

METHODS: Four samples of peanut shells were collected in Florida from a commercial peanut shelling operation. Representative sub-samples were analyzed in duplicate using a commercial enzyme-linked immunosorbent assay (Neogen Veratox® Peanut Allergen) with a lower limit of quantitation of 2.5 parts per million peanut (ppm, µg/g). Later, 5 samples were received from a Georgia family with a peanut-allergic child after a commercial firm had installed topsoil dressing to their lawn that showed visual evidence of peanut hulls. These samples were analyzed using the same ELISA method.

RESULTS: Peanut protein was detected in 50% (2/4) of the samples from Florida ranging from 80-150 ppm peanut while the other 2 samples had no detectable peanut at the limit of quantitation (2.5 ppm). Peanut protein was detected in 60% (3/5) of samples collected from the Georgia family ranging from 50-2200 ppm peanut.

CONCLUSIONS: Peanut protein was detected in variable amounts among samples of raw peanut shells obtained from several sources. While we are unaware of allergic reactions occurring from the presence of peanut hulls in compost or top dressing for lawns, a potential risk seems to exist especially in terms of potential skin-contact reactions. Peanut-allergic individuals should be made aware of the potential for compost materials to contain peanut hulls so that they might select alternative products.

890 In Vitro Assessment of the Allergenicity of Novel H1N1 Influenza Vaccine Produced in Dog Kidney Cells in Subjects with Dog Allergy

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RATIONALE: A licensed inactivated seasonal influenza virus produced in canine kidney cells (MDCK 33016-PF) contains no egg proteins and did not trigger degranulation in rat basophilic leukemia (RBL) cells passively sensitized with human anti-dog IgE, supporting its safe use in dog-allergic individuals. The canine kidney cell-derived H1N1 pandemic vaccine, however, was adjudicated with the emulsion adjuvant MF59®, and support for its similar safe use was sought. We evaluated allergenicity of the adjuvanted canine kidney cell-derived H1N1 vaccine in subjects with dog allergy, with utilization of an in vitro mediator release assay.

METHODS: RBL-2H3 cells transfected with human IgE receptor-1 were sensitized with sera from adult dog-allergic subjects and stimulated with serial dilutions of H1N1 vaccine and dog dander extract. β-N-hexosaminidase release (NHR) was used as a marker of RBL degranulation.

RESULTS: Median dog dander-specific IgE in 30 dog-allergic subjects was 27.7 kU/L (range 10.1; >100); and in 5 dog-non-allergic subjects was <0.35 kU/L. Median (range) maximum NHR in dog-allergic subjects was: 1) H1N1 vaccine- 1.1% (0- 4.4); 2) Dog dander-6.9% (0.7-37.3); P<0.001. Median (range) maximum NHR in dog non-allergic subjects was: 1) H1N1 vaccine -2.3 % (1.5-2.8); 2) Dog dander-2.2% (2.0-2.4); P=0.6. There was no difference in peak mediator release upon stimulation with H1N1 vaccine in dog allergic versus dog non-allergic subjects, P=0.4.

CONCLUSION: MF59-adjuvanted H1N1 influenza vaccine produced in canine kidney cells did not trigger degranulation in RBL cells passively sensitized with human anti-dog IgE, supporting its safe use in dog-allergic individuals.

891 Amoxicillin-induced Aseptic Meningitis with Neutrophil Predominance

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RATIONALE: Amoxicillin-induced aseptic meningitis (AIAM) is extremely rare and there are only 6 reported cases. Cerebrospinal fluid (CSF) of all the patients in the reported cases showed a lymphocytic predominance. We report a case of AIAM with neutrophil predominance.

METHODS: Diagnosis of drug-induced aseptic meningitis was based on published criteria: a temporal relationship with drug intake (with likely positive re-introduction), CSF pleocytosis, negative microbiological test and rapid complete resolution after drug discontinuation.

RESULTS: A 58-year-old woman with multiple food allergies presented to the hospital with fever of 103°F, nausea, vomiting and headache 4 hours after receiving 2g amoxicillin orally for dental procedure. She did not take any other prescribed or over-the-counter medications. Physical exam was unremarkable. Head CT did not show acute hemorrhage. CSF showed total cell count of 624 with 17 RBC, 561 (90%) neutrophils and 25(4%) lymphocytes. CSF did not show any organisms. CSF routine cultures and HSV PCR were negative. HIV was negative. Amoxicillin was stopped within 48 hours of onset. She had a similar but milder episode a year ago 6 hours after receiving 2g of oral amoxicillin, with resolution of symptoms within 24 hours.

CONCLUSION: Neutrophil predominant aseptic meningitis can be induced by amoxicillin.
The Impact of Parasite Infestation Associated With Hyper-IgE on Tolerance of Aspirin and Desensitization

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RATIONALE: Parasites are highly prevalent worldwide particularly in underdeveloped regions including Vietnam. Hyper-IgE may be a consequence of parasite infection. Presently, it is unknown how parasite infestation associated with Hyper-IgE affects ASA sensitivity and desensitization.

METHOD: The patient was a 76-year-old Vietnamese male with coronary artery disease requiring a stent, which necessitated aspirin. Urticaria complicated the use of aspirin and prevented a trial to desensitize the patient. At the same time the patient was found to have an IgE of 1337 IU/L and parasite infestation with Lumbricoides, Toxocara and Liver fluke. ASA desensitization was re-attempted after treatment with abendazole.

RESULTS: The second aspirin desensitization was successful without the complication of urticaria; however, the IgE level persisted over 1000 IU/L. The patient has been able to tolerate aspirin on a regular basis after treatment of his parasite infection. Our report documents a safe and successful desensitization to aspirin in an individual with hyper IgE caused by helminthic parasite infection who had recurrent urticaria whenever aspirin was introduced; however, after treatment of his parasite infection he was able to tolerate repeat desensitization with aspirin and continued aspirin use.

CONCLUSIONS: The combination of parasite infection and use of aspirin resulted in urticaria and inhibited attempts to desensitize the patient to aspirin. Treatment of the parasite infection allowed aspirin desensitization to be successful and the continued use of aspirin to be tolerated.

Prevalence and Co-morbidities of Ocular Allergy in Adolescents

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RATIONALE: The prevalence of ocular allergy (OA) and its association with asthma, rhinitis and atopic dermatitis (AD) have not been well established. The aim was to describe the prevalence of OA and associated co-morbidities in adolescents.

METHODS: 3468 subjects from seventh and eighth grades from Curitiba volunteered to self-complete a standardized and validated questionnaire on symptoms of OA, asthma, rhinitis and AD. OA was defined as more than 3 episodes of ocular itching occurred in the last 12 months. Definitions of asthma, rhinitis, and AD symptoms in the last 12 months followed the ISAAC written questionnaire for 13 - 14 year olds.

RESULTS: 3120 adolescents completed the questionnaire, mean age was 13.3±1.1 years, 51.2% were female. OA was identified in 647 (20.7%) subjects. At least one OA co-morbidity occurred in 75.3%, most frequently rhinitis (64.6%). Association with asthma was observed in 31.4% and AE in 13.1%. OA, asthma, rhinitis and AD were combined in 3.6% of children. The risk of adolescents with ocular allergy show up with asthma, rhinitis and atopic eczema was [OR=5.7; CI95%: 4.5 to 7.1]; (OR=3.6; CI95%: 3.0 to 4.3) and (OR=2.6; CI95%: 2.0 to 3.5), respectively. The association between asthma and ocular allergy was greater among those with both ocular allergy and rhinitis (36.8% versus 20.5%; p<0.01).

CONCLUSIONS: Ocular allergy is common in adolescents and frequently associated with rhinitis, asthma and AD. The link between OA and asthma was stronger in those with OA who had associated nasal symptoms.
**AB238 Abstracts**

**How Commonly Does Symptom Severity Vary by Season in Nonallergic Rhinitis?**

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**RATIONALE:** Nonallergic rhinitis (NAR) is a heterogenous disease. In this study, we describe the seasonal variation in symptom severity in patients with NAR.

**METHODS:** We performed a retrospective study of patients that presented to a subspecialty rhinitis and sinusitis clinic between January 1, 2010 and June 30, 2011. Each patient in this clinic was asked to complete a questionnaire, which included a rating of nasal or sinus symptom severity by month (1-10 scale). Seasonal variation in symptom severity was defined as an increase in symptom score by 2 points in 2 of 3 months of a season above the best symptom score recorded in any month. Patients were excluded if there was a clinical or radiological diagnosis of chronic rhinosinusitis, no documentation of rhinitis symptoms, or no record of negative skin prick or serum-specific IgE tests to relevant allergens.

**RESULTS:** We identified 144 patients that had complete seasonal symptom data and met our definition of rhinitis. Eighty-six of the 144 patients were excluded because they had allergic rhinitis, and another 17 were excluded due to chronic rhinosinusitis. The mean age of the 41 included patients was 54 years-old and 56% were female. A pattern of seasonal variation was present in 59% of NAR patients. NAR patients with seasonal variation were not different by age (p=0.50) or gender (p=0.76). Nearly all patients (88%) demonstrated worsening of symptoms over baseline in 2-3 seasons.

**CONCLUSIONS:** Patients with NAR report significant seasonal variation in symptom severity. Environmental triggers may be important for the majority of patients with NAR.

**Exhaled NO May Predict Development of Allergic Rhinitis in Children**

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**RATIONALE:** As a non-invasive parameter of lower airway inflammation, fraction of exhaled nitric oxide (FeNO) concentration has been known to be related with bronchial hyperreactivity in asthma patient. FeNO may be increased in atopy related diseases (e.g. allergic rhinitis) but relationship of FeNO and development of allergic rhinitis in asthma is unknown. The aim of this study was to investigate whether measurement of FENO in asthma children can predict development of allergic rhinitis.

**METHODS:** Fifty-three children with mild to moderate persistent asthma aged from 5 to 15 years who were measured with FENO, total eosinophil count and IgE were included. FeNO was measured through chemiluminescence analyzer. Prospectively, the patients were followed after 6 years by interview with questionnaire and FeNO levels of the patient who developed allergic rhinitis (allergic rhinitis group and control group) were evaluated.

**RESULTS:** There were no difference of peripheral blood total eosinophil count, serum IgE, age, sex, family history, history of atopic dermatitis, or degree of asthma severity between allergic rhinitis group and control group. FeNO was significantly higher in allergic rhinitis group compared to control group (29.4±24.6 parts per billion [ppb] vs 13.6±11.8 ppb; p = 0.003).

**CONCLUSIONS:** Measurement of FeNO can be a useful tool to predict development of allergic rhinitis in asthmatic children.
Are Pseudopods On Skin Prick Testing Reproducible?  
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RATIONALE: Pseudopod development on skin prick testing is used widely by allergists to denote severe sensitivity to a given allergen. We attempted to evaluate if a patient will consistently develop a pseudopod to a particular allergen.

METHODS: Patients aged 2-17 were enrolled in our outpatient hospital based allergy clinic. Any patient who developed a pseudopod during their skin prick testing associated with their visit were enrolled. For the purpose of objectivity a pseudopod was defined as an asymmetric foot like projection on the wheel of a skin prick test that projects > 5 mm away from the natural contour of the wheel and with no other identifiable cause for the asymmetry. 2 subsequent pricks to the allergen were applied to a neutral central area of their back. Skin tests were measured, documented with tape tracings, and photographed.

RESULTS: A total of 42 skin prick tests were applied to 22 patients. All initial skin pricks met the definition of a pseudopod. Of the subsequent pricks there were 27% (95% CI: 30-48) of patients that had both follow up skin pricks being positive for a pseudopod. 55% (95% CI: 40-69) of the total follow up skin prick tests were positive for a pseudopod.

CONCLUSIONS: Pseudopod development on skin prick testing is a not a reliably reproducible phenomenon even when using an objective measure of what a pseudopod is. Based on these findings we suggest using caution when interpreting pseudopod development as a marker for severity of allergic disease.

Optimal Concentration Of Dermatophagoides Pteronyssinus allergen Extract (Dp) For Skin Prick Testing (SPT) In Thai Population With Allergic Rhinitis (AR)  
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RATIONALE: It is noted that sizes of SPT to Dp in some allergic Thai patients are large. We hypothesize that lower concentration of Dp may be used for the Thais.

METHODS: Forty AR patients with positive SPT to Dp and 69 healthy volunteers (all > 15 years) were recruited. SPT with Dp at concentration of 30, 100, 300, 1000, 3000 and 10,000 AU/ml were performed in duplicates, in all, SPT sizes were recorded. Nasal challenge test with Dp allergen extract (50 AU/side) were performed to accurately verify Dp-induced AR. Sensitivities, specificities, accuracies and receptive operative curve (ROC) were analyzed at various Dp concentrations.

RESULTS: 35 patients had positive nasal challenges to Dp. 10 subjects in healthy group had positive challenge and were excluded. By ROC, areas under the curve (AUCs) of Dp at 30 and 100 AU/ml were significantly smaller than that of 10,000 AU/ml (p < 0.001) while AUCs of 300, 1000, 3000 and 10,000 AU/ml were similar (p > 0.05). Further analysis at cut-point of 3 mm wheal size, the accuracies of 300, 1000, 3000, 10,000 AU/ml were 72.5%, 79.8%, 82.6% and 85.3%. The accuracies of 1000, 3000, and 10,000 AU/ml were not significant different from one another (p > 0.05). Sensitivities and specificities of 1000, 3000, 10,000 AU/ml were 53.3/ 98.4%, 64.4/95.3% and 80/89.1%.

CONCLUSIONS: Despite the fact that the best sensitivity was noted at Dp 10,000 AU/ml, similar accuracies between 3000 and 10,000 AU/ml was observed. Concentration of between 3000 and 10,000 AU/ml should be further investigated.

Histamine Skin Prick Test (SPT) Titration Following Antihistamine Administration: Wheel Comparison of Histamine Strength Using Different Devices  
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RATIONALE: Histamine positive control establishes patient skin reactivity in order to validate skin test results and reveal impairment due to antihistamines or other factors. In the US, different histamine concentrations and devices are used for SPT. The purpose of this study is to evaluate histamine concentrations and SPT devices for positive and negative wheal responses in subjects under antihistamine-induced inhibition.

METHODS: SPT was performed simultaneously with 1, 3 and 6mg/mL histamine base using devices from 3 manufacturers; Lincoln Diagnostics, Greer, and Hollister-Stier. A 50% glycerol-saline negative control was included. Some subjects were also tested with Standardized Bermuda allergen extracts at 3,000-10,000BAU/mL. SPT was first done after withholding antihistamine for at least 5 days. A single dose of an OTC antihistamine was taken and SPT completed again after 12, 36 and 42hr. Wheal sizes were recorded 10-15 minutes after skin testing. Results were scored as either positive or negative based on a wheal size of either ≥3mm or ≥5mm.

RESULTS: The wheal size increased as histamine concentration increased. Depending on the device and cutoff criteria used, diagnostic results varied, with low histamine concentrations appearing negative under antihistamine inhibition while high histamine concentrations sometimes appeared positive. This effect was also seen with different Bermuda concentrations.

CONCLUSIONS: Due to differences in the wheal size produced with different devices and histamine, proper cutoff ranges must be established for each system. Determining positive reactions under various conditions is especially important for individuals under the influence of antihistamines or other factors that reduce skin responses.
Evaluation of Fungal Sensitivity in the Greater New Orleans Area

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Rationale: In post-Katrina New Orleans, there was an increase in atmospheric fungal exposure. Fungal allergy is associated with increased severity of rhinitis and asthma. Our institution’s allergen panel was expanded in response to possible increases in fungal sensitization. However, recent studies have shown that fungal sensitization in New Orleans is not above the national average as was once hypothesized. We retrospectively examined skin test results with the intention of simplifying our testing of fungal allergy and eliminating redundancy.

Methods: Four years of skin prick test results of 1208 patients were analyzed for rates of monosensitization and multisensitization. A cluster analysis was performed to identify fungal allergens with higher levels of concordance suggesting cross-reactivity rather than unique sensitization.

Results: Of the 28,992 fungal skin tests performed in 1208 patients, 3.3% were positive. Of the patients with a unique fungal sensitization, Alternaria had the highest degree of monosensitization at 26%, and Stenphylium was the only fungus with no monosensitization. We determined that 102 patients were uniquely sensitized to one fungal allergen, and 162 patients were sensitized to two or more allergens.

Conclusions: Most fungal extracts identified patients that were monosensitized to fungus. Others appeared to be positive in patterns suggestive of cross-sensitization consistent with phylogenetic relationships. Based on rare sensitizations and apparent cross-sensitizations, several fungal extracts can be eliminated from our testing panel.

Comparison of Skin Prick Testing and ImmunoCAP Testing in the Diagnosis of Cat Allergy


Background: Cat-specific serum IgE levels are sometimes used to augment or replace skin prick testing (SPT) in the diagnosis of allergic rhinoconjunctivitis. The purpose of this study is to compare SPT and the cat-specific ImmunoCAP test in the diagnosis of cat allergy.

Methods: Subjects between the ages of 18 and 55 were enrolled in the study based on the presence or absence of nasal-ocular symptoms in the presence of a cat. All subjects underwent SPT to cat and had cat-specific serum IgE measurement by ImmunoCAP (Phadia Ab, Uppsala, Sweden). Subjects then underwent a conjunctival challenge to standardized cat extract. A positive cat ImmunoCAP test was defined as a level >0.35 kU/L. True positives were defined as having a history of cat allergy symptoms and a positive conjunctival challenge, while true negatives lacked symptoms of cat allergy and were challenge negative.

Results: 13 true positive and 31 true negative subjects were identified. All (13/13) true positives had a positive SPT, and 29/31 true negatives had a negative SPT (Sens. 100%, Spec. 94%, PPV 87%, NPV 100%). 41 of the 44 subjects had serum available. Most (9/13) true positives had a positive cat ImmunoCAP test, and all (28/28) of the true negatives had a negative cat ImmunoCAP test (Sens. 69%, Spec. 100%, PPV 100%, NPV 87.5%).

Conclusion: SPT is more sensitive but less specific than ImmunoCAP testing when evaluating patients for cat allergy. The high sensitivity of SPT makes it more effective in ruling out cat allergy.

Photoaging Attenuates Skin Test Response to Histamine but not Morphine

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Rationale: Clinical experience suggests that skin test reactivity is often decreased in photo-exposed skin versus sun-protected skin in older individuals. The current study was designed to address whether photoaging or natural aging of skin causes a greater diminution in skin test response to either histamine (a mast cell-independent stimulus) or morphine (a mast cell-dependent stimulus).

Methods: Prick-puncture skin tests to histamine and morphine were performed on sun-exposed and sun-protected areas in younger (n = 61, age 20-50) and older (n = 63, age 60-87) adult volunteers. The skin was scored for photoaging by physical examination and coloration was measured by a colorimeter.

Results: Photoaging was significantly correlated with decreased skin reactivity to histamine on the upper back (a sun-exposed area) as compared to the lower back (a sun-protected area), p<0.01. Skin reactivity to morphine was not correlated to photoaging, but did show significantly decreased flare response in older versus younger volunteers, p<0.05.

Conclusions: Skin test reactivity to histamine correlates negatively to the degree of photoaging and is independent of patients’ chronological age. This result has clinical implications for patients with significant cutaneous solar damage, suggesting that care should be taken to perform skin testing on anatomic sites in sun-protected areas. In patients with severe photoaging, allergen-specific IgE testing should be considered to avoid possible false-negative interpretation of skin-prick testing. The inverse correlation of the morphine flare response to chronological age may reflect decreased mast cell response or mast cell number in older individuals.

Relative Prick and Intradermal Skin Test Reactivities of Non-Standardized Alternaria alternata Extracts from Two U.S. Manufacturers

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Rationale: Non-standardized Alternaria alternata extracts from different U.S. allergen manufacturers are prepared from diverse A. alternata strains, cultures or culture fractions using variable cultivation, extraction or processing procedures. This study compared the prick and intradermal skin test reactivities of Alternaria extracts prepared by Greer (1:20 weight/volume) and ALK Abello (1:10 weight/volume).

Methods: An open-label study was conducted at two allergy clinics in the Midwest and Southeastern U.S. with a total of 17 subjects exhibiting a significant positive prick test response to Alternaria allergens (>20 mm erythema). Each subject was prick tested with both Greer and ALK Alternaria extract concentrates in 50% glycerin, followed by quantitative intradermal testing (ID50) using 5-fold serial dilutions of both extracts until graded responses were observed (bracketing a 50 mm sum of erythema). Wheal and erythema responses were measured and evaluated for statistical significance.

Results: All 17 subjects demonstrated positive prick test responses to either the Greer or ALK Alternaria extracts. The mean wheal and erythema diameters for the Greer extract were significantly larger than those observed with ALK extract (wheal: 6.5 mm vs. 4.6 mm, p < 0.001; erythema: 29.9 mm vs. 15.7 mm, p < 0.001). Intradermal skin test titrations on these subjects yielded mean D50 values of 10.10 for Greer extract and 8.60 for ALK extract, resulting in a relative potency ratio (Greer/ALK) of 5.16 for these product lots.

Conclusions: Alternaria extracts obtained from two different U.S. manufacturers displayed significantly different prick and intradermal skin test reactivities with patients from two allergy clinics.
908 Comparison Of The IgE Interaction In Depigmented-polymerized And Native Allergen Extracts By Surface Plasmon Resonance Biosensor Analysis
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RATIONALE: It has been demonstrated that chemically modified allergens (allergoids) have a reduced allergenicity respect to native extracts. The reduction of the allergenicity is calculated by ELISA studies and respect to the native extract, however, the reduction of the IgE binding cannot be quantified. The objective was to compare the strength of a depigmented-polymerised (Dpg-Pol) and a native extracts, using a surface plasmon resonance (SPR) biosensor analysis.
METHODS: SPR measurements were performed on a Biacore T100. Monoclonal anti-human IgE was immobilized on a C1 series S chip. Afterwards, specific IgE from a pool of sera from allergic individuals to D. pteronyssinus was injected. Finally, native and Dpg-Pol D. pteronyssinus extracts were injected at two different concentrations (0.2 and 0.4 mg/ml) and the interaction measured. The constant of dissociation (Kd) and average time (t½) for both allergenic extracts was determined.
RESULTS: Dpg-Pol extract have a significantly higher Kd and lower t½ average time (t½) for both allergenic extracts was determined. When injecting 0.4 mg/ml results were for native: Kd 2.54E-05 and t½ 19628, and for Dpg-Pol 1.25E-04 and 5522.8, respectively. When injecting 0.2 mg/ml results were for native: Kd 2.54E-05 and t½ 27265; and for Dpg-Pol extract: 1.26E-04 and 5489.3.
CONCLUSIONS: These results demonstrated that depigmented-polymerized extracts are dissociated rapidly than native, supporting and explaining the higher safety of Dpg-Pol extracts for allergen immunotherapy. The method used can be considered a potent tool for the design of allergy vaccines.

909 Relationship Between The Levels Of Total Serum IgE And Skin Reactivity In Patients With Allergic Rhinitis (ar)
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RATIONALE: Immunoglobulin IgE is the producer of the hypersensitivity reaction in the nasal mucosa in allergic rhinitis what motivates the chain of symptoms that occur in this disease. This condition is the most common allergy in the world so any study to be performed to better understand the immunopathology of this clinical entity is very important.
METHODS: Most of the allergens arrive by air, and here arises a question mark does the number of antigens that react with IgE attached to mast cells of the skin in the skin tests directly related to serum IgE levels? If we can clarify this mystery we could predict total IgE levels to those allergens to calculate a patient would react. We selected 50 patients of the Immunological Department of the Juarez Centro Hospital in Mexico, residents of the Valley of Mexico with confirmed diagnosis of allergic rhinitis, by making a selection rigorous to avoid factors that altered the results, prick skin tests for immediate reading with common allergens in this area were performed (40 allergens), and quantified the levels of total serum IgE (IgE normal levels 100 IU) to compare whether total IgE levels were related to the number of positive skin tests.
RESULTS: We found that there was no correlation between the number of tests that gave a positive skin response and total serum IgE levels in the patients studied.
CONCLUSIONS: The use parameter to correlate the total IgE levels with the number of positive skin tests have no prognostic significance in patients with allergic rhinitis.

910 Suppression of Allergic Airway Inflammation by Low Dose, Intranasally Administered Der p 1 Derived Peptides, in a Murine Model of Dust Mite Allergy
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RATIONALE: Recently, we demonstrated the induction of immune tolerance in a murine model of cat allergy following systemic administration of a T cell epitope peptide (Campbell et al., J. Exp. Med 2009). In the current study we hypothesized that exposure to Der p 1 (major house dust mite [HDM] allergen)-derived peptides intranasally (local mucosal environment) could modulate markers of allergic airways disease in a murine model of HDM allergy.
METHODS: Female Balb/c mice (Charles River, 6-8 w/o, n=8-11/group) were sensitized to HDM via 10 days of intranasal HDM (1.5ig), allowed a 9 day rest, treated with Der p 1-derived peptides (10, 1 or 0.1ig) or vehicle intranasally for five days and immediately recall challenged twice with HDM (15ig). Twenty-four hours post final challenge invasive measures of airway resistance were made during a methacholine dose-response test. Subsequently, mediastinal lymph nodes (LN), lung tissue and broncho-alveolar lavage (BAL) were collected. LN and lung tissues were stained for surface markers and cytokines, and acquired on a FACS Canto II. BAL cells were Wright-Giemsa stained and differentiated by morphological features.
RESULTS: 10 μg of Der p 1 derived peptides significantly reduced BAL eosinophilia, while 1μg of peptides significantly improved AHR, as compared to vehicle treated mice (P < 0.05, one-way ANOVA and post-hoc student’s t-test). These functional changes were associated with reduced IL-4 and IL-5 T-cells, total iNKT and increased percentage of CD4+IL-10+ cells in the lung.
CONCLUSIONS: Low dose Der p 1-derived peptides reduced Th2 inflammation associated with allergen recall, in a murine model of HDM allergy.

911 A Comparison of the Local and Systemic Effects of AZD3199, an Inhaled Ultra-long-acting β2-adrenoceptor Agonist (uLABA), With Formoterol in Patients With Asthma
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RATIONALE: To compare the local and systemic effects, tolerability, and safety of single doses of inhaled AZD3199, a novel, ultra-long-acting β2-adrenoceptor agonist, with formoterol in patients with mild-to-moderate asthma.
METHODS: Patients were randomized to receive AZD3199 (120, 480, and 1920 μg), formoterol (9 and 36 μg) or placebo delivered via Turbuhaler in a double-blind, 6-way crossover, single-dose study (NCT00736489). Repeated assessments of forced expiratory volume in 1 second (FEV1) were used to compare local bronchodilatory effects; serum potassium level was used as the primary marker of systemic effects, with heart rate, corrected QT interval (QTcB), pulse, blood pressure, tremor, and palpitations as secondary variables.
RESULTS: Overall, 37 patients (32 men) were randomized. Dose-dependent effects on FEV1 derived outcome variables were seen for both AZD3199 and formoterol, with statistically significant peak effects at all dose levels versus placebo. At 22-26 hours post-dose, the mean FEV1 was statistically significantly greater following AZD3199 doses of 480 and 1920 μg or formoterol 36 μg than placebo. At comparable peak effects, AZD3199 showed a longer duration of bronchodilation. Statistically significant systemic effects were only seen for the highest dose of AZD3199 and formoterol. The effect on serum potassium levels and tremor was greater for formoterol, whereas the effect on heart rate and QTcB was similar for both drugs.
CONCLUSIONS: At eqeueffective doses, inhaled AZD3199 maintained bronchodilation longer than formoterol, and caused fewer sistemically mediated effects such as hypokalemia and tremor, suggesting a more favorable therapeutic index for AZD3199.
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912 Selective Blockade of Pulmonary Epithelial Stat3 for the Treatment of Asthma
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RATIONALE: Asthma affects 22 million people in the US and 300 million worldwide. Treatment of asthma remains difficult. In the last 5 years, Stat3 has gained interest due to its central role in the pathogenesis of asthma. In the last of several series of experiments, each of 3 groups of C57BL/6 mice (10 each) received one of the following regimens by intranasal inhalation: phosphate buffered saline (PBS)/10% DMSO (50 ul; control group); PBS/10% DMSO followed by IL6 (100 ng in 50 ul PBS; stimulated-control group); or C188 (75ug in 50ul PBS/10% DMSO) followed by IL6 (treatment group). Mice were humanely euthanized 60 min later, and their lungs harvested for measurement of pStat3 and total Stat 3 levels using Luminex technology.

RESULTS: IL6-stimulated pStat3 lung levels (1,254 ± 6 U; p<0.001), to levels similar to the PBS-control group (247 ± 17 U; p=0.981).

CONCLUSION: C188 inhibition blocks IL6-mediated Stat3 activation and may be a promising, novel treatment for asthma. Studies testing the efficacy of C188 inhalation (75ug in 50ul PBS/10% DMSO) in a DM asthma model are underway.

913 Maternal Ashmi Therapy Reduces Offspring Susceptibility To Developing Airway Inflammation In A Murine Model
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RATIONALE: Maternal asthma increases asthma risk in children, and poor asthma control during pregnancy is associated with higher risk of childhood asthma. The anti-asthma herbal medicine (ASHMI) showed therapeutic effects in human asthmatics and animal models. The aim of this study was to investigate the effect of maternal ASHMI therapy on offspring asthma susceptibility in a murine model.

METHODS: Female BALB/c mice (pre-mother mice) with established experimental asthma, induced by ovalbumin (OVA) sensitizations/challenges, received six weeks daily oral treatment of ASHMI, or water (Sham), or intraperitoneal dexamethasone (Dex). After treatment all mice were mated with naïve males. Naïve pre-mothers served as controls. 14 day old offspring from all groups were sub-optimally sensitized with 5 mcg OVA + 1mg alum then challenged intranasally with OVA or PBS on days 28, 29 and 30. Assessment of pulmonary inflammation by bronchoalveolar lavage fluid (BALF) cell counting and differential staining was performed on day 31.

RESULTS: Offspring of sham-treated mothers (O-Sham) showed marked (51%) elevation of total BALF cell numbers compared to offspring of naïve mothers (O-Naive). Offspring of ASHMI-treated mothers (O-ASHMI) and offspring of Dex-treated mothers (O-Dex) showed equally decreased numbers of total BALF cells compared to O-Sham (P<0.05), and were not different from O-Naive. However, eosinophil counts were decreased in O-ASHMI (52% reduction) but not O-Dex BALF. Reduction in neutrophil counts was also greater in O-ASHMI than O-Dex BALF (79% and 47% respectively) when compared to O-Sham.

CONCLUSIONS: Maternal ASHMI therapy reduced offspring susceptibility to induction of airway inflammation, and appeared to be superior to Dexamethasone.

914 Myeloid Derived Suppressor Cells Attenuate Murine Allergic Airway Inflammation
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RATIONALE: Myeloid derived suppressor cells (MDSCs) are a heterogeneous population of cells that expand during cancer and other pathogenic conditions. These cells have remarkable abilities to suppress T cell responses and to induce Treg cell expansion. As asthma is a chronic disease with imbalance of Th2, Th17, Th1 and Treg responses, we hypothesize that adoptive transfer of MDSCs generated in vitro can ameliorate murine allergic airway inflammation.

METHODS: MDSCs were generated in vitro through co-culturing bone marrow cells with hepatic stellate cells (HSCs) in the presence of GM-CSF. Cultures lacking HSCs will induce mature dendritic cells (DCs), serving as a control. Airway inflammation was induced by intraperitoneal sensitization and intranasal challenges with OVA. MDSCs, DCs or saline were adoptively transferred to mice on the same day as OVA sensitization (i.v.) and one day before intranasal challenge. Mice were sacrificed 3 days after nasal challenges.

RESULTS: Mice in saline and DCs groups developed obvious allergic airway inflammation. However, mice receiving MDSCs exhibited significant decreases in inflammatory cell accumulation in bronchoalveolar lavage fluids, lung inflammation and mucus production, serum IgE levels, and the levels of IL-4, IL-13, IL-10 and IFN-γ in lung tissue and in supernatants of splenocytes stimulated by OVA. Furthermore, this transfer down-regulated the percentages of Th2, Th17 and MDSC cells in spleen when compared with controls.

CONCLUSIONS: Adoptive transfer of MDSCs ameliorated OVA-induced allergic airway inflammation through down-regulating Th2 and Th17 responses, suggesting that adoptive transfer of MDSCs may provide a potential approach in asthma treatment.

915 Expression of the Regulatory Protein Caveolin-1 is reduced in Asthma
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RATIONALE: Caveolin-1 has emerged as a critical regulator of signaling pathways involved in lung fibrosis and inflammation. There are several reports of loss of caveolin-1 in fibrotic foci of lungs in patients with scleroderma lung disease and idiopathic lung fibrosis. Recently, loss of caveolin 1 in the lungs was reported following allergen challenge in a sensitized murine model of asthma. Therefore, the objective of this study was to investigate if caveolin-1 is deficient in patients with asthma compared to controls.

METHODS: Monocytes were isolated from peripheral blood of asthmatics (all severities) and controls (n=10). Endobronchial biopsy sections were obtained from 5 subjects with mild asthma and 4 healthy controls. Western blotting analysis and immunostaining was employed to study protein expression. Clinical markers of airway inflammation were collected. Caveolin-1 expression was also studied in a murine model of asthma.

RESULTS: Caveolin-1 expression is reduced in peripheral blood monocytes, and in the lungs of asthmatics compared to controls. Loss of caveolin-1 is most evident in the bronchial epithelial cells of asthmatics. Low caveolin-1 is associated with increased collagen and tenascin deposition, and increased number of fibrocytes in the lungs of asthmatics vs. controls. Furthermore, caveolin-1 expression decreased following aspergillus challenge in a sensitized murine model of asthma.

CONCLUSIONS: To our knowledge, this is the first investigation of a role for caveolin-1 in humans with asthma. We have demonstrated a novel regulatory protein that may play an important role in airway inflammation and fibrosis characteristic of asthma.
916 Mechanical Skin Injury Induces TLR4/MyD88-Dependent IL-23 Expression in Epidermal Keratinocytes

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RATIONALE: Scratching and epidermal hyperplasia are hallmarks of atopic dermatitis. IL-23 is a cytokine that induces epidermal hyperplasia. We examined the hypothesis that mechanical skin injury by tape stripping, a surrogate of scratching, induces IL-23 expression in the skin.

METHODS: Ear skin of mice was tape stripped then examined 6 hrs later for IL-23 expression by quantitative RT-PCR and immunohistochemistry. Low molecular weight hyaluronic acid (HA) was injected intradermally, and 3 hrs later, skin was harvested. Langerhans cells were depleted by i.p. injection of 1 μg diphtheria toxin (DT) into langerin-eGFP-DTR mice, and 24 hrs later ear skin was tape stripped then harvested. The keratinocyte cell line, PM212 cells was treated with HA (50 μg/ml) for 3h

RESULTS: Tape stripping induced epidermal IL-23 expression of WT, but not TLR4 and MyD88 deficient mice. IL-23 induction by tape stripping in germ free mice was comparable to that in specific pathogen free mice. Skin of LC-depleted mice showed the same level of IL-23 induction compared to intact mice. Intradermal injection of the endogenous danger signal molecule, HA induced IL-23 expression in the skin of WT, but not TLR4 deficient mice. HA treatment induced IL-23 expression by PM212 cells in vitro.

CONCLUSION: Scratching may contribute to epidermal hyperplasia in AD through the release of the endogenous danger signal molecule HA, which directly induces IL-23 expression from keratinocytes through TLR4/MyD88 signaling.

917 Human Dendritic Cells Stimulated with a Novel Peanut Protein Express High Levels of RALDH2 and Induce RA-Sensitive Genes in Naïve T Cells

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RATIONALE: Dendritic cells instruct naïve T-cells to differentiate into various effector cells determining immune responses such as allergy or tolerance. Our objective was to identify peanut extract (PE)-induced changes in gene expression in human myeloid dendritic cells (mDC), and assess the role of differentially expressed genes in the induction of T-cell differentiation.

METHODS: mDC (CD11c+B2CDA1+) and naïve Th-cells (CD4+CD45RA+) were isolated from blood donors. mDC were incubated for 24h with medium alone, PE, or control stimulants (LPS, CT). mRNA was isolated for use in expression array and qRT-PCR. To assess T-cell differentiation, mDC were cocultured for 6d with autologous naïve T-cells and the RALDH2 substrate retinal.

RESULTS: PE induced a unique expression profile in mDC, including the gene that encodes RALDH2, the rate-limiting retinoic acid (RA)-producing enzyme. qRT-PCR confirmed the ~20-fold induction of this gene in PE-treated mDC. PE-treated mDC also demonstrated a 7-fold increase in enzymatic activity of RALDH2. Naïve T-cells cocultured with PE-treated mDC showed a 3-fold increase in production of IL-5 and in expression of the RA-sensitive surface markers CD38 and z4β7-integrin. Size exclusion purification and mass spectrometry suggest the RALDH2-inducing constituent to be a member of the plant glycine-rich proteins superfamily, which is not recognized as a major allergen.

CONCLUSIONS: A previously undescribed peanut protein induces RALDH2 in mDC, leading to RA production which can act on T-cells to induce gut-homing integrin and IL-5 production. RA has been implicated in potentiating gut-homing T-cell differentiation. RALDH2 induction by PE could be an important factor determining allergic or tolerant responses to peanut.

918 Interaction With Myd88-dependent CD8-CD11c+ Cells Mediates Rapid Induction Of Antigen-specific IgE-suppressive Gamma Delta T Cells

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RATIONALE: Antigen-specific IgE-suppressive gamma delta T cells (Vγ4+) can be induced in mice that are repeatedly exposed to inhaled antigen. Here we investigate the requirement for the induction of this regulatory gamma delta T cell subset by using a “three-mouse model”.

METHODS: CD8-CD11c+ cells or control cells from other populations were purified using a MoFlo XDP cell sorter from either Myd88 sufficient or deficient “inhaler mice” that were exposed via the airways to ovalbumin (OVA). 1x106 of these purified cells/mouse were injected via the tail vein into an antigen-inexperienced recipient mouse (“incubator mouse”). At different time points after the injection, Vγ4+ gamma delta T cells were purified from the “incubator mouse” and 3x104 cells/mouse were i.v. injected to a third mouse (“indicator mouse”) shortly before immunization with OVA- or HEL/alum i.p. injection. 14 days later, sera were harvested from the “indicator mice” and ELISA assay was used to determine total IgE levels in the serum samples.

RESULTS: CD8-, but not CD8+ CD11c+ cells from “inhaler mice” are able to induce Vγ4+ γδ T cells to become IgE-suppressive in a time-span as short as 24hrs. The induced γδ T cells are Ag-specific because they suppress OVA - but not HEL-induced IgE. The non-T inducer cells must be derived from Myd88+ mice.

CONCLUSIONS: Without direct exposure to inhaled antigen, Ag-specific IgE-suppressive gamma delta T cells can be quickly induced through interacting with Myd88-dependent CD8-CD11c+ cells from mice that are repeatedly exposed to inhaled antigen.

919 Combined Blockade Of The Histamine H1 And H4 Receptor Suppresses Peanut-Induced Diarrhea And Intestinal Inflammation By Regulating Dendritic Cell Function

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RATIONALE: Histamine receptors play an important role in allergic responses. Dendritic cells (DCs) are involved in peanut allergy but the importance of histamine receptors on DCs in the pathogenesis of peanut-induced intestinal allergy has not been defined.

METHODS: Histamine H4 receptor-deficient (H4R−) mice and wild-type (WT) mice were sensitized and challenged with peanut extract. In some experiments, sensitized WT mice were treated orally, twice daily (5-20 mg/kg) with loratadine and/or the H4 receptor antagonist JNJ7777120 during peanut challenge. Bone marrow-derived DCs (BMDCs) were generated and differentiated. Symptoms, intestinal inflammation, and intestine mucosal DCs were assessed. The effects of loratadine and/or JNJ7777120 on BMDC chemotaxis and calcium mobilization were measured.

RESULTS: Peanut-induced diarrhea and intestinal inflammation were attenuated in sensitized and challenged H4R− mice compared to WT mice. The percentage of myeloid DCs and expression of CD80 and CD86 in lamina propria DCs were decreased in H4R-/- mice compared to WT mice. Peanut-induced diarrhea and intestinal inflammation and decreased the percentage of myeloid DCs and expression of CD80 and CD86 in lamina propria DCs. In vitro, the combination of loratadine and JNJ7777120 suppressed DC calcium mobilization and chemotaxis.

CONCLUSIONS: These data support the premise that combined inhibition of both H1 and H4 receptors synergistically prevent peanut-induced intestinal allergy by altering DC function. The combination of histamine H1 and H4 receptor blockade provides an effective therapeutic strategy for the treatment of peanut-induced intestinal allergy.
**920 Upregulation Of Glucocorticoids Beta Receptors In Severe Rsv Bronchiolitis In Infants**

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**RATIONALE:** The majority of studies on glucocorticoids treatment in RSV bronchiolitis conclude there are no beneficial effects. We hypothesized that RSV infected patients may have an up-regulation of the GCR-β expression, the isofrom that is unable to bind cortisol and exert an anti-inflammatory action.

**METHODS:** We studied by RT-PCR the expression of β and β’ GCR in the peripheral blood mononuclear cells (PBMC) obtained from 50 RSV infected infants (less than 1 year of age) of diverse clinical severity, evaluated by a modified Tal’s clinical score (1=mild to 8=severe). In plasma we analyzed the level of cortisol by RIA and inflammatory cytokines: IL-6, IL-8,TNF-α, IL-1β, IL-12 and IL-10 by cytometric beads assay. Statistical analysis was performed by ANOVA.

**RESULTS:** There has found a significant up-regulation of β’ GCR in patients with severe illness compared to those with mild disease (p<0.001) and also to a group of healthy control (p<0.01). The β/β’ GCR ratio was significantly decreased in infants with severe disease (p<0.05) compared to those with mild illness and with normal controls (p<0.01). The expression of β GCR has been positively correlated with the clinical score of severity (r=0.51; p<0.0006). IL-6, IL-8 and cortisol in plasma were significantly increased in severe infected infants compared with mild infected (p<0.05) and healthy controls (p<0.01).

**CONCLUSIONS:** The decrease of the β/β’ GCR ratio by an up-regulation of β receptors may partly explain the insensitivity to corticoids treatments in RSV infected infants.

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**922 Risk of Childhood Asthma Following Infant Bronchiolitis During RSV Season**

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**RATIONALE:** Infant respiratory syncytial virus (RSV) infection is common and is associated with recurrent wheezing and asthma. The aim of this study was to determine what proportion of childhood asthma is attributable to infant bronchiolitis.

**METHODS:** We conducted a population-based birth cohort study of infants from 1996-2008 who were cared for under the California Kaiser Permanente Medical Care Program (KPMCP) or Tennessee Medicaid (TennCare). Eligible infants had a minimum gestational age of 32 weeks and no chronic lung disease. Bronchiolitis was defined during RSV season using ICD-9 codes, and asthma was defined using an algorithm of ICD-9 codes and medication utilization between ages 4.5-6 years.

**RESULTS:** Among 260,460 children, 13% were diagnosed with asthma. The proportion of children among the KPMCP and TennCare cohorts with a history of infant bronchiolitis during RSV season was 29% and 33%, respectively, for those with asthma, and 14% and 19%, respectively, for those without asthma. The population attributable risk (PAR) for asthma contributed by infant bronchiolitis during RSV season, was 16% for the KPMCP cohort, and among the subset of children with bronchiolitis during infancy, the attributable risk was 56% (95%CI:53%,58%). In TennCare it was 16% and 48% (95%CI:47%,49%), respectively.

**CONCLUSIONS:** In two representative US populations, nearly 50% of asthma cases in children with a history of infant bronchiolitis during RSV season were attributable to bronchiolitis, and on a population level, 16% of asthma was attributable to bronchiolitis. Thus, infant bronchiolitis is an important target to determine if prevention would be an effective primary asthma prevention strategy.
924 Bacterial Detection In The Fall Is Associated With Increased Viral Respiratory Infections

Rationale: Bacterial colonization has been associated with wheezing in children. We evaluated bacterial detection during peak viral season in children with and without asthma to determine if underlying detection at the start of the season affected subsequent viral infectivity.

Methods: 310 children ages 4-12 years provided five consecutive weekly nasal samples from September 1 through October 5 in the fall of 2007-2009. Viral diagnostics were performed on all nasal samples and the first (baseline) sample of each child was tested for Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis with PCR.

Results: Baseline samples of 282 children (151 asthmatic, 131 non-asthmatic) were analyzed. Detection rates were 48%, 17% and 5% for H influenzae, S pneumoniae and M catarrhalis, respectively, and independent of asthma status. Subjects with S pneumoniae and H influenzae had increased number of virus-positive weeks over the fall season (2.44 vs. 1.93, p<0.05; 2.22 vs. 1.82, p<0.05, respectively). Baseline viral infection increased rates of S pneumoniae detection from 12% to 27% (p<0.005). A similar trend was observed for H influenza detection (45% to 55%, p=0.09).

Conclusion: Baseline detection of S pneumoniae and H influenzae is associated with increased number of virus-positive weeks in the fall, and S pneumoniae detection was higher in those with co-infection of virus at baseline. Further investigation is needed to determine if bacterial detection represents colonization or infection; if it persists and relates to viral infectivity; and if there is an association with bacterial detection and illness severity.

925 Proton-sensing Receptor GPR65 Regulates Allergic Gastrointestinal Esophagitis
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Rationale: Extracellular acidosis has been observed in allergic inflammatory diseases. However, the effect of an acidic microenvironment on inflammatory cells is poorly understood. Recently, we demonstrated that eosinophil viability was increased by acidic pH in a GPR65-dependent manner, suggesting that GPR65 is important in regulating eosinophil cell survival in an acidic environment; GPR65 was required for optimal eosinophil accumulation in allergic lung inflammation. Additionally, our preliminary data identified GPR65 expression on mast cells, another cell type critical for allergic responses especially in the gastrointestinal tract. Therefore, we investigated the role of GPR65 in gastrointestinal allergic inflammation.

Methods: OVA-sensitized, GPR65-deficient and wild type (WT) mice were orally challenged with OVA or saline. OVA-specific antibody levels were measured by ELISA. The number of eosinophils and mast cells in the jejunum was examined by MBP and CAE staining, respectively.

Results: Allergen-challenged, GPR65-deficient mice showed significantly decreased eosinophila in the jejenum compared with allergen-challenged WT mice (59.1±9.2% decrease, n=4 experiments). The degree of sensitization was comparable between WT and GPR65-deficient mice, suggesting that GPR65 affects local inflammatory responses in the jejunum. The levels of the eosinophil chemokines eotaxin-1 and -2 were comparable in the jejunum of WT and GPR65-deficient mice. These findings, together with our prior in vitro data showing GPR65 affects eosinophil viability, suggest that GPR65 regulates eosinophil accumulation by affecting eosinophil survival during inflammation. Despite expression of GPR65 on mast cells, the accumulation of mast cells was not affected by GPR65 deficiency.

Conclusions: GPR65 selectively regulates eosinophil accumulation in allergic gastrointestinal inflammation.

926 Twin Shared Environment Increases Risk of Eosinophilic Esophagitis in Families
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Rationale: Eosinophilic esophagitis (EoE) has evidence of genetic and environmental contributions. Family studies support increased risk in EoE patients’ first degree relatives. However, no studies have examined EoE in monozygotic (MZ) and dizygotic (DZ) twins. By comparing concordance between siblings and twins, contributions of shared environment and genetics may be better understood.

Methods: A retrospective study was conducted to examine EoE familial risk using reported family history in the clinical record (January 2008-July 2011). A second retrospective study enrolled MZ and DZ twins (proband with EoE). In twins, EoE was ascertained by pathology report or slide confirmation of an esophageal biopsy (EGD) with ≥15 intraepithelial eosinophils per high power field. EoE absence was ascertained by negative symptoms or EGD. Recurrence risk ratios (RRR) and proband-wise concordance were calculated for family members and twins, respectively. To compare groups, X²1df=1 or Fisher’s Exact test were used.

Results: In 554 families, 3.3%, 0.7%, 3.8%, and 1.6% of fathers, mothers, brothers and sisters (respectively) had EoE. RRR ranged from 12-70. The twin sample included 24 MZ and 46 DZ pairs. EoE concordance was not significantly different in MZ (45%) versus DZ (33%) twins (p>0.05), but frequency non-proband twins (22.8%) was higher than non-twin siblings (p<0.0001).

Conclusions: We confirmed increased EoE recurrence risk in families, supporting genetic inheritance. However, EoE concordance is surprisingly similar in MZ and DZ twins. Twins’ markedly higher RRR than non-twin siblings support an unexpected strong effect of environmental factors in EoE etiology and point to the importance of early life events.
**927** Interleukin (Il)-15 Overexpression In The Esophagus Promotes IgE Associated Experimental EoE

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**RATIONALE:** We previously reported that total IgE, B cells, and immunoglobulin IgG isotype switching genes are involved in human eosinophilic esophagitis (EoE); however, the IgE’s role in EoE is not well understood. Recently, we showed that IL-15 mRNA and protein are highly expressed in the blood and esophageal biopsies of EoE patients and are critical for promoting experimental EoE. Therefore, we tested the hypothesis that esophageal IL-15 overexpression promotes IgE-associated experimental EoE.

**METHODS:** Immunohistochemical analysis was performed to quantitate eosinophil in esophageal tissue sections from mice overexpressing IL-15. The mRNA and protein levels of IL-15 and Ig class switching genes were measured by performing real time qPCR and ELISA analysis.

**RESULTS:** Our analysis indicates that DOX-induced rtTA-CC-10-IL-15 transgenic mice promote IL-15 concentration-dependent esophageal eosinophilia. B cell, total IgE, IgG1, and IgG2a levels were induced in DOX-exposed IL-15 overexpression mice compared to unexposed mice. Similarly, we observed induced mRNA levels of Ig class switching genes (GL3, GL4, GL5, and GL7) in the esophagus of DOX-exposed IL-15 overexpression mice compared to unexposed mice. Further, we validated our data by performing in vitro experiments, which established that IL-15 promotes a concentration-dependent increase in B cell proliferation, activation, and IgG class switching. Further studies, using IL-15 gene-deficient mice, are in progress to test whether IL-15 is required for induction of IgE-associated EoE.

**CONCLUSIONS:** IL-15 promotes B cell activation, Ig class switching, IgE production, and esophageal eosinophilia in DOX-induced IL-15 overexpression mice.

**928** Increased CD3+CD69+ T-Cells and CD40+ Eosinophils in the Esophageal Tissue of Eosinophilic Esophagitis

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**RATIONALE:** Eosinophilic esophagitis (EoE) is a disorder that is increasing in incidence and prevalence. Data suggests an interaction between eosinophils, acting as antigen presenting cells (APC), and T-cells in the pathogenesis of disease. We investigated the number of CD3+ T-cells, and activated CD69+CD3+ T-cells in the esophageal biopsies of EoE patients. We also studied the presence of CD40, an APC co-stimulatory marker, on EG2+ eosinophils.

**METHODS:** Esophageal tissues were processed via standard immuno-histochemistry techniques. For the T-cell studies, biopsies were co-stained with CD3(Vector Laboratories) and CD69(Abcam). For the eosinophil studies, biopsies were co-stained with EG2(kind gifts of Dr. Raggam Reinhard and Phadia) and CD40(Abcam). Stained cells were counted per high-powered field (400x) at 3 different sites with the mean count used.

**RESULTS:** The number of CD3+ cells was significantly higher in EoE patients (n=5, mean=36.6) versus healthy controls (HC) (n=3, mean=3.2). (P=0.04). More CD3+CD69+ cells were present in EoE (mean=35.7) versus HC (mean=0.3). (P=0.04), as well as a higher proportion of CD3+ T-cells that were CD69+ (EoE=98%; HC=9%). In the CD40 study, virtually all EG2+ eosinophils in EoE (n=11, mean=25.5) were CD40+ (99%). In the HC (n=3), no eosinophils were present.

**CONCLUSIONS:** We demonstrate an increase in CD3+ T-cells, and activated CD69+CD3+ T-cells in patients with EoE versus HC. Additionally, all eosinophils in EoE were CD40+. These findings suggest further evidence that eosinophils are acting as APC, interacting with T-cells in EoE. Continuing studies are underway to investigate expression of other proteins potentially involved in this interaction such as HLA-DR, CD80, CD86 and CD40L.
931 Financial Impact of Late Diagnosis of Severe Combined Immunodeficiency: Why It is Fiscally Sound for States to Invest in the Implementation of Newborn Screening

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RATIONALE: Screening for severe combined immunodeficiency (SCID) has begun in ten states as part of the newborn screening (NBS) panel. An obstacle in some states is the requirement for legislation to approve funds for implementation and follow-up. While multiple compelling clinical reasons exist to support NBS for SCID, state governments need to know the cost benefits associated with screening. Earlier reports evaluate theoretical cost-effectiveness of SCID NBS models based on SCID natural history simulations. We analyzed actual hospital charges for SCID in a multicenter, retrospective analysis, reporting the preliminary findings from one center.

METHODS: Retrospective chart review of five SCID cases diagnosed and treated in the past five years at All Children’s Hospital in Florida was performed as a pilot study. Total and itemized charges for each hospitalization from pre-diagnosis to post-transplant were evaluated to compare costs associated with early diagnosis (<3.5 months) vs. late (3.5 months). Clinical conditions associated with SCID such as infectious complications, growth parameters, and transplant outcomes were compared.

RESULTS: Only one case, identified by family history, had early diagnosis at 1.3 months and successful transplant at 3.5 months. Four cases were diagnosed between 4.8 to 12.8 months, with only one achieving successful transplant. Total charge for the early case was $606,759 versus median late charges of $1,871,650. Later diagnosis was associated with high mortality, failure to thrive, and opportunistic infections at diagnosis with all cases positive for Pneumocystis infection.

CONCLUSIONS: Early identification of SCID leads to better outcomes and lower hospital costs.

932 Tolerability of Subcutaneous Immunoglobulin (SCIG) in Patients Receiving Antiplatelet (AP) and Anticoagulant (AC) Therapy

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RATIONALE: SCIG is an effective form of antibody replacement in patients with primary and secondary immunodeficiency. Advantages include steady serum IgG levels and ease of use, particularly in those with difficult venous access or contraindications to IVIG. These patients often have comorbid conditions which necessitate treatment with AP or AC agents. Physicians may be hesitant to prescribe SCIG in such patients due to concerns about infusion site bruising/bleeding, as these adverse effects might negatively impact adherence. To our knowledge, there have been no studies examining the tolerability of SCIG in this population.

METHODS: This case series describes five patients receiving SCIG with concurrent AP or AC therapy.

RESULTS: Patients 1 and 2 (both with common variable immunodeficiency, CVID) were taking clopidogrel and ASA. Patient 1 had a history of coronary artery disease (CAD), stroke and chronic kidney disease. SCIG was prescribed due to concerns of potential hyperviscosity with IVIG. Patient 2 (with CAD requiring stents) initially received IVIG but was switched to SCIG for personal preference and to improve IgG levels. Patient 3 (on SCIG for hypogammaglobulinemia following rituximab) developed a DVT after back surgery and was treated with IV heparin before transitioning to coumadin. Patients 4 and 5 (on SCIG for CVID) used ASA for primary cardiovascular prevention. None of the patients reported significant ecchymoses, bleeding or other infusion site reactions. IgG levels remained steady in all patients (mean, 996 mg/dL).

CONCLUSIONS: SCIG is well-tolerated in patients receiving AP/AC therapy. This safe and effective option should be considered for patients requiring these medications.

933 Discrepancies Between Guidelines and International Practice in the Treatment of Hereditary Angioedema: Results from a World Allergy Organization Survey of Physicians

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RATIONALE: Hereditary angioedema (HAE) is an autosomal dominant disorder characterized by decreased expression or loss of function of C1 esterase inhibitor (C1 INH). In 2010, international guidelines were published regarding the management of both acute HAE attacks and prophylactic treatment. Additionally, several clinical trials for emerging HAE therapies were published in 2010. The purpose of this study was to assess the adherence of internationally-based physicians to the current evidence-based studies and the 2010 International Consensus Algorithm in the treatment of HAE patients.

METHODS: Internationally-based physician members of the World Allergy Organization were surveyed between November 2010 and February 2011 regarding their diagnosis and management of patients with HAE. Only physicians who treat HAE patients were included in the analyses.

RESULTS: Among the 201 responding physicians, the most highly-used therapies for acute HAE attacks were C1 INH (59%), fresh frozen plasma (42%), and icatibant (32%). For their preferred long-term prophylactic therapy, 74% use attenuated androgens and 18% use anti-fibrinolytics. Physicians in Latin and South America in particular were less likely to prescribe C1 INH and more likely to prescribe attenuated androgens and fresh frozen plasma than their international counterparts, while European physicians were the most likely to prescribe icatibant. Over a third of physicians described themselves as ‘unfamiliar’ with emerging HAE therapies.

CONCLUSIONS: Many international physicians neither follow current evidence-based studies nor adhere to the 2010 Consensus Algorithm for treating HAE. Expansion in both physician education and the availability of certain medications are likely necessary to improve the management of HAE internationally.

934 Cost of Treating Hereditary Angioedema with Newly Available Medications in Five Different Settings

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RATIONALE: Hereditary angioedema (HAE) is an autosomal dominant disorder characterized by decreased expression or loss of function of C1 esterase inhibitor (C1 INH). In 2010, international guidelines were published regarding the management of both acute HAE attacks and prophylactic treatment. Additionally, several clinical trials for emerging HAE therapies were published in 2010. The purpose of this study was to assess the adherence of internationally-based physicians to the current evidence-based studies and the 2010 International Consensus Algorithm in the treatment of HAE patients.

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CONCLUSIONS: Many international physicians neither follow current evidence-based studies nor adhere to the 2010 Consensus Algorithm for treating HAE. Expansion in both physician education and the availability of certain medications are likely necessary to improve the management of HAE internationally.
How Molecular Diagnosis Can Change Allergen-specific Immunotherapy Prescription In A Complex Area Of Pollen Sensitization (madrid, Spain)


RATIONALE: The identification of the disease-eliciting allergen is an essential prerequisite for the accurate prescription of Allergen-Specific Immunotherapy (SIT). The aim of this study was to evaluate whether molecular diagnosis (MD) may change indication and allergen prescription of SIT.

METHODS: 141 patients with allergenic rhinoconjunctivitis and/or asthma sensitized to pollen with or without concomitant food allergy were included. In all patients skin prick test (SPT) with a panel of aeroallergens and a microarray-based panel of allergens (ISAC, Phadia, Sweden) were performed. Three authors made a consensus, in a blind fashion, on indication of SIT and use of allergens, based on clinical history and skin prick test results before and after knowing ISAC results, following EAACI recommendation. Agreement coefficient (kappa index) was used to analyze results.

RESULTS: 59% were female with mean age of 31±13.63. In only 62 (46%) patients there was an agreement (Kappa=0.1057±0.0413) in indication of SIT before and after ISAC results. Concerning allergens used in the most common prescriptions before and after MD results we obtained the following results: K=0.117±0.0825 for grass; K=0.1624±0.0639 for olive pollen; K=0.0505±0.0548, for olive and grass pollen; K=0.1711±0.0471 for grass and cypress; K=0.1897±0.0493 for grass and London plane; K=±0.0842 for olive and cypress, and K=0.3586±0.0798 for other combinations.

CONCLUSIONS: There was a very low agreement concerning indication and use of allergens for SIT before and after a MD results. This emphasizes the usefulness of MD, at least in areas of complex sensitization to pollen, to make a correct indication of SIT.

Bispecific Antibody-induced Allergen-specific Regulatory T cells (Tregs) Suppress Der-P-1-induced Airway Inflammation

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RATIONALE: Earlier, we had shown that targeted engagement of CTLA-4, using a bispecific antibody (BsAb), can induce antigen specific Foxp3+ Tregs and down modulate TH1 type autoimmune responses. This study wanted to determine if BsAb therapy can induce allergen-specific Tregs and suppress airway inflammation.

METHODS: Anti-CD11c and anti-CTLA4 monoclonal antibodies were chemically coupled into BsAb. BsAb coated bone marrow dendritic cells (BMDCs) were generated by culturing bone marrow cells with GM-CSF. Mice were immunized two times with Der-p-1 allergen isolated from the dust mite Dermatophagoides pteronyssinus. Immunized mice were treated with either PBS buffer (PBS), allergen-pulsed BMDCs or allergen-pulsed BMDCs coated with BsAb (BsAb). Subsequently, mice were intranasally challenged 2 times with Der-p-1. Immune response and lung pathology were compared.

RESULTS: Comparison of Der-p-1 immunized and PBS treated mice with controls confirmed induction of allergic response in Der-p-1-immunized mice characterized by elevated numbers of eosinophils and Der-p-1 specific IgG1 and IgE antibodies in broncho-alveolar lavage (BAL). In contrast, BsAb coated-BMDC treated mice showed reduced numbers of eosinophils, IgG1 and IgE, and increased numbers of Foxp3+ and IL-10 secreting CD4+ T cells (Tregs) in the BAL. These Tregs were more potent in suppressing Der-p-1 specific T-cell response in vitro than Tregs from PBS or BMDC treated mice.

CONCLUSIONS: Our data indicate that BsAb successfully induced Der-p-1 specific Tregs that suppressed Der-p-1 specific IgE response and related eosinophilia. These and our earlier studies show that BsAb therapy may be useful in suppressing both TH1 and TH2 type inflammatory responses.

Long-term Safety Of A 300IR Sublingual Tablet Of 5-grass-pollen Allergen Extract In Adults With Grass-pollen-induced Allergic Rhinoconjunctivitis

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RATIONALE: Discontinuous administration of 300IR sublingual tablet of 5-grass-pollen allergen extract has demonstrated a favorable safety profile in single season studies. Here we report the safety over three consecutive grass pollen seasons of an ongoing trial.

METHODS: 633 adults were randomized to placebo or 300IR pre- and co-seasonally for three grass pollen seasons starting 4 months [4M] or 2 months [2M] prior to the season each year. Safety was assessed by means of AE reporting, laboratory data and physical examination findings.

RESULTS: During Year 1, 327 patients (51.7%) reported at least one TEAE with an investigator assigned causality to treatment. Year 2, 200 (39.4%). Year 3, 133 (28.6%). The most commonly reported were oral pruritus and throat irritation. Across the three treatment years, 38 patients (four Placebo, seventeen 300IR [2M], and eighteen 300IR [4M]) withdrew due to TEAEs (mostly application site reactions). Thirty of these withdrew in Year 1. There were no reports of anaphylaxis. Three serious TEAEs, all 300IR [4M] during Year 1, had causality assigned to the treatment by the Investigators. Two were application site reactions. The third, gastroenteritis, reportedly occurred concomitantly with an infection. All events resolved. No notable differences regarding laboratory results or physical examination findings were observed between groups.

CONCLUSIONS: The safety profile of 300IR sublingual tablet of 5-grass pollen allergen extract administered discontinuously for three consecutive years was consistent with that observed in single grass pollen season studies. The frequency of TEAEs decreased over the three treatment periods.
938 Ragweed Allergy Immunotherapy Tablet Reduces Nasal and Ocular Symptoms of Allergic Rhinocconjunctivitis Over the Peak Ragweed Pollen Season in North America

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RATIONAL: Peak season nasal and ocular symptoms of allergic rhinocconjunctivitis (ARC) are bothersome and can profoundly impact quality of life. The effects of sublingual ragweed allergy immunotherapy tablet (AIT) on nasal and ocular symptoms were investigated in North American ragweed allergic adults with or without asthma.

METHODS: 565 adults were randomized to daily ragweed AIT 6 or 12 Amb a 1-U (Amb) or placebo. Treatment was initiated approximately 4 months before and continued throughout ragweed season (RS). Daily four nasal and two ocular symptoms were assessed on a scale from 0 (no symptoms) to 3 (severe). The peak RS was defined as the 15 consecutive days with the highest 15-day moving average pollen count.

RESULTS: The ragweed AIT 12 Amb a 1-U and 6 Amb a 1-U groups showed mean improvement in total nasal scores compared to placebo of 14.8% (diff = -0.58 points; p = 0.03) and 11.7% (diff = -0.46 points; p = 0.09), respectively during peak RS. Total ocular scores revealed improvements of 21.8% (diff = -0.37 points; p = 0.01) and 18.9% (diff = -0.32 points; p = 0.03) for the 12 Amb a 1-U and 6 Amb a 1-U doses. Furthermore, a significant effect (p < 0.05) on individual symptoms was noted for 12 Amb a 1-U dose on watery and itchy eyes, runny nose and sneezing. Treatment with ragweed AIT was well tolerated with no observed difference between 6 and 12 Amb. There were no reports of systemic allergic reactions.

CONCLUSIONS: These results demonstrate that once-daily administration of ragweed AIT effectively treats the nasal and ocular symptoms of ragweed-induced ARC.

939 Age-related Differences in Antigen Sensitization and the Allergic Airway Responses in Acute and Resolved Viral Respiratory Infection

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RATIONAL: Clinical data suggests that viral respiratory infections in younger patients may promote allergic sensitization. This project investigated age-related effects of acute and resolved viral respiratory infection on antigen sensitization and allergic airway response in mice.

METHODS: Six-week and 18-month BALB/c mice (5-10/group) were infected with non-lethal dose of influenza virus A (H1N1)X1). Young and aged mice were ovalbumin (OVA) sensitized during acute-infection (3-days post inoculation) or during resolved-infection (30-days post inoculation), and OVA-challenged 3 times intratracheally at weekly intervals. Aged-matched, non-infected OVA-sensitized/challenged, infected-alone and naive mice were controls. Forty-eight hours after final OVA-challenge, airway hyperreactivity (AHR) to acetylcholine provocation was determined by airway-pressure time-index (APTI); bronchoalveolar fluids (BALF), sera, and lung tissues were collected.

RESULTS: APTI-values significantly increased in both young (p = 0.001) and aged (p < 0.05) mice sensitized during acute-infection compared to non-infected, antigen-sensitized/challenged mice. However, APTI values were significantly elevated in young, but not aged mice sensitized after resolved-infection. Serum OVA-specific IgE was significantly increased in young mice sensitized during acute-infection (105.6 ± 5.1 ng/ml) compared with young non-infected/OVA-sensitized (74.6 ± 1.3 ng/ml; p = 0.0001). OVA-specific IgE was not significantly different between aged mice sensitized during acute-infection (177.5 ± 23.27 ng/ml) or non-infected/OVA-sensitized (207.2 ± 22.58 ng/ml; p = 0.38) mice. OVA-specific IgE was significantly decreased in young (36.3 ± 5.8 ng/ml) and aged mice (16.8 ± 4.2 ng/ml) when sensitized after resolved infection. BALF eosinophil numbers were increased in aged, but decreased in young mice sensitized during acute-infection, and decreased in both ages when sensitized after infection was resolved.

CONCLUSION: There are several age-related differences including AHR, airway inflammation, and IgE production in the response to antigen sensitization and timing of viral infections.

940 Diesel Exhaust Particles Induce Cysteine Oxidation and S-Glutathionylation in House Dust Mite Induced Murine Asthma

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RATIONAL: Diesel exhaust particle (DEP) exposure enhances allergic inflammation and has been linked to the incidence of asthma. Oxidative stress on the thiol molecules cysteine (Cys) and glutathione (GSH) can promote inflammatory host responses. We hypothesized that DEP exposure would alter the Cys or GSH oxidation-reduction state in the asthmatic airway.

METHODS: Bronchoalveolar lavage fluid was obtained from a house dust mite (HDM) induced murine asthma model exposed to DEP. GSH, glutathione disulfide (GSSG), Cys, cystine (CySS), and s-glutathionylated cysteine (CySSG) were determined by high pressure liquid chromatography.

RESULTS: Compared with HDM exposure alone, DEP co-administered with HDM decreased total Cys (0.058 μM vs. 0.024 μM, p < 0.001), increased CySS (0.0043 μM vs. 0.025 μM, p < 0.0001), and increased CySSG (0.11 μM vs. 0.21 μM, p < 0.05) without significantly altering GSH or GSSG.

CONCLUSIONS: DEP exposure promotes oxidation and s-glutathionylation of cysteine amino acids in the asthmatic airway, suggesting a novel mechanism by which DEP may enhance allergic inflammatory responses.

941 The Gut Mucosa Microenvironment Affects Allergic Sensitization vs tolerance to Food Proteins

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RATIONAL: Oral administrations of food proteins may influence further oral tolerance or sensitization by changing the gut mucosa microenvironment.

METHODS: In a first experiment, BALB/cJ mice were sensitized by gavage with the purified cow’s milk (CM) allergen bovine β-lactoglobulin (BLG) mixed with Cholera toxin (CT). Mice were then gavaged with CM, without adjuvant. In a second experiment, mice were first tolerized to BLG by gavage1 and then sensitized to CM by gavage with CT. In both experiments, the specific antibodies to the different CM proteins (CMPs) were determined in sera collected from individual mice.

RESULTS: No specific antibodies to any CMPs were evidenced in control mice gavaged with CM without adjuvant. Conversely, mice previously sensitized to BLG produced specific IgG1 antibodies against caseins, β-lactalbumin and lactoferrin. Mice tolerized with BLG did not produce anti-BLG IgE or IgG1 antibodies after sensitization with CM+CT. Interestingly, the concentrations of antibodies against all the other CMPs were also significantly reduced in this group.

CONCLUSIONS: BLG present in CM likely elicits a specific local allergic reaction in mice previously sensitized with BLG which may then favour a Th2-type response to other bystander proteins. On the other side, the Treg cells induced after gavage with BLG alone would result in a pro-regulatory microenvironment and induction of a tolerogenic response to other CMPs. These results demonstrate the crucial role of the gut mucosa microenvironment in the nature of the immune response to a food protein.

1Adel-Patient et al., Allergy. 2011, 66(10):1312-21
**942 Rhinovirus Matures Dendritic Cells (DCs) and Primes Them for Antigen Presentation**

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**RATIONALE:** Rhinovirus infections are the leading cause of asthma exacerbations in children and adolescents. Understanding the immune mechanisms driving these exacerbations is contingent upon studying RV-targeting CD4 and CD8 T cells; which requires the use of autologous antigen-presenting cells. RV does not infect DCs. We speculated that in the presence of high concentrations of RV, DCs would be matured to cross-present RV antigens thereby permitting investigation of the presence and phenotype of responding T cells.

**METHODS:** DCs were generated from magnetic affinity purified CD14+ monocytes using GM-CSF and IL-4 supplemented with 10% autologous serum for 5 days. RV strain A39 was generated in epithelial cells and gradient purified. RV loading was accomplished with 20,000 pfu equivalent inoculum (~50 μg of viral protein). DC phenotype was established by flow cytometry as expression of CD11chi/CD14low/HLA-DR and RV-induced maturation via upregulation of CD80 (51.6 ± 11.3% to 56.4 ± 10.2%) and CD86 (76.5 ± 5.7% to 85.8 ± 2.3%) (p < 0.05) although not CD83. Functional status was confirmed as expansion of peripheral T memory lymphocytes.

**RESULTS:** DC differentiation was confirmed as high CD11c/HLA-DR expression and absence of CD14. Maturation by the RV was confirmed as upregulation of CD80 and CD86. Functional status was confirmed as expansion of peripheral T memory lymphocytes.

**CONCLUSIONS:** We developed methodology to identify and expand RV-specific CD4+ and CD8+ T cells. Expansion of RV-specific T cells permits elucidation effectors (Th1 v. Th2) and regulatory (IL-10) phenotypes.

**943 Leukocyte Ig-like Receptor LILRB4 (LILRB4) Downregulates Key Events in the Migration of Antigen (Ag)-bearing Lung Dendritic Cells in Th2 Inflammation**

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**RATIONALE:** We previously reported that Lilrb4−/− mice have an exacerbated Th2 immune response and pulmonary inflammation compared with Lilrb4+/+ animals when sensitized with ovalbumin (OVA) and low-dose lipopolysaccharide (LPS) followed by challenge with OVA. In addition, LILRB4 is selectively upregulated on Ag-bearing lung and draining lymph node (LN) dendritic cells (DCs). Moreover, Ag-challenged Lilrb4−/− mice exhibit increased migration of Ag-bearing DCs to LNs and accumulation of IL-4- and IL-5-producing LN lymphocytes. We therefore sought to determine how the absence of LILRB4 leads to more DCs in the LNs of Ag-challenged mice.

**METHODS:** Mice were sensitized intranasally with PBS alone or containing OVA and LPS on days 0, 1, and 2, and challenged with OVA on day 14. Four hours after challenge, lungs were evaluated by immunohistology, and lung mononuclear cells were isolated for flow cytometry.

**RESULTS:** After sensitization and challenge, the lung lymphatic vessels of Lilrb4−/− mice expressed more CCL21, a chemokine that directs the migration of DCs from peripheral tissue to draining LNs. In addition, lung DCs of challenged Lilrb4−/− mice expressed more CCR7, the CCL21 receptor. The lungs of challenged Lilrb4−/− mice also contained significantly greater numbers of CD4+ cells expressing IL-4 or IL-5, consistent with the greater number of Ag-bearing DCs and Th2 cells in LNs and the attendant exacerbated Th2 lung pathology.

**CONCLUSIONS:** Our data reveal that LILRB4 downregulates expression of two key molecules that induce the migration of Ag-bearing lung DCs to LNs, thereby attenuating Th2 cell accumulation in LNs and lung and ensuing pathologic inflammation.