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1 Paradoxical Bronchospasm With a Near-Fatal Reaction to Albuterol-HFA and Levalbuterol Inhalation Solution Leading to Intubation in an Adult Asthmatic

S. Amara, N. Gupta, B. Silverman, Y. A. K. Rao, A. T. Schneider; Long Island College Hospital, Brooklyn, NY

OBJECTIVE: We present a case of life-threatening bronchospasm to Albuterol-HFA and Levalbuterol inhalation solution. The literature reveals several cases of paradoxical bronchospasm with Albuterol-CFC and HFA, but no case with such convincing documentation has been reported with Levalbuterol until now.

METHODS: 59 year-old male with mild-intermittent asthma was treated with Albuterol-CFC and Albuterol-HFA prn. With each use, he experienced severe chest tightness and flu-like symptoms. Six months prior, he experienced severe dyspnea immediately after using Albuterol HFA and called 911. EMS found him unconscious and apneic. He was immediately intubated and rushed to the ED, where he received high-dose Solumedrol and Benadryl. He was extubated after 3 days and discharged on prednisone taper and Xopenex/Atrovent.

RESULTS: Later, pre and post B-agonist spirometric evaluation using Xopenex portable nebulizer revealed an obstructive pattern on the pre B-agonist curve; surprisingly, the post curve showed greater obstruction with acute wheezing. This episode resolved with Epipen, Solumedrol, and antihistamines. Beta-receptor genotyping was normal (Arg-Gly).

CONCLUSIONS: This is the first documented case of near-fatal reaction to Levalbuterol relieved with Epipen and high-dose steroids. Of note, while the patient was intubated, B-agonist therapy was continued, despite convincing history implicating its adverse effects; one must conclude that simultaneous high-dose steroids may have prevented further deterioration. Documented spirometry finally confirmed that Xopenex use, as first reported by this patient, resulted in severe obstruction secondary to acute bronchospasm. Even though paradoxical and contrary to conventional wisdom, physicians should be aware that the possibility of bronchospasm to B-agonists, even levalbuterol, exists.

2 Gata-3-specific DNAzyme As An Approach For Asthma-therapy

T. Dicke, M. Wegmann, S. Sel, H. Renz, H. Gam; Medical Faculty, Philipps University, Marburg, GERMANY

RATIONALE: The transcription factor GATA-3 is a key regulator of Th2 cell differentiation. Since Th2 cells play a principal role in the initiation and maintenance of allergic airway inflammation, GATA-3 represents a promising target for therapeutic intervention.

METHODS: DNAzymes are single-stranded desoxy-nucleotides combining the specificity of DNA base pairing with an inherent RNA-cleaving enzymatic activity. The most effective GATA-3 mRNA-specific enzyme was used as treatment in an acute and in a chronic model of experimental asthma. Its specificity of DNA base pairing was assessed by gel electrophoresis.

RESULTS: The GATA-3-specific DNAzyme gd21 was able to cleave more than >80% of GATA-3-mRNA within 30 minutes in a cell-free system. Similar RNA cleavage activities were observed in vitro after transfection of EL-4 cells. In mouse model of experimental asthma, intranasal application of gd21 resulted in reduced allergic airway inflammation. Especially the amount of eosinophils was markedly reduced in an acute as well as in a chronic model of experimental asthma. A diminished IL-5/IFN-γ ratio further indicated a lessened Th2 activity, that was accompanied by reduction of goblet cell hyperplasia and normalization of airway hyperresponsiveness as assessed by head-out body-plethysmography.

CONCLUSIONS: The downregulation of GATA-3 expression by application of a GATA-3-mRNA-specific DNAzyme may be a novel tool for therapeutic intervention in allergic diseases such as asthma.

Funding: Deutsche Forshungsgemeinschaft SFB/TR22 Z2

3 Bronchial Thermoplasty in Refractory Asthma: Interim Results in a Severe Asthma Population (Research in Severe Asthma (RISA) Trial)

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RATIONALE: Bronchial Thermoplasty (BT) reduces the amount of airway smooth muscle and potentially bronchoconstriction. The RISA Trial evaluated safety and efficacy of BT in subjects with asthma who were refractory to optimum care in specialty asthma clinics.

METHODS: Adult subjects with severe persistent asthma who remained symptomatic despite taking >750 µg fluticasone (or equivalent) +/-maintenance oral-corticosteroids and long-acting beta-agonists were enrolled. BT subjects underwent 3 BT sessions to treat all accessible airways. Control subjects underwent 3 office visits. Subjects remained on baseline asthma medications through 22 weeks following the last BT session.

RESULTS: Thirty-two subjects were enrolled (BT group: 15, Control group: 17). Changes from baseline in efficacy parameters for the BT vs Control groups at 22 weeks following completion of BT were: %change in Pre-BD FEV1, %Predicted: 14.9 ± 17.40 vs -0.94 ± 22.34 (p = 0.039); Rescue Medication Use (puffs/SABA/7days): -25.56 ± 40.05 vs -1.47 ± 11.66 (p = 0.046); AQLQ Score: 1.21 ± 1.05 vs 0.15 ± 0.75 (p = 0.003); and ACQ Score: -1.04 ± 1.03 vs -0.13 ± 1.00 (p = 0.020). Hospitalization rate for respiratory-related events during the Treatment Period was higher in the BT group (8 in 45 bronchoscopies) compared to the Control group (no hospitalizations), but was similar for both groups during the post-treatment period.

CONCLUSIONS: We have shown clinically and statistically significant improvements in key efficacy measures at 22 weeks following BT in patients with severe asthma. There was a short-term increase in hospitalizations but the benefits of the procedure suggest an acceptable risk/benefit profile. Follow-up is planned through 12 months to assess the durability of the treatment effect and its impact on asthma maintenance medication requirements.

Funding: AsthmaX, Inc, USA

4 Compatibility of Levalbuterol Inhalation Solution Mixed with Budesonide, Ipratropium Bromide, Cromolyn Sodium or Acetylcysteine Sodium

W. K. McVicar, P. Bonasia, S. Ong; Sepracor Inc., Marlborough, MA.

RATIONALE: Nebulized formulations of asthma medications are often mixed together in order to simplify therapeutic regimens. It is therefore important to determine whether mixtures of these medications are chemically and physically compatible. In this study, levalbuterol inhalation solution was mixed separately with one dose each of commercially available, nebulized formulations of budesonide, ipratropium bromide, cromolyn sodium, or acetylcysteine.

METHODS: Admixtures were prepared from XOPENEX® (levalbuterol HCl Inhalation Solution concentrate 1.25 mg/0.5 mL) and solutions of either Pulmicort Respules® (budesonide inhalation solution, 0.5 mg/2 mL), Atrovent® (ipratropium bromide, 0.5mg/2.5 mL), Intal® (cromolyn sodium, 20 mg/2 mL), or Mucomyst® (acetylcysteine, 1000 mg/5 mL). At time points immediately and 30 minutes after preparation, admixtures were inspected visually, pH was assessed, and HPLC assay of the active level for each drug was performed.

RESULTS: There was no evidence of precipitation, haze, or physical incompatibility immediately or at 30 minutes after mixing of the samples. Compatibility was maintained over the period of study for all admixtures; drug recoveries were 93.2-102.6% of initial or control values. Admixture pH values were close to the pH of the other drugs due to the relatively smaller dose volume of the levalbuterol but showed little change (-0.10 to 0.24 pH units) over the assessed study period.

CONCLUSIONS: Compatibility was maintained for at least 30 minutes at room temperature when an inhalation solution of levalbuterol concentrate
(1.25 mg/0.5 mL) was mixed with inhalation solutions of budesonide, ipratropium bromide, cromolyn sodium, or acetylcysteine.

**Funding:** Sepracor Inc

5 **A Comparison of Bronchodilator Expressions to Identify the Asthmatic Child**

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**RESULTS:** Three hundred forty six asthmatics, 51 non asthmatics, predominantly Hispanic children, ages 4 to 17 years were evaluated. All BDR expressions were significantly greater in the asthmatics regardless of severity (P < .001), and increased with severity. Positive BDR values established for FEV1 % initial, but had higher +LR, and was less dependent on initial FEV1 and lung size factors. We suggest that the BDR expression ΔFEV1 % predicted be a routine part of evaluating childhood asthma regardless of baseline FEV1.

**Funding:** California Wellness Foundation

6 **Adrenergic β2 Receptor Genotyping in Asthma: Case Reports**

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**RATIONALE:** Recent publications have suggested a possible relationship between a specific polymorphism of the β2 adrenergic receptor gene (ADRB2) and adverse effects of regular β-agonist use in subjects with asthma. Thus, individuals who are homozygous for alanine at codon 16 of the ADBR2 gene may experience a decrease in morning peak expiratory flow rate, and an increase in asthma symptoms with regular use of short- or long-acting bronchodilators, with or without concomitant use of inhaled corticosteroids (Wechsler et al, Am J Respir Crit Care Med. 2006;173:519).

**METHODS:** Poorly controlled asthmatic patients seen in the Pediatric Allergy and Immunology clinic at our center underwent genotyping of codon 16 of the ADRB2 gene using PCR with gene and polymorphism-specific primers.

**RESULTS:** We report 3 cases of asthma in subjects with the Arg/Arg ADRB2 genotype who had poorly controlled asthma while on maintenance therapy with a combination of a high-dose inhaled corticosteroid and a daily long-acting β2 agonist (LABA). All three patients had significant improvement in their pulmonary function tests as well as clinical symptomatology and decreased use of rescue bronchodilator medications within one month of discontinuing treatment with LABA. FEV1 pre- and post- LABA were as follows: 51% vs 102%, 66% vs 87%, and 59% vs 92%, respectively.

**CONCLUSIONS:** Prospective randomized controlled studies are needed to confirm the possible relationship between the Arg/Arg ADRB2 genotype and potential adverse effects of regular use of β2-agonist medications.

7 **Effect of Budesonide and Formoterol Administered Via One Pressurized Metered-dose Inhaler on Lung Function in Adults and Adolescents With Moderate to Severe Persistent Asthma**


**RATIONALE:** To compare treatment effects on lung function of budesonide and formoterol in one pressurized metered-dose inhaler (pMDI) with budesonide pMDI, formoterol dry powder inhaler (DPI), budesonide and formoterol in separate inhalers (budesonide pMDI + formoterol DPI), and placebo.

**METHODS:** This 12-week randomized, double-blind, double-dummy, placebo-controlled, multicenter study (SD-039-0717) included 596 patients aged ≥12 years with moderate to severe asthma previously treated with inhaled corticosteroids. After a 2-week run-in period on 2 inhalations budesonide pMDI 80 μg bid, patients were randomized to receive 2 inhalations of one of the following: budesonide/formoterol pMDI 160/4.5 μg, budesonide pMDI 160 μg + formoterol DPI 4.5 μg, budesonide pMDI 160 μg, formoterol DPI 4.5 μg, or placebo. Lung function variables included morning predose forced expiratory volume in 1 second (FEV1), 12-hour mean postdose FEV1 (serial spirometry), and morning and evening peak expiratory flow (PEF).

**RESULTS:** Mean changes from baseline in predose FEV1 at end of treatment and 12-hour FEV1 at week 2 were greater (P ≤ .049) for budesonide/formoterol pMDI (0.19 L and 0.34 L, respectively) versus budesonide pMDI (0.10 L and 0.15 L), formoterol DPI (-0.12 L and 0.19 L), and placebo (-0.17 L and -0.03 L) but similar versus budesonide pMDI + formoterol DPI (0.14 L and 0.32 L). Improvements in morning and evening PEF were greater with budesonide/formoterol pMDI versus all groups (P < .001) except budesonide pMDI + formoterol DPI.

**CONCLUSIONS:** Twice-daily budesonide/formoterol pMDI provides improvements in lung function significantly greater than its monocomponents or placebo and similar to that of budesonide pMDI + formoterol DPI.

**Funding:** AstraZeneca

8 **Efficacy and Safety of Intravenous Aminophylline in Children with Acute Exacerbation of Asthma: A Multicenter Randomized Trial**

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**RATIONALE:** Use of aminophylline or theophylline as an additional treat- ment for acute asthma is controversial. IV aminophylline is a “classical” bronchodilator but may have therapeutic advantages in its putative anti-inflammatory effect and availability to peripheral airways where inhaled drugs may inadequately reach at. The study was performed to assess if the addition of IV aminophylline to standard treatment for acute exacerbation of asthma would enhance the recovery without serious adverse events.

**METHODS:** Children aged 2 to 15 years with acute asthma who did not respond to repeated inhalations of beta2 agonists were enrolled. All sub- jects were treated with inhaled salbutamol and IV methylprednisolone/hy- drocortisone and were randomized to receive additional IV aminophylline (Group A) or none (Group B). Asthma symptom score and time when wheeze disappeared were compared.

**RESULTS:** Fifty subjects were enrolled with 26 randomly allocated to group A and 24 to B. The groups were well matched at baseline. One in Group A and 7 in B dropped out because of exacerbation or non-compliance and outcome was analyzed in 24 from A and 17 from B. Faster improvement in symptoms were seen in Group A and there was a significant difference in symptom score at 24 h after treatment between the groups (p<0.05). The time to resolution of wheezing was significantly shorter in Group A than in B (median 46 h and 70 h, respectively; p<0.01). Four minor adverse events were observed in Group A but all completed the treatment.

**CONCLUSIONS:** Addition of aminophylline may be a beneficial thera- peutic option for children with acute asthma.

**Funding:** Nikken Chemicals Co. Ltd
Functional Role of Glucocorticoid Receptor β In The Steroid-induced Suppression Of IL-8 In Airway Epithelial Cells

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RATIONALE: There are few reports detailing the effect of GRβ on steroid-induced suppression of inflammatory cytokines, and in particular, whether GRβ can act as a dominant negative inhibitor of this activity. We investigated the functional role of GRβ in the steroid-induced suppression of IL-8.

METHODS: GR-β was overexpressed by transfection of pCMV GRβ using lipopentamime plus method. TNF-α was used as an activator of IL-8. mRNA of IL-8 was measured by RT-PCR and amounts of IL-8 secretion were measured by ELISA. Activities of histone acetylase and histone deacetylation were measured with GRβ overexpression. Immunoprecipitita- tion and chromatin immunoprecipitation were done.

RESULTS: GRβ was expressed in abnormal conditions such as long-term glucocorticoid treatment or inflammation induced by TNF-α. GRβ was able to inhibit glucocorticoid-induced transcriptional activation mediated by binding to glucocorticoid response elements (GRE's). The suppressive effect of dexamethasone on the transcription and TNF-α-induced IL-8 was not affected by GRβ over-expression, rather GRβ had its own weak activity suppressing TNF-α-induced IL-8 secretion. Histone deacetylase activities were increased by GRβ overexpression without changes of histone acetyltransferase activity and GRβ formed a complex with HDAC1 as demonstrated by co-immunoprecipitation experiments. TNF-α induced histone H4 acetyla- tion at the IL-8 promotor was decreased with GRβ overexpression.

CONCLUSIONS: The study suggests that GRβ may not act as a dominant negative inhibitor of GRo in the steroid-induced suppression of IL-8 in airway epithelial cells and GRβ induce its own histone deacetylase activity by recruiting histone deacetylase.

Funding: Korea Health 21 R&D Project, Ministry of Health & Welfare, Korea (Grant No. 03-PJ10-PG13-GD01-0002)

Development of Asthma Study Technologies in an Environmental Chamber (ASTEC)

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RATIONALE: The development of ASTEC to study the effects of dust mite allergen (DMA) on asthma in a more natural setting will provide etiological and therapeutic insights.

METHODS: Spent dust mite culture powders were aerosolized after particle size reduction through a controlled ball-milling process that leads to known particle size distributions to include typical respirable particles, 5 μm and 10 μm with unit density. Particle size (aerodynamic diameter) and number, and chamber temperature (T) and relative humidity (RH), were monitored continuously. Airborne DMA, der p1, concentrations were measured with ELISA. The goodness-of-fit of linear relationships was assessed by correlation coefficients (R² ~1 correlative) and statistical significance with linear regression (p<0.05).

RESULTS: Particle aerosolization was size-dependent with smaller particles aerosolizing in higher numbers. The effects of T/RH on aerosolization were minimal on larger particles with slopes of RH versus particle aerosolization counts of -9.62E+02 and -4.56E+02 for 5 μm and 10 μm compared to -1.54E+05 and -5.14E+04 for 0.5 μm and 1 μm particles, respectively. DMA correlated highly with particle number for the largest well-aerosolized particles (5 μm, 10 μm), both with R² = 0.99 (p<0.05) compared to correlations for smaller particles, with R² 0.67 and 0.64 for 0.5 μm and 1 μm particles, respectively. Using these determined particle/environmental parameters, homogeneous DMA levels within the chamber are achieved to tight tolerances with low relative standard deviations (<15%) within the 30-200 ng/m³ range at 24°C. 35% RH.

CONCLUSIONS: Calibration of inhalant particle characteristics and environmental chamber conditions are necessary for tight control of dust particle aerosolization and DMA exposure, which are required to develop ASTEC for the study of asthmatic patients.

Funding: Allied Research International

Cutaneous CpG Administration Reduces Th2-type Airway Inflammation But Induces Airway Hyperreactivity

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RATIONALE: We recently demonstrated in mice that sensitization with natural rubber latex (NRL) via cutaneous route plays an important role in the elicitation of asthmatic symptoms after airway NRL exposure. In this study we investigated the possibility to prevent the development of latex induced asthma by administration of immunostimulatory CpG motifs intradermally together with NRL.

METHODS: Balb/c mice were given CpG or mutated CpG intradermally with NRL or PBS for four weeks followed by three day NRL airway challenge. Measurement of airway hyperreactivity (AHR) and collection of specimens were conducted on subsequent day.

RESULTS: NRL-induced pulmonary eosinophilia was significantly re- duced whereas the numbers of lymphocytes, neutrophils and CD11c+ cells were increased in the airways after CpG administration. CpG treatment also elicited reduction in mucus secretion, downregulation of Th2 type cy- tokines and upregulation of Th1 type cytokines in the lungs. Expression of regulatory cytokines TGF-β and IL-10 and, Foxp3, a specific marker for regulatory T cells, was significantly enhanced in the airways of CpG treated mice. Moreover, the levels of NRL-specific IgE were reduced and NRL-specific IgG2a levels were increased in NRL sensitized mice treated with CpG. Unexpectedly, significantly elevated AHR to inhaled metacho- line was observed after CpG treatment.

CONCLUSIONS: Intradermal CpG treatment during cutaneous NRL sen- sitization suppresses the development of Th2-type lung inflammation and systemic IgE responses. Surprisingly however, CpG administration significa- ntly increases AHR, the characteristic manifestation of clinical asthma. This unexpected side-effect should be taken in consideration when plan- ning prophylaxis and treatment of human asthma with cutaneous CpG in- jections.

Funding: Ansell Healthcare Corporation, The Clinical Research Institute HUCH and TB-Foundation
12 New Treatments for Suppression of Ongoing Human and Murine IgE Responses

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RATIONALE: There is currently no therapy available to decrease IgE production in humans. An optimal therapy should suppress IgE responses in iso- type specific manner, allowing unrelated immune responses to go forward.

METHODS: We investigated the ability of minocycline (mino), doxycycline (doxy) and chemically modified tetracyclines lacking antibiotic activity (CMT) to suppress human and murine IgE responses in vivo and in vitro (UnicAP Total IgE fluorescence immunoassay, ELISA, ELISPOT assay). Allergic adults with moderate to severe persistent asthma used mino for one year as add-on therapy (N = 5). BPO-KLH sensitized mice were fed with mino or doxy at the peak of the hapten specific IgE response. The ability of mino, doxy and/or CMT to suppress in vitro induction of nonspecific (anti-CD40/IL-4) IgE responses and ragweed specific memory IgE responses by human PBMC and murine spleen cells was also investigated.

RESULTS: Mino treated adults had decreased serum IgE levels (~60% per annum). Mino and doxy treated BPO-KLH sensitized mice had strongly suppressed hapten specific IgE responses (>90%); suppression was isotype specific and dose dependent. Mino, doxy and/or CMT sup- pressed in vitro induction of a nonspecific (anti-CD40/IL-4) IgE re- responses (>80%) and (b) ragweed specific memory IgE responses (>95%) by PBMC from asthmatic donors; specific suppression was isotype specific and dose dependent.

CONCLUSIONS: Mino/doxy/CMT are suitable candidates for anti-IgE therapy. The mechanism(s) by which mino/doxy suppressed IgE responses in vivo may be due to antibiotic or other activities of these pleotropic mole- cules, but suppression of in vitro induction of nonspecific and memory IgE responses does not involve antibiotic activity.

Funding: New York State Research Grant

13 Formoterol Treatment plus Tiotropium Results in Greater Improvements in Lung Function Compared with Tiotropium Administered Alone in Patients with COPD

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RATIONALE: Bronchodilators are the foundation for the treatment of chronic obstructive pulmonary disease (COPD). Anticholinergics and ß2-adrenergic receptor agonists are 2 distinct bronchodilator agents that differ in their mechanisms of action. Therefore, their combination may elicit com- plementary effects on lung function. Treatment with formoterol plus tio- tropium was thus compared with tiotropium alone in patients with COPD.

METHODS: In a 12-week, randomized, placebo-controlled, parallel- group, multicenter, double-blind study, patients aged ≥40 years received treatment with tiotropium (18 mcg QD) plus formoterol (12 mcg BID; TIO/FORM) or tiotropium (18 mcg QD) plus placebo (TIO).

RESULTS: TIO/FORM combination treatment (n = 115) significantly improved FEV1 AUC0-6 hrs compared with TIO treatment alone (n = 122) at all time points post-baseline, with mean normalized treatment dif- ferences (95% CI) that reached clinical significance (>100 ml change); 150 ml (84.4, 216.4), 162 ml (95.7, 228.4), 213 ml (137.3, 289.3) and 189 ml (124.9, 253.8) at Weeks 4, 8, 12, and endpoint, respectively (endpoint = Week 12- Last Observation Carried Forward, P < 0.0001 for all). At end- point, TIO/FORM resulted in significantly greater trough measurements (10 min pre-dose) of FEV1 and FVC from baseline, with normalized treat- ment differences of 99 ml (P < 0.006) and 200 ml (P < 0.003), respectively. Secondary parameters, including trough FEV1 and FVC (30 min pre-dose), showed similar findings at Weeks 4, 8, and 12, demonstrating significant improvements with TIO/FORM treatment compared with TIO treatment alone.

CONCLUSIONS: TIO/FORM treatment results in significantly greater improvements in lung function that persist over 12 weeks of treatment than TIO treatment alone.

Funding: Schering-Plough

14 Montelukast Added to Usual Therapy during the September Epidemic of Asthma Exacerbations in Children


RATIONALE: An epidemic of asthma exacerbations in children occurs annually following school return after summer vacation.

METHODS: In a double blind randomized placebo-controlled trial, 194 children aged 2-14 stratified by age and sex added montelukast or placebo to usual therapy between September 1 and October 15 2005. Entry criteria included; physician diagnosed asthma; rescue inhaler needed in the last year; school absence due to asthma in the last year; history of asthma exacerbations associated with apparent respiratory viral infections.

RESULTS: A 53% reduction in days with worst asthma symptoms occurred with montelukast compared to placebo, (3.9% versus 8.3%, p < 0.02), and a 78% reduction in unscheduled physician visits for asthma (4 versus 18, p = .011). The benefit of montelukast occurred both in those using and not using regular inhaled corticosteroids. Boys 2-5 years showed the greatest benefit from montelukast, (0.4% versus 8.8% days with worse asthma symptoms, p<.001), with a lesser effect among 6-9 year olds (2.0% montelukast versus 7.0% placebo, p = .12), and a minimal effect in 10-14 year olds (6.3% montelukast versus 8.2% placebo, p = 0.44). In girls the treatment effect was minimal in 2-5 year olds (5.7% with montelukast, 6.9% with placebo) and in 6-9 year olds (4.5% versus 4.6%) but significant and in 10-14 year olds (4.6 % with montelukast versus 17.0% with pla- cebo, p = 0.03).

CONCLUSION: Montelukast added to usual treatment substantially re- duced the risk of worsening asthma symptoms and unscheduled physician visits during the September asthma epidemic. Treatment effect differences observed between age and sex groups require further investigation in future studies.

Funding: Merck Frosst Canada Ltd

15 Addition of Omalizumab Improves Quality of Life in Moderate- Severe Asthmatics Receiving Fluticasone 500 μg/Salmeterol 50 μg

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RATIONALE: A significant number of patients with moderate-severe asthma are not well controlled despite treatment with high-dose inhaled corticosteroids (ICS) and long-acting β-agonists (LABAs). We describe the effect of omalizumab (OMA) on quality of life (QoL) in patients with moderate-severe persistent IgE-mediated asthma receiving inhaled fluticasone 500 μg/salmeterol 50 μg (FLU/SAL) combination treatment in a 28-week clinical trial (INNOVATE).

METHODS: INNOVATE was a double-blind, randomized, placebo (PBO)-controlled trial that evaluated OMA in 419 patients uncontrolled on high-dose ICS and LABAs. A subgroup analysis was performed on pa- tients receiving inhaled FLU/SAL 50/50 μg bid. The change from base- line in the Juniper Adult Asthma Quality of Life Assessment (AQLQ) scores (overall and 4 individual domains: activity, symptoms, emotional, and environmental) was analyzed using analysis of covariance. Least squares mean (LSM) differences were calculated and a 95% confidence in- terval was constructed.

RESULTS: There were 80 patients (45 OMA, 35 PBO) in the FLU/SAL subgroup. Mean age was 42.2 y, 38% were male, and baseline FEV1 was 60%-79% of predicted in 51% and <60% of predicted in 45% of patients. Treatment with OMA vs. PBO resulted in significant improvement in overall AQLQ score (LSM change 1.1 OMA, 0.5 PBO; LSM difference 0.60 [95% CI: 0.08, 1.12; p = 0.0241]). While all domains of AQLQ improved, greatest LSM differences were seen in changes in emotional and environ- mental scores (0.83 and 0.84, respectively).

CONCLUSIONS: The addition of omalizumab improved quality of life measures in patients with moderate-severe persistent IgE-mediated asthma inadequately controlled by FLU/SAL 50/50 μg.

Funding: Novartis Pharmaceuticals Corporation
Effects Of MN-001 In Patients With Mild-to-moderate Asthma In A Randomized, Double-blind And Placebo-controlled Phase II Study


**Rationale:** To investigate MN-001, an oral anti-inflammatory agent (e.g., inhibitor of phosphodiesterase IV, 5-lipoxygenase, leukotriene receptors), for control of asthma.

**Methods:** Mild-to-moderate asthmatics (147) were randomized to receive MN-001 (500 mg tid, 750 mg bid, 750 mg qd) or placebo orally for 4 weeks in this multi-center, double-blind study. Subjects had asthma for ≥3 months, an FEV1 ≥65% of predicted, no inhaled corticosteroids ≥1 month, ≥12% improvement in FEV1 after albuterol, a symptom score on 4 symptoms ≥3 on ≥2 days and ≥8 puffs albuterol within a 7-day run-in and a methacholine PC20 ≤8 mg/mL. 24 hr serial spirometry was performed on Days 1 and 14. The primary outcome was FEV1 change from baseline at 4 weeks. Secondary outcomes included change in PEFR, rescue albuterol use, change in methacholine PC20, serial spirometry measures, asthma symptom scores and nighttime wakings.

**Results:** FEV1 was significantly improved after 4 weeks of 500 mg MN-001 tid vs. placebo (0.158L; p = 0.021). A similar trend was observed for 750 mg bid (0.117L; p = 0.058). Positive trends in secondary outcomes were also observed in the 500 mg tid group. MN-001 was well tolerated with 89% of patients completing 4 weeks of treatment. There was no apparent difference between placebo and any MN-001 group in adverse event (AE) discontinuations or in AEs attributable to treatment. No serious AEs were reported.

**Conclusions:** MN-001 may effectively control bronchial asthma.

**Funding:** MediciNova, Inc.

Safety of Budesonide and Formoterol Administered Via One Pressurized Metered-dose Inhaler (Budesonide/Formoterol pMDI) In Patients (≥12 Years) With Moderate to Severe Persistent Asthma


**Rationale:** To compare the safety of budesonide/formoterol pMDI with budesonide pMDI, formoterol dry-powder inhaler (DPI), budesonide pMDI + formoterol DPI, and placebo.

**Methods:** This 12-week, double-blind, double-dummy, placebo-controlled, multicenter study (SD-039-0717) included 596 patients aged ≥12 years with moderate to severe asthma previously treated with inhaled corticosteroids. After a 2-week run-in period on 2 inhalations budesonide pMDI 80 μg bid, patients were randomized to receive 2 inhalations bid of one of the following: budesonide/formoterol pMDI 160/4.5 μg, budesonide pMDI 160 μg + formoterol DPI 4.5 μg, budesonide pMDI 160 μg, formoterol DPI 4.5 μg, or placebo. Safety variables included adverse events (AEs), postdose electrocardiograms (ECGs) and laboratory evaluations, 24-hour Holter monitor assessments, vital signs, and physical examinations.

**Results:** AEs occurred in 76 (61.3%), 73 (63.5%), 64 (58.7%), 77 (62.6%), and 54 (43.2%) patients receiving budesonide/formoterol, budesonide + formoterol, budesonide, formoterol, and placebo; AEs judged related to study medication occurred in 12.9%, 8.7%, 5.5%, 7.3%, and 5.6% of patients in these respective treatment groups. Most AEs were of mild or moderate intensity. The incidence of asthma reported as an AE was low and similar across treatment groups (budesonide/formoterol, 2.4%; budesonide + formoterol, 0%; budesonide, 2.8%; formoterol, 3.3%; placebo, 3.2%). The incidence of other potentially asthma-related AEs and cardiac-related AEs was generally low and similar across treatment groups. No clinically relevant differences were observed across treatment groups in ECG and laboratory values, Holter monitor assessments, vital signs, and physical examination results.

**Conclusions:** Budesonide/formoterol pMDI was well tolerated, with a safety profile similar to the individual monocomponents.

**Funding:** AstraZeneca

The Effects of Mometasone DPI on Airway Hyperresponsiveness and Markers of Airway Inflammation

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**Rationale:** Exhaled nitric oxide (eNO) and exhaled breath condensate pH (EBC pH) may be useful markers of airway inflammation, a cardinal feature of asthma. The ability of inhaled corticosteroids to influence these parameters concomitantly with FEV1 and methacholine responsiveness has not been elucidated. This study examines the effects of mometasone DPI on these markers of airway inflammation in asthma.

**Methods:** Twelve adult steroid naïve patients with mild to moderate persistent asthma (FEV1 ≥60% predicted and PC20 methacholine <8 mg/mL) were treated with mometasone furoate DPI 400 mcg daily for 8 weeks, followed by a 4-week washout. FEV1, methacholine PC20, eNO and EBC pH were measured at baseline, during active treatment (weeks 1, 4 and 8) and during mometasone washout (post-treatment weeks 1 and 4).

**Results:** Median FEV1 at baseline was 2.99 L (89% of predicted), and was unaffected during the study. Methacholine PC20 increased by 4.1 doubling doses by treatment week 4, and remained higher throughout post-treatment week 4 (p = 0.01). Median eNO decreased from 24.6 ppb to 15.1 ppb by treatment week 1 and remained significantly lower through week 8 (p = 0.05), reverting to baseline by post-treatment week 4. Median EBC pH increased from 7.81 to 8.02 by treatment week 4, and then plateaued, although statistical significance was not achieved.

**Conclusions:** Treatment of asthma with mometasone DPI is associated with significant improvements in methacholine responsiveness and eNO, and a trend towards increased EBC pH. These data suggest that inhaled corticosteroids affect eNO more rapidly and transiently, but airway hyperresponsiveness more slowly and persistently.

**Funding:** Schering-Plough

Objective evidence of omalizumab treatment assessed by Forced Oscillation (FO)

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**Rationale:** Omalizumab is approved for treatment of moderate to severe asthmatic patients dependent on systemic steroids (SS) or requiring high dose inhaled corticosteroids (ics); and results in subjective clinical improvement and decreased SS and ics dose requirements, with marginal or no objective improvements in lung function.

**Methods:** Twelve moderate to severe asthmatic patients were evaluated in an open-label safety study of omalizumab using the Impulse Oscillometry System (IOS), a form of FO, in addition to spirometry. IOS measures included low frequency resistance (R at 5 Hz, R5), and low frequency integrated reactance (AX).

**Results:** IOS indices were significantly improved after 3 to 4 months of treatment; but were not paralleled by changes in spirometry (FEV1). Mean AX prior to, and after 4 months treatment with omalizumab were 26.9 and 18.0 cm H2O/L (p < 0.002). Mean R5 was 5.8 prior to and 4.8 cm H2O/Ls after 4 months of treatment (p < 0.003). Mean FEV1 was 2.02 L before and 1.98 L after 4 months treatment (p = 0.66).

**Conclusions:** We conclude that low frequency FO indices provide objective evidence of omalizumab efficacy, while such objective evidence is not available from spirometry. These data provide further support for the utility of FO in clinical management of asthma: airflow resistance and low-frequency reactance quantify lung mechanical responses noninvasively and unobtrusively, with increased patient comfort compared to spirometry.

**Funding:** Genentech
**20 Saccharomyces (S.) Cerevisiae Mannan Facilitates Airway Epithelial Repair**

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**RATIONALE:** In asthmatic airways, repeated epithelial damage and repair occur. We have previously shown that S. cerevisiae mannan inhibits airway hyperreactivity in allergen-sensitized mice (JACI 113:816, 2004). Studies were conducted to investigate the effects of mannan on airway epithelial repair.

**METHODS:** Either primary normal bronchial epithelial cells (NHBEc) or 16HBEC were cultured in 6 or 12 well plates to confluence at 37°C and 5% CO₂ using a pipette tip. Wounds were inflicted across the diameter of the wells. Wounded plates were cultured with mannan (0.5-2 mg/ml, 0-24 hr) or vehicle control. In some cases active or heat-inactivated (50°C, 3 hr) beta-hexosaminidase A (HexA, 50 nM) was added as an endogenous ligand for mannose receptor. Cells were stained with rhodamine-phalloidin. Wound size was measured over time and wound edge cell morphology was examined and expressed as average lamellipodial width (area/length). 16HBEC cells grown in culture on a nylon sheath were incubated with gold (10 nm)-labeled mannos-bovine serum albumin (ManBSA) or gold-BSA (control) for 30 min and processed for electron microscopy.

**RESULTS:** Average lamellipodial width of wound edge cells at 24 hours after wounding was significantly increased in mannan treated (n = 10) versus control 16HBEC (n = 6) (4.47 ± 0.90 vs. 1.57 ± 0.59 microns, p<0.05). Whereas active HexA retarded repair process, inactivated enzyme facilitated repair. Similar findings were observed in NHBEc. Colloidal gold-Man BSA was endocytosed via clathrin-coated pits in 16HBEC, indicating a receptor-mediated phenomenon.

**CONCLUSIONS:** Collectively, these data suggest that S. cerevisiae mannan facilitates human bronchial epithelial repair, possibly via a mannose receptor.

**Funding:** LeBonheur, Accredo and NIH

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**21 Streptomyces cerevisiae 1,3/1,6 Beta-glucan Prevents Airway Hyperreactivity and Pulmonary Inflammation in a Murine Asthma Model**

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**RATIONALE:** Beta-glucans (BG), known immunomodulators, have antitumor activity and reduce post-operative infections. Particulate BG and water-soluble BG have variable immunomodulating effects. We investigated whether oral particulate or water-soluble BG has an effect on a murine asthma model.

**METHODS:** Prior to sensitization, AKR mice were treated with oral BG [particulate 1 mg (P-1), particulate 6 mg (P-6), water-soluble 1 mg(S-1), or water-soluble 6 mg(S-6)] on 5 consecutive days per week for 4 weeks. Treatment continued throughout the sensitization and challenge phase. Sham-treated and naïve mice served as controls. BG-treated and sham-treated mice were sensitized to ovalbumin using our published protocol.

Airway pressure time index (APTI) data was acquired, and bronchoalveolar lavage fluid (BALF) and blood samples were taken.

**RESULTS:** Sham-treated mice showed increased APTI (517.98±27.55, P<0.001) compared to naïve mice (145.74±24.76, P<0.001). BG-treated mice had decreased APTI compared with sham-treated mice [(P-1) 267.86±27.80, P<0.001; (P-6) 284.36±18.76, P<0.001; (S-1)210.46±13.92, P<0.001], with the exception to S-6 mice (524.25±98.35, P = 1). Sham-treated mice BALF content increased total leukocyte counts (15.4 x 10⁵±2.17 x 10⁵, P<0.001) compared to naïve mice (2.2 x 10⁵±0.2 x 10⁵, P<0.001). All treated groups had decreased leukocyte counts in BALF compared to sham [(P-1) 5 x 10⁵±1.18 x 10⁵, P<0.001; (P-6)11.4 x 10⁵±1.8 x 10⁵, P<0.001; (S-1) 3.8 x 10⁵±0.37 x 10⁵, P<0.001; (S-6) 4 x 10⁵±1.5 x 10⁵, P<0.001]. Sham-treated mice had elevated mean percent eosinophils in BALF (20.33±7.1%, P<0.008) compared to naïve (0.1%±0.01%, P<0.008). Percent eosinophils in BALF of treated mice was decreased compared to sham treated mice [(P-1) 3.2±2.9%, (P=0.011; (P-6) 1.3%±0.5%, P = 0.007; (S-1) 2.1%±1.5%, P = 0.006; (S-6) 6.2%±4.2%, P = 0.17]. Splenocytes stimulated with OVA showed increased IL-4 only in cultures from sham-treated mice, while P-1 and P-6-treated mice showed increased IFN-γ compared to sham-treated mice.

**CONCLUSIONS:** 1,3/1,6-glucan prevents airway hyper-reactivity and pulmonary inflammation in a murine asthma model.

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**22 The Effect of Discontinuing Omalizumab Therapy on Free IgE Concentration**

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**RATIONALE:** Omalizumab, an anti-IgE antibody, has proven efficacy in patients with moderate-to-severe and severe persistent allergic (IgE-mediated) asthma.

**METHODS:** We investigated the effect of omalizumab on free IgE levels during and for 16 weeks after 28 weeks’ treatment in a randomized, placebo-controlled trial (INNOVATE study). INNOVATE enrolled patients with inadequately controlled severe persistent allergic asthma despite high-dose ICS plus LABA ± additional controller medication. Omalizumab was administered by subcutaneous injection every 2 or 4 weeks based on baseline IgE and bodyweight using a dosing table to target a free IgE level of ≤50 ng/ml (20.8 IU/ml). A prior population PK/PD stoichiometric model based on free IgE, total IgE and omalizumab was used to simulate the free IgE concentration time course for different cells of the dosing table.

**RESULTS:** 95% (198/209) of omalizumab-treated patients achieved free IgE concentrations ≤50 ng/ml compared with 6% (12/200) for placebo. Target free IgE concentrations were achieved for both the 2-weekly and 4-weekly dosing schedules. Median free IgE ranged from 14.5-18.3 ng/ml. Following discontinuation of therapy, IgE levels rose towards pre-treatment levels. Some patients exceeded the 50 ng/ml efficiency threshold within 4 weeks of the last 2 weekly dosing, or 8 weeks after cessation of 4 weekly dosing. Omalizumab pharmacokinetics, free and total IgE were well fitted by the model. The return of patients’ free IgE to baseline occurred as expected from the PK/PD model.

**CONCLUSIONS:** Upon discontinuation of 28 weeks of omalizumab therapy, free IgE returns towards baseline levels in line with omalizumab reduction.

**Funding:** Novartis Pharma AG
There was a trend toward decreased emotional QOL scores associated with increased child asthma severity (p = 0.007) and increased missed school days (p = 0.001). There was a notable decrease in activity QOL scores associated with increased child asthma severity (p<0.001), increased missed school days (p=0.001), increased emergency room visits (p = 0.001), and number of parents with asthma (p = 0.007).

CONCLUSIONS: Pediatric asthma negatively affects the QOL of caregivers of underserved children with asthma and lower QOL scores are associated with increased asthma related morbidity.

Funding: USPHS Health Disparities Program MD00532-03, MD Cigarette Restitution Fund and Southern CA Asthma and Allergy Foundation

24 Asthma Control Test: reliability, validity, and responsiveness in Korean patients
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RATIONALE: Asthma Control Test (ACT) is a simple, patient-based tool for identifying patients with poorly controlled asthma which has been validated in USA. We evaluated a Korean translation of ACT and sought to evaluate the reliability and validity of the ACT in a longitudinal study of Korean asthmatic patients in the care of an asthma specialist.

METHODS: Patients (n = 117, baseline visit) completed the ACT and the Quality of Life Questionnaire for Korean Asthmatic Adults (QLQA-KA) at multiple physician visits (2-5 visits; 298 total visits, 4-12 weeks apart). Pulmonary function was measured, and asthma specialists rated asthma control.

RESULTS: Internal consistency reliability of the ACT was 0.79 (baseline, n = 117) and 0.74 (total visits, n = 298). Test-retest reliability was 0.77. Criterion validity was demonstrated by significant correlations between baseline ACT scores and baseline specialists’ ratings of asthma control (r = 0.81, P<0.001) and QLQA-KA scores (r = 0.69, P<0.001). Discriminant validity was demonstrated, with significant (P<0.001) differences in mean ACT scores across patients differing in asthma control, pulmonary function, and treatment recommendation. Responsiveness of the ACT to changes in asthma control and lung function was demonstrated with significant correlations between changes in ACT scores and changes in specialists’ ratings (r = 0.72, P<0.001), QLQA-KA scores (r = 0.60, P<0.001), and percent predicted FEV1 values (r = 0.39, P<0.001). An ACT score of 20 or less provided optimum balance of sensitivity (85%) and specificity (93%) for detecting uncontrolled asthma.

CONCLUSIONS: The Korean translation of ACT is reliable, valid, and responsive to changes in asthma control over time in patients under the care of an asthma specialist.

Funding: Clinical Research Center for Chronic Obstructive Airway Disease Grant 0412-CR03-0704-0001 from Korean Ministry of Health and Welfare

25 Self Reported Provider Adherence to NAEPP Guidelines for Control of Factors Contributing to Asthma Severity
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RATIONALE: One of the major components of the NAEPP guidelines stresses the need to identify and reduce exposures to allergens and irritants that exacerbate asthma. Through a self-reported survey questionnaire we attempt to identify physicians’ usage of this component of the guidelines and hypothesize that it is under-utilized.

METHODS: A 28 item one-page survey questionnaire designed for self completion by participants was distributed to Internal Medicine Residents at a primary care clinic.

RESULTS: 40 of 48 residents completed the survey. Only 40% of this study population reported awareness of the NAEPP guidelines. Interestingly however, of the questions recommended by the NAEPP, all residents reported asking about smoking (100%), and most residents about exposure to secondhand smoke (87.5%), seasonal changes (97.5%), the specific season of asthma exacerbation (95%), occurrence of year round symptoms (94.9%), exposure to pets (92.5%), and history of nasal congestion (85%). Residents were also more likely to ask questions regarding exposure to triggers like mold (67.5%), fumes (65%), dampness (62.5%), heartburn (52.5%) and occupational exposures (52.5%) than exposure to cockroaches (42.5%), use of aspirin (37.5%), use of beta blockers (35%), and sulfite sensitivity (20%).

CONCLUSIONS: Awareness of the NAEPP guidelines was found to be sub-optimal. However, residents report asking many of the assessment questions recommended by the NAEPP for control of allergens and irritants in asthmatics. Our study suggests that there is opportunity for further improvement in physicians’ control of factors contributing to asthma severity. Self-reported studies often over-estimate adherence to guidelines and our study may be limited by this.

26 Race, Asthma Exacerbations and Leaving against Medical Advice
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RATIONALE: Leaving against medical advice (LAMA) is a frustrating event for physicians and medical staff and a costly behavior for patients. In asthma exacerbation, this decision by patients can lead to death. This study was to assess the determinants, characteristics and prevalence by race of LAMA in patients admitted for asthma exacerbations.

METHODS: Healthcare Cost and Utilization Project (HCUP) data are used. The study focuses on years 1997-2004 and only 2004 results are reported. Both national and state data are used.

RESULTS: It is found that LAMA is more prevalent in the uninsured (4.4%), low income ($0-35,999) (1.8%), and Medicaid recipients (1.9%). LAMA is highest in young asthmatics (ages 18-44, 4.3%), followed by middle age adults (ages 45-64, 1.7%). The very young (ages <1 and 1-17) and the older adults (ages 65+) have minimal LAMA rates. Males have higher rates than females (1.6%) vs. (1.3%) respectively. The LAMA rates by race were CA (2.8, 1.1, and 1.7), MA (2.4, 1.8, and 1.5), NY (3.26, 3.82, and 1.96), and FL (1.3, 1.7, and 1.5) for blacks, Hispanics, and whites respectively in California, Massachusetts, New York and Florida.

CONCLUSION: LAMA, a marker of non-adherence/noncompliance in hospitalized patients coincides with male gender, young age, uninsurance and poverty (MYUP) and depends on the concentration of the minority population in the US. Educational measures used to combat non-adherence/noncompliance behaviors can be used to help these patients.
27 Use of a Validated Asthma Symptom Questionnaire to Predict Obstructive Flow Volume Loop in School-Aged Children
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RATIONALE: To determine if a validated questionnaire can identify obstructive flow-volume loop (FVL) in grade school children.
METHODS: A group of 170 students, from an urban setting, completed with a parent the 15-item Kids Asthma Check Life Quality Test (KACLQT) prior to a school asthma screening in a mobile asthma unit. FVL and a limited examination were performed. Data were analyzed using a logistic regression model with either the total questionnaire score as a predictor or all individual questions as independent concurrent predictors. FVL results (normal vs. obstructive) was the outcome variable.
RESULTS: 62 children presented with obstructive FVL, 108 with normal FVL. 50% of the children endorsed more than three questions. The obstructive FVL group scored significantly higher on the KACLQT (median score: 5, range: 0-15) than the normal group (median: 3, range: 0-12), p<0.01. Logistic regression analysis revealed a moderate (but statistically significant) increase in risk for obtaining obstructive FVL results associated with a one point increase in the questionnaire score (OR = 1.18, 95% CI: 1.07-1.29, p<0.001). When all 15 KACLQT items were concurrently included as predictors of FVL results, endorsing the question “colds make me cough or wheeze” was the best predictor of obstructive results (OR = 2.2, p = 0.05).
CONCLUSIONS: The questionnaire used in this study is a useful tool for predicting obstructive FVL in children 9-11 years of age. Higher KACLQT scores were associated with increased probability of obstructive results. Endorsing the item “colds make me cough or wheeze” appears to be the best predictor of an obstructive FVL.

28 Real-World Evaluation of Asthma Control and Treatment (REACT): Findings from a National Web-Based Survey
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RATIONALE: Despite health initiatives for advancing management of asthma, evidence suggests that many asthmatics have uncontrolled disease. We assessed the prevalence of, and the risk factors for, uncontrolled asthma in a nationally representative population of moderate-to-severe asthmatics on standard asthma therapy.
METHODS: A web-based survey was administered to a census-representative sample of adult (≥18 years) moderate-to-severe asthmatics diagnosed with asthma for at least one year and currently receiving multiple controller medications. The Asthma Control Test (ACT) was used to stratify respondents into controlled (score 20-25) and uncontrolled (score 5-19) cohorts. Multivariable analysis identified independent risk factors for uncontrolled asthma.
RESULTS: A total of 1,812 patients were evaluated; 809 (45%) had controlled asthma and 1,003 (55%) had uncontrolled asthma. The majority of patients had healthcare coverage (88% of controlled, 86% of uncontrolled; P = NS) and received care from a general practitioner for their asthma; however, a large proportion of controlled (74%) and uncontrolled (65%) patients reported never receiving an asthma action plan. Inhaled corticosteroid plus long-acting beta-agonist was the most common medication regimen used in controlled (60%) and uncontrolled patients (48%). Uncontrolled patients reported significantly higher rates of healthcare utilization. Gastroesophageal reflux disease, chronic sinusitis, and high blood pressure were predictive of uncontrolled asthma.
CONCLUSIONS: Uncontrolled asthma is highly prevalent (55%) in patients on standard asthma therapy. Our results support the need for a more global evaluation of asthma control, assessment of comorbid conditions, and alternative therapies for patients with difficult-to-control asthma despite guideline-based treatment.
Funding: Funded by Genentech, Inc., and Novartis Pharmaceuticals Corp.

29 Keeping Asthmatics Out of the Emergency Department and Hospital: Evidence for Asthma Controller Medication Usage for Intermittent Asthmatics
RATIONALE: Novel approaches are needed to decrease asthma-related emergency department (ED) visits and hospitalizations.
METHODS: Complete pharmacy and diagnostic coding records from 109,774 asthma patients were analyzed. Subjects were stratified into two asthma severity categories (intermittent or persistent) based on pharmacy utilization data in 2002, and tracked for occurrence of outcome events (ED visits or hospitalizations for asthma) in 2003.
RESULTS: Of the 4070 subjects with an outcome event, 2022 (49.7%) were classified as intermittent asthmatics, as defined by low usage of asthma controller and reliever medications during the stratification year. Of 5281 total outcome events, 2341 (44.3%) occurred in patients with intermittent asthma. Within this group, patients with a previous history of ED visit or hospitalization were at eight-fold greater risk for an outcome event compared to those with no history of prior emergency hospital event (p < 0.0001). Prescription of asthma controller medication in the previous year was associated with reduced risk of outcome events in the next year. The effect appeared to be greater for those with a previous history of emergency hospital event (O.R. 0.68, CI.0.57-0.81) than for those with no previous history of emergency hospital event (O.R. 0.79, CI.0.73-0.86).
CONCLUSIONS: Patients with intermittent asthma, as defined by low pharmacy utilization for asthma, account for a substantial proportion of overall asthma-related emergency hospital events. Reduction of future emergency hospital utilization can be achieved by prescribing asthma controller medications to these patients, with the greatest impact seen in patients with a history of previous ED visit or hospitalization.

30 Childhood Asthma Control Test: Reliability, Validity And Responsiveness
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RATIONALE: Presently available assessment tools can not full-fill the quick and easy measurement for the degree of asthma control and outcome correctly in children.
METHODS: We used a 7- items questionnaire, Childhood Asthma Control Test (CACT), to assess asthma symptoms (daytime and nocturnal) on daily function in totally 150 asthmatic children age between 4-11 yrs enrolled from three hospitals around Tainan area. All enrolled children received at least twice outpatient visits and evaluation separately from 4-8 weeks (the baseline visit and follow up visit).
RESULTS: The CACT at baseline showed significant correlation with physician scores (PT) (r = 0.555, P<0.05) except in predicted PEFR percentage (r = -0.036, P = 0.723). PT also showed no significant correlation with PEFR predicted value (r = 0.175, P = 0.086). The mean childhood ACT was 21.9 (SD, 3.7) with ranges 9 to 27 for intermittent group and persistent group revealed 19.2 (SD, 4.3) ranging from 5 to 27 (P<0.01). The mean PT among intermittent group was 21.4 while 18.3 among persistent group (P<0.01). The internal consistency reliability of the CACT survey was 0.78 (n = 112) at the baseline, and 0.78 at the follow-up visit (n = 76). The test -retest reliability among 76 patients with the same specialist rating of asthma control at the baseline and follow-up visits was r = 0.413 (p<0.001). CACT scored of patients whose therapy needed to stepped up were significantly lower than patients with no change in therapy or with stepped-down therapy (P = 69.8, P< 0.001).
CONCLUSIONS: Childhood ACT is reliable, valid, and responsive to changes in asthma control over time.
31 Achieving and Maintaining Control of Asthma with Regular Participation in an Urban Pediatric Disease Management Program: The Breathmobile® Program
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RATIONALE: National guidelines suggest that, with appropriate care, most patients can control their asthma. This study evaluates the degree to which children in a lower socioeconomic urban setting achieve and maintain control of asthma with regular participation in a disease management program that provides guideline-based care.

METHODS: Interdisciplinary teams of asthma specialists use mobile clinics to offer ongoing care at schools and county clinics. A guideline-derived construct of asthma control is recorded at each visit.

RESULTS: 2185 enrollees were eligible to evaluate the time to first achieve control, while 1591 patients were eligible to evaluate subsequent control maintenance. Depending on severity, 70-87% of patients with persistent asthma achieved control by visit 3, and 89-98% were controlled by visit 6. Subsequent control maintenance was highly variable. 39% of patients displayed well-controlled asthma (control at >90% of subsequent visits) while 13% displayed difficult to control asthma (<50% of subsequent visits). Patients from each baseline severity category were found in each group. Maintenance of control was influenced by physician-estimated compliance with the treatment plan, baseline severity, and the interval between clinic visits.

CONCLUSIONS: Many children can achieve asthma control with regular visit intervals and guideline-based care, however long term control can be highly variable among patients in all severity categories. These findings highlight the need, and feasibility, for systematically tracking each patient’s clinical response in order to individualize therapy and guide the use of population management strategies.

Funding: Southern California Chapter of the Asthma and Allergy Foundation of America, Genentech, Merck

32 Implementation of GINA Guidelines in Poor Countries May Have Resulted in an Unnecessary Expenditure on Pharmacotherapy
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RATIONALE: Wheezing episodes (WEs) are common in school children with persistent asthma (PA) and asthma induced by viral infections (VA). GINA’s guideline encourages the chronic use of controller medication in PA, but omits recommendations for VA. As in poor Peruvians WEs are mild and are not associated to atopy, we estimated the cost of GINA’s omission.

METHODS: Based on two previously published RCT, WEs in VA (Doull, BMJ 1997) and WEs in PA/CAMP, NEJM 2001; we estimated the number of emergency room visits and hospitalizations prevented per 100 children treated per year. Market price of medications and services were included in the analysis.

RESULTS: In Peru, the cost of inhaled corticosteroid per 100 children per year is $48,000 dollars. In the most likely scenario (WEs by VA): no single benefit would be obtained for the money spend. In the least likely scenario (WEs in PA): ten urgent care visits ($25.00 each) and two hospitalization ($350.00 each) would be prevented. The $750 saved on resources corresponds to 2% of the amount spent on chronic treatment.

CONCLUSIONS: GINA guideline lacks recommendations for WEs induced by viral infections. Public health interventions based on GINA guidelines in poor populations, where WEs are mostly induced by viral infections, do not favor societal interests. GINA’s omission must soon be corrected.

33 No Correlation Between Airway Obstruction Measured by FEV1/FVC and Asthma Control Test Scores
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RATIONALE: Asthma symptoms do not correlate significantly with airway obstruction measured by FEV1 or PEF. In recent years, the Asthma Control Test (ACT) has been validated as a tool for identifying patients with poor control. The ratio of FEV1 to FVC has been described as a potentially more sensitive indicator of expiratory flow limitation (Chest 2006;129:369). We studied associations between symptoms and lung functions to confirm previously reported low correlation and to determine if ACT correlates better with FEV1/FVC.

METHODS: We retrospectively analyzed visits with complete ACT scores and spirometric data (FEV1 and FEV1/FVC) from January-June 2006. Scatterplots were constructed and Spearman’s correlation coefficients were calculated. Patients with ACT scores >15 and FEV1 < 60% were classified as poor perceivers.

RESULTS: There were 295 visits for 236 asthma patients with mean age 47; of these 73% were female, 70% Caucasian, 28% had severe asthma; <5% were poor perceivers. ACT scores and spirometric values correlated poorly: FEV1 % predicted (0.28) and FEV1/FVC (0.08). Severe asthma subjects had slightly higher correlations of ACT scores with FEV1 % (0.16-0.37). Daytime and nocturnal symptoms, rescue medication use, limitations on everyday functioning or self rating of asthma control were not significant predictors of spirometric measurements. Adjusting for age, sex, race, and asthma severity, associations remained extremely weak.

CONCLUSIONS: We confirmed previous findings of low correlation between ACT scores and FEV1 in a population of <5% poor perceivers. There was no correlation between ACT scores and FEV1/FVC. These results support the contention that symptoms and spirometric measures are independent dimensions of asthma and proper management requires assessment of both.

Funding: William Wagner Memorial Research and Education Fund

34 Does A WwB-based Interactive Computer Program change asthma Outcomes, Quality of Life and Asthma Knowledge
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RATIONALE: In 2001 we gained financing for our project www.astamcenter.dk., which is an internet based, interactive asthma program. The purpose of this was to enhance children’s knowledge of asthma, self-management of asthma, quality of life and to reduce asthma morbidity and health costs.

Was there a difference between a group of asthma children allocated to this interactive program and a similar group of asthma children allocated to a program with the same asthma information but without the interactivity feasibility.

METHODS: 83 asthmatic children between ages 6 and 14 were randomly allocated to either the interactive or the non-interactive program. Two visits one year apart were scheduled. Peak-flow and forced expiratory volume in one second (FEV1) was recorded. A Quality of Life questionnaire and a questionnaire about asthma knowledge was completed. Information on number of admissions to hospital, visits to the emergency room (ER) and unscheduled visits to general practitioners (GPs) during the year prior to each visit were obtained.

RESULTS: 81 children completed the study. No differences between the two groups were found concerning peak-flow (P = .29) , FEV1 (P = .72), Quality of Life (P = .19), GP contacts, hospitalisation or ER-visits (P = .22). The knowledge of asthma improved (P = .000).

CONCLUSIONS: The present study includes only a small group of probably selection-biased children and the results are therefore merely indicative. The results might be explained by the fact that all the children had already received good medical treatment and were well informed about asthma.

Funding: The County of North Jutland
CONCLUSIONS: The addition of OMA improved control in adolescents with moderate-severe persistent IgE-mediated asthma.
Funding: Novartis Pharmaceuticals Corporation

37 Assessment of Asthma Control in a United States Population
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Rationale: Asthma control has been recently introduced as a method to assess the adequacy of current treatment and inform asthma management. The purpose of this study is to measure asthma control using the Asthma Control Test (ACT) in a population of adult asthma sufferers and evaluate the level of control by age, gender, and region.
Methods: A patient education website to assess asthma control (www.asthmacontrol.com) was previously developed. Respondents completed the ACT and provided age, gender, and region. ACT is a self-completed, validated tool for patients 12 years and older. ACT scores <15 may indicate uncontrolled asthma within a scoring range of 5-25. Descriptive statistics and logistic regression were performed.
Results: In a sample of 2,425 adults, 66% were female, mean age of 38 years, 24% in Midwest, 13% Northeast, 40% South, and 23% West. The mean ACT score was 12 in 91% of subjects suggesting that the majority were uncontrolled. The mean ACT score was lower for women than men (12 v. 13). Males had a lower probability of uncontrolled asthma when compared to females (OR = 0.69; 0.519 - 0.918). ACT scores did not vary by region.
Conclusions: These national, real-world data demonstrate that asthma is inadequately controlled, particularly in women, and does not vary by region. These data correlate with other studies demonstrating higher morbidity and mortality in women. These findings strongly suggest a need for future asthma management strategies targeted towards improvement of asthma control.
Funding: GlaxoSmithKline

38 Risk Factors for Asthma-Related Emergency Hospital Utilization Differ Between High and Low Users of Asthma Medications
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Rationale: Patterns of asthma medication use vary widely among patients seen in the emergency department (ED) for asthma. We examined risk factors for emergency hospital utilization among patients with a history of high versus low usage of asthma medications.
Methods: Complete pharmacy and diagnostic coding records from 109,774 asthma patients (age 5-56) were analyzed to determine risk factors for asthma-related emergency hospital events among high and low users of asthma medications. High utilizers (HU) received 4 or more canisters of asthma medication during the stratification year; the remaining subjects were classified as low utilizers (LU). Subject stratification and risk factor analysis was performed using year 2002 data, outcome events (asthma-related ED visits or hospitalizations) were measured in year 2003. Odds ratio (OR) were statistically significant if the p value < .05.
Results: Risk factors for asthma-related emergency hospital utilization that were common to both HU and LU included prior emergency hospital utilization (OR 7.83 and 9.34 respectively) and beta-agonist usage (OR 1.06, 1.55). Female sex (OR 1.26), and oral corticosteroid use (OR 1.36) were risk factors only for HU. Use of asthma controller medications was associated with reduced outcome risk in LU (OR .76) but not in HU (OR 1.00).
Conclusions: Risk factors for asthma-related emergency hospital utilization differ between high and low users of asthma medications. Use of asthma controller medication is associated with reduced outcome risk in LU, but not in HU. Female sex is linked to increased outcomes in HU only.
Change (A) in Percent Forced Expiratory Volume in the First Second (FEV1) in 10 patients on Omalizumab Over 23 Months

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RATIONALE: To determine if, and when, there is a plateau in FEV1 following initiation of omalizumab.

METHODS: Retrospective review of omalizumab patients (n = 19) (Age range:12-18) with >2 FEV1s after initiation of omalizumab (9 patients excluded). Change in % FEV1 was generated for patients meeting inclusion criteria (n = 10; 5M/5F) by comparing each patient’s % FEV1 immediately preceding initiation of omalizumab to % FEV1s obtained over a 23 month study period following initiation of therapy. Spirometry was obtained (Kokomax), and graphs were generated to plot change of percentage of FEV1 vs. time. FEV1s obtained while on concomitant oral steroids were excluded.

RESULTS: Average time on omalizumab per patient: 19.7 months. Range of % FEV1 prior to initiation of omalizumab: 51-129. Average increase in FEV1 was 0.92% (0.017L/mo) per month. Average total FEV1 increase of 0.384L per patient per study period. No plateau in FEV1 was appreciated throughout the 23 month study period.

CONCLUSIONS: This pilot study demonstrates that our patients on omalizumab following initiation will not achieve maximal FEV1 improvement. This illustrates that patients stopping omalizumab prior to 23 months following initiation of therapy will not achieve maximal FEV1 improvement. Additional studies are required to determine if, and when, FEV1 plateaus subsequent to treatment with omalizumab.

Pulmonary Function Test Values Predictive of Success in Decreasing Inhaled Corticosteroid Doses in Asthmatics: A Chart Review

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RATIONALE: Maintaining asthma control at the minimal effective inhaled corticosteroid (ICS) dose is a goal of asthma therapy.

METHODS: A retrospective chart review was performed on patients who had been prescribed a reduction in ICS and who had returned for re-evaluation within 90 days. Various spirometric parameters were correlated with the success or failure of the patient to tolerate the decreased ICS dose as assessed at the follow up visit.

RESULTS: Forty-two patients met the criteria for inclusion in this study with data dating from 2000 to 2006. Twenty-seven (27) patients tolerated the dose decrease, while fifteen (15) patients did not. Using the Chi Square test, several spirometric parameters measured at Visit 1 pre-dose reduction were predictive of tolerating the ICS reduction as follows: An FEV1/FVC ratio of ≥100% predicted, p = 0.039; an FEV1 25-75% predicted of ≥90% predicted, p = 0.022; and an FEV1 25-75% predicted that was greater than the FEV1 % predicted, p = 0.033. FEV1 % predicted values did not significantly predict outcomes after ICS dose reduction.

CONCLUSION: Careful attention to the FEV1/FVC ratio and FEV1 25-75 as they compare with predicted values and to the relationship between the FEV1 and FEV1 25-75 may help to identify patients for whom ICS dose reduction may be appropriate and well tolerated.

Evaluation and Standardization of Enzyme-Linked ImmunoSpot (ELISPOT) Assay for Measurement of Pathogen-Specific T-cell Responses in Normal Donors

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RATIONALE: Methods for evaluation of cell-mediated immune responses are essential for understanding immunopathology, developing intervention strategies against old and emerging pathogens, as well as for clinical decision-making in treatment of compromised immunity, recurrent infections, and critical illness. The goal of this study was to evaluate immune responses to a recall antigen panel in normal donors using ELISPOT assay.

METHODS: Peripheral blood mononuclear cells (PBMC) from 21 normal donors were evaluated for reactivity to common recall antigens (tetanus toxoid, Candida albicans, cytomegalovirus (CMV), tuberculosis PPD, mumps, and varicella zoster virus (VZV)), and a CEF (CMV, EBV, and influenza) peptide mixture using IFNγ ELISPOT assay. Samples were tested in triplicate and results were reported as a number of IFNγ secreting cells (spot forming cells, SFC) per 300,000 PBMC over background. Responses to CMV, mumps, and VZV were also characterized by ex-vivo stimulation followed by cytokine analysis.

RESULTS: Donors demonstrated distinct patterns and levels of antigen recognition, which were highly reproducible from day to day. Most donors reacted to mumps (95% of donors responded, average 126 SFC) and VZV (81%, average 73 SFC). CMV induced the highest level of reactivity (62% responded, average 443 SFC). Positivity thresholds for each pathogen were calculated using 2 SdCutoff above the average value for negative donors. ELISPOT results correlated with ex-vivo IFNy measurements (Spearman rank r = 0.81, 95% CI: 0.52-0.94).

CONCLUSIONS: The ELISPOT assay is an excellent tool for evaluation of low frequency pathogen-specific T-cell responses. Positivity thresholds determined for recall antigens are useful for evaluation of cell-mediated immunocompetence and for vaccine development.

ComéJ-Netherton Syndrome - New Insight Into The Molecular Basis of this Rare Syndrome Characterized by Atopic Diathesis and Immune Deficiency

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ComéJ-Netherton syndrome (NS) (OMIN: # 256500) is a autosomal-recessive inherited disease characterized by congenital ichthyosis, bamboo hair, and atopic diathesis. Associated recurrent infections have been recognized, but the immune system of NS patients hasn’t been extensively investigated. Mutations in the gene SPINK5 encoding a serine-protease inhibitor, called LEKTI, have been shown to cause NS. LEKTI is mainly expressed in epithelial cells of skin, mucosa, and thymus with hypothesized function in matrix and immune modulation.

We report seven patients who presented with classic NS phenotype. All patients had recurrent skin infections and presented with upper and lower respiratory tract infections and gastroenteritis. Mutations in the gene SPINK5 were found in six of the seven patients. Protein expression was altered by immunohistochemistry in buccal-mucosa and/or skin in all patients. Patients did not respond well to anti-allergic treatment, but those treated with immunoglobulin replacement showed significant improvement of their clinical course. Immunologic evaluation revealed abnormal responses to bacterial phospho- phiX174 including impaired class-switching and memory amplification; serum immunoglobulin levels, lymphocyte proliferation and B-cell-immunophenotyping showed only minimal alterations. Interestingly, effector CD8 cells were significantly elevated in most patients and cytokine/chemokine assessment showed an increase in the serum concentration of pro- and anti-inflammatory markers suggesting a generalized immunedysregulation of unknown mechanism. Protein function analysis is in process and might explain details about allergy and immuneregulation. We would like to define NS as a multisystem disorder with immunedysregulation and defects in specific antibody production caused by decreased expression of LEKTI resulting in altered extracellular matrix in the affected structures.

Funding: NIH
43 European Consensus for Gynecological and Obstetric Management of Women with Hereditary Angioedema due to C1-Inhibitor Deficiency (HAE): PREHAEAT

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RATIONALE: A lack of literature about handling of gynecological/obstetric problems in female patients with HAE has been observed.

METHODS: This consensus was elaborated by the European Working Group on C1 INH deficiency (PREHAEAT) and represents a consensus among clinicians specialized in dealing with HAE in major European centers, with assessment of a gynecologist with experience in HAE (de Carolis C). It is based on a full review of literature, on PREHAEAT work package o 5 (Bouillet L) and on expert experience.

RESULTS: Long term treatment with attenuated androgens: Specific side effects in women include menstrual irregularities and masculinization. Contraception: Estrogens should be avoided. Progesterone-only pills, intrauterine device and condom are preferred.

Pregnancy: The potential for masculinization of a female fetus contraindicates the use of attenuated androgens in pregnancy. If possible, therapy should be discontinued before conception. Tranexamic acid or human C1 inhibitor concentrate (hC1INH) could be used.

Parturition: Complications of C1INH deficiency are rare in vaginal delivery. Prophylactic transfusion of hC1INH during labor and delivery does not appear warranted, but hC1INH should be available in the delivery suite. Nevertheless, individual approach should be taken according to HAE activity. hC1INH prophylaxis is advised if forceps or vacuum extraction is necessary.

Caesarean (abdominal delivery): Regional anesthesia is preferred to endotracheal intubation. hC1INH prophylaxis is necessary.

Breast cancer: Avoid attenuated androgens.

Other issues addressed: lactation, amniocentesis, abortion, menopause treatment, infertility, ¼.

CONCLUSIONS: A consensus which seeks to further assist clinicians in the management of female patients with hereditary angioedema is presented.

Funding: European Commission. Concerted Action. QLRT-CT-2002-01359

44 Tolerance To Allogegenic Thymus Transplantation In Complete DiGeorge Syndrome

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RATIONALE: Assess long-term tolerance to transplanted allogegenic thymus tissue in patients with complete DiGeorge syndrome.

METHODS: Six subjects with DiGeorge syndrome and athymia were given allogeneic postnatal cultured thymus transplants in the first year of life. No HLA matching to the thymus tissue was present in one subject; partial matching was seen in the others. The subjects were assessed at different times after transplantation by mixed lymphocyte cultures for allograft reactivity against thymus donor peripheral blood mononuclear cells (PBMCs) or cryopreserved donor thymocytes. Long-term thymic function was followed by evaluating both naïve T cell (CD3+CD45RA+CD62L−) production and T cell proliferation to the mitogen phytohemagglutinin (PHA) and to tetanus toxoid antigen.

RESULTS: All subjects had markedly less T cell proliferation against thymus donor PBMCs and cryopreserved donor thymocytes versus controls in mixed lymphocyte cultures performed at 11 to 70 months post-transplantation. No association was observed between tolerance to the thymus tissue and the degree of HLA matching (recipient to donor). All subjects had full long-term T cell reconstitution, seen by increasing naïve T cell numbers and the development of normal T cell proliferative responses to PHA and tetanus toxoid.

CONCLUSIONS: Tolerance to allogeneic thymus tissue is present in subjects with complete DiGeorge syndrome after thymus transplantation. HLA matching is not required for such tolerance. Both tolerance to the thymus tissue and excellent thymic function are maintained long-term in these subjects.

Funding: 2006 American Academy of Allergy, Asthma, & Immunology 3rd Year FIT Research Award; National Institutes of Health

45 Development Of A Newborn Screening Test For Severe Combined Immunodeficiency Using ELISA And Dried Blood Spots

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RATIONALE: Early detection of infants with SCID improves outcomes and survival rates. A PCR-based test for SCID has been developed, but lacks adequate specificity alone. A second-tier test would improve the accuracy of SCID screening. Due to abnormal T-cell development, patients with untreated SCID have higher levels of IL-7, and may also have higher levels of IL-15. We investigated the use of these cytokines in newborn SCID screening.

METHODS: Samples were obtained from healthy adults, blotted cards from the state of Texas newborn screening program, and individuals with treated and untreated primary immunodeficiencies. Using commercially available ELISA kits, IL-7 and IL-15 levels were measured in 1) plasma, 2) dried plasma spots, and 3) dried blood spots. Spiked samples were used for measurement of IL-7 and IL-15 decay. For correlation, plasma samples were compared to dried blood spots from the same individuals.

RESULTS: IL-7 is recoverable from blotted samples, but has a half-life of 18 days. Higher concentrations of IL-7 will be more affected by IL-7 instability, and may result in reduced screening sensitivity. IL-15 can also be detected in dried blood spots, but hemolysis adversely affects the detection sensitivity. Strategies for avoiding the interference from hemolysis are explored.

CONCLUSIONS: Dried blood spots can be used to measure cytokine levels as an initial newborn screening test for SCID. The half-life of IL-7 may not have sufficient stability to be reliable unless samples are assayed shortly after collection. IL-15 is a possible alternative, but requires further verification with SCID patients and avoidance of hemoglobin contamination.

Funding: American Academy of Pediatrics, National Institutes of Health
METHODS: NK cells and NK cell lines were control treated or treated with varying doses of Wiskostatin with or without additional cell activation. Filamentous actin content was determined by flow cytometry after staining with AlexaFluor-647-conjugated phalloidin. Cytotoxicity against EBV-transformed MHC-class I negative B cells was evaluated using 51Cr release assays. IFN-gamma production from target cell stimulated NK cells was evaluated by ELISA.

RESULTS: High concentrations of Wiskostatin were toxic to NK cells. Viability was maintained in moderate concentrations of Wiskostatin and resulted in loss of cytotoxicity as well as activation-induced increases in filamentous actin content. Lower concentrations of Wiskostatin were also effective in inhibiting IFN-gamma production.

CONCLUSIONS: Wiskostatin is a reasonable tool for studying the mechanism of WASp inactivity in NK cells because it effectively mimics the WAS phenotype in NK cells in vitro. Additional mechanistic assessments of Wiskostatin specificity and comparison to WASp deficiency are ongoing.

Funding: University of Pennsylvania, NIH A155062

47 Defective Pneumococcal Polysaccharides-induced Cytokine Production in Common Variable Immunodeficiency
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RATIONALE: Common variable immunodeficiency (CVID) is associated with defective specific antibody response to pneumococcal polysaccharides. Streptococcus pneumoniae stimulates monocytes to induce production of cytokines, which can stimulate B cell differentiation and antibody production. Therefore, we hypothesized that decreased specific antibody response in CVID may be due to a defect in pneumococcal polysaccharides-induced cytokine production.

METHODS: Peripheral blood mononuclear cells (MNCs) from patients with CVID (n = 14) and healthy matched controls (n = 13) were cultured in vitro in the absence or presence of various concentrations of Pneumovax-23 vaccine or LPS (positive control) for 24 hours and supernatants were analyzed for IL-1β, TNF-α, IL-6, and IL-10. Since all these cytokines are produced by B cells, T cells and monocytes, these subsets were purified to determine the source of above cytokines. Statistical analysis was performed by the Mann-Whitney test and the Kruskal-Wallis test.

RESULTS: MNCs from patients with CVID produced significantly lower levels of Pneumovax-23-induced IL-6 (p = 0.043) and TNF-α (p = 0.03). Cytokines were produced by monocytes; neither B cells nor T cells in healthy controls or CVID produced detectable levels of cytokines.

CONCLUSIONS: Patients with CVID demonstrate a defect in pneumococcal polysaccharide-induced monocyte-derived cytokine production, which may play a role in poor specific antibody responses in CVID. Signaling pathways (TLRs) to understand the mechanisms for this defect are currently under investigation.

Funding: University of California, Irvine

48 Helicobacter pylori Infection As A Triggering Factor Of Attacks In Patients With Hereditary Angioedema
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RATIONALE: Helicobacter pylori infection is considered among the causative factors of urticaria and angioedema. Having conducted a study on 65 patients, Hungarian authors reported in 2001 that successful eradication of H. pylori is followed by a significant reduction in the number of attacks in patients with hereditary angioedema (HAE).

METHODS: Within the framework of the PREHAEAT project launched by the EU, further 152 patients were studied in seven collaborating centers, and participants of the earlier study were followed up in order to detect any relationship between H. pylori infection and the occurrence of attacks in HAE patients.

RESULTS: Nine subjects of the previous Hungarian study who underwent eradication therapy for dyspepsia were followed up for an additional 4 years. In these patients, attack frequency remained consistently low. The proportion of patients experiencing frequent (≥5/year) abdominal attacks was higher (p = 0.002) among the H. pylori infected participants of the international study who underwent eradication as compared to the rest of patients. Successful eradication of H. pylori significantly (p = 0.001) reduced the number of attacks in these patients as well.

CONCLUSIONS: As shown by experience from the Hungarian and the international trial, the number of frequent, edematous abdominal attacks may decrease substantially following the eradication of H. pylori from HAE patients infected with this pathogen. Therefore screening of HAE patients for H. pylori infection seems warranted. Eradication of H pylori may lead to a marked improvement in quality of life.

49 Genetic Analysis of Autosomal Dominant Common Variable Immunodeficiency
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RATIONALE: Common Variable Immunodeficiency (CVID) is an acquired hypogammaglobulinemia occurring by immune dysregulation resulting in impaired secretion of immunoglobulins. CVID may present itself with different inheritance patterns. We report a kindred of 11 affected members spanning 2 generations.

METHODS: A total of 14 siblings and a father of one family unit were evaluated for CVID. Serum immunoglobulin, IgG subclasses, antibody responses and lymphocyte enumerations were performed commercially. The serum was sent for further testing including flow cytometry, lineage analysis, genotyping, and co-stimulatory testing.

RESULTS: Eleven of the 15 family members met the criteria for CVID based on laboratory data. Each affected family member presented differently within the wide spectrum of CVID. Three of the children needed IVIG infusions. Chromosome number 3q is the likely site of the genetic defect. Initially both CD80 and CD86 were of great interest in this kindred of CVID, however, flow cytometry analysis proved to demonstrate the defect lies in a different region. Additional genotyping and linkage analysis is ongoing.

CONCLUSIONS: We report the largest familial pedigree afflicted with CVID. With results from genetic analysis of this family the following conclusions were made. The family was excluded from the chromosome 4q mutation from D4S405 to D4s 1652 and excluded from links to the chromosome 116q locus between D16S12621. This family is also unlikely to suffer from TACI deficiency since neither D17S122 nor chromosome 17q is the likely site of the genetic defect. Initially Both CD80 and CD86 were of great interest in this kindred of CVID, however, flow cytometry analysis proved to demonstrate the defect lies in a different region. Additional genotyping and linkage analysis is ongoing.

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SATURDAY
**50 Role of Toll-like Receptor Signalling Defects in Human Susceptibility to Invasive Infection by Streptococcus Pneumoniae**

S. E. Turvey, A. F. Hirschfeld, R. E. Victor; Children’s Hospital and University of British Columbia, Vancouver, BC; CANADA.

**RATIONALE:** Defective Toll-like receptor (TLR) signalling, due to IRAK4-deficiency and ectodermal dysplasia with immunodeficiency (EDA-ID), greatly enhances human susceptibility to pneumococcal infection. Nevertheless, the importance of TLR signalling defects in a larger population of children with invasive pneumococcal infections remains unclear. Should all children with invasive pneumococcal infection be assessed for abnormal TLR function?

**METHODS:** We developed and optimized a peripheral blood TLR assay that readily identified patients with TLR defects resulting from IRAK4-deficiency and X-linked EDA-ID. We studied TLR function in population predicted to be enriched for TLR defects—healthy children who had developed invasive pneumococcal infection without classic risk factors for infection.

**RESULTS:** By testing 36 healthy control neonates, children and adults we demonstrated that TNF-α and IL-6 most accurately report human TLR function and that TLR function was stable over the first six-decades of life. We tested 50 children with a history of invasive pneumococcal infection and although TLR defects were predicted to be over-represented in this population, we did not identify any TLR abnormalities.

**CONCLUSIONS:** Although TLR signalling defects are associated with greatly enhanced susceptibility to invasive pneumococcal infection, our results suggest that routine clinical screening for TLR defects in healthy children who develop invasive pneumococcal infection is not justified.

**Funding:** CIHR and SickKids Foundation

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**51 Guidelines for “10 Warning Signs of Primary Immunodeficiency” Neither Sensitive Nor Specific**

F. P. Aloi, S. S. Mishra, A. J. MacGinnitie; Children’s Hospital of Pittsburgh, Pittsburgh, PA.

**RATIONALE:** Primary immunodeficiency (PID) is rare, but can lead to significant morbidity and mortality, especially if left undiagnosed. It is often challenging to identify which patients need to be evaluated for PID. Guidelines emphasizing “10 Warning Signs of PID” have been promulgated, but are based solely on expert opinion. We sought to validate the “10 Warning Signs of PID” from the Modell Foundation. We also investigated the relationship between documented IgE-mediated allergy and PID.

**METHODS:** A retrospective analysis of 130 consecutive outpatient charts from university affiliated pediatric tertiary care Allergy and Immunology Clinic was undertaken. Records were evaluated for meeting one or more of the “10 Warning Signs”, documented IgE-mediated allergy based on skin prick testing or IgE RAST, and immunologic work-up and diagnosis.

**RESULTS:** Of the 130 charts studied 40 patients had documented immune deficiency. The sensitivity of the “10 Warning Signs” is only 56% (95% CI 41.4-69.7%) and the specificity is 16.3% (95% CI 9.3-26.6%) if one of the ten warning signs were met. If meeting the criteria for two or more warning signs was used as a screen, sensitivity was 27.5% (95% CI 15.1-44.1%) and specificity was 77.8% (95% CI 67.5-85.6%). The presence of an IgE-mediated allergy carried a 63% relative risk reduction for having a PID, but several patients with PID also had allergic sensitization.

**CONCLUSIONS:** The “10 Warning Signs of PID” are neither sensitive nor specific for PID, as one-third of patients in this series did not meet a single warning sign. Diagnosing an IgE-mediated allergy does not exclude PID. However, in some patients referred for an immunologic evaluation, diagnosing and treating an IgE-mediated allergy maybe a practical initial step.

**Funding:** CIHR and SickKids Foundation

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**52 Reimbursement Driven Medicare Patients Receiving IVIG in the Hospital vs. the Physician’s Office**

M. Eagan, R. W. Hostoffer, Jr; Lake Erie College of Osteopathic Medicine, Erie, PA; Case Western Reserve University, Cleveland, OH.

**RATIONALE:** Intravenous immune globulin (IVIG) therapy is an important part of the treatment process for certain immunodeficiency conditions. The recent change in the reduction in Medicare reimbursements for IVIG and the increased prices of IVIG have resulted in patients not being able to provide IVIG treatments to Medicare patients in their office. This has obligated patients to go to hospitals to receive their treatments.

**METHODS:** We have developed a questionnaire comprised of 16 questions asking about the way infusion treatments are being given in the hospital compared with the office and inconveniences imposed on patients due to these changes. 19 Medicare patients have been interviewed by telephone.

**RESULTS:** The majority of patients said that there were no benefits of going to the hospital for treatment rather than the office and most preferred to be able to go back to the office. Overall patient dissatisfaction was immense for receiving treatments at the hospital due to various reasons. The most common concerns patients had were the long hours in the hospital, exposure of serious illnesses in which immunocompromised individuals do not prefer and affects their quality of life which they strive for, not being able to see the Doctor at each infusion visit like they used to, and there is actual increase of cost for Medicare and the health system.

**CONCLUSIONS:** This data suggests that the present state of reimbursements for IVIgG have adversely affected the Medicare patients. The data will be further summarized and presented to governmental officials.

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**53 Hypo-IgM Syndrome: A Secretion Defect?**


**RATIONALE:** Hypo-IgM syndrome has an incidence of 0.03% in the general population. Little is known about the mechanism of disease. We have addressed this mechanism by examining a child with this syndrome.

**METHODS:** We present a case of an eleven-year-old boy with history of mild-asthma and an incidental lab finding of low IgM. His father also has a low IgM of 28 mg/dL (normal 56-352). However, 11 other relatives have normal serum IgM. The patient had been healthy without recurrent infections. T- and B-cell mixing studies were performed. The child’s and mother’s T- and B-cell enriched cell fractions were obtained by e-rosetting, mixed, and stimulated with Pokeweed (PWM) for six days. CD19+ blasts were surface-stained for IgG and IgM and analyzed by FACScan.

**RESULTS:** PWM and Phytohemagglutinin proliferation indices were normal. However, the Concana-valin A response was decreased. Mixing maternal T-cells with the child’s B-cells produced 69% IgM+ and 27% IgG+ IgG+ IgM+ CD19+ blasts. Identical results were obtained by mixing the child’s B-cells with his own T-cells. However, the child’s T-cells mixed with maternal B-cells produced only 33% IgM+ and 57% IgG+ IgG+ IgM+ CD19+ blasts. Mother’s T-cells mixed with her B-cells also showed similar results (36% and 54% respectively).

**CONCLUSIONS:** We present a case of a child with hypo-IgM whose B-cells preferentially express surface IgM immunoglobulin only when stimulated with PWM in the presence of either autologous or HLA haplo-identical T-cells. This suggests that IgM expression in this patient is an intrinsic B-cell defect.
54 Allergic Reaction and Anaphylaxis to IVIG when Administered Through Bromobutyl Vial Closure.

M. Solomon, R. W. Hostoffer, Jr.; Case Western Reserve University Cleveland, OH.

RATIONALE: Medication vial closures have been thought to cause reactions in latex sensitive individuals. Limited reports have attributed anaphylactic reactions to trace amounts of denatured proteins present in natural rubber vial closures. Bromobutyl closures have been substituted in several IVIgG products with no reported case of anaphylaxis with subsequent puncture. We report two cases of allergic reactions occurring during the infusion of intravenous immunoglobulin (IVIg) after dispensing the medication through the bromobutyl vial closure.

METHODS: Patient one experienced a rash during IVIg infusion and headaches post infusion. Patient two experienced anaphylaxis during the infusion of IVIg. Patient two reported a thickened tongue, dyspnea, and chest tightness. The infusion was immediately stopped, epinephrine was administered, and the patient recovered without sequelae.

RESULTS: Intraderal skin testing revealed latex sensitivity for both patients. Further tests compared subcutaneous skin reactions between IVIg drawn through the bromobutyl vial and the solution administered in the absence of the vial closure. Both patients produced positive reactions at the site of the IVIg inoculation when drawn through the vial closure. IVIg infusions performed in absence of the bromobutyl vial closure were tolerated without complications by both patients.

CONCLUSIONS: Our reports support proposals that bromobutyl vial closures may induce allergic reactions and anaphylaxis in individuals with latex sensitivity. This data suggests that the potential exist for anaphylaxis during an IVIgG infusion when the product is withdrawn through a bromobutyl closure.

55 NEMO (IKKγ) Mutation Can Be Associated With Opportunistic Infection Without Impairing TLR Function

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RATIONALE: Patients with mutations in NEMO (IKKγ) are generally described as having mycobacterial and pyogenic infections and ectodermal dysplasia.

METHODS: A 6-month old boy with previously normal growth and development was diagnosed with Pneumocystis pneumonia and was CMV-positive in stool and serum. Hair, teeth and sweat production were normal.

RESULTS: Quantitative immunoglobulins showed serum levels of IgG 467, IgAA NEMO mutation in the first coiled-coil region. Mother was a carrier of the mutation. Examination of the patient’s PBMC response to various Toll-like receptor (TLR) ligands were surprisingly, essentially normal.

CONCLUSIONS: This patient demonstrated a novel mutation in NEMO which resulted in an aspartic acid to asparagine substitution at position 113, and lies within the first coiled-coil domain. The most commonly reported NEMO mutations are farther downstream in the 10th exon in the zinc finger domain. IKKβ binds to NEMO in this first coiled-coil region and this mutation should impair its activation and function. This particular NEMO mutation highlights a dispensability of the region including aa 113 for full IKKγ function.

Funding: This work was supported by a USIDnet grant.

56 Primary Immunodeficiency Disorders: 30 Years of Experience in Shanghai, China

T. Chen, D. Ying; Shanghai Jiao Tong University School of Medicine, Shanghai, CHINA.

RATIONALE: The understanding of the frequency of different primary immunodeficiency disorders (PIDs) in children will increase the awareness of primary care physicians in the diagnosis and treatment of such diseases in China.

METHODS: Ninety three cases of PIDs from Xinhua Hospital diagnosed between 1974 to 2003 were analyzed retrospectively. When possible, practice parameters published by Joint Council of Allergy, Asthma & Immunology were used to make the diagnosis.

RESULTS: The most common PID is antibody deficiency (39.8%), followed by combined immunodeficiency (22.6%) and T lymphocyte deficiency (14%). Other deficiencies include children with immunodeficiency accompanied by other major defects (12.9%), phagocytic deficiency (9.7%), and complement deficiency (1.1%). Of note is the trend of increased cases diagnosed in more recent years. Among the PIDs summarized, 54% were diagnosed since 1996. Sixteen children with combined immunodeficiency died shortly after diagnosis, indicating its high mortality. The gender distribution of all disorders was 3:1 for boys versus girls.

CONCLUSIONS: The types of various PIDs in Shanghai, China are comparable with reports in developed country. With improved diagnostic techniques, more cases have been identified in the last few years. Primary care physicians should be aware of these disorders in order to make early diagnosis. On the other hand, it is essential to establish a national registry of PIDs in China. Such a registry will help to understand the prevalence of PIDs in China. It will also provide a base for standardized therapy of such disorders.

57 Antibody Deficiency Disorders in Recurrent/persistent pneumonia and Chronic Sinusitis in Thai Children at Queen Sirikit National Institute of Child Health

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RATIONALE: To study the incidence of antibody deficiency disorders in Thai children, age 0-15 years old, who have recurrent/persistent pneumonia and/or chronic sinusitis without HIV infection and other secondary causes of immunodeficiency diseases.

METHODS: Children who met the inclusion criteria were enrolled and interviewed. Inform content and record form were completed. Blood sample was investigated for B and T cell subset study; including CD3, CD4, CD8, CD19, CD65/56; serum IgG, IgA, IgM and IgG subclasses levels.

RESULTS: 51 patients who met the criteria were included. The boy to girl ratio is 1.68:1.0. Majority of patients; 39 patient (79.8%); were diagnosed within the first 2 years of life. Average age of onset is 18.3 months old. Data shows abnormal CD3 level = 21.6% (n = 11), CD4 level = 19.6 % (n = 10), CD8 level = 23.5% (n = 12) and CD19 level = 9.8% (n = 5). There are 16 patients who are abnormal serum immunoglobulins and serum IgG subclass which can be categorized to 4 groups, (a) hypogammaglobulinemia = 6 patients (11.76%), (b) selective deficiency Ig A = 1 patients (1.96%), (c) transient hypogammaglobulinemia of infancy = 2 patients (3.92%) and (d) Ig G subclasses deficiency = 7 patients (13.72%) The latter can be subcategorized into Isolated IgG2 deficiency 1 patients (1.96%), IgG2 & Ig G 4 deficiency 2 patients (3.92%) and Isolated Ig G4 deficiency 4 patients (7.84%) respectively.

Conclusions: Children with non-HIV, recurrent/persistent pneumonia and/or chronic sinusitis showed abnormal B and T lymphocyte subsets between 9.8% to 23.5% and abnormal serum immunoglobulins and serum IgG subclass 31.37%. Thus we suggest to consider immunologic working up in children with recurrent/persistent pneumonia and/or chronic sinusitis who have neither HIV infection nor other secondary cause of immunodeficiency.
58 Subcutaneous Bioavailability of Gamunex® in Rabbits
M. Pamarthi, G. Taylor, P. Scuderi, V. Arora; Talecris Biotherapeutics, Research Triangle Park, NC.

RATIONALE: Gamunex® is a 10% intravenous immunoglobulin (IGIV) approved for use in treatment of Primary Immune Deficiency. There has been a rapid growth in demand from this patient population for self-administering Gamunex® as a weekly subcutaneous infusion for antibody replacement. The current preclinical pharmacokinetic studies were conducted to assess plasma fractional availability following subcutaneous dosing. Rabbits were used as a model because of prior literature characterizing pharmacokinetics of IGIV in that species.

METHODS: Naïve male New Zealand White rabbits (n=5/group) were administered Gamunex® at an intravenous dose of 200 mg/kg. The area-under-curve (AUC) of the plasma IgG concentration vs. time curve was compared to subcutaneously-dosed rabbits at 100%, 120%, 137% and 150% dose levels.

RESULTS: The data showed that the AUC (0-12 days) for the intravenous group was 421 ± 35 (mean ± SD) hr*mg/mL. The AUC of animals dosed subcutaneously at 100%, 120%, 137% and 150% of the intravenous dose was 330 ± 40, 397 ± 14, 401 ± 44 and 408 ± 15 hr*mg/mL, respectively. The fractional availability (F) in plasma for these subcutaneous doses was 0.78 ± 0.10, 0.94 ± 0.03, 0.95 ± 0.11 and 0.97 ± 0.04, respectively. All subcutaneous dose levels tested, with the exception of 100%, were statistically indistinguishable from the intravenous dose or from each other (p>0.05).

CONCLUSIONS: We conclude that subcutaneous administration of Gamunex® provides comparable plasma fractional availability to intravenous administration, when used at a dose level of 120% or more of the intravenous dose.

Funding: Talecris Biotherapeutics Inc.

59 Infants With Decreased Immunoglobulin Levels
S. J. McGeady, S. Kung; Thomas Jefferson University, Philadelphia, PA.

RATIONALE: The cause(s) of deficiency and clinical course of infants having abnormally low immunoglobulins and intact antibody formation are unknown.

METHODS: Sixty eight term infants presenting with recurrent infections were found to have decreased levels of one or more immunoglobulin isotypes, but normal antibody production to vaccine antigens. These infants were evaluated for immune function and followed prospectively until immunoglobulin levels normalized.

RESULTS: There were 46/68 (67.6%) male children and the mean age at diagnosis was 10.35 months. IgA was decreased most commonly with 66/68 (97%) decreased. IgG was decreased in 40/68 (58.8%) and IgM in 7/68 (10.2%). In 36/68 (51.4%) immunoglobulins normalized at a mean age of 37.5 months (range 10-179 months), while others continue to be decreased. Flow cytometry for CD3, CD4, CD8, CD19 and CD16/56+ cells was performed in 38/68 subjects and was normal in all. No patient developed life threatening infections and none were treated with IVIG.

CONCLUSIONS: Male children predominate in this cohort with IgA being the most commonly deficient immunoglobulin. Immunoglobulin levels normalize at various times in these children, but they do not require replacement therapy with IVIG. The cause(s) of diminished immunoglobulin levels remains unknown. Transient hypogammaglobulinemia of infancy can be identified only in retrospect.

Funding: nemours foundation

60 Idiopathic CD4+ T-Lymphocytopenia (ICL) in a Child with Persistent Cryptococcal Meningitis
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RATIONALE: ICL is a condition of the CD4+ T-cell count that is less than 200/µL with the remaining CD4+ T-cells normal. This case treated with rIL-2 which seems to be both effective and well tolerated.

METHODS: A 16-year-old male with a past history of schizoaffective disorder, presented with neck pain, increased psychotic behavior, and fever. WBC was 8,300 cells/µL with 82% neutrophils and 13% lymphocytes. CSF showed 75 nucleated cells/HPF with 44% neutrophils, 29% lymphocytes, and 21% monocytes, protein 175 mg/dL and glucose 44 mg/dL. India ink stain showed budding yeast cells. Cryptococcus neoformans was isolated from CSF and blood. Amphotericin B and fluconazole were initiated. He had normal Ig levels (IgG 649, IgM 150 mg/dL), CD19 (28%; 318/µL), CD3 (64%; 717/µL), and CD8 (37.6%; 417/µL), but low CD4 (19%; 213/µL) and CD4:CD8 (0.5). HIV ELISA and PCR were negative, which fulfills ICL criteria. He developed pancreatitis and renal failure; the former resolved, but renal function only improved. He was hospitalized 3 times during 5 months for recurrent cryptococcal meningitis despite prophylactic fluconazole. Recombinant IL-2 was added twice weekly as 50,000 U/m² during week 1, 100,000 U/m² during week 2, then maintained at 250,000 U/m² from week 3 onwards. It has been well tolerated and meningitis did not recur.

CONCLUSIONS: To our knowledge this is the first reported pediatric ICL case treated with rIL-2 which seems to be both effective and well tolerated.

Funding: Robert A. Good Chair in Immunology
Mannose-Binding Lectin Deficiency in a Family with Frequent Respiratory Infections

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RATIONALE: Mannose-binding lectin (MBL) mediates complement activation through the lectin pathway. The gene encoding MBL, MBL2, contains several common polymorphisms that influence transcription and polymerization of the molecule.

METHODS: Five members from one family with no history of immunodeficiency were evaluated in this case series. The son, presented at age 16, had recurrent otitis media, sinusitis and pneumonia since childhood. His MBL and IgG levels were 0.009 µg/ml (normal 0.03-4.94 µg/ml) and 400 mg/dl (normal pediatric 528-2190 mg/dl), respectively. The 48 year-old mother suffers from recurrent sinusitis. She had undetectable levels of MBL and an IgG level of 547 mg/dl (normal 700-1600 mg/dl). The 15 year-old daughter had undergone multiple sinus surgeries and courses of antibiotics for recurrent sinus infections. Her MBL and IgG levels were 0.02 µg/ml and 462 mg/dl, respectively. Other serum immunoglobulins, antibody responses to protein and polysaccharide antigens and complement levels were normal in all three patients. Two additional healthy family members, the father and another daughter, had MBL levels of <0.05 µg/ml and 1,363 µg/ml, respectively.

RESULTS: MBL genotypes obtained following informed consent strongly correlated with MBL serum levels: LXPA/LYPB (parents), LYPB/LYPB (son), LXPA/LYPB (affected daughter) and LXPA/LXPA (unaffected daughter).

CONCLUSIONS: Although usually clinically silent, low MBL levels are associated with increased susceptibility and severity of infections, particularly in an immunocompromised host. Our series is unique in that although all three affected subjects have borderline hypogammaglobulinemia, they were able to make normal antibody responses to both protein and polysaccharide antigens. This case series illustrates the value of determining MBL levels in patients with recurrent infections but no apparent immunodeficiency.

Pediatric Patients With Refractory Autoimmune Cytopenias Displaying Autoimmune Lymphoproliferative Syndrome (ALPS) Phenotypes - Role For Anti-cd20 (Rituximab™) Therapy

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RATIONALE: Here we describe 2 pediatric cases of refractory autoimmune cytopenias that demonstrate features of autoimmune lymphoproliferative syndrome (ALPS) and common variable immune deficiency (CVID) that were responsive to anti-CD20 therapy.

METHODS/RESULTS: Two 15 year old males presented with autoimmune cytopenias (thrombocytopenia, neutropenia, and anemia) that were refractory to standard therapy with intravenous immunoglobulin (IVIG) and high-dose steroids. Immune phenotyping analysis revealed specific lymphocyte abnormalities consistent with ALPS and CVID. Flow cytometry in both patients demonstrated elevated percentages of TCRab+CD4-CD8+ (double negative) T cells typically observed in ALPS as well as diminished percentages of total memory (CD19+CD27+) and switched memory (CD19+CD27+IgD+) B cells seen in CVID. In addition, both patients had elevated percentages of CD19+CD21+B cells observed in various autoimmune syndromes. Due to their refractory disease, both patients were treated with anti-CD20 (Rituximab™) resulting in resolution of their cytopenias.

CONCLUSIONS: 1) A specific subset of primary immune deficiency patients exists that develops refractory cytopenias and has flow cytometry findings consistent with both ALPS and CVID phenotypes. 2) Refractory autoimmune cytopenia can be treated successfully with anti-CD20 therapy. 3) Screening for CVID and ALPS phenotypes within the context of autoimmune cytopenias is prudent.

Funding: Medical College of Wisconsin

β-tubulin Induced Murine Model of Autoimmune Hearing Loss and Regulation of T Cell Cytokines of the Mice

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RATIONALE: Fifty nine percent of Meniere’s disease patients produce antibodies to a 55 kD inner ear membranous and neural protein, β-tubulin. However, the immunological role of β-tubulin in autoimmune hearing loss remains obscure.

METHODS: In the present study, we generated an experimental autoimmune hearing loss by immunizing mice with β-tubulin. BALB/c mice were subcutaneously injected with β-tubulin in dosage of 100, 200 or 300 µg per mouse for immunization. Acoustic brain stem response was measured for hearing loss. Lymphocytes were isolated from the spleen and CD4 T cells were counted by FACS. TH1, TH2, and regulatory T cell cytokines were measured from the supernatants of the lymphocytes.

RESULTS: Hearing loss was induced in a dose-dependent manner, two and six weeks after immunization with β-tubulin. Profferative responses of CD4 lymphocytes to β-tubulin were also observed. The production of TH1 cytokines such as IFN-γ, IL-2, IL-12, and TNF-alpha was increased in the lymphocytes from the β-tubulin-immunized mice compared to those from control mice. The production of TH2 cytokines such as IL-4, IL-5, and IL-13 did not show any difference between the immunized mice and control mice. Furthermore, the production of regulatory T cell cytokines such as IL-10 and TGF-beta was decreased in the lymphocytes from the immunized mice.

CONCLUSIONS: In this study, we successfully generated an experimental autoimmune hearing loss by immunizing mice with β-tubulin. The possible immunologic mechanisms of this hearing loss may be the upregulation of TH1 response and the downregulation of regulatory T cell response.

Funding: NIH

The Clinical Significance Of Isolated Antinucleolar Antibodies

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RATIONALE: The antinucleolar pattern seen by indirect immunofluorescence on HEP-2 cells is strongly associated with systemic sclerosis, but its importance in unselected patients is unknown. Our objective was to determine the true clinical significance of antinucleolar antibodies in an unselected patient population.

METHODS: Antinucleolar antibody (ANA) positive samples were identified in the Immunology laboratory during routine screening and case notes reviewed using a structured questionnaire. Of 7842 samples, 104 patients with ANoAs were identified (overall prevalence of 1.3%). Titters ≥1:40 were considered positive, and classified into homogenous, clumpy and speckled antinucleolar subtypes. Tests for antibodies against extractable nuclear antigens (ENA) were added to all the positive samples.

RESULTS: Of 104 patients, there were 87 females (mean age ± SD= 56.8± 17.4 years) and 17 males (mean age ±SD= 61.4± 19.4 years). The number (%) of the three nucleolar subtypes detected were homogenous 57 (55%), clumpy 15 (14%) and speckled 32 (31%). Only 2 patients had evidence of antibodies against ENA (weak SS-A and U1RNP). Systemic sclerosis was evident in only two (1.8%) patients. Other rheumatologic disorders identified were polymyalgia rheumatica (11.5%), polymyositis/dermatomyositis (4.8%), rheumatoid arthritis (2.8%), crystal arthropathy (2%) and all others (3.1%). 22 patients (21%) had malignancy, 73% of whom had a homogenous nucleolar pattern compared with 50% of patients without malignancy, but this was not statistically significant (p>0.05).

CONCLUSIONS: Presence of antinucleolar antibody and specific subtype has low specificity for systemic sclerosis. The finding of anti-nucleolar antibody does not warrant testing for antibodies against ENA.
66 Prostate Specific Antigen: Responsible Allergen In Human Seminal Plasma Allergy
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BACKGROUND: Human seminal plasma allergy (HSPA) in women is rare. There is paucity of information about the nature of the antigen involved in HSPA. Several seminal plasma allergens have been identified and their molecular masses were reported to range from 12 to 75 kDa, but the real origin of the allergens as well as if there is only one or multiple allergenic components involved in HSPA are still uncertain.

CASE REPORT: A 38-year-old nulligravida woman suffered anaphylactic reactions immediately after ejaculation during sexual intercourse. Symptoms had begun several years earlier. The husband had been the patient’s only sexual partner. The patient had a family and personal history of atopy. SDS-PAGE immunoblotting was carried out with the husband’s seminal plasma under two different conditions: with and without 2-mercaptoethanol.

Proteomics study was performed for identification of the allergen. The selected band was cut out from the gel and subjected to in-gel trypsin digestion. Peptides were analyzed using a Voyager-DE STR Biospectrometry Workstation instrument (Applied Biosystems, Foster City, CA) and identified by matrix-assisted laser desorption ionization-time-of-flight-mass spectrometry (MALDI_TOF_MS).

RESULTS: SDS-PAGE was carried out for allergen isolation and the immunoblotting identified an IgE-binding band of 26 kDa in non-treated samples. The mass spectrometry identify the 28 kDa band in the non-reducing gel as a prostate specific antigen precursor (PSA).

CONCLUSIONS: In this study we have identified and characterized by mass-spectrometry the responsible allergen for a case of HSPA as the PSA. To our knowledge this is the second case of HSPA where the implicated allergen is the PSA. Until date we are the second research group to characterise the causative allergen of HSPA. Despite using different methods, we both agree in identifying the PSA as the causative allergen for HSPA.

67 Development of Hypocomplementemic Urticular Vasculitis Syndrome Following Intracoronary Stent Placement
S. L. Cole, D. K. Ledford; University of South Florida, Tampa, FL.

RATIONALE: Hypocomplementemic urticarial vasculitis syndrome (HUVS) is an uncommon autoimmune disorder of unknown etiology. HUVS has not been reported following a delayed hypersensitivity reaction to an intracoronary stent.

METHODS: A 54-year-old male cigarette smoker without a significant past medical history had an acute myocardial infarction with subsequent intracoronary stainless steel stent placement (ACS Multi-Link RX50, Guidant, St. Paul, MN). Within a few days he reported respiratory complaints and urticaria, which was resistant to oral antihistamines. He continued to experience urticaria and subsequently developed intermittent facial angioedema, uvetitis, alopecia, subcutaneous nodules, and inflammatory polyarthropathy with joint stiffness.

RESULTS: Laboratory evaluation revealed hypocomplementemia with a negative ANA. The FEV1 was 40% of the predicted value and did not reverse with bronchodilator inhalation. Patch testing was positive to the stent material at 48 hours with erythema and edema. Biopsy of the patch test site was consistent with a cellular hypersensitivity reaction with an infiltrate of lymphocytes, neutrophils, and eosinophils. The intracoronary stent could not be removed, and he was treated with oral antihistamines, systemic and inhaled corticosteroids, leukotriene modifiers, and bronchodilators. His urticaria, angioedema, and uvetitis resolved, and his respiratory complaints improved. The polyarthropathy was treated unsuccessfully with methotrexate and hydroxychloroquine but later improved with NSAIDs.

CONCLUSIONS: Based on a computerized search of the medical literature, this is the first description of HUVS following placement of an intracoronary stent. Although an immunologic association between these events is hypothetical, it is suggested by the timing of symptom onset and the positive patch test to the stent material.

Funding: University of South Florida

68 Treatment of Hypoglycemia with Intramuscular Immunoglobulin in Insulin Dependent-Diabetics with Insulin Antibodies
S. A. MacLeish, S. Wallace, Z. Madhun, R. Hostoffer, Jr.; Case Western Reserve University Cleveland, OH.

RATIONALE: Treatment of diabetic patients with insulin may produce insulin antibodies, resulting in hypoglycemia. It is hypothesized that insulin antibodies bind to insulin, acting as a reservoir, and then releasing the insulin at inappropriate times. Usually these episodes resolve without treatment. Glucocorticoids have been used if the episodes last for an extended time or if they resulted in life-threatening hypoglycemia, although glucocorticoid refractory cases have been reported.

METHODS: We present a case of a 42 year old woman with maturity onset diabetes of the young of 20 years duration and recent onset of severe hypoglycemia of hypoglycemia due to insulin antibodies resident to steroid therapy. She was started on intramuscular immunoglobulin once weekly with frequent blood glucose monitoring. This case closely parallels the cases we presented last year, of a 37 year old woman with type I diabetes for 2 decades before the onset of hypoglycemic episodes, also due to insulin antibodies.

RESULTS: Our patient has not required any emergency medical attention since starting immunoglobulin treatment. She is hypoglycemic 1-2 times per week; her lowest blood sugar was 43, and she has warning for these episodes and is able to treat herself.

CONCLUSIONS: Both case studies show the patients with a history of insulin-dependent diabetes and severe hypoglycemia due to auto antibodies who are refractory to treatment with steroids may be successfully treated with intramuscular immunoglobulin therapy. Further prospective controlled studies are needed.

69 A Case of a Child with Autoimmune Polyglandular Syndrome Type 1 associated with Metaphyseal Dysplasia
T. J. Pitt, N. K. Maclaren; St Vincent Hospital Manhattan, Department of Pediatrics, New York, NY.

RATIONALE: APS-1 or Autoimmune Polyglandular Syndrome type 1 results from a recessive mutation of the autoimmune regulator gene (A.I.R.E). Concomitant skeletal abnormalities are rarely reported.

METHODS: We present a case of a 9 year old male with chronic mucocutaneous candidiasis and chronic lower leg pains secondary to metaphyseal dysplasia of the tibias who was referred for possible APS-1.

RESULTS: Clinical evaluation revealed a 9 year old Hispanic male with enamel hypoplasia and pain in both his ankles and wrists. Lab evaluation demonstrated: 21-OHP antibodies 2.1(n=1), Smooth Muscle antibody positive (titer 1:20), AST 58 (n=0-40 U/L), ALT 74 (n=5-40 U/L), normal levels of IgG, IgA and IgM and a homozygous 13 base deletion (c123 del c) confirming APS-1. A plain film showed metaphyseal dysplasia of the knees and ankles. No pharmacologic treatment was necessary at this time, albeit future Addison’s disease was anticipated.

CONCLUSIONS: This patient with Autoimmune Polyglandular Syndrome Type 1 was found to have Metaphyseal Dysplasia of the knees and ankles. To our knowledge this case documents the third with this association. Of the more than 80 APS-1 patients we follow, this is the only known instance of metaphyseal dysplasia. This is an insightful clinical report that outlines a unique presentation of APS-1 with mucocutaneous candidiasis, and impending adrenal insufficiency accompanied with a skeletal dysplasia in a pre-adolescent child.
**70 Behçet Disease in a Patient with Autoimmune Polyendocrine Syndrome - Type 1**

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**INTRODUCTION:** Autoimmune Polyendocrine Syndrome Type 1 (APS-1), known as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) syndrome, is seen in childhood and characterized by the coexistence of several autoimmune diseases affecting endocrine and non-endocrine glands. However, the first manifestation is usually mucocutaneous candidiasis. APS-1 is caused by mutations in a gene called AIRE (autoimmune regulator). Here, we first time report an APS-1 patient with Behçet Disease.

**PATIENT/METHODS:** 8-year-old, white-female, well-nourished, but asthma, polyneuropathy, and type 1 DM.

caused by recurrent serous otitis media; and hypertension, probably owing to Behcet disease due to recurrent fever, rash, oral/vaginal ulcers, and high ESR.

At age 2, she had mouth ulcers associated with candidiasis and GI discomfort due to colitis. She suffered from hearing loss, speech delay caused by recurrent serous otitis media; and hypertension, probably owing to steroid use. At age 6, hypocalcemia detected. In the family, father has asthma, polyneuropathy, and type 1 DM.

**RESULTS:** CBC and BMP were normal except for calcium of 4.7 mg/dL. PTH was low. Vitamin D, T4, TSH, DHEA, ACTH and cortisol levels were normal. ANA and RF were negative with an elevated ESR. CH50, specific antibody titers, lymphocyte subpopulation and responses to mitogens/autoantibodies were negative. Throat culture grew Candida albicans. Biopsies showed gastritis, duodenal mucosal atrophy, colitis and ileitis. Brain MRI, chest/sinus CT was normal. AIRE mutation [967-979del13bp] was positive in the patient.

**CONCLUSIONS:** This case suggests that rheumatologic symptoms may also be early manifestations of APS-1.

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**71 Autoimmune Neonatal Chondrodysplasia Punctata and Maternal Lupus**

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**RATIONALE:** Classic rhizomelic chondrodysplasia punctata (RCDP) is a rare autosomal recessively inherited disorder, characterized by proximal shortening of the limbs, punctuate calcifications of the epiphyses, cataract and developmental delay. A distinctive biochemical profile is characteristic for each of the several defects of peroxisomal metabolism, but several cases were associated with mothers with connective tissue disease. We present a newborn with RCDP, whose mother developed systemic lupus erythematosis (SLE) eight months after delivery, emphasizing the importance of autoantibodies, not maternal disease status.

**CASE REPORT:** A newborn male was diagnosed with features suggestive of RCDP, whose mother developed a pruritic erythematous rash on the dorsum of the hands, axillary and inguinal areas accompanied by joint pains of hands and feet, eight months after delivery.

**RESULTS:** Study of the newborn failed to demonstrate a defect in either plasmalogens or cholesterol biosynthesis, while maternal lab revealed a slightly elevated ESR and discoid lupus erythematosus on skin biopsy. Maternal autoantibodies profile demonstrated ANA with a 1:640 titer, positive anti-SSA (Ro) 133.4 (<25.1 EU/ml), positive anti-SSB (La) 149.7 (<25.1 EU/ml), consistent with SLE.

**CONCLUSIONS:** Mothers of infant with CDP should be followed for signs of autoimmune disease, while newborn born to mothers with SLE should be evaluated for features of CDP. Studying the antibody profiles should be evaluated for features of CDP. The causative mechanism, but neither the presence of autoantibodies nor the status of maternal disease can be the only factor to predict the occurrence of CDP.

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**72 Hyperinsulinemia Hyperammonemia Syndrome in a Patient with autoimmune disease**

R. V. Basavaraju; Kansas University Medical Center, Kansas City, KS.

**RATIONALE:** Hyperinsulinemia Hyperammonemia (HIHA) syndrome is a little known syndrome caused by an inborn error of metabolism involving glutamate dehydrogenase.

**METHODS:** 10 year old caucasian female presented with arthralgias, headache and a positive ANA titer. She was treated with nonsteroidal anti-inflammatory agents and hydroxychloroquine. Two years later her symptoms progressed to severe headaches, tremor and slurred speech. On exam she had malar erythema, livedo reticularis, normal joint exam, mild obesity and round facies. Laboratory data included a positive ANA 1:80, negative rheumatoid factor and random blood sugar of 76 mg/dL. CT scan and MRI of the head were normal. Brain SPECT study showed decreased perfusion in the left parietotemporal area, temporal lobes and occipital lobes consistent with possible vasculitis. She was given oral prednison 30 mg a day which improved her speech, headaches and arthralgias.

On tapering of steroids her symptoms recurred. Serial blood sugars were consistently below 35 mg/dL. Glucose tolerance test showed high insulin levels, and normal anti-insulin and anti-islet cell antibodies. Her serum ammonia levels were elevated at 114 mmol/L (normal 21-50 mmol/L). **RESULTS:** She was diagnosed with HIHA syndrome due to inappropriately elevated insulin levels and high ammonia levels.

**CONCLUSION:** Severe hypoglycemia due to HIHA syndrome may cause CNS vasocostriction and mimicking CNS vasculitis. Prednisone may have stabilized her blood glucose and caused relief of her symptoms. She has done well on diazoxide and controlled diet, but continues to have arthralgias.

**Funding:** Kansas University Medical Center.

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**73 Fever of Unknown Origin (FUO) and Anemia as Sole Presenting Features of Sarcoid**

T. Chacko, D. Ledford, R. F. Lockey; University of South Florida College of Medicine, Tampa, FL.

**RATIONALE:** This is a case report of sarcoid with the unusual presentation of fever of unknown origin (FUO) and anemia without other systemic findings.

**METHODS:** A 61-year-old white male presented with fatigue, fever up to 38.9°C (102°F), and shortness of breath for 2 months. Six weeks prior, he was hospitalized and had a low CD4 count (absolute number unavailable), chest CT showed small subsegmental atelectasis, and bronchoscopy was unremarkable. He was discharged on antibiotics for presumed pneumonia.

**RESULTS:** On this hospitalization, vital signs were normal except for a temperature of 38.9°C (102.2°F). The physical was normal. Laboratory results revealed a hemoglobin of 9.3 g/dL (normal 14-17 g/dL), hematocrit of 27.5% (normal 39-50%) and normal WBC, platelet count, comprehensive metabolic panel, and chest radiograph. CD4 T cell count was 365 10^6/L (normal 800-3340 10^6/L). CD8 T cell count 179 10^6/L (220-960 10^6/L) and CD4/CD8 ratio 2.1 (normal 1-4.5). High resolution chest CT was normal. Blood cultures, ACE level, HIV PCR and multiple studies to rule out an infectious etiology were normal. A bone marrow biopsy revealed noncaseating granulomas (negative cultures for bacteria, fungi, and mycobacteria).

Three months after starting prednisone, 40 mg daily, he felt well, and his lymphopenia resolved with a normal CD4, CD8 and CD4/CD8 ratio.

**CONCLUSION:** Isolated sarcoidosis of the bone marrow can present as lymphopenia, FUO, and anemia without lymphadenopathy or abnormal chest imaging.

**Funding:** Joy McCann Culverhouse and Mabel and Ellsworth Simmons Endowments
Pancytopenia and Myelofibrosis in Autoimmune Polyglandular Syndrome Type I


Autoimmune Polyglandular Syndrome Type I (APS I) is due to a defect in the autoimmune regulator gene (AIRE). Mucocutaneous candidiasis, Addison’s disease, hypoparathyroidism, other endocrinopathies, neural ectodermal dysplasia, malabsorption, and autoimmune hepatitis are clinical features of APS I. Immune mediated cytopenias are common. We describe myelofibrosis as an unusual complication of APS I.

A 16 year old adolescent female, with clinical diagnosis of APS I and all attributes described above, including pernicious anemia and neutropenia, presented with pancytopenia. She was DAT positive, hypergammaglobulinemic with positive ANA and dsDNA titers. A bone marrow biopsy revealed a mildly hypocellular marrow with myeloid left shift, mild erythroid and megakaryocytic hyperplasia and increased lymphoplasmacytic infiltrate with delicate reticulin fibrosis. There were rare positive CD3 cells and scattered positive CD20, CD34 and CD117 cells. Bone marrow biopsy performed two years earlier demonstrated a cellular marrow with erythroid preponderance and marked megaloblastic and dysplastic changes, presence of giant bands and hypersegmented neutrophils, and scattered CD 117 positive plasma cells without evidence of fibrosis.

AIRE encodes a transcription factor that enables negative selection of autoreactive thymocytes and may promote development of the regulatory T-cell subset. Myelofibrosis has been observed in other autoimmune diseases, most notably systemic lupus erythematosus. Additionally, primary autoimmune myelofibrosis was recently characterized as a syndrome associated with lymphocytic infiltration of the bone marrow interstitium. Accordingly, we postulate that myelofibrosis is a manifestation of APS I driven by autoreactive T cells.

Funding: UCLA

Autoimmune Thyroiditis Developing In A Survivor Of Catastrophic Antiphospholipid Syndrome: A Case Report

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RATIONALE: We report a case of autoimmune thyroiditis developing in a patient after an episode of Catastrophic Antiphospholipid Syndrome (CAPS), a life-threatening, multi-organ thrombosis occurring acutely. A Medline search failed to show prior reported events except for a few reports on Antiphospholipid Syndrome (APS) associated with thyroiditis.

METHODS: A Case Report.

RESULTS: This is a case of a 31 year-old female, G2P1 (1001), diagnosed with hyperthyroidism 2 years prior, given methimazole for 1 month, rendering her euthyroid. FT3 was low on her 9th week of this pregnancy, which normalized during her 24th week without any medications. Post-caesarean delivery, she developed sudden hypotension, oliguria, dyspnea, tachypnea and bradycardia. Laboratory findings showed thrombocytopenia, elevated liver enzymes, prolonged activated partial thromboplastin time, elevated D-dimer and Troponin-I. On echocardiography, multispectral wall motion abnormality and ejection fraction of 30% were seen. CAPS was entertained, and she was treated with enoxaparin, hydrocortisone, and intravenous immunoglobulin with dramatic improvement. Eight months later, she developed hyperthyroidism with high titers of anti-thyroglobulin and anti-thyroid peroxidase, confirming the diagnosis of an autoimmune thyroiditis. She was given neomercazole for a month when she became hypothyroid. She was refractory to levothyroxine, hence total thyroidectomy was done.

CONCLUSIONS: This case report identifies an association between 2 autoimmune phenomena, namely, the catastrophic antiphospholipid syndrome and autoimmune thyroiditis.

Ischemic Events in Patients with Systemic Lupus Erythematosus

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RATIONALE: The aim of our study was to determine the frequency of ischemic events in patients with Systemic Lupus Erythematosus (SLE), recognize the ischemic events more common and typify the risk factors.

METHODS: We studied the clinic histories from the department of immunology of the Ciudad Hospitalaria “Dr. Enrique Tejera”, Valencia-Carabobo, years 1990 to 2006. There were 369 patients with diagnosis of SLE. For the recollection of the data a filing card created by the authors was used, in whom data like: age, sex, diagnosis, ischemic event and risk factors were registered.

RESULTS: The mean age of our cohort was 32 years. Ischemic events occurred in 87 patients (23.5%). The most common systemic ischemic event occurred was non digital ulcer (36.2%). Hypertension was documented in 40.5%, Raynaud phenomenon in 22.8%, and hyperlipidemia in 16.3% of patients. We also found that patients with more than two risk factors the risk for ischemia was increased more than seven times.

CONCLUSIONS: The management of the risk factors for developing ischemic events will help the physician to prevent them in SLE patients.

Antibodies Anti-cmv In Patient With Myocardial Ischemia


RATIONALE: The direct action of the CMV or their antigenic determinant can induce changes in the vascular endothelium, contributing to the development of the atheromatous plaque. The objective of the present study was to look the presence of antibodies anti CMV in patient with acute myocardial ischemia (AMI).

METHODS: It was studied 29 patients with diagnostic of AMI hospitalized in the area of coronary cares of the C.H.E.T: The determination of IgM and IgG, anti CMV (ELISA) was made in the first 48 hours. A control group of 30 healthy individuals, without antecedents of ischemic cardiopathy equivalent in age and sex.

RESULT: 3.4% of the patient were IgM+ anti-CMV, in the control group was not positive cases. Serum concentrations of IgG in 48 hours were more risen in the group of patient with heart attack that in the group with chest angina (4.52±3.34 IU/ml- 3.69±2.39 IU/ml).

They were not significant differences among the serum concentrations of IgG anti CMV between the total group of patient and the control group.

CONCLUSION: Among the patients with acute myocardial ischemia illness the presence of IgM anti CMV was evidenced. The serum concentrations of IgG anti CMV is bigger when it exists myocardium necrosis that only ischemia.

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A 54 Year-Old Woman with Acquired Angioedema, Coagulopathy, and Lymphoma

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RATIONALE: Acquired angioedema (AAE) is a rare condition of adulthood due to C1 esterase inhibitor deficiency, which occurs in the absence of a family history of angioedema. C1 esterase inhibitor deficiency can potentially lead to activation of the coagulation cascade due to interconnections between the complement and coagulation pathways.

METHODS: A literature review of PubMed and Ovid for angioedema, acquired angioedema, C1 esterase inhibitor deficiency, coagulopathy, lymphoproliferative disorder, and lymphoma was performed. We describe a 54 year-old woman with recurrent episodes of facial swelling.

RESULTS: Most patients presenting with AAE have an underlying lymphoproliferative disorder or autoimmune process. Although there is an interconnection between the complement and coagulation cascades at several levels, our literature review failed to demonstrate other cases of coagulopathy in association with AAE and lymphoma. Laboratory evaluation in our patient revealed low C1 esterase inhibitor, C2, C4, and CH50 levels, low C1q binding assay, normal C3 level, and an elevated prothrombin time and INR. Further evaluation revealed non-Hodgkin’s lymphoma.

CONCLUSIONS: AAE is a rare condition with known possible association with lymphoma. This is the first documented case of AAE and lymphoma associated with coagulopathy. Evaluation of the coagulation system should be considered in the evaluation of patients with AAE.

Abdominal pain, Nausea, and Vomiting as the Initial Presenting Symptoms of Systemic Lupus Erythematosus

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RATIONALE: Systemic lupus erythematosus (SLE) is usually diagnosed with evidence of renal, rheumatologic, cutaneous and neurological target organ damage and positive serological markers. However, isolated abdominal pain, nausea, and vomiting, as the initial presentation of SLE, is rare.

METHODS: This is a case report of a patient who presented with abdominal pain, nausea, and vomiting as the initial and sole clinical manifestation of SLE.

RESULTS: A previously healthy 18-year-old female presented to emergency department with nausea, vomiting, and abdominal pain. The physical exam was consistent with an acute abdomen, and radiological studies revealed diffuse ascites and prominent small bowel wall thickness and mucosal edema. The laboratory studies showed an ANA of 1:1280, a positive anti-ds DNA of 1250, anti-Smith antibodies, low C3 and C4 of 35 and <10 respectively, and autoimmune hemolytic anemia. She improved with two courses of intravenous methylprednisolone, 1 gm each given 2 subsequent days, and was discharged on tapering oral prednisone and hydroxychloroquine. Repeat CT scan showed no evidence of ascites and resolved bowel wall edema.

CONCLUSIONS: Gastrointestinal manifestations occur in approximately 30 percent of patients with SLE; however, these symptoms are frequently overlooked in the presence of renal, rheumatologic, cutaneous and cerebral complications. The pathophysiology resulting in abdominal pain is unknown, but may occur as a consequence of vasculitis resulting in ischemia and/or infarction. This case report is similar to a few other patients described in the literature. SLE should be considered in a young woman who presents with abdominal pain associated with nausea and vomiting.

Mucosal administration of Escherichia coli Heat-labile toxin B and Classical swine fever E2 Chimeric antigen inhibits collagen-induced rheumatoid arthritis

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RATIONALE: Since the nontoxic B subunits of LT and CT are known to suppress Th1 (Thelper type 1)-mediated autoimmune diseases, we demonstrate role of LTB and CSFV E2 subunit chimeric antigen in the pathogenesis of rheumatoid arthritis.

METHODS: LTB, E2 protein obtained by E.coli system were administered to CIA mice orally. We analyzed gene expression, phenotypical changes of immune cells and IgG production.

RESULTS: Administration of LT inhibited both the CIA-induced infiltration of immune cell population, and CIA-induced Th1 cytokine gene expression.

CONCLUSIONS: Oral administration of LTB chimeric proteins reduced the CIA incidence.

IgE-Mediated Hypersensitivity Reactions to Cannabis in Laboratory Personnel

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RATIONALE: There have been sporadic reports of hypersensitivity reactions to plants of the Cannabinaceae family (hemp and hops), but it has remained unclear whether these reactions are immunologic or non-immunologic in nature.

METHODS: Two laboratory workers at the Bavarian State Office of Criminal Investigation suffered from nasal congestion, rhinitis, sneezing and asthmatic symptoms upon occupational contact to hashish or marihuana which they had handled frequently for 25 and 16 years, respectively. They both had no history of atopic disease. Serum was analyzed for specific IgE antibodies to hashish or marihuana extract by CAP-FEIA, and histamine release was triggered by hashish and marihuana extracts was assessed. Results were matched to those of 4 non-atopic and 10 atopic control subjects with no known history of recreational or occupational exposure to marihuana or hashish.

RESULTS: Patient 1 had CAP class 2 levels of IgE to both hashish and marihuana, patient 2 had CAP class 2 levels to marihuana only. Controls remained unclear whether these reactions are immunologic or non-immunologic in nature.

METHODS: Two laboratory workers at the Bavarian State Office of Criminal Investigation suffered from nasal congestion, rhinitis, sneezing and asthmatic symptoms upon occupational contact to hashish or marihuana which they had handled frequently for 25 and 16 years, respectively. They both had no history of atopic disease. Serum was analyzed for specific IgE antibodies to hashish or marihuana extract by CAP-FEIA, and histamine release was triggered by hashish and marihuana extracts was assessed. Results were matched to those of 4 non-atopic and 10 atopic control subjects with no known history of recreational or occupational exposure to marihuana or hashish.

RESULTS: Patient 1 had CAP class 2 levels of IgE to both hashish and marihuana, patient 2 had CAP class 2 levels to marihuana only. Controls proved negative for specific IgE except for 2 individuals with CAP class 1 to marihuana and 1 individual with CAP class 1 to hashish. Histamine release was triggered by hashish and marihuana extracts in both patients and 4 control subjects. There was no association of specific IgE-levels to atopic disease.

CONCLUSIONS: Our results suggest an immunologic pathomechanism for hypersensitivity reactions to marihuana or hashish.

Funding: Ludwig-Maximilians-Universität
82 Multiple Chemical Sensitivity: an Unusual Case of Vocal Disorder
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RATIONALE: Multiple Chemical Sensitivity (MCS) is a phenomenon observed in patients who reported sensitivities involving any and every organ system, following exposure to environmental agents including pesticides, solvents, and others. A 39-year-old white man was accidentally exposed to an extremely high concentration of petroleum aromatic hydrocarbons (AH) vapors at his job. Since that time he developed voice disorder attacks every time he smelt gasoline or other HC vapors. These episodes delayed about one hour, and occurred at the work environment, at home or at the gas station. He had no previous history of allergy or vocal cord dysfunction. Investigational procedures for gastro-esophageal reflux and a video-laryngoscopy did not show abnormalities.
METHODS: Double blind challenge tests were performed with 5 different chemical compounds supplied by the employer. He was exposed to inhalation for one minute and the results were evaluated for the occurrence of voice disorder and accompanied by video-laryngoscopy.
RESULTS: Voice disorder associated with vocal cord edema was observed immediately after provocation with samples 1, 2, and 4. They were composed by a mixture of nafta derivatives (ND) and at least 15% of AH. Samples 3 and 5 did not produce voice disorder or anatomic modifications on the vocal cords. They were composed by NH4OH plus Na2S, and ND plus 10% of AH, respectively.
CONCLUSIONS: These results showed evidences that AH could be involved in the observed events. The voice disorders were well correlated with video-laryngoscopy findings. AH could be listed as a potential agent involved in MCS.

83 Effect of Training on Asthma and Allergy Symptoms in Recreational Roadrunners
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RATIONALE: Intensive training among elite athletes has been associated with impact on asthma. Our objective was to ascertain the impact of training on allergy and asthma symptoms in recreational roadrunners.
METHODS: A validated questionnaire consisting of 18 questions encompassing demographics, allergy and asthma symptoms, specialty evaluation and therapy and impact of training was administered to roadrunners.
RESULTS: There were an estimated 4000 roadrunners of whom 350 (8.8%) completed the questionnaire. Their demographics were as follows: 204 male (58%) 124 females (35%), 22 non-designated (6%), 290 Caucasians (83%), 53 Non-Caucasian (15%), 7 non-designated (2%). There were 18(5%) roadrunners age 1-10 years, 29(8%) ages 10-20 years, 55(15.4%) ages 20-30 years, 71 (20%) 30-40 years, 104(30%) 40-50 years, 61 (17%) ages 50 years-60 years, 8(2.3%) ages 60-70 years, 3(0.9%) ages 70-80, 2 non-designated (0.6) with a mean and median range of 40-50 years. There were 104(30%) with questionnaire symptoms consistent with asthma, 184(53%) with symptoms of allergy alone, 70(20%) with both allergy and asthma symptoms. Training was for a median of 7-10 hours/week (mean 6.5 hours/week). Training impacted 13 roadrunners with allergy symptoms alone (7%), 22 with asthma alone (21%) and 12(17%) with both allergy and asthma symptoms. Training had significant impact on runners with allergy symptoms (p<0.001), asthma symptoms (p<0.001) and those with both allergy and asthma symptoms (p<0.001) but significantly more impact on asthma than allergy symptoms alone (p<0.01) by chi square analysis with one degree of freedom. In contrast asthma did not impact on training (>10 hours/week vs <10 hours/week, p=0.097).
CONCLUSION: Training for a median of 7-10 hours/week, range 1to 20 hours, impacted significantly on allergy and asthma symptoms in recreational roadrunners but asthma had no significant impact on training.
Funding: Schering Corporation $1000

84 Occupational Mouse Allergen Exposure and Incident Skin Test Sensitivity
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RATIONALE: An understanding of how the risk of allergic sensitization varies across a range of allergen exposure is necessary for developing rational approaches to primary prevention of allergic sensitization. Results from cross-sectional studies suggest that high level aeroallergen exposure may protect against allergic sensitization, but there are scant prospective data to support these findings.
METHODS: 144 new employees at a mouse facility were enrolled in a prospective cohort study. Skin testing, assessment of personal mouse allergen exposure, and questionnaire administration were performed at 0, 6, and 12 months. Survival analysis methods were used to analyze relationships between exposure and skin test sensitivity.
RESULTS: Fifty-seven percent of study participants were female. The median follow-up time was 6 months. The incidence rates of mouse skin test sensitivity at 6 and 12 months were 8.8% and 15.3%, respectively. Atopy was an independent predictor of skin test conversion (hazard ratio [95% CI]: 7.5 [1.0-59.3]). The median cumulative personal Mus m 1 level was 1.1 ng/ml (IQR: 0.1-5.1 ng/ml). Participants in the lowest and highest exposure tertiles had the lowest incidence rates of mouse sensitization at 12 months (6.7% and 11.2%, respectively; p = 0.59, log-rank test), and participants in the middle exposure tertile had the highest incidence rate of mouse sensitization (31.2%; p = 0.15, log-rank test).
CONCLUSIONS: The highest risk of skin test conversion may be associated with moderate, rather than high, levels of mouse allergen exposure in laboratory mouse workers. Substantial reductions in exposure may be required to reduce the risk of allergic sensitization.
Funding: NIH

85 Hypersensitivity Pneumonitis Caused by Trichoderma Viride
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RATIONALE: Hypersensitivity pneumonitis can be induced by exposure to molds contaminating humidifiers and heating-ventilation systems.
METHODS: A 54-year-old woman was seen in the emergency room with dyspnea, cough, chest pain and fever. Her chest X-ray revealed interstitial infiltrates and blood tests showed leukocytosis and severe hypoxemia. She was admitted at the intensive care unit requiring non-invasive mechanical ventilation. She showed a marked improvement within a few days after treatment with antibiotics, oxygen therapy, bronchodilators and systemic corticosteroids. She complained about the presence of pigeons and cats near her house. She had kept a canary for years. She had installed an ultrasonic humidifier at home a year ago. We carried out laboratory tests, pulmonary function tests, high-resolution computed tomography (HRCT) of the chest, bronchoscopy with analysis of BAL fluid and pulmonary biopsy. Precipitating antibodies to common micro-organisms were assessed. Water samples from the ultrasonic humidifier were cultured.
RESULTS: The laboratory test showed leukocytosis with neutrophilia. Chest HRCT showed diffuse micronodular infiltrates and ground-glass opacification. Her pulmonary function tests showed restrictive changes with impaired diffusing capacity. Lymphocytosis and an increase CD4+ / CD8+ ratio in the BAL fluid were observed. Transbronchial lung biopsy demonstrated lymphocytic interstitial pneumonitis and microgranulomas. The cultures of the humidifier water samples grew Trichoderma viride. Precipitating IgG antibodies to Trichoderma viride were detected in patient’s serum by ELISA.
CONCLUSIONS: Home ultrasonic humidifiers should be thought of as a possible cause of HP caused by indoor moulds. To our knowledge, this is the first report of HP caused by Trichoderma viride.
An Age-stratified Assessment Of The Incidence Allergic Diseases Among Patients From Western Hungary

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RATIONALE: The incidence of allergic diseases is increasing worldwide. Prior investigations have shown that the peak incidence of allergy is in young adulthood. The aim of the present investigation is assessment of the age stratification characteristics of patients diagnosed as being allergic among those who presented at the Allergy Outpatient Clinic in Szombathely, Hungary from 2002 to 2003. The clinic receives patients from the western region of Hungary, an area with a population of 300,000.

METHODS: From 2002 to 2003 the outpatient clinic evaluated 7090 sent to the allergy clinic by their general physicians for assessment of possible allergic disease. The patients ranged in age from infancy to 94 years. Disease assessment included clinical history, physical examination, and tests for the presence of allergen sensitization including skin prick tests and allergen-specific IgE determination.

RESULTS: The average incidence of allergy per year over the investigated period among all age groups was 2,363 cases/100,000 population/year. The peak of incidence of allergic diseases was in the age group 5 to 6 years old (174 cases average/year; 5,794 cases/100,000 population/year), while second in incidence was the age group 6 to 14 years old (149 cases average/year; 4,961 cases/100,000 population/year). Both of these pediatric age groups had incidences of allergic disease which was greater than the birth year; 4,961 cases/100,000 population/year. The adolescent (14 to 18 years old) and the young adult (19 to 29 years old) age groups had nearly the same incidence of allergy diagnosis (135 cases average/year; 4,495 cases/100,000 population/year). The group 30 to 60 years old had an average incidence of 89 cases/year (2,964 cases/100,000 population/year); the group 60-80 years old had an average incidence of 24 cases/year (0,800 cases/100,000 population/year), and the group over 80 years old had an average incidence of 3 cases/year (0,100 cases/100,000 population/year) with respect to allergic disease diagnosis.

CONCLUSIONS: In contrast to previous observations, the peak of incidence of allergic diseases was in the age group 3–6 years of age among our patients in western Hungary. There was an impressive decrease in the incidence of allergic diseases in the more elderly age groups. Incidence patterns may not necessarily follow the prevalence distribution of diseases which occur in the “Atopic March”. Further studies are necessary to investigate the causes of this shift in the peak incidence of allergic disease from young adulthood to early childhood. One possible explanation is the growing epidemic of allergic disease in Hungary resulting in increased incidence of allergy in the very young, recently sensitized population of western Hungary.

IgE and Skin Test Reactivity in relation to Anti-parasitic treatment

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RATIONALE: Parasite specific IgE (PsIgE) is a very important parameter of acquired immunity and protection against parasites. It correlates with intensity of infection & competes with household allergens specific IgE for Fc(ε)R1 receptors (HsIgE) with consequent diminished or negative skin test reactivity and corresponding clinical manifestations. We tried to throw light on parasite-allergy relationship.

METHODS: Nineteen asthmatic patients aged 20–40 years, with Schistosoma & Ascaris infestations were subjected to:
1. Serum total IgE (TlgE).
2. Serum Bilharzial antibody titre (BAB).
3. Schistosoma & Ascaris specific IgE (SsIgE) & (Aslge).
4. Skin Test reactivity (ST) to Schistosoma (SWAP), Ascaris antigen (ASA) & common household Allergens (HHA).
5. Parameters were tested before and 6 months after giving Praziquantil & Mebendazol in 3 courses over 3 weeks.

RESULTS: TlgE, SsIgE & Aslge demonstrated significant decrease compared to pre-treatment levels as following:
(1581.1±882.61 IU/ml versus to 413.8±239.15 IU/ml) P= 0.000
(36.37±14.23 IU/ml versus to 4.68 ±2.52 IU/ml) P=0.000
(18.29±9.2 IU/ml versus to 4.58 ± 2.93 IU/ml) P=0.000 respectively.

On the other hand, skin test reactivity wheal to Schistosoma & Ascaris antigens decreased up to 1/3 of the pre-treatment size. Concomitantly, 16% of patients were converted to positive after treatment & 84% demonstrate up to 3 folds increase of pre-treatment wheal diameter.

CONCLUSION: Parasitic infestations induce significant elevation of both TlgE & SsIgE that down regulate IgE-mediated allergic diseases & skin test reactivity to HHA. Treatment with anti-parasitic drugs induce reciprocal effect.
OCCUPATIONAL CONTACT URTICARIA SYNDROME CAUSED BY HANDLING LETTUCE AND CHICORY: CROSS-REACTIVITY BETWEEN LETTUCE AND CHICORY

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RATIONALE: Contact urtica syndrome (CUS) due to lettuce and chicory, belonging to the Compositae family, has rarely been reported.

METHODS: A 30-year-old man, who had been a cook for the past 11 years, was referred to our hospital due to several anaphylactic reactions during cooking. He started developing urtica on his hands, accompanied by generalized urtica, abdominal pain, vomiting, and dyspnea, when he washed lettuce at the age of 27. He also began to feel itchiness on his lips and oral cavity after ingestion of lettuce. Thereafter, he limited his exposure to lettuce by using gloves and avoiding ingestion. Two years later, he experienced generalized urtica and dyspnea when he handled chicory for the first time. The patient underwent prick–prick tests with lettuce and chicory and skin prick tests (SPTs) with pollen extracts. Furthermore, specific IgE against pollens and the allergens of lettuce and chicory were detected by CAP-RAST and IgE-immunoblotting, respectively.

RESULTS: The prick–prick tests with lettuce and chicory were positive, whereas SPTs with ragweed and mugwort were negative. Serum total IgE was 1,587 IU/ml. CAP-RAST revealed positivity to ragweed. The patient’s serum bound to proteins at 32-kDa and 32–34 kDa in the lettuce and chicory extracts, respectively, in IgE-immunoblotting.

CONCLUSIONS: We reported a rare case of occupational CUS caused by handling lettuce and chicory. Our study showed that 32–34 kDa proteins of lettuce and chicory were responsible for CUS in our case, indicating that CUS after first handling of chicory might be caused by cross-reactivity with lettuce.

Funding: Department of Dermatology, Yokohama City University, Yokohama, Japan

ASTHMA PREVALENCE AND MORBIDITY AMONG RURAL SCHOOLCHILDREN IN THE MISSISSIPPI DELTA

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RATIONALE: Reports on asthma among school-aged rural children in the United States are limited and there are no reports on high-risk pediatric populations in rural environments.

METHODS: Children at risk for asthma were identified using a cross-sectional asthma screening survey. Surveys were distributed to students enrolled in Marvell and Eudora school districts in the Arkansas region of the Mississippi Delta. School nurses distributed and collected surveys during the 2005-06 school year.

RESULTS: The survey response rate was 81% (964/1190). Of the 964 children completing the survey, the mean age was 10.3 years (range 4-17), 85% were African-American, and 78% were below poverty level. Twenty-eight percent (268/964) were categorized as being at risk for asthma by previous physician diagnosis (33%), asthma algorithm diagnosis (16%), or both (51%). Of the 268 at-risk children, 14% reported no current symptoms while 7% reported intermittent and 79% reported persistent symptoms. Sixty-five percent reported both daytime and nocturnal symptoms in the past 4 weeks and 62% reported rescue asthma medication use in the past 4 weeks. Activity limitation was reported by 81% and 50% reported being treated in the emergency department or hospital for asthma in the past 2 years.

CONCLUSIONS: These findings suggest that asthma diagnosis and active symptoms are prevalent among this predominately minority and low-income rural population in the Arkansas region of the Mississippi Delta. High rates of inadequately controlled asthma are evidenced by activity limitation, medication use, and increased healthcare utilization. Further studies on asthma should focus on high-risk populations in rural locales.

Funding: UAMS Dean’s Research Development Fund

ASTHMA AND MYCOPLASMA PNEUMONIAE INFECTION

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RATIONALE: Mycoplasma pneumoniae is the first ranking aethiological agent of community-acquired pneumonias in children over five years of age. Some previous studies suggested that M. pneumoniae take part in the initiation and asthma exacerbation. Some studies did not. The aim of this study was to evaluate the association between M. pneumoniae infections and asthma in children.

METHODS: A survey was performed in children visited to Sanbon Medical Center of Wonkwang University. 102 subjects with asthma (47 subjects with previously diagnosed asthma and hospitalized for acute asthma exacerbation, 19 subjects with first asthma attack, 36 subjects with stable asthma) were evaluated. The presence of anti-M. pneumoniae antibodies was assessed.

RESULTS: Of 47 patients, M. pneumoniae was identified in 13 (27.7%) patients during acute exacerbation. Of 19 patients, M. pneumoniae was identified in 5 (26.3%) patients during first asthma attack. Of 36 patients with stable asthma, M. pneumoniae was identified in 3 (8.3%) patients (P < 0.005).

CONCLUSIONS: M. pneumoniae seems to be considered a triggering factor in acute exacerbation of asthma. As a consequence, the diagnosis of M. pneumoniae infection is important in patients with asthma and it should be treated properly.

Funding: Wonkwang University

IS OBESITY RELATED TO SEVERITY AND FREQUENCY OF ASTHMA SYMPTOMS?

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RATIONALE: Obesity is postulated to increase the frequency and severity of asthma symptoms resulting in poorer control of asthma. This study is conducted to determine the effect of obesity on control and severity of moderate to high-risk asthma in inner city children.

METHODS: A retrospective chart review of 109, 16-18 yrs old asthmatic patients was performed. Patients were divided in obese and non-obese groups based on BMI. Obesity defined as BMI > 95%. Number of hospitalizations, ER visits, number of steroid bursts and spirometry were used to compare control and frequency of symptoms in 2 groups over a period of 2 years.

RESULTS: The obese group had 43 patients versus 66 patients in the non-obese group. The obese group accounted for 71 hospitalizations versus 30 for the non-obese group (p=0.004), 194 ER visits versus 30 ER visits (p=0.0003), and 168 steroid bursts versus 50 steroid bursts (p=0.0004) over a two-year period. Obese patients also had a lower FEV1/FVC of 76% vs. 85% (p=0.0002), however there was no statistical significance in the FEV1 between the obese and non-obese group (83% vs. 87%, p=0.3).

CONCLUSIONS: An alarming finding in our moderate to high-risk asthmatics was the obesity prevalence rate of 39% compared to 16-20% of the general pediatric population. Frequency of hospitalizations, ER visits, steroid bursts, was significantly more severe in the obese group then in non-obese asthmatics. FEV1 was not significantly different. This discrepancy may be due to other conflicting issues (e.g. OSA) that should be investigated further.

Funding: medicaid matching fund
Conclusions: An HRA system can consistently identify a high rate of asthma-related health outcomes. Methods are being tested to assure uniform use for all patients seen in the clinic setting.

Funding: Southern California Chapter of the Asthma and Allergy Foundation of America

95 The Asthma Day Care Project: Identifying and Managing Asthma in Brooklyn Preschools

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Rationale: Asthma is a leading cause of school absenteeism and hospitalizations for Brooklyn’s children 0-4 years old. Asthma programs have been established to screen school-aged children, but such interventions do not exist for younger children, and a large number remain undiagnosed and untreated. Our objective is to initiate a large-scale, preschool-based system for early asthma identification and management in inner city children.

Methods: Twenty day care centers in central Brooklyn with high asthma hospitalization rates were selected for the study with 2886 enrolled children. The Brief Respiratory Questionnaire (BRQ), a validated, bilingual, 9-question asthma survey was used to quantify asthma risk. A “yes” response to at least one question identified children with “likely asthma”. The parents would then receive an Asthma Action Plan (AAP) to be completed by their physician, if asthma was confirmed.

Results: A total of 2069 BRQs were distributed, of which 1263 (61%) were received from 15 participating sites. Using the BRQs, “likely asthma” was identified in 386 (31%) children and 137 (35%) were diagnosed with asthma from the returned AAPs.

Conclusions: This preliminary data demonstrates that the BRQ can be used to identify children at risk for asthma in a preschool setting. We hope to establish decreased absenteeism (missed school and parent work days) and hospitalizations following implementation of the BRQ at the time of inner city preschool enrollment.

Funding: New York City Department of Health and Mental Hygiene

96 Dust And Airborne Concentrations Of Endotoxins In Strasbourg And In A Rural Environment (Haut-Doubs)

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Rationale: To compare dust and airborne concentrations in Strasbourg (STG) and rural environment.

Methods: 100 dwellings were randomly selected to be representative of the type of dwellings in STG area. In the Haut-Doubs, 49 farms with cow producing milk and 50 non-farming dwellings used as controls were also randomly selected. Samples were performed in all dwellings in the dust of the oldest mattress and the floor of the room where the mattress was located. 2 airborne samples were performed using a portable pump. Endotoxin measurements were performed using the limul test (Chromogenix®). A standardized questionnaire was filled for each home visit with supplementary questions in the rural area.

Results: The levels of endotoxin in the mattress dust were significantly higher in the rural area than in STG (farm: mean ± SD : 2.9 ± 4.1, control farm: 1.09 ± 2.4, STG: 0.85 ± 2.7 μg/g p<0.001). In the air, no difference was found between the 3 groups.

Conclusions: Endotoxin concentration in dust were higher in the rural area than in STG area. However, no difference was found in the air. Our results underlined the difficulty to assess endotoxin exposure.

Funding: Centre Scientifique et Technique du Bâtiment
97 Allergy To Cumaru (Dipterix micrantha Harms) Tropical Wood F. de la Losa, Sr.; DIATER Laboratories San Martin de la Vega SPAIN.

RATIONALE: Wood dust may produce allergic rhinitis, asthma, or contact dermatitis in sensitized patients, being tropical woods frequently implicated in occupational allergy in last years. However, the knowledge about wood allergens is still limited. Shihuahuaco (Dipterix micrantha Harms), internationally known as Cumaru, is a tropical wood very appreciated for wood floors. The aim of this study was to identify allergens involved in a case of asthma due to the tropical wood Cumaru, which has never been reported to be allergenic so far.

METHODS: A 47-years-old man suffered from acute dry cough and asthma in several occasions after polishing Cumaru wood. He did not suffer any symptom when working with other woods. An in vitro study was performed to determine the presence and the possible pattern of IgE sensitization to this wood. Specific IgE to Cumaru wood dust was determined with enzymatic method. Extract proteins were separated by SDS-PAGE and SDS PAGE immunobloting was performed with serum from patient.

RESULTS: Specific IgE was 2.2 IU/L (EAST: HYTEC, HYCOR Biomedical Ltd.UK). SDS-PAGE Immunobloting showed two IgE-binding bands of 28 and 90 kDa.

CONCLUSIONS: In vitro sensitization to Cumaru wood has been demonstrated, being implicated two bands of 28 and 90 kDa, recognized by the serum of the patient. To our knowledge, this is the first case reported so far of asthma due to Shihuahuaco wood dust, where an IgE mediated mechanism has been suggested.

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RATIONALE: Asthma absenteeism may be a useful indicator of asthma morbidity, but is difficult to track with available data. We estimated the impact of asthma absences on total school absences.

METHODS: In response to a survey question, 1203 elementary school nurses in upstate NY reported the number of students who missed school due to asthma. The National Asthma Survey/NY State (unpublished data) estimated that students who missed school due to asthma averaged 8.6 asthma absences per year. We estimated the impact of asthma absenteeism by calculating the ratio of asthma absences (the number of students who missed at least one day of school due to asthma multiplied by the average number of days missed due to asthma) to total school absences (NY State Education Department attendance data).

RESULTS: The ratio of estimated asthma absences to total school absences was 25.6 per 1000 absences (95% CI 24.0-27.2). The ratio varied by geographic location from 9.7 to 27.3 asthma absences per 1000 absences and increased with the number of school environmental triggers reported by school nurses (test for trend, p<0.001). A higher ratio of asthma absences to total absences was correlated with physical activity limitations (r=0.54) and visits to the health office (r=0.50) but not with asthma management practices.

CONCLUSIONS: The effect of asthma on total absenteeism may vary by school demographics and environmental conditions. Development of a model to estimate the impact of asthma absenteeism has proved challenging using existing data. Improved tracking and methods of estimating asthma absenteeism are needed.