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ORAL ABSTRACT SESSION ALLERGEN IMMUNOTHERAPY 1

1
Ultra-Rush Specific Immune Therapy with Depigmented and Polymerized Allergen Extracts is Effective and Safe in Patients With Severe SAR Highly Sensitized against Pollen Allergens

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Background: Procedures for specific immune therapy (SIT) vary widely. We were interested whether a pre-seasonal ultra-rush treatment with depigmented and polymerized allergen extracts is effective and safe in patients with severe SAR.

Methods: 31 pts (21 f, 10 m, mean age 39.7 years, range: 17–69 years) with severe SAR and partial asthma attacks (31.3%) during pollen season (mean total IgE level 152 kU/L, range: 5–5113 kU/L; mean Phadia CAP class 3.7 and 3.5 against birch pollen and Bet v1, resp.; mean Phadia CAP class 3.7 and 3.3 against grass pollen and Phl p1,5, resp.) were treated with an ultra-rush schedule receiving the maximum dose of 0.2 plus 0.3 mL of a allergen extract (DepiQuick, Novartis, Germany) on day one, followed by further injecting the maximum dose of 0.5 mL at weekly intervals for 5 weeks. Patients were interviewed by a questionnaire 2 months after the pollen season.

Results: 75.8% of patients reported a good or very good effect of SIT with respect to their symptoms during the pollen season after having received only one cycle of ultra-rush SIT; 18.4 did not notice any effect after the first cycle; one patient reported an increase of symptoms. 56.5% of patients did use less anti-allergic medication in comparison with their mean need before SIT; in 18.8% the need of medication was comparable to the year before. In 77.8% of all cases ultra-rush SIT was well tolerated subjectively. Local swelling at the injection site was reported in 25.9% (immediate) and 42.4% (delayed); 4 patients felt a mild discomfort after injection with pruritus, fatigue, or dizziness, respectively. The systemic symptoms disappeared spontaneously without medication.

Conclusions: Even for patients with clinically severe SAR and high specific sensitization against birch or grass pollen the pre-seasonal ultra-rush SIT regimen with depigmented, polymerized allergen extracts showed a good efficacy and tolerability.

2
Dose Optimizing Study of a Depigmented Polymerized Allergen Extract of Birch Pollen by Means of Conjunctival Provocation Test

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Background: Clinical efficacy of a depigmented polymerized birch pollen extract has been shown in 2 large phase III studies with 1000 DPP/mL. To date dose-response studies are required to show optimal efficacy at a defined allergen dose. The conjunctival provocation test (CPT) is a possible outcome parameter and from the regulatory authorities accepted test procedure.

Methods: 301 (PP) patients with confirmed rhinitis and/or rhinoconjunctivitis were treated in a double-blind study with 4 doses of 100 DPP/mL, 1000 DPP/mL, 5000 DPP/mL and 10.000 DPP/mL allergen extract over 22 weeks in Germany, Poland, and Lithuania. A 1-day build-up phase applying 0.1 mL and 2 times 0.2 mL allergen extract was followed by a maintenance period applying 0.5 mL in 3 to 4 weeks intervals. Before treatment a CPT was performed with semi-logarithmically increasing doses up to 10,000 SQ-U/mL of native birch extract, after treatment the CPT was repeated with doses up to 100,000 SQ-U/mL. The main parameter was the percentage of patients with an increase of allergen extract to provoke a positive CPT after SIT. Secondary parameters were specific IgE, IgG1 and IgG4 as well as safety. The main parameter was investigated using a hierarchic test procedure comparing the highest dose against the lowest, if statistically significant testing the next lower dose against the lowest until the difference was no longer significant.

Results: An increase in allergen amount to provoke a positive CPT after SIT was reached in 37.5% of the 100 DPP/mL, 50.7% of the 1000 DPP/mL, 54.9% of the 5000 DPP/mL and 55.8% of the 10,000 DPP/mL group. Results compared to the lowest dose were statistically significant for the 5000 DPP/mL ($P = 0.0236$) and 10,000 DPP/mL group ($P = 0.0159$). Specific IgEs remained stable in all groups whereas specific IgG1 and IgG4 showed dose-dependent increases. Grade 1 systemic reactions occurred in 18% (100 DPP/mL), 14.8% (1000 DPP/mL), 17.4% (5000 DPP/mL) and 25.3% (10,000 DPP/mL) of patients.

Conclusions: We determined increased allergen amounts to obtain a positive CPT after SIT from 1000 to 10,000 DPP/mL depigmented polymerized birch pollen extract. The 5000 DPP/mL dose extract suggest a good benefit/risk ratio with the potential for further development.

3
Double-blind Study of the Use of Transfer Factor (TF) Combined With Sublingual Immunotherapy in Management of Patients With Allergic Rhinitis in Mexican Population

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Background: Allergic diseases affect 20% of world population and allergic rhinitis (AR) is the most common, alone or associated with asthma. Antigen-specific immunotherapy has been world-desensitizing type studied showing that it is capable of modifying the natural history of the disease through changes in the immune response increasing the role of clones of lymphocytes T helper type I (LTh1) and inhibiting the activity of type 2 (LTh2). Dialyzable leukocyte extract or transfer factor (TF) has shown the same stimulatory effect.

Objective: Evaluate the synergistic effect of TF associated with SLIT in patients with RA.

Material and Methods: We studied 94 patients with RA. We included randomized into 2 groups (47 each one) both received antigen-specific sublingual immunotherapy (SLITAE) and also in group 1 was given oral TF Unit at one 200 mg monthly for 3 months, and group 2 placebo. We used a control group only to compared the normal results. All patients underwent complete blood count (BHC), immunoglobulins, quantification of cell-type lymphocyte CD3, CD4, CD8, interleukin (IL2, IL4, IL5, IL10, TNF and

IFN). The nasal symptoms were evaluated monthly for 3 months, with test score symptoms questionary 4 (TSSQ4) and auto-evaluation by scale Linker.
Results: We studied 94 AR patients (50% women and 50% men, range age between 5 and 40 years). Indoor antigens (mites, house dust and cockroach) were the main cause of allergy. Allergic patients had more eosinophiles and IgE than the healthy controls ($P < 0.05$). The number of CD8+ lymphocytes was slightly reduced in group 2 after treatment ($P < 0.05$), whereas the amount of IL-4 and IFN ƒnwere increased in both groups ($P < 0.005$) and the amount of IL-10 was significantly increased in group 1 ($P < 0.01$) after treatment. Clinical evaluation was with initial TSSQ4 of 11.6 before handling and 5.1 (44%) after, with significant improvement ($P < 0.0001$) and Likert score was reduced 69% than the star the treatment.
Conclusions: The TF along with SLITAE in the treatment of patients with RA did not alter the clinical improvement induced by SLITAE alone for 3 months of treatment, but the combination increased production of IL 10 and production of IFNg.

4

The Risk of Severe Treatment Related Adverse Events is Significantly Lower in Children Compared to Adults When Treated With Standardized Timothy Grass Allergy Immunotherapy Tablets: Post Hoc Analysis of 7 Clinical Trials

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Background: Allergy immunotherapy tablets (AIT) provides a safer and more convenient alternative to subcutaneous specific immunotherapy treatment. However, severe adverse events occur infrequently. These events are rare and therefore pooled safety data from 1 phase II/III and 6 phase III clinical trials (5 in adults, 2 in children (5–17 years)) with grass AIT (Grazax, *Phleum pratense* 75,000 SQ-T/2800 BAU, ALK, Denmark) were analysed.
Method: All trials were randomised, double-blind, placebo-controlled multi-centre trials. Subjects suffered from grass pollen induced allergic rhinoconjunctivitis with or without asthma, had positive skin prick test and specific IgE to *Phleum pratense*. Subjects received once-daily sublingual treatment with grass AIT or placebo for approximately 24 weeks. The 5 adult trials comprised 2095 treated subjects (AIT = 1060, placebo = 1035) and the 2 children trials comprised 597 treated subjects (AIT = 301, placebo = 296). Adverse events were assessed by the investigator as treatment-related (possible or probable) or unlikely related and for seriousness. Application site-related events were defined as adverse events in relation to the oral cavity.
Results: In the adult trials, 71% of AIT-treated subjects reported treatment-related adverse events compared to 24% for placebo. In the children trials the corresponding numbers were 63% for AIT and 27% for placebo. Of the AIT-treated subjects 2 children (0.7%) and 32 adults (3.0%) experienced severe treatment-related events. The odds for severe events was 4.7 times lower in children compared to adults (odds-ratio with 95% CI, 0.22 [0.025-0.85], $P = 0.019$). Both AIT-treated children (0.7%) and 18 (1.7%) of the AIT-treated adults experienced severe treatment-related events that were application site-related. The odds for having severe related application site adverse events was 2.6 times lower in children compared to adults (odds-ratio with 95% CI, 0.39 [0.04-1.63], $P = 0.27$, not statistically significant). No serious treatment-related adverse events were reported.
Conclusion: This pooled analysis of over 2000 subjects in 7 clinical trials shows that the risk of experiencing severe treatment-related adverse events was significantly lower in children compared to adults when treated with of Timothy grass allergy immunotherapy tablets. This analysis provides evidence that Timothy grass AIT is an important and safe immunotherapy treatment option in children with grass pollen induced rhinoconjunctivitis.

5

Posttreatment, Long-Term Clinical Efficacy of a 300 IR Sublingual Tablet of 5-Grass Pollen Allergen Extract in Adults With Grass Pollen Induced Allergic Rhinoconjunctivitis

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Background: A 5-year study of adults with grass-pollen related rhinoconjunctivitis has demonstrated the sustained efficacy of discontinuous treatment with a 300 IR sublingual tablet of 5-grass pollen allergen extract, initiated 4 or 2 months before each pollen season and continued for its duration for 3 consecutive years. Here we report on the persistence of efficacy during the first of 2 post-treatment pollen seasons.
Methods: 633 adults were randomized to either placebo or one of 2 active groups receiving pre- and co-seasonal treatment for 3 pollen seasons starting each year either 4 months [4M] or 2 months [2M] prior to the pollen season. Patients were followed during the subsequent, treatment-free, grass pollen season. The primary endpoint for the Year 4 assessment of the post-treatment long-term efficacy was the Average Adjusted Symptom Score (AAdSS, adjusting the Rhinoconjunctivitis Total Symptom Score for rescue medication usage) during the fourth pollen period. Secondary efficacy criteria included the Average Rescue Medication Score (ARMS) and the overall Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score.
Results: Statistically significant differences compared to Placebo in the mean AAdSS during the Year 4 pollen period were observed for both 300 IR (4M) and 300 IR (2M). The treatment effect for 300 IR (4M) was estimated as the difference in LS Means of −1.14 (95% CI, [−2.03 to −0.26], $P = 0.0114$), corresponding to a relative LS Mean difference from Placebo of −22.9%, whilst the treatment effect for 300 IR (2M) is estimated as the difference in LS Means of −1.43 (95% CI, [−2.32 to −0.53]), $P = 0.0019$), corresponding to a relative LS Mean difference from Placebo of −28.5%. The primary results were confirmed over the worst pollen period. Compared to placebo, the active treatment groups (4M and 2M) also showed a statistically significant LS Mean difference in ARMS (−24.6%; $P = 0.00184$ and −27.9%; $P = 0.0082$) and in overall RQLQ score (−32.8%; $P = 0.0001$ and −37.6%; $P < 0.0001$). No unexpected risk was identified in this study.
Conclusions: The post-treatment, long-term efficacy of 300 IR sublingual tablets of grass pollen allergen extract was demonstrated during the first of 2 post-treatment pollen seasons. This persistent improvement was clinically meaningful to patients.

6

Escherichia coli Heat-Labile Enterotoxin (LTS61K) Modulates Dendritic Cell Function and Attenuates Airway Inflammation in Mouse Model of Allergic Asthma

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Background: *Escherichia coli* heat-labile enterotoxin (LT) with different mutant forms has been used as adjuvant for vaccines due to its ability to enhance immune response to specific antigen in vivo. We hypothesis that LTS61K or LTS61K mixed with dust mite allergen, Der p, (LTS61K/Der p) can modulate dendritic cells (DCs) s' functions thus alleviate allergen-induced airway inflammation.

Methods: Two protocols (ie, preventive and therapeutic protocol) were designed to evaluate the effects of LTS61K in Der p sensitized and challenged mouse model of asthma.
Results: Both intranasal inoculations with LTS61K or LTS61K/Der p decreased allergen-induced airway inflammation and alleviated systemic T_H2-type immune response. In addition, bronchoalveolar lavage (BAL) fluids and sera from LTS61K/Der p treated mice have higher concentrations of Der p-specific IgA than those of other groups. In the in vitro study, bone marrow-derived dendritic cells (BMDCs) and DC cell line, DC2.4 cells stimulated with LTS61K/Der p both secreted pro-inflammation cytokines IL-6 and TNF-a. In contrast, after LTS61K treatment, only BMDCs decreased production of IL-6 and TNF-a as well as decreased maturation. Furthermore, we found that pre-treatment BMDC with LTS61K inhibited Der p-induced NF-kB translocation which might explain the delayed maturation and decreased productions of IL-6 and TNF-a in LTS61K pre-treated BMDCs. Intratracheally adoptive transferred with LTS61K- or LTS61K/Der p-primed DC2.4 cells or BMDCS into Der p-sensitized mice decreased inflammatory cells infiltration and T_H2-type chemokines in BAL fluids and alleviated airway inflammation.
Conclusions: Our results show that LTS61K may influence DCs maturation and its cytokine production. On the other hands, LTS61K/Der p may induce more Der p-specific IgA production to decrease allergic T_H2 cytokine responses and alleviate airway inflammation in murine model of asthma. These finding suggested that LTS61K may have clinical application as an immune-modulator effect on the diseases of allergy and asthma.

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7
Comparison of Efficacy and Safety of a Dipigmented Polymerized Allergen Extract of Grass and Birch with Placebo in Patients With Type-1 Allergic Rhinoconjunctivitis

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Background: The safety and efficacy of specific immunotherapy (SIT) with depigmented and polymerized allergen extracts of pollen is well documented in several clinical trials. We investigated efficacy and safety of an extract containing 2 taxonomically non-related pollen species (birch and grasses) in a subcutaneous immunotherapy over 2 pollen seasons in co-sensitized allergic patients with rhinitis and/or rhinoconjunctivitis with or without allergic asthma.
Methods: 269 (ITT) patients with confirmed rhinitis and/or rhinoconjunctivitis were treated during 2009 and 2010 in Germany, Romania, Poland, Lithuania, and Bulgaria. For each patient a 1-day build-up phase applying 0.2 mL and 0.3 mL of 1000 DPP/mL allergen extract was applied. During the remaining 18-month period maintenance 500 DPP were administered in 4 to 6 weeks intervals. Patients were randomised to the treatment groups on a 2:1 basis (175 verum: 94 placebo). The main parameter in this study was the combined symptom and medication score during the birch and grass pollen season 2010 over 7 weeks. Secondary parameters were symptom score, medication score, IgE, IgG4 as well as quality of life.
Results: During the 2010 season a statistically significant difference ($P = 0.0385$) was observed between treatment groups: in patients treated with the allergen extract the median time weighted AUC of the combined symptom and medication score was 5.70, in patients treated with placebo 7.07. This effect was predominantly due to the reduction of symptom score by 21% over placebo. The intake of recue medication was very low during both seasons leading only to a 10% reduction (ns). Birch and phleum specific IgE did not change during the course of the study in both groups whereas respective IgG4 levels increased only in the verum group and remained nearly unchanged in the placebo group ($P < 0.0001$). Total QoL score was improved in verum patients ($P = 0.0254$). 5.4% of the patients in the verum group and 4.0% of the patients in the placebo group developed mild systemic reactions.
Conclusions: The results show that specific immunotherapy with a depigmented polymerized extract of 2 taxonomically non-related pollen (birch and grass) was effective and safe demonstrated by clinical and immunological parameter.

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Allergenic Composition of Polymerized Allergen Extracts of *Betula verrucosa*, Dermatophagoides Pteronyssinus and Phleum Pratense

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Background: Allergoids have been successfully used in the treatment of respiratory allergic diseases. They are modified allergen extracts that allow the administration of high allergen doses, due to their reduced IgE binding capacity.They maintain allergen-specific T-cell recognition. Since they are native allergen extracts that have been polymerized with glutaraldehyde, identification of the allergenic molecules requires more complicated methods. The aim of the study was to determine the qualitative composition of different polymerized extracts and investigate the presence of defined allergenic molecules using Mass spectrometry.
Methods: Proteomic analysis was carried out at the Proteomics Facility of the Hospital Nacional de Parapléjicos (Toledo, Spain). After reduction and alkylation, proteins were digested with trypsin and the resulting peptides were cleaned using C18 SpinTips Sample Prep Kit; peptides were separated on an Ultimate nano-LC system using a Monolithic C18 column in combination with a precolumn for salt removal. Fractionation of the peptides was performed with a Probot microfraction collector and MS and MS/MS analysis of offline spotted peptide samples were performed using the Applied Biosystems 4800 plus MALDI TOF/TOF Analyzer mass spectrometer. ProteinPilot Software V 2.0.1 and the Paragon algorithm were used for the identification of the proteins. Each MS/MS spectrum was searched against the SwissProt 2010_10 database, Uniprot-Viridiplantae database and Uniprot_Betula database.
Results: Analysis of the peptides revealed the presence of native allergens in the polymerized extracts: Der p 1, Der p 2, Der p 3, Der p 8 and Der p 11 in D. pteronyssinus; Bet v 2, Bet v 6, Bet v 7 and several Bet v 1 isoforms in B. verrucosa and Phl p 1, Phl p 3, Phl p 5, Phl p 11 and Phl p 12 in *P. pratense* allergoids. In all cases, potential allergenic proteins were also identified, including ubiquitin, actin, Eenolase, fructose-bisphosphate aldolase, luminal-binding protein (Heat shock protein 70), calmodulin, among others.
Conclusions: The characterization of the allergenic composition of allergoids is possible using MS/MS analysis. The analysis confirms the presence of native allergens in the allergoids. Mayor allergens are preserved during polymerization.

9
A Proteomic Style Approach to Characterize a Grass Mix Product Reveals Potential Immunotherapeutic Benefit

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Background: Grass allergy immunotherapies often consist of a mix of different grass extracts each containing several proteins of different physiochemical properties; however the subtle contributions of each protein are difficult to elucidate. This study aimed to identify and characterise the

group 1 and 5 allergens in a 13 grass extract and to standardise the extraction method.

Methods: The grass pollens were extracted in isolation and pooled and also in combination and analysed using a variety of techniques including enzyme-linked immunosorbent assay (ELISA), liquid chromatography-mass spectrometry (LC-MS) and sodium dodecyl sulphate polyacrylamide gel electrophoresis (SDS-PAGE).

Results: Gold-staining and IgE immunoblotting revealed a high degree of homology of protein bands between the 13 species and the presence of a densely stained doublet at 25 to 35 kD along with protein bands at approximately 12.5, 17 and 50 kD. The doublet from each grass species demonstrated a high level of group 1 and 5 interspecies homology. However, there were a number of bands unique to specific grasses consistent with evolutionary change and indicative that a grass mix immunotherapeutic could be considered broad spectrum.

Conclusions: SDS-PAGE and IgE immunoblotting showed all 13 grasses share a high degree of homology particularly in terms of group 1 and 5 allergens. IgE and IgG ELISA potencies were shown to be independent of extraction method.

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Seasonal Versus Symptom-based Evaluation of a Depigmented Grass-Birch Allergoid

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Background: The safety and efficacy of specific immunotherapy (SIT) with depigmented and polymerized allergen extracts of pollen is well documented in several clinical trials. The results of such clinical studies are highly dependent on the quantity and quality of pollen exposure and their measurements. To identify a pollen-independent efficacy assessment we compared the combined symptom and medication score (SMS) measured during the pollen season with the SMS defined by a minimum symptom score of the placebo group in a subcutaneous immunotherapy with a depigmented Grass-Birch allergoid over 2 years.

Methods: 269 (ITT) patients with confirmed rhinitis and/or rhinoconjunctivitis were treated during 2009 and 2010 in Germany, Romania, Poland, Lithuania, and Bulgaria. Patients were randomised to the treatment groups on a 2:1 basis (175 verum: 94 placebo). The main parameter in this study was the combined symptom and medication score during the birch and grass pollen season 2010[1]. In addition the SMS of the actively treated patients was analyzed following the placebo treated patients eliciting a considerable symptom burden >2.

Results: The clinical results following the seasonal approach are given in the other abstract of our group[1]. Taking all days with mean symptom score >2 in the placebo group as calculation basis, the combined SMS values were considerably lower for actively treated patients than for placebo treated patients. For both seasons, the differences between the treatment groups were highly statistically significant (median; 2009: 5.06 vs 7.97, 2010: 4.26 vs 6.43; ITT set) with *P*-values of 0.0038 and 0.003.

Conclusions: The results show that the efficacy assessment of specific immunotherapy might be better discriminated in relation to the actual symptoms of the placebo group rather than following the days of pollen exposure.

REFERENCE

1. Abstract # 3093: Biedermann T, Pfaar O, Sager A. "Comparison of efficacy and safety of a depigmented polymerized allergen extract of grass and birch with placebo in patients with type-I allergic rhinoconjunctivitis.".

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Efficacy and Tolerability of HDM Injective Immunotherapy With Monomeric Allergoid

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Background: Subcutaneous immunotherapy (SCIT) is an effective treatment of respiratory allergy and carbamylated monomeric allergoids (monoids), by virtue of their reduced IgE-binding activity, resulted clinically safe by sublingual administration. Purpose of this study was to investigate the efficacy and tolerability of immunotherapy with house dust mites (HDM) monoid administered by injective route in patients with allergic rhinoconjunctivitis (AR).

Methods: A preparation of 0.70 mL of 10 BU/mL containing modified extract with 50% *Dermatophagoides pteronyssinus* and 50% *Dermatophagoides farinae* (amount of major allergen: 4 μg of group 1 per milliliter) was delivered monthly for 12 months, following a 5-week build-up induction phase (0.10–0.20–0.30–0.50–0.70 mL), to 58 patients (60% males, mean age 25.1 ± 12.7) suffering from AR due to mites for at least 2 years, whereas 60 patients with similar baseline characteristics were observed as controls. All patients were allowed to assume traditional drug therapy for their condition. At the end of the study changes from baseline in symptoms scores, in number of days with drug assumption, in severity of AR (according to ARIA classification) were compared between the 2 groups; moreover an overall assessment of clinical efficacy and tolerability was based on patients' and physicians' judgements (unsatisfactory, mild, good, optimal).

Results: In respect to baseline both groups showed, after 1 year, an improvement in symptoms score ($P < 0.001$) with a significant difference in favour of SCIT group ($P < 0.05$). Days of drug intake were significantly lower in patients receiving SCIT ($P < 0.05$). The number of patients with severe AR decreased in the first group while no variation was observed in controls. The subjective clinical overall assessment was optimal in 31 cases and good in 24 according to physicians' and patients' judgements; similarly 38 patients judged tolerability as optimal and 18 as good, whereas according to physicians it was optimal in 37 patients and good in 19; in only 1 patient the treatment was considered unsatisfactory.

Conclusions: In this prospective controlled study, SCIT with HDM carbamylated allergoid was associated with a significant clinical benefit observed through objective and subjective outcomes; the traditional safety of monomeric allergoids was confirmed by the subjective judgements of tolerability.

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12
Comprehensive Detection of Allergens in Grass Pollen Extracts by Mass Spectrometry

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Background: More than 40% of type 1-allergic individuals suffer from hypersensitivity to grass pollen. Patients are treated traditionally with specific

immunotherapy using pollen extracts derived from one or several different *Pooideae* species. While for several species the most important allergens (group 1 and group 5) have been identified, other allergens have either not been identified or sequence data are still missing. We have used mass spectrometry (MS) together with genetic and immunological methods to identify allergens in various grass pollen extracts.

Methods: Pollen extracts of 6 different grass species (*Phleum pratense*, *Holcus lanatus*, *Lolium perenne*, *Dactylus glomerata*, *Festuca pratensis*, *Poa pratensis*) and a mixture thereof were analyzed. For identification of allergens by MS, extracts were subjected to enzymatic digestion. Resulting peptides were separated by liquid chromatography and analyzed by tandem mass spectrometry. Protein identification was performed by searching both the NCBIPlant release and an individually designed database. The presence of individual allergens was confirmed with allergen-specific monoclonal antibodies. Unknown sequences were determined following cDNA synthesis from pollen RNA and allergen sequence amplification by PCR.

Results: Fes p 1 and Fes p 5 were identified by the PCR approach. MS analysis of pollen extracts from the 6 individual species resulted in detection of all known allergens including the newly identified Fes p 1 and Fes p 5. Based on the homology of allergens from different grass species, previously unknown sequences of representatives of groups 2, 3, 4, 7, 11, 12 and 13 were detected by MS in investigated extracts with high sequence coverage. Group 6 allergens could not be identified in some of the analyzed extracts. These findings are supported by immunological analyses and thus demonstrate the specificity of the applied method. Members of all allergen groups were identified in an extract mix prepared from pollen of all 6 grass species studied.

Conclusions: The most important grass allergens (group 1 and group 5) were detected in all extracts. In addition all other known allergens of the assayed species and homologues thereof could also be identified, thus demonstrating the quality of the tested extracts.

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Gene Expression Pattern of Arabidopsis EXPB1, a Nonallergenic Homologue of Grass Group 1 Pollen Allergens

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Background: Grass pollen allergy is one of the most common allergies worldwide. Group I allergens constitute the major allergenic component of grass pollen with more than 85% of grass pollen allergic patients showing IgE reactivity. These are highly immunologically cross-reactive glycoproteins specifically expressed in pollen of all grasses. Alignments of the amino-acid sequences of grass group I allergens derived from diverse grass species reveal up to 95% homology. It is therefore likely that these molecules share a similar biological function.

Methods: RT-PCR analysis, In situ hybridisation, Promoter-GFP construct design, plant transformation and analysis of transgenic plants.

Results: Sequence comparison has identified a homologue (β-expansin clone At2g20750 or EXPB1) in *Arabidopsis* of the Cyn d 1 gene. The EXPB1 protein is 42% similar to the Cyn d 1 protein. This gene represents a member of a small multigene family in Arabidopsis. RT-PCR analysis showed expression only in floral not vegetative tissues. In situ hybridisation using 150 bp region of the 3′ UTR of the *Arabidopsis* gene as probe showed specific expression in mature *Arabidopsis* pollen. We further cloned the promoter region for the Arabidopsis EXPB1 and prepared and GFP fusion constructs. These constructs were then introduced in to Arabidopsis plants by floral dip method. GFP-promoter fusions showed high level of expression in tri-cellular pollen.

Conclusions: Our study provides evidence that EXPB1, a non-allergenic homologue of grass group 1 pollen allergens, gene is expressed in mature pollen.

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Comprehensive Expression of Recombinant House Dust Mite Allergens for Component-Resolved Diagnosis

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Background: Allergen-specific immunotherapy (SIT) is the only promising treatment of allergy. However, current SIT has limitations such as a need for long-term medication and a risk of systemic anaphylaxis. Those issues are raised mainly because current SIT procedure is carried out using crude allergen extract, which may also induce a harmful neo-sensitization. Use of defined recombinant allergens would be a preferable alternative for the next generation SIT vaccine as well as for the development of component-resolved diagnosis (CRD), which enables to prescribe a patient-tailored vaccine. Objective of this study is to construct a production system of recombinant house dust mite (Dermatophagoides farinae) allergens, and to test their usefulness for molecular diagnosis.

Methods: Thus far, the WHO/IUIS allergen nomenclature subcommittee has approved 24 Dermatophagoides allergens. Among them, we sought to express 20 groups of D. farinae allergens (Der f 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 13, 14, 15, 16, 17, 18, 20, 21, and 22) using the Escherichia coli cold shock expression system. We also tried to express additional new antigens [Mag133 (a highly-conserved UK114/YER057c/YjgF family member), DFA22 (a new group 2 family member), and DFA67 (peroxiredoxin)] that we originally identified as major allergens with high IgE-binding frequencies. IgE-binding ability of those recombinant allergens was assessed by western blot analysis. We also tested whether these allergens were applicable for the development of CRD.

Results: We confirmed successful expression of above D. farinae allergen molecules as soluble recombinant proteins. Western blot analysis revealed that these recombinant allergens retained IgE-binding capacity. We also found that house dust mite-allergic patients showed differential IgE-binding signatures against them, suggesting that our recombinant allergens are useful to determine sensitized allergen molecules in individual patients.

Conclusions: Here we carried out the comprehensive expression of recombinant D. farinae major allergens. The recombinant allergen repertoire offers an essential platform for the future molecular diagnostics of dust mite allergy.

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A Bioinformatic Approach to Allergen Nomenclature Applied to Allergens From the Non-Biting Midge *Chironomus thummi thummi*

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Background: Representatives of the family Chironomidae (non-biting midges; order Diptera) are found worldwide. Freeze-dried chironomid larvae, predominantly of the species *Chironomus thummi thummi* are frequently used as fish food and are an allergen source for fish keepers and persons employed in the manufacture of fish food. At present, 9 allergens of *C. thummi thummi* have been assigned an official designation by the WHO/IUIS allergen nomenclature sub-committee: Chi t 1 to 9. All of them are hemoglobins with

molecular weights of 16 kDa. IgE binding and cross-reactivity was clearly demonstrated for all these proteins. However, the assignment of 9 distinct allergen numbers to members of the same protein family is quite unusual.
Methods: Currently, the IUIS allergen database contains 12 allergen and isoallergen sequences from C. thummi thummi. The Uniprot database has demerged entry P02225, listed in the database for Chi t 7, into 7 entries, 5 from *C. thummi thummi* and 2 from *C. thummi piger* that are identical to 2 of the sequences from *C. thummi thummi*. Consequently, the 16 unique amino acid sequences of the mature *C. thummi* allergens were aligned using ClustalX2, a neighbor-joining tree was generated from the alignment and a percent sequence identity matrix was built to evaluate appropriate nomenclature.
Results: Pairwise sequence alignments showed that sequences belonging to allergens Chi t 5, 6, 7 and 8 possess sequence identities to Chi t 3 of between 51 and 63%. Chi t 1, 2, 4, and 9 diverge to a greater extent from Chi t 3 (<50% identical) and from each other. Phylogenetic tree analysis suggests the clustering of Chi t 3, 6, 7, and 8, while Chi t 1, 2, 4, 5, and 9 form separate clades.
Conclusions: Based on these analyses, the IUIS Allergen Nomenclature Sub-Committee renames Chi t 5, 6, 7 and 8 isoallergens of Chi t 3, even though their sequence identities to Chi t 3 are below the 67% threshold previously defined for isoallergens. The remaining hemoglobins, previously designated Chi t 1, 2, 4 and 9 will retain their previous names.

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Pollen Allergens Differ From Nonallergenic Pollen Proteins by Their Lower Extent of Evolutionary Conservation

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Background: Pollen contains hundreds of different proteins. However, only a small fraction of them have been identified to be allergenic. We aimed to test the hypothesis that most pollen proteins are non-allergenic due to their high extent of sequence conservation among non-related species.
Methods: Data on the composition of pollen proteomes of birch (*Betula pendula*), pellitory (*Parientaria judaica*) and timothy grass (*Phleum pratense*) were obtained from the literature. Sequences were downloaded from UniProt and manually classified into allergens and non-allergens. Complete proteome sequences of 3 dicotyledonous species (*Arabidopsis thaliana*, *Populus trichocarpa* and *Vitis vinifera*), 2 monocotyledons (*Oryza sativa* subsp. japonica and *Zea mays*) and one moss (*Physcomitrella patents*) were downloaded from ENSEMBL Plants. Sequences of pollen proteins were compared to these proteomes by using BLAST and the hits yielding the highest sequence identity recorded taking into account only sequence alignments at least 40 residues in length. The distributions of maximum sequence identities of allergens and non-allergens from each species were compared using the Mann-Whitney test.
Results: Allergens from birch and pellitory pollen were significantly ($P < 0.001$) less similar to proteins from monocots than non-allergenic pollen proteins. Median sequence identities to the nearest rice and maize homologues were 49 and 52% for birch allergens, 86 and 85% for birch non-allergens, 37 and 37% for pellitory allergens, and 87 and 89% for pellitory non-allergens. Similarly, timothy grass pollen allergens were significantly ($P < 0.0001$) less similar to dicot proteins than non-allergenic pollen proteins. Median sequence identities to the nearest homologues were 43 to 44% for allergens and 81 to 83% for non-allergens. A comparison of all 3 pollen proteomes to sequences from the moss *P. patens* yielded similarly significant differences.
Conclusions: Pollen allergens belong to evolutionary less conserved protein families than non-allergenic pollen proteins. The continual exposure of the human immune system to nearly identical and hence highly cross-reactive conserved proteins from multiple pollen and plant food species most likely leads to the induction of immunological tolerance rather than allergic sensitization.
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Sensitization to *Betula verrucosa* and RBET V1 in Spain

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Background: Sensitization to *Betula verrucosa* pollen is common in North Central Europe. In Spain, it is also common in patients from Galicia, a region located in the Northwest of Spain. Birch trees are abundant in this region and several birch species have been described. The main objectives were to determine the differences in the IgE reactivity to *B. verrucosa* and rBet v 1 between patients from Sweden and Spain, as well as the contribution of the major allergen Bet v 1 to the overall reactivity of *B. verrucosa*. Allergenicity was also compared using a serum pool derived from sera of North American (USA) patients.
Methods: IgE reactivity to *B. verrucosa* and rBet v 1 was measured in sera from 44 Spanish and 21 Swedish patients. rBet v 1 was produced as N-terminal His-tagged fusion protein and purified as originally described. All of them were sensitized to the pollen of this tree species and suffered from allergic rhinitis during the pollination period. rBet v 1 contribution was determined by inhibition ELISA using 3 pools of sera: from Spanish, North American and Swedish patients. IgE binding pattern was evaluated by Western blots using the same pools of sera. Specific IgE binding was expressed in arbitrary units.
Results: Specific IgE to *B. verrucosa* was detected in 50 from the 65 sera analyzed (mean = 3.77 ± 3.71 Units). Specific IgE levels to rBet v 1 were 3.13 ± 3.32 Units. Immunoblot assays confirmed specific IgE binding to rBet v 1, and also to other allergens present in the extract. The Spanish pool presented reactivity to more allergens than the Swedish pool. ELISA Inhibition assays, performed with a native extract and rBet v 1, revealed a significant contribution (>80% inhibition) of rBet v 1 to the allergenicity of the extract, with no differences according to the origin of the sera.
Conclusions: Bet v 1 has a great importance in birch allergy in Galicia and Sweden. Nevertheless, there are differences in the IgE recognition pattern according to the rest of birch allergens. Mayor allergen from birch, Bet v 1, significantly contributes to the allergenicity of *B. verrucosa* in Galicia.

ALLERGEN STRUCTURE 2

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Proteomic and Immunological Characterization of Ragweed Allergens

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Background: The prevalence of sensitization to ragweed has risen in North America and across Europe. Although the pectate lyase Amb a 1, the major allergen of ragweed, was identified as long ago as the 1960s, little is known about the allergenicity of the 5 Amb a 1 isoallergens and other allergens present in ragweed pollen. Ragweed extracts and purified Amb a 1 isoallergens have now been characterized for their allergenic potential to determine whether a single Amb a 1 isoallergen, several isoallergens or a combination with other allergens should be included in a recombinant SIT vaccine.

Methods: Extracts from North American short ragweed (*Ambrosia artemisiifolia*) pollen were investigated by mass spectrometry (MS), 2D-PAGE and immunoblotting. Furthermore, Amb a 1 isoallergens were purified and IgE reactivity determined by immunoblotting and IgE inhibition.
Results: 2D-PAGE and MS of ragweed extract proved the presence of all 5 known Amb a 1 isoallergens, of which Amb a 1.01 represents the dominant form. Additionally all other ragweed allergens known by sequence (Amb a 3, Amb a 4, Amb a 5, Amb a 6, Amb a 8, Amb a 9, Amb a 10) were identified. The highest IgE reactivity by immunoblotting was observed for Amb a 1.01 followed by Amb a 1.03; other Amb a 1 isoallergens as well as other detected ragweed allergens showed only weak IgE reactivity. All isoallergens with the exception of Amb a 1.04, which is only of low abundance in ragweed extract, were purified. Similar to the immunoblot analysis with crude extract, the purified isoallergens Amb a 1.02 and Amb a 1.05 showed weak IgE binding, whereas Amb a 1.01 and Amb a 1.03 had high IgE reactivity. First IgE inhibition experiments suggest that Amb a 1.01 contains all relevant IgE epitopes.
Conclusions: Amb a 1.01 is the most abundant Amb a 1 isoallergen, and presumably the most important ragweed allergen. However, a larger panel of ragweed-allergic subjects has to be analyzed with regard to IgE and T cell reactivities, to be able to choose a candidate for a recombinant vaccine for specific immunotherapy of ragweed allergy.

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Proteomic Analysis of Major and Minor Allergens From Isolated Pollen Cytoplasmic Granules

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Background: Grass pollen is one of the most important vectors of aeroallergens. Under atmospheric conditions, pollen grains can release pollen cytoplasmic granules (PCGs). The allergens associated with these intrinsic sub-fractions induce, in laboratory animals as well as in asthmatic patients allergic and inflammatory responses. The aims of this study were to characterize and identify the intrinsic allergens of PCGs, to compare them with those of pollen grains.
Methods: PCGs were isolated from *Phleum pratense* pollen by osmotic shock. The water-soluble proteins were extracted from pollen grains and their PCGs. Nine out of 26 grass sensitized patient sera were selected on the basis of previous ELISA and immunoblotting results showing IgE specific binding to numerous grass pollen allergens. IgE-binding proteins were analyzed by 1- and 2D-immunobloting using grass pollen-sensitized patient sera. Once located, allergens were characterized by mass spectrometry.
Results: 2D gels of pollen and PCGs extract revealed about 100 and 40 proteins respectively, with a large spectrum of Mr (10–>94 kDa) and pI (<4.5–10.0). More proteins as well as more allergens in pollen than in PCGs were detected by immunoblotting. Several of the allergens listed in the IUIS nomenclature - Phl p 1, 4, 5, 6, 11 and 12 - were found in pollen and PCGs extracts while Phl p 11 was found only in PCGs and Phl p 2 as well as Phl p 13 only in pollen extract. Some other allergens, not listed in the IUIS nomenclature, were also characterized in both pollen and PCGs extracts.
Conclusions: Since the major grass pollen allergens were found in PCGs and because of their small size, these sub-micronic particles should be considered as very potent sensitizing and challenging respirable vectors of allergens. We demonstrate here that PCGs are at least as much dangerous as pollen grains.

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Cross-Reactivity Between Olive Pollen and 3 Species of Grasses in Madrid, Spain

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Background: The most common allergenic pollens in patients with pollinosis in Central Spain are grasses and olive pollen, with a prevalence of positive skin prick test results of 94 and 61%, respectively. Shared proteins have been described in olive and grasses, such as profilins, polcalcin and trypsin inhibitors, but there are few in vitro studies analyzing the potential cross reactivity between both species. The aim of the present study was to analyze the protein composition of both allergen extracts, and the allergenic cross-reactivity between *O. europaea* and different grass pollen species.
Methods: Seventy-two (72) patients (mean age 10.4 years) were included in the study. All of them suffered rhinoconjuntivitis and/or asthma and were sensitized to olive and/or grass pollen. Specific IgE of the individual patients against *O. europaea*, and to the grass species: *Dactylis glomerata, Phleum pratense* and *Trisetum paniceum* were determined by ELISA. Inhibition assays were performed to verify allergenic crossreactivity between grass species and olive. Mass spectrometry analysis was performed to characterize the extracts and establish if there are common proteins in both, grass and olive pollens, that could act as cross reactive proteins.
Results: Three different sensitization patterns were observed: 1) sensitization to olive and grass pollen, 2) sensitization to olive and not to grasses and 3) sensitization to grasses and not to olive. Different pools of sera were mixed according to this classification and used for the different assays. Correlation coefficients found for the 3 grass species were significant ($P < 0.0001$; Spearman), but not for olive pollen ($P = 0.14$; Spearman). Proteomic analysis revealed the presence of more than 40 common proteins in grasses and olive pollens, but inhibition assays demonstrated no allergenic cross-reactivity between both families.
Conclusions: There is no in vitro crossreactivity between *O. europaea* and Grass pollen extracts, in spite of the allergens and the large number of common proteins shared by these pollens. We can conclude that sensitization to olive and grasses is species specific.

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Molecular Properties and Immunological Reactivity of Arabidopsis EXPB1, a Nonallergenic Homologue of Grass Group 1 Allergens

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Background: Grass group 1 allergens are glyco-proteins of about 30kDa that are highly soluble and profusely released by grass pollen upon hydration. They bind to IgE antibodies that initiate the allergic response causing hay fever, seasonal asthma, and related immune responses in humans. Bermuda grass (*Cynodon dactylon*; subfamily Chloridoideae) is an important source of seasonal aeroallergens in warm tropical and sub-tropical areas worldwide. Improved approaches to diagnosis and therapy of allergic diseases require a thorough understanding of the structure and epitopes on the allergen molecule that are crucial for the antigen-antibody interaction. In order to understand structural basis of IgE reactivity of group 1 allergen Cyn d1, we have pursued a comparative genomic approach to search for hypoallergenic or non-allergenic homologues.
Methods: Gene cloning, Protein expression in bacteria, protein structure modeling, IgE reactivity analysis through Immunoblotting.

Results: EXPB1, an *Arabidopsis* protein (belonging to the beta expansin multi gene family), showed significant sequence and structural similarity to Cyn d 1. This protein was expressed in *E. coli* and the recombinant protein did not react with serum IgE from grass pollen allergic patients, suggesting that EXPB1 represented a non-allergenic homologue of grass group 1 allergens. It is proposed that differences in the amino acid sequence are responsible for the difference in the allergenicity profile of the *Arabidopsis* and grass pollen proteins.
Conclusions: Our study provides valuable data for further investigations of the molecular basis of allergenicity and cross-reactivity of grass group 1 allergens.

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Protein-Protein Interactions Determine IgE Reactivity to Polygalacturonase From *Cupressus sempervirens* Pollen

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Background: In a recent proteomic study, we identified in Italian cypress (*Cupressus sempervirens*, *Cups*) pollen grains, 2 proteins at 43 and 60 kDa, homologous to already known Cupressaceae polygalacturonase (PG) proteins. The 60-kDa PG is suspected to be a multi-protein complex including the 43-kDa PG and one or more proteins with lectin-like properties
Objective: In the present study, cypress pollen PGs were further characterized and the molecular basis of their allergenicity including the presence of specific IgE directed against cross-reactive carbohydrate determinants (CCDs) were investigated.
Methods: *Cups* pollen PBS extracts were characterized using 2- and double one-dimensional electrophoresis followed by IgE immunoblotting. The IgE reactivity to carbohydrate- versus peptide-specific determinants was investigated using both bromelain inhibition and Con A-binding assays. Pollen proteins were also prefractionated in their native forms using size exclusion chromatography. The presence of multi-protein complexes were investigated by using 2-D blue native (BN)-PAGE/SDS-PAGE electrophoresis.
Results: Upon bromelain inhibition assay, we revealed that 70% of tested patients displayed CCD-specific IgE to the 43-kDa PG while its isoenzyme of 60 kDa appeared to be exclusively recognized for its peptide-specific determinants. The specific binding of the Con A lectin to the 43-kDa PG, and not to the 60-kDa isoenzyme, demonstrated the presence of exposed mannose-containing oligosaccharides only on the 43-kDa protein. This fact reflects fundamental differences between specific IgE-binding epitopes involved in the recognition of the 43-kDa and 60-kDa proteins making these 2 cypress pollen PGs immunologically distinguishable. The present results suggest that in the 60-kDa protein complex, the CCDs of the 43-kDa PG are not exposed due to the binding of a lectin-like protein exhibiting peptidic IgE reactive epitopes recognized by 25% of tested patients.
Conclusion: The current study demonstrates that the sensitization to the *Cups* pollen PG is mainly due to CCD bromelain-type epitopes and directly associated with an increased prevalence of IgE reactivity to cypress pollen extracts due to CCD interference. However, the *Cups* pollen PG and its carbohydrate-specific determinants seem to play a key role in the dynamics of protein-protein interaction in cypress pollen and may confer to protein complexes a higher allergenicity.

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Grafting of BET V 1 Epitopes onto its Homologue API G 1 Reveals Patient-Specific IgE Recognition Profiles

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Background: Up to 70% of birch pollen-allergic individuals show adverse reactions to certain plant foods. This cross-reactivity is caused by sensitisation to the major birch pollen allergen Bet v 1 and binding of Bet v 1-specific IgE antibodies to homologous plant food allergens. We aimed to assess the importance of selected conformational epitopes for IgE binding to Bet v 1.
Methods: Chimeras of Bet v 1.0101 and its homologue Api g 1.0101 were constructed. In each of the 4 chimeras, roughly one fourth of the surface residues of Api g 1.0101 were replaced by corresponding residues of Bet v 1.0101. The proteins were expressed in *Escherichia coli* and purified by chromatographic methods. Secondary structures were checked by CD-spectroscopy. IgE ELISA with Bet v 1.0101, Api g 1.0101 and the chimeras were performed with sera of 63 Bet v 1-sensitized birch pollen allergic patients. For inhibition ELISAs, chimeras were coated and inhibition was performed with the chimeras or Api g 1.0101.
Results: IgE binding to Api g 1.0101, Api-Bet-1, -2, -3 and -4 was observed for 22, 81, 79, 70 and 38% of the sera, respectively. To assess the relevance of the grafted regions for IgE binding to Bet v 1, the amounts of IgE binding to the chimeras were compared with those to Api g 1.0101. Most of the sera recognised either 3 chimeras (39%) or all 4 chimeras (21%) better than Api g 1.0101. Only a minority of the sera showed increased binding to a single chimera. Inhibition ELISAs confirmed the presence of IgE specific for the grafted regions.
Conclusions: Our study indicates that the epitope recognition profile of Bet v 1-specific IgE is highly patient specific. Due to the different IgE binding patterns to Bet v 1, determined by binding of IgE to different chimeras, the existence of a single major IgE epitope on Bet v 1 can be excluded. Moreover, the Bet v 1-specific IgE repertoire is polyclonal and the IgE epitopes are distributed over the whole surface of Bet v 1.
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ALLERGIC MODELS OF INFLAMMATION

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Common and Rare Variation in the T Helper 2 Gene Pathway Predicts Allergic Asthma Phenotypes

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Background: The T helper 2 (Th2) inflammatory pathway, including the Th2-activating cytokine interleukin 33 and its receptor interleukin 1 receptor-like 1 have been strongly implicated in asthma susceptibility (Moffatt MF, et al NEJM 2010). However, the role of Th2 pathway genetic variation in asthma progression and severity is not well understood. Our research group recently developed a clustering algorithm based on comprehensive phenotype information to assign subjects with asthma in the Severe Asthma Research Program (SARP) to 5 primary clusters; 3 of which represent increasing severe

allergic asthma (Moore WC, et al AJRCCM, 2010). We hypothesized that common and potentially deleterious rare variation in this pathway would be associated with severe asthma based on SARP cluster designation.

Methods: To evaluate common variants (minor allele frequency or MAF >5%), 419 SARP non-Hispanic white participants with a cluster assignment were genotyped for 182 single nucleotide polymorphisms (SNPs) in Th2 pathway genes using whole-genome SNP data. Individual SNPs and a cumulative model of significant SNPs were evaluated using contingency tables with a chi-square test for trend and ordinal regression models adjusted for age, sex, and principal components. Rare (MAF <5%) amino acid changes and splice site alterations in this pathway were tested for association with asthma severity outcomes in 20 SARP subjects with whole exome sequence data.

Results: Individual Th2 pathway variants were associated with overall SARP cluster assignment, and allergic clusters of increasing severity (1, 2, and 4), including GATA3 polymorphism rs1244186 ($P = 0.005$). In an 18-SNP additive model, an increasing number of Th2 pathway risk genotypes were highly associated with severe allergic asthma ($P = 3.9 \times 10^{-6}$). For example, in cluster 4, the percentage of subjects with at least 9 risk genotypes was 83% compared to 35% in cluster 1. Additionally, there was evidence that subjects with rare variants in this pathway were more likely to report allergy symptoms ($P = 0.006$), especially in the fall ($P = 0.003$), compared to subjects with no rare variants.

Conclusions: Common Th2 pathway variants predict an increased likelihood of severe allergic asthma and rare variants were associated with increased seasonal allergy symptoms.

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Role of Myeloid Derived Suppressor Cells in Asthma

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Background: We know that a heterogeneous group of myeloid cells termed myeloid derived suppressor cells (MDSC) accumulate in almost all pathological conditions, which elicit an inflammatory signal. The exact role played by these cells in asthma is not known. In this study we investigated the function and role of these cells in asthma.

Methods: Accumulation of MDSC and other subsets of myeloid cells were analyzed from peripheral blood mononuclear cells from patients with non-severe asthma (FEV_1) >60) and severe asthma (FEV_1 <60) by multicolor-flowcytometry and compared to healthy controls. Allergic mouse models were used to determine the role of microRNA-142 (miR-142) in regulation and expansion of MDSC.

Results: There is a significant increase in the proportion of MDSC in severe versus non-severe asthmatics and controls, corresponding to a decrease in myeloid dendritic cells. Allergic mice had significant increased levels of MDSC expansion which were associated with increased levels of IL-6 and downregulation of miR-142. miR-142 overexpression induced MDSC differentiation.

Conclusions: An accumulation of MDSC is associated with severe asthma in humans and mice. In an allergic mouse model, IL-6 levels increase. miR-142 may play an important role in regulation and differentiation of MDSC, leading to altered immunity.

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MIR-150 Suppresses Lung Inflammation in a Mouse Model of Experimental Asthma

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Background: Asthma is a complex disorder of the immune system caused by a combination of genetic predisposition with environmental exposures. The environmental factors play a predominant role in the etiology of asthma. It is hypothesized that epigenetic changes in miRNAs play a critical role in pathogenesis of asthma as an interface between genetic makeup and environmental exposures. (Wang, Jia-wang; Li, Kunyu; Hellermann, Gary; Lockey, Richard F.; Mohapatra, Subhra; and Mohapatra, Shyam. Regulating the Regulators: microRNA and Asthma. *World Allergy Organization Journal*. June 2011, Volume 4, Issue 6).

Methods: In the present study, we used miRNA array profiling in a mouse model of ovalbumin-induced asthma to identify differentially regulated miRNAs and characterized miR-150 in terms of cellular and humoral involvement and analysis of lung inflammation markers.

Results: We found that miR-150 was downregulated in CD4 T lymphocytes during asthmatic inflammation and Th1 and Th2 induction. Over-expression of miR-150 delivered by chitosan nanoparticles inhibited lung inflammation and decreased Th1 and Th2 cytokine levels. miR-150 suppressed Akt3, Cbl1 and Elk1 oncogenes, which are involved in inflammation and cytokine production. Transgenic mice overexpressing miR-150 are resistant to asthma induction, demonstrated by reduced AHR and cytokine inflammation production.

Conclusions: These results suggest that deregulation of miRNAs may be involved in the pathogenesis of asthma and miR-150 may suppress inflammation in asthma by inhibiting cytokine production by downregulating critical genes such as Akt, Elk1 and Cbl1. miR-150 may be an attractive candidate for asthma gene therapy.

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Serine Protease Inhibitor Attenuates Ova Induced Inflammation in Mouse Model of Allergic Airway Disease

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Background: Serine proteases promote inflammation and tissue remodeling by activating proteinase-activated receptors, urokinase, metalloproteinases and angiotensin. In the present study, AEBSF (4-(2-Aminoethyl) benzene-sulfonyl fluoride) a serine protease inhibitor, was evaluated for prophylactic and therapeutic treatment in mouse model of airway allergy.

Methods: BALB/c mice were sensitized by i.p route on 0 and 14 day and challenged with OVA (25, 26 and 27 day) by i.n. route. Mice were treated i.n. with AEBSF, 1 hour before/after challenge and sacrificed on day 29 to collect BALF, blood and lungs. OVA specific immunoglobulins were measured in serum. Proteolytic activity, total cell/eosinophil count, eosinophil peroxidase activity (EPO), IL-4, IL-5, IL-10, cysteinyl leukotrienes and 8-isoprostane (oxidative stress marker) were determined in BALF. Haematoxylin and eosin stained lung sections were examined for cellular infiltration and airway inflammation.

Results: Mice exposed to OVA and treated with PBS showed significantly high levels of IgE, IgG1 and IgG2a as compared to sham mice. Both prophylactic and symptomatic AEBSF treatment reduced serum IgE and IgG1 significantly ($P \leq 0.05$) than control, however there was little increment

in IgG2a level. AEBSF could effectively reduce the proteolytic activity in BALF. IL-4 and IL-5 decreased significantly ($P \leq 0.05$) after AEBSF treatment while a significant ($P \leq 0.05$) increase was observed in IL-10 in BALF. Airway inflammation reduced significantly as revealed by lung histopathology, EPO activity and cysteinyl leukotrienes in BALF after treatment. AEBSF also suppressed oxidative stress in terms of 8-isoprostane in BALF. Among the treatment doses, 10 and 50 μg of AEBSF were most effective in reducing majority of the inflammatory parameters.
Conclusions: Prophylactic and therapeutic treatment of AEBSF attenuates the airway inflammation in mouse model of airway allergy and have potential for the treatment of inflammatory allergic diseases.

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Potential Role of Scavenger Receptors in Human Mast Cell Cytokine Response to Oxidized ldl

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Background: Human atherosclerotic lesions contain mast cells and oxidatively modified low-density lipoprotein particles (oxLDL). Scavenger receptors are cell surface receptors that bind and internalize oxLDL, and they play an important role in macrophage foam cell development, a key event in the initiation and development of atherosclerotic lesions. The purpose of the study was to analyze expression of the most common scavenger receptors in mast cells, and determine whether oxLDL particles can induce them to secrete pro-inflammatory cytokines that are potentially capable of inducing and amplifying atherogenic processes.
Methods: Mast cells were differentiated from human cord blood-derived CD34+ progenitor cells in vitro (CBMC), and their expression of scavenger receptors was analyzed by conventional RT-PCR, flow cytometry and Western blot techniques. Fluorescently-labeled oxLDL was used to investigate LDL internalization by mast cells. Secretion of pro-inflammatory cytokines into the incubation medium and degranulation of the mast cells in response to oxLDL were assayed by ELISA and a colorimetric-enzymatic test for beta-hexosaminidase, respectively.
Results: CBMC expressed mRNA and protein for LOX-1, SR-AI and CD68, but not for CD36, and the expression of LOX-1 and SR-AI was upregulated by incubation of the cells with oxLDL. CBMC internalized oxLDL more efficiently than native LDL, while simultaneous neutralization of CD68, SR-AI and LOX-1 with monoclonal antibodies resulted in reduced oxLDL uptake. Moreover, in response to oxLDL, CBMC showed increased release of β-hexosaminidase, and a dose-dependent secretion of the pro-inflammatory cytokines IL-8 and MCP-1.
Conclusion: Our results reveal that cultured human mast cells express scavenger receptors that are upregulated by oxLDL. In atherosclerotic lesions, oxLDL may activate MC to secrete pro-inflammatory cytokines, and so they cause mast cells to act as a cellular link between oxLDL and the inflammatory response in atherosclerosis.

ALLERGIC RHINITIS

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Allergic Rhinitis to Ragweed Pollen

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Background: The prevalence of pollen allergy is estimated around 40% in general population. Ragweed (ambrosia artemisiifolia) pollen represents a major source of allergen but was rare in Romania. The aim is to evaluate the symptoms and associated factors in patients with allergic rhinitis to ragweed pollen in the northwest region of Romania.
Methods: 74 patients (pts) (mean age 27.97 ± 13.85 years) with allergic rhinitis to ragweed pollen were included in the study. The patients were clinically evaluated regarding the severity of the symptoms on a scale from 0 to 3 and their duration. A total score over 6 indicates a moderate/severe form of rhinitis. We evaluated the association with other allergic manifestations (asthma and urticaria). All the patients had skin prick tests to inhalant allergens. The obtained data were statistically analyzed using Anova, Chi-square and Fischer tests, with a significance of $P < 0.05$.
Results: 50.94% of the pts were female. 58.1% of them presented mild allergic rhinitis, while 41.9% moderate severe forms. 27% of the pts were monosensitised to ragweed pollen and 73% of the pts were polisensitised. The patients monosensitised to ragweed had moderate/severe forms of rhinitis (14 vs 86%, $P = 0.004$) compared with polisensitised group. The symptoms score was higher in pts with monosensitisation compared with polisensitisation pts (7.05 vs 5.28, $P = 0.02$). In monosensitized group the ocular szmptoms were more frequently present (65 vs 18%, $P = 0.02$) and were more severe (0.65 vs 0.33, $P = 0.01$). The number of pts with association of allergic rhinitis and asthma was higher in the polisensitised group compared to the monosensitised one (44.4 vs 11.11%, $P = 0.029$). The interval between the onset of the symptoms and diagnosis of rhinitis is higher in polisensitised pts and significantly increased in pts with asthma. There is no correlation between environment (rural–urban), age, sex, family and personal allergic history and the type of sensitisation and severity of the symptoms.
Conclusions: Ragweed produces intense allergogen pollen and determines severe forms of allergic rhinitis and also the presence of ocular symptoms. Polisensitisation increases the risk of associated asthma and also increases the interval betweeen the onset of the symptoms and diagnosis.

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Ragweed Allergy – What Role Does It Play in Bavaria?

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Background: Ragweed (*Ambrosia artemisiifolia*), is increasingly spreading in Southern Germany and Central Europe. Little is yet known about the sensitization and allergy rates in Bavaria.
Methods: In 2008 to 2010 patients from a Bavarian university allergy unit were enrolled into the study. The patient's history was recorded by a standardised questionnaire concerning allergies. Sensitization rates were measured by skin prick test (SPT) for seasonal aeroallergens including ragweed. Patients sensitized to ragweed were further characterized by measuring specific serum immunoglobulin E (IgE) for ragweed specific allergens (by ImmunoCAP and ELISA). To determine the clinical relevance challenge tests (nasal/conjunctival) with ragweed were performed.
Results: 1022 patients were enrolled in the study (665 female, 357 male). 289 patients were sensitized to ragweed (SPT positive). In ragweed sensitized patients the sensitization rate to mugwort was 61.8% whilst in patients not sensitized to ragweed it was 7.4%. The sensitization to birch was 78.1% resp. 36.4%. In 120 ragweed sensitized patients challenge tests with ragweed extract were performed (nasal n = 110; conjunctival n = 60) with positive results in 29 (26%) resp. 12 (20%) patients. In 232 ragweed sensitized patients specific IgE to nArt v 1 was observed significantly more frequently than to nAmb a 1.
Conclusions: The results of this 3-year study show that in a Bavarian allergy unit sensitization to ragweed is frequent. Often ragweed-sensitized patients have sensitivities to multiple seasonal aeroallergens. There is a coexistence of ragweed and mugwort specific allergens. One fourth of the challenged

patients that are sensitized to ragweed show clinical allergy symptoms. With sufficient ambient allergen exposure, a prolonged allergy season can be expected for this at-risk population.
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Nasal Nitric Oxide and Nasal Polyposis as Determinants of Asthma Control

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Background: The relationship between asthma control, its comorbidities and noninvasive markers of airway inflammation has been investigated with controversial results. The aim of this study was to analyze the relationship between level of asthma control (evaluated by ACT and ACQ questionnaires), its main comorbidities (rhinitis, chronic rhinosinusitis - CRS, obesity), exhaled nitric oxide (FENO) and nasal nitric oxide (nNO).
Methods: Forty-one consecutive asthmatic patients (mean age: 50 years, range: 21–80; 21 females; 2 smokers) were enrolled into the study. All patients were investigated to assess diagnosis of rhinitis, CRS (with or without nasal polyps) and obesity (by measuring the BMI). All patients underwent skin prick tests for a panel of common inhalant allergens, spirometry, FENO and nNO, and completed ACT and ACQ questionnaires. An univariate analysis was performed to identify determinants of asthma control (defined by means of ACT and ACQ values).
Results: Twenty-seven (65.9%) patients had ACQ values indicating asthma control (ACQ $\leq$1), while, according to ACT, only 14.6% of patients were completely controlled (ACT = 25), 48.8% partially controlled (20$\geq$ ACT $<$25) and 36.6% uncontrolled (ACT $<$20). ACT and ACQ values were negatively correlated with nNO levels ($R^2 = -0.175$ and $R^2 = 0.013$ respectively). The univariate analysis showed that the the only significant determinants of lack of asthma control were nNO and the diagnosis of CRS with nasal polyps ($P = 0.020$ and 0.018 respectively).
Conclusions: Nasal nitric oxide was the only biomarker, amongst those evaluated, which was correlated to asthma control. This finding suggests that nNO may reflect particular aspects of airway inflammation which may be more strictly correlated with asthma, underlying the importance of CRS with nasal polyps in loosing asthma control.

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Peak Nasal Inspiratory Flow Levels in Children With Allergic Rhinitis and Their Health Related Quality of Life (HRQL)

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Background: Allergic rhinitis impairs the quality of life children. There is paucity of data with regards to clinical profile and health related quality of life (HRQL) of children with Allergic rhinitis in India and hence we studied the clinical profile and measured Peak nasal inspiratory flow (PNIF) of children with allergic rhinitis in an urban population, and assessed their Quality of life.
Methods: Children with moderate to severe persistent Allergic rhinitis, diagnosed as per Allergic Rhinitis and Impact on Asthma (ARIA) guidelines, in the age group of 6 to 18 years were included in this study. The quality of life questionnaire, pediatric and adolescent by Juniper et al was used. PNIF was measured by using 'In- Check' peak nasal inspiratory flow meter.
Results: Of the 100 children studied, 70 (70%) were in the age group of 6 to 11years and 30/100 (30%) were between 12 and 18 years of age. An equal distribution of sex was observed in 6 to 11 year age group, and in the 12 to 18 year age group there was a male preponderance (1.9:1). Majority (87%) of children in our study had Moderate Allergic rhinitis and 13% had severe Allergic rhinitis. Bronchial asthma, a commonly reported entity in Allergic rhinitis was seen in 19% of the cases. 66% of children in our study had PNIF values of the fifth to 50th percentile where as 24% were in the third to fifth percentile and 10% had their PNIF values less than third percentile. PNIF showed a linear correlation with severity of allergic rhinitis. HRQL assessment showed that children in the 6 to 11 year group had derangement in the activity and physical symptoms domain while children in the12 to 18 year group had predominately involvement of emotional and practical problem domains. Quality of life score worsened with decrease in PNIF.
Conclusions: PNIF is very useful tool to quantify the nasal obstruction in Allergic Rhinitis. PNIF is easy to administer, reproducible and correlates well with the severity of the disease. HRQL assessment helps us to do psycho educational training to adhere compliance.

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Exhaled Nitric Oxide and Airway Function in Seasonal Allergic Rhinitis

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Background: Seasonal allergic rhinitis could predispose to the development of chronic bronchial inflammation. However, association between seasonal allergic rhinitis and airway function, especially exhaled nitric oxide [FENO], are not fully understood.
Objectives: The aim of this study was to evaluate the relationship among FENO and airway function and nasal symptoms in patients with seasonal allergic rhinitis without asthma.
Methods: We included 37 subjects [9 males and 28 females] in this study. Total serum IgE were investigated and specific IgE for 4 pollen allergens and 5 perennial antigens were determined by RAST. Sensitization to a specific allergen was defined as over RAST score 2. We compared 4 groups. Group A: 7 nonatopic subjects [no nasal symptoms and RIST, RAST negative, 1 males and 6 females, mean age: 33.2 24–52 years]. Group B: 10 atopic subjects with a sensitization to Japanese ceder without medication [6 males and 4 females, mean age: 44 20–58 years]. Group C: 10 atopic subjects with a sensitization to Japanese ceder who took oral anti-histamine medicine during pollen season [2 males and 8 females, mean age: 34.9 24–52 years]. Group D: 10 atopic subjects with a sensitization to Japanese ceder who receive intranasal corticosteroid treatment during pollen season [2 males and 8 females, mean age: 40.2 26–56 years]. Score of nasal symptoms, FENO, spirometry, total eosinophils, nasal eosinophils, were investigated before, during, and after pollen season.
Results: Regardless of having treatment or not, in comparison with the subjects without the allergy, FENO showed a statistically significant increase in all patients with a sensitization to Japanese after pollen season. In group D, v 50/v 25 was the tendency to adversely affect after the pollen season, and correlation between FeNO rate of the change and v 50/v25 rate of the change admitted. As for the other indexes, a statistically change were not showed in the comparison of each group.
Conclusions: These results suggest that FENO is a primarily marker of bronchial inflammation in patients with seasonal allergic rhinitis during pollen season and intranasal corticosteroid treatment may be effective for improvements in lower airway outcome.

ANAPHYLAXIS

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Immunologic Evaluation of the Patients With Ranitidine Anaphylaxis

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Background: There have been a few reports of hypersensitivity reactions to Ranitidine and cross-reactivities between H2-receptor antagonists. The pathogenic mechanisms of H2 receptor antagonist induced hypersensitivity reactions are not understood. The purpose of this study was to observe the clinical characteristics of the patients with Ranitidine anaphylaxis and investigate the pathogenic mechanisms with detection of serum specific IgE antibody to Ranitidine-HSA conjugate.

Methods: Ten patients with anaphylaxis to Ranitidine were enrolled from Ajou University Hospital and Seoul National University Bundang Hospital. Skin prick test (SPT) using Ranitidine extract were performed in 7 patients. Serum specific IgE and G1 antibodies were detected by ELISA using Ranitidine-HSA conjugate. The study subjects were divided into 2 groups according to the presence of serum specific IgE antibody to Ranitidine-HSA conjugate: 3 subjects had high serum specific IgE (Group I) and 7 subjects showed negative results (Group II), when positive cut off value was determined from mean + 3 SD of absorbance values of healthy controls.

Results: Six (60%) were female and 9 (90%) were atopics. 6 (86%) patients had positive responses to ranitidine on SPT, however, high serum specific IgE to Ranitidine-HSA conjugate was detected in only 3 patients (30%), while serum specific IgG1 was detectable in one patient (10%). There were no significant differences in clinical characteristics including age, sex, atopy and serum total IgE level between group I and II.

Conclusions: We confirmed the presence of serum specific IgE to Ranitidine-HSA conjugate by ELISA, suggesting that IgE mediated response is a major pathogenic mechanism of Ranitidine induced anaphylaxis. Further studies will be needed to investigate other immunologic and non-immunologic mechanisms and cross-reactivity among other H2 receptor antagonists.

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Body Mass Index (BMI) and Immediate ("STAT") Dose of Epinephrine im (EPI IM) Needed to Treat Subcutaneous Allergen Immunotherapy (SCIT) Systemic Reactions (SRS)

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Background: The purposes of this study are to document the number of SRs to SCIT, the relationship between BMI versus the severity of SRs [World Allergy Organization (WAO) Grade 1 to 5 reactions], and the possible relationship between BMI and the total amount of epi IM needed to treat the SRs.

Methods: This is a retrospective study of SRs to optimal dose SCIT with any combination of approximately 20 allergens (pollens, animal emanations, molds, and Hymenoptera) in 840 subjects representing 13,812 encounters over 12 months (June 2010–May 2011). Nurses administered stat epi IM (1:1000 v/v), 0.2 mg, immediately into the arm or thigh for any systemic signs or symptoms (SS) of a SR, including, but not limited to, itchy eyes, nose, pharynx, palms; rhinorrhea, nasal congestion, sneezing; and generalized erythema, pruritus, or urticaria. Repeat doses of epi IM were administered as necessary.

Results: 32 subjects (3.8%) each had one SR: 21 (66%) Grade 1, 10 (31%) Grade 2, 1 (3%) Grade 3, and Grades 4 or 5. BMIs were missing in 3 subjects. Fifteen of 29 were in the normal weight range (BMI 18.5–24.9), 9 Grade 1 (mean epi IM, 0.27 mg) and 6 Grade 2 (mean epi IM, 0.3 mg). Mean epi IM was 0.28 mg. Eight of 29 subjects were overweight (BMI 25–29.9), 7 Grade 1 (mean epi IM, 0.23 mg), and 1 Grade 3 (mean epi IM, 0.3 mg). Mean epi IM was 0.24 mg. Six of 29 were obese (BMI >30), 4 Grade 1 (mean epi IM, 0.3 mg) and 2 Grade 2 (mean epi IM, 0.2 mg). Mean epi IM was 0.27 mg.

Conclusions: SRs occurred in 3.8% of SCIT subjects. No significant association was found between BMI and the WAO Grade severity ($P = 0.13$ by Fisher's exact test) and BMI and total epi IM dose given ($P = 0.82$ by Kruskal-Wallis test). BMI should not influence risk assessment of SCIT or IM epi administered for SR.

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Muscle Relaxant Induced Allergic Reactions

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Background: Both eperisone and afloqualone act by relaxing both skeletal muscles and vascular smooth muscles to improve circulation and suppress pain reflex. These drugs are usually prescribed combined with non-steroid anti-inflammatory drugs (NSAIDs) as pain killers. Although there have been no report on serious adverse reactions to muscle relaxant, this is the first report of 3 anaphylactic reactions caused by eperisone and afloqualone.

Methods: All 3 patients had previous histories of anaphylaxis after oral intake of multiple pain killers including muscle relaxant and NSAID for chronic muscle pain. Open label oral challenge tests were performed with each drug to find out which drugs caused systemic reactions.

Results: All experienced the same reactions within an hour after oral intake of eperisone or afloqualone. The severity of these reactions ranged from laryngeal edema to hypotension. To confirm the systemic reaction caused by eperisone or afloqualone, skin prick testing and intradermal skin tests with eperisone or afloqualone extract were performed in vivo, and the basophil activity tests were performed with stimulation with these drugs in vitro. In one patient with laryngeal edema, intradermal test with afloqualone results showed positive result and CD63 level increased after the stimulation with afloqualone dose-dependently.

Conclusions: We report 3 allergic reactions caused by oral muscle relaxants that might be mediated by non-IgE-mediated responses. As muscle relaxant, eperisone and afloqualone, commonly prescribed drugs for chronic muscle pain, can induce severe allergic reactions therefore we should prescribe them carefully.

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Features of 51 Patients With Perioperative Anaphylaxis History

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Background: To evaluate the prevalence and the etiology of perioperative anaphylaxis (APEO) referred to an outpatient clinic specialized in adverse drug reactions.

Methods: We evaluated 806 patients throw the questionnaire "*European Network for Drug Allergy" (ENDA*) in the period from October 2006 to June 2011. Patients with a history of APEO were selected. The diagnostic criteria for anaphylaxis were based on the World Allergy Organization. Etiological investigation was made with skin tests for latex, neuromuscular blockers (NMBs), antibiotics, hypnotics, opioids and local anesthetics. Provocation tests for antibiotics, NSAIDs, local anesthetics and latex were also done. Specific IgE was tested for antibiotics (Penicillin G and V, Ampicillin and amoxicillin) and latex.

Results: We identified 51 (6%) patients with a history of APEO. Among them, 16 patients (31%) had hypersensitivity reactions with positive cutaneous test, 14 patients (27%) abandoned the investigation and 8 patients (16%) completed the investigation with all tests negative. Currently 12 patients (23%) are being investigated and one of them (2%) performed tests to drugs to use in the next sirgury. The main cause of APEO was latex allergy (22%), followed by NMB hypersensitivity (6%). Three patients had positive tests for 2 different agents.
Conclusions: Latex allergy is the main cause of APEO in this study. The importance of testing all the possible agents involved was demonstrated by the occurrence of 3 cases with positive test for 2 agents.

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Drug Induced Anaphylaxis in a University Hospital in Sao Paulo, Brazil

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Background: Adverse drug reactions (ADRs) are common in clinical practice, most of them presented only with mucocutaneous symptoms. Drug induced anaphylaxis is rare, but it is responsible for most deaths due to ADRs. The aim of this study was to evaluate drug induced anaphylaxis treated in an Allergy Outpatient Clinic of a University Hospital.
Methods: Retrospective analysis of medical records from patients who seek assistance because of ADR. We looked for clinical criteria for diagnosing anaphylaxis, as recommended in WAO Guidelines. Criteria were classified in numbers 1 to 3:1) Acute onset of an illness (minutes to several hours) with involvement of the skin-mucosal tissue and respiratory and/or cardiovascular compromise; 2) Two or more of the following that occur rapidly after exposure to a likely allergen: involvement of skin-mucosal tissue, respiratory, cardiovascular and/or gastrointestinal compromise; 3) Reduced blood pressure after exposure to known allergen for that patient. We analyzed patients gender and age, drugs involved in reactions and administration of epinephrin.
Results: We studied 806 patients with history of ADR, of whom 123 (15.3%) presented clinical criteria of anaphylaxis (mean age 39.0 year old, female 101). The first clinical criteria was found in 60.2% and the second one in 38.2%. Epinephrin was injected in only 42 patients (34.1%). Non-steroidal anti-inflammatory drugs (NSAIDs) were most commonly suspected culprit drugs involved in anaphylactic reactions, with 59 patients (47.9%), followed by 40 patients with perioperative anaphylaxis (32.5%), 6 cases due to local anesthetics (4.9%) and 4 to antibiotics (3.2%). Between perioperative anaphylaxis, latex was involved in 10 reactions and neuromuscular blocking agents in 3.
Conclusions: We found a high prevalence of anaphylaxis, probably because patients with severe ADRs tend to be followed in university hospitals. Nevertheless, anaphylaxis is underdiagnosed in emergency departments, as we observed less than 35% of patients with drug induced anaphylaxis were treated with epinephrin. NSAIDs are still the most common drugs involved in ADRs in Brazil, including severe reactions, as anaphylaxis. In our country, latex still is an important agent incriminated in perioperative anaphylaxis, but anaphylaxis due to antibiotics are less common than in other countries.

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Analysis of Anaphylactic Reactions to Biological Agents Reported to the Italian Pharmacovigilance Database

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Background: Spontaneous reporting of adverse drug reactions (ADR) to biological agents used for cancer and immuno-mediated disease treatment is important for furthering knowledge regarding the safety of these new drugs. An analysis was carried out in Italy on reports of anaphylaxis caused by biological agents.
Methods: Data were extracted from the national Spontaneous Reporting Database. Since biological drugs refer to different ATC (Anatomical Therapeutic Classification) codes, in this study they have been extracted by the presence of "mab" and/or "cept" suffixes. Cases were defined as following: A) reports with the string "anaph" in the description of the event or in the WHO-ART (Adverse Reactions Terminology) coded preferred terms; B) reports with adverse reactions referring to at least 2 of selected System Organ Classes (skin, respiratory, cardiovascular and gastrointestinal disorders) with an onset within 24 hours after administration. All selected cases were reviewed and the case definition from the "Second Symposium on the Definition and Management of Anaphylaxis" was applied to evaluate the reports (JACI 2005;115(3):584–591).
Results: The Italian database up to March 2011 contains 3820 reports related to biologicals. According to selection criteria, a total of 334 reports were extracted: 65 for group A and 269 for group B. By application of the anaphylaxis case definition, 2 cases belonging to group A and 139 to group B were excluded after individual review. Out of 193 reports meeting the case definition, 8 (4.1%) were reported in children and adolescents up to 18 years of age. The most reported responsible drugs were infliximab with 83 (43%) cases, followed by cetuximab (41–21%) and rituximab (28–14%); other 11 different biologicals were associated with the remaining 32 cases (22%), with up to 8 reports each.
Conclusions: Spontaneous reporting is an important source to provide further knowledge on the reactogenicity of biological agents. Three-fourths of Italian reports of anaphylaxis concern 3 chimaeric antibodies containing a murine component. In our study, the best identification of cases of anaphylactic reactions came out of the combination of selected reported terms, application of case definition and expert review of individual reports.

ATOPIC DERMATITIS 1

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Contribution of IL-33 and Nuocyte to Experimental Allergic Dermatitis

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Background: IL-33 is a member of the IL-1 family cytokines and the ligand of ST2 (IL-33R alpha chain). IL-33 stimulates Th2 cells, basophils, mast cells, and nuocyte, a recently discovered new lymphocyte, to produce various cytokines. We have previously shown that the serum level of IL-33 is significantly elevated in patients with Japanese cedar pollinosis[1] and IL-33 has the potential to induce Th2 cytokine-mediated allergic conjunctivitis[2]. As these results suggest that IL-33 may also have some relations to allergic dermatitis, we now examined the pathological role of IL-33 in dermatitis. First, we investigated an immediate reaction of skin by challenging BALB/c mice with DNFB repeatedly. We also tested the involvement of natural helper cells (nuocyte) in dermatitis of NC/Nga mice.
Methods: (1) Wild-type BALB/c mice or ST2 KO mice were sensitized and repeatedly challenged with DNFB on the left ear at 1 week intervals. When they are challenged 4 or 5 times, the ear shows biphasic (bimodal) responses which consist of an immediate phase and a delayed-type reaction. (2) When NC/Nga mice are raised in conventional (non-SPF) circumstances, skin

lesions that are clinically similar to human atopic dermatitis spontaneously appears on the skin. We separated lymphocytes from the inflamed skin of NC/Nga mice using collagenase I (Sigma-Aldrich) and counted the numbers of nuocytes (ST2+/Sca-1+/lineage marker-negative) by FACS.

Results: (1) The reactions were hapten specific. Wild-type BALB/c mice showed both immediate and delayed-type reactions, whereas ST2 KO mice did not show any immediate reaction. (2) When IL-33 was administered subcutaneously, NC/Nga mice showed increase of serum IgE level. The number of nuocytes in inflamed skin of NC/Nga mice significantly increased compared to non-inflamed skin. The nuocytes showed very weak expression of ST2 in non-inflamed skin, whereas the expression of ST2 in inflamed skin was very significant.

Conclusions: These results suggest that IL-33 may have an important role in the mechanism of immediate contact hypersensitivity, and nuocytes may contribute to the development of atopic dermatitis-like skin lesion in NC/Nga mice.

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S100A8/A9, a Damp Molecule Activated by IL-17 and House Dust Mite is Upregulated in Atopic Dermatitis

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Background: S100A8/A9 (Calgranulin A/B, Calprotectin), a heterodimer of 2 calcium-binding proteins originally found in the cytoplasm of neutrophils and membrane of monocytes. It has emerged as an important pro-inflammatory mediator, so called "damage-associated molecular pattern (DAMP)" molecule in acute and chronic inflammation. Our previous proteomics data showed that S100A8/A9 was significantly downregulated after immunotherapy with house dust mite in patients with atopic dermatitis (AD).

Methods: The purpose of this study was to evaluate S100A8/A9 expression in serum and lesional skin of AD patients, and then to assess S100A8/A9 expression in HaCaT cells and primary human keratinocytes, which were cultured with Th2, Th17 cytokines and house dust mite (HDM) extracts.

Results: Compared with healthy controls, serum S100A8/A9 levels were higher in AD patients and correlated with eczema area and severity index (EASI) scores ($P < 0.01$, $r^2 = 0.2037$). S100A8/A9 was strongly expressed in the upper epidermis of AD tissues by immunofluorescence. IL-17A strongly induced S100A8/A9, and enhanced S100A8/A9 expression in HaCaT cells and human keratinocytes which were cultured with Th2 cytokines. S100A8/A9 mRNA and protein levels were also increased in HaCaT cells and human keratinocytes which were stimulated with *Dermatophagoides farinae* by time dependent manner. IL-17A also strongly enhanced S100A8/A9 expression in HaCaT cells which were cultured with *D. farinae*, but Th2 cytokines did not.

Conclusions: These results suggest that elevated S100A8/A9 levels of AD patients may reflect the importance of DAMP-associated inflammation, which could be triggered by Th17 cytokines and HDM allergens in AD.

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Polyprenol Could Prevent Loss of Filaggrin in Epithelial Cells in Atopic Dermatitis

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Background: In epithelial cells loss of filaggrin correlates with atopic dermatitis (AD) presence and activity. Dysregulation of DPAGT1 (Dolichylphosphate (UDP-N-acetylglucosamine) N-acetylglucosaminephosphotransferase 1 (GlcNAc-1-P transferase) causes disturbances in filaggrin expression. The resent results are in favour of the idea that N-glycosylation in keratinocytes cells is limited by Dolichyl Phosphate Cycle (DPC) intermediates. The aim of the present study is to investigate the effect of Polyprenol (PP), which provides a dolichol phosphate (DolP) substitute on regulation of filaggrin expression.

Methods: Filaggrin expression was measured in skin biopsies from 42 persons with AD and 36 with normal skin and cultured keratinocytes; PP concentration in the culture medium made up 10^{-2} to 10^{-6}. Immunohistochemical and Western blotting methods were used to detect the changes in the expression levels of filaggrin and DPAGT1. IL-4 and IL-13 was determined using ELISA. Intermediates of DPC fractions were analysed by HPLC method.

Results: Overexpression of DPAGT1 was 5-fold higher in AD skin biopsies than in normal skin biopsies. AD cells differ from normal one in filaggrin content lost by 3 to 4 times. IL-4 and IL-13 cause overexpression and abberant N-glycosylation of filaggrin in DPC. The study showed overexpression of DPAGT1 and 6-fold DPC intermediates decrease in keratinocytes in presence of IL-13 and 2-fold in presence of IL-4 cells. Treatment of keratinocytes with PP resulted in downregulation of DPAGT1. It is established that PP in the concentration 10^{-2} M could overcome DPAGT1 overexpression which leads to regulation of filaggrin N-glycosylation.

Conclusions: IL-13 could cause DPAGT overexpression and dysregulation of N-glycosylation in keratinocytes which leads to AD fenotype affecting the stability of tight assembly and adherence junctions in skin. The findings indicate that DPAGT1 overexpression in keratinocytes treated with IL-4 and IL-13 can be overcomed by PP, which provides a DolP substitute for DPAGT1 normal expression, N-glycosylation and filaggrin loss prevention without neutralization of interleukins. Polyprenol could be a promising agent for atopic dermatis prevention and control.

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Role of Sweating on Impaired Skin Barrier Functions in Atopic Dermatitis

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Background: Atopic dermatitis (AD) is known to have skin barrier dysfunction and impaired sweating. To assess the relationship between sweating and skin barrier function, we measured 2 parameters reflecting skin barrier function; transepidermal water loss (TEWL), and water holding capacity of stratum corneum. Sweating function was evaluated by quantitative sudomotor axon reflex test (QSART) system in AD patients and non-atopic controls.

Methods: Thirty-nine AD patients (21 males and 18 females, mean ± SD age 37.8 ± 10.9 years) and 37 normal controls (17 males and 20 females, mean ± SDage 34.9 ± 10.1 years) were enrolled in this study. For measurement of TEWL and water holding capacity of stratum corneum on axilla, cubital fossa, scapular, and elbow. By using the QSART in which the axon reflex is stimulated by acetylcholine iontophoresis we measured the axon reflex (AXR) sweating volume for 5 minutes on cubital fossa. The measurements were performed at room temperature (21–22°C) and at relative humidity of 54%.

Results: The AD patients showed higher TEWL and lower water holding capacity value compared with normal controls on all 4 points. And the AD patients showed lower volumes of AXR sweating than normal controls on cubital fossa. We could not find out correlation between TEWL and AXR sweating volume. The same result was observed between water holding

capasity and AXR sweating volume. To our knowledge, elevated TEWL and decreased water holding capacity are believed to skin barrier dysfunction. It was surprising that we found positive correlation between TEWL and water holding capacity in AD.

Conclusions: The results of TEWL and water holding capacity suggest that the barrier function of stratum corneum is impaired in AD patients. On the one hand, further studies should be required to explain the unexpected correlation between TEWL and water holding capacity. Both TEWL and water holding capasity didn't correlate with AXR sweating volume. This appeared that the 2 factors are not under the influence of the AXR sweating at the same site.

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The Risk of Atopic Dermatitis in Children Exposed to Pets During Pregnancy

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Background: Although the mechanism is uncertain, some studies have linked prenatal and early-life pet exposure to a decreased risk of atopic dermatitis (AD).

Methods: 675 participants in a southeast Michigan population-based birth cohort were evaluated at age 2 to 4 years. Based on medical history and examination, a study physician was asked to determine whether there was evidence of current AD or a past history consistent with AD. Information regarding the presence of indoor dogs or cats was prospectively collected from the participants' mothers during pregnancy.

Results: Of 675 maternal-child pairs, 255 (37.7%) mothers reported living with a pet during pregnancy and 150 children (22%) were diagnosed with either current or prior atopic dermatitis by age 2 to 4 years. Compared to mothers not exposed to indoor pets during pregnancy, the risk of AD was lower among offspring of 255 mothers that lived with an indoor pet prenatally [OR = 0.6, 95% CI, (0.4-0.9), $P = 0.01$]. The lower risk was seen primarily among 137 mothers reporting indoor dogs only [OR = 0.5, (0.3, 0.8), $P = 0.009$] or 43 that had lived with both indoor cat(s) and dog(s) [OR = 0.4 (0.1, 1.0), $P = 0.05$]. There did not appear to be a similar effect among 75 mothers with cat only prenatal exposure [OR = 0.9 (0.5, 1.6), $P = 0.79$]. When analyses were restricted to the presence or absence of dog exposure (not considering cat co-exposure), offspring were also less likely to have had current or prior AD [OR 0.5(0.3, 0.8), $P = 0.002$]. Results of analyses further restricted to dog exposure and "current AD" (AD present at the 2–4 year evaluation) were similar [OR 0.5 (0.3, 0.9), $P = 0.013$]. These results were not substantially different in logistic regression models adjusting for the child's total IgE level or the presence of atopy as assessed by positive allergen-specific IgE tests or positive skin prick tests to a panel of common allergens.

Conclusions: Prenatal dog exposure is associated with a lower risk of AD in young children. The mechanism(s) responsible for this relationship require further study.

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Economic Analyses of Partially Hydrolyzed Infant Formulas in Prevention of Atopic Dermatitis: Results From 5 European Countries

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Background: Economic analyses (EAs) were performed in 5 European countries to determine costs, outcomes and cost-effectiveness of a partially hydrolysed 100% whey-based infant formula (PHF-W) in the prevention of atopic dermatitis (AD) in 'at risk' children when compared to standard cow's milk formula (SF) or extensively hydrolyzed formula (EHF).

Methods: The EAs were performed in France, Germany, Spain, Denmark and Switzerland, using decision-analytic models describing AD treatment pathways, as well as resource utilisation and costs associated with the treatment of AD in healthy yet 'at risk' newborns who could not be exclusively breastfed. A time horizon of 12 months including 6 months of formula consumption was applied, with country-specific resource use and costs. In 4 settings, SF was the main comparator. The outcomes of the EAs were the number of avoided cases and the incremental cost per avoided case (ICER) of AD when comparing subjects who used PHF-W versus SF. An ICER represents the additional cost for obtaining each additional clinical outcome gained; in this instance each avoided case. Given a lack of significant differences in efficacy between PHF-W and EHF, a cost-minimization approach was used in all settings to compare them. A negative ICER represents savings. Three perspectives were applied: the Ministry of Health (MOH), the family and society.

Results: In the base case analyses selecting PHF-W over SF yielded numbers of avoided cases of AD ranging from 1653 (Switzerland) to 13,356 cases (France) for respective "at risk" birth cohorts of 22,933 and 185,298 infants. The analyses of PHF-W versus SF generated ICERs ranging from €801 to €1343 (MOH), from −€1796 to −€454 (family) and from −€995 to €719 (society). The costs of formula and time loss were the main cost drivers. When comparing PHF-W to EHF in prevention, PHF-W demonstrated savings ranging from €4 to €120 million for society, or €1.3 to €64 million for the MOH perspective. The robustness of the models and the direction of the results were confirmed by one-way and probabilistic sensitivity analyses.

Conclusions: In 5 European countries, PHF-W appears to offer a better prevention than SF at a reasonable cost, and at a lower cost than EHF.

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Prevalence and Associated Risk Factors for Atopic Dermatitis Symptoms in Mexican Children

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Background: Describe AD prevalence and identify associated risk factors in Mexican children.

Methods: Multi-centric, cross-sectional ambiental survey. We applied the standardized Spanish-version ISAAC questionnaire to children's tutors aged 6 to 7 years in 8 Mexican cities. Sampling units randomly selected from local schools with advisable sample size of 3000 questionnaires per centre. Questions to evaluate actual AD: Has your child had itchy rash at any time in the past 12-months? Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks or around the neck, ears or eyes? A risk analysis was made through multivariate logistical regression, central tendency and dispersion measures were obtained with respective 95% confidence intervals.

Results: A total of 25,809 questionnaires were applied at 274 schools. For current AD symptoms 18,095 questionnaires were analyzed and for severe current AD symptoms 19,173. Current AD symptoms mean global prevalence was 6.1% (95% CI, 5.7-6.4%). Mean prevalence and 95% CI per center: Monterrey 4.2% (3.5-4.9%), Mexicalli 6.3% (5.3-4.9%), Ciudad Victoria 2.3% (1.8-2.9%), Tijuana 4.9%(4.1-5.7%); North DF 8.5% (7.6-9.4%), Southeasat DF 9.4% (8.0-10.7%), Toluca 5.4% (4.6-6.2%); Veracruz 5.3% (4.3-6.2%); Villahermosa 8.6% (7.3-9.8%). Severe current AD symptoms mean global prevalence was 0.7% (95% CI, 0.6-0.9). Mean prevalence and 95% CI per center: Monterrey 0.6% (0.3-0.9%), Mexicalli 0.8% (0.5-1.2%), Ciudad Victoria 0.3% (0.1-0.6%), Tijuana 0.9% (0.5-1.2%); North DF 1.1% (0.7-1.5%), DF Southeast 1% (0.5-1.4%), Toluca 0.3% (0.1-0.5%); Veracruz 0.7% (0.4-1.1%); Villahermosa 1.2% (0.8-1.7%). Identified risk factors for current AD symptoms: presence of allergic rhinitis symptoms OR 1.94 (95% CI, 1.53-2.14; $P \leq 0.005$); conjunctivitis symptoms OR 1.81 (95% CI, 1.53-2.14; $P \leq 0.005$); accumulated asthma symptoms OR 1.51 (95% CI, 1.3-1.76; $P \leq 0.03$). Identified risk factors for severe current AD symptoms: presence of conjunctivitis symptoms OR 2.20 (95% CI, 1.42-3.4; $P \leq 0.005$); accumulated asthma symptoms OR 2.16 (95% CI, 1.38-3.39; $P \leq 0.005$); use of acetaminophen in the first year of life OR 1.80 (95% CI, 1.21-2.69; $P \leq 0.005$).

Conclusions: Current AD symptoms prevalence was higher at north DF, followed by Toluca and southeast DF; current severe AD symptoms were higher at Villahermosa, followed by north DF and Tijuana. The presence of rhinoconjuntivitis and accumulated asthma symptoms doubles the risk for current AD and current severe symptoms in Mexican children and Acetaminophen use in the first year of life was associated with severe current AD symptoms.

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Involvement of Human Histamine N-Methyltransferase Gene Polymorphisms in Susceptibility to Atopic Dermatitis in Korean Children

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Background: Histamine N-methyltransferase (HNMT) catalyzes one of 2 major metabolic pathways for histamine. Histamine is one of the mediators for pruritus of atopic dermatitis. The aim of this study was to evaluate the role of HNMT polymorphisms in children with atopic dermatitis.

Methods: We genotyped 763 children for allelic determinants at 4 polymorphic sites, which were −465T>C, −413C>T, 314C>T and 939A>G in the HNMT gene, and the functional effect of the 939A>G polymorphism was analyzed. The genotyping was screened using the TaqMan fluorogenic 5' nuclease assay (ABI, Foster City, CA, USA).

Results: Among these 763 children, 520 had eczema and 542 had atopy. Distributions of the genotype and allele frequencies of HNMT 314C>T polymorphism were significantly associated with non-atopic eczema ($P = 0.004$) and those of HNMT 939A>G polymorphism were significantly associated with eczema in atopy groups ($P = 0.048$). However, those of HNMT 654T>C and 413C>T polymorphisms were not. In addition, subjects with the homozygous AA or heterozygous AG of the 939A>G polymorphism showed significantly higher IgE levels than those with the homozygous GG genotype ($P = 0.009$). In U937 cells, the variant genotype reporter construct showed significantly higher mRNA stability ($P < 0.001$) and HNMT enzyme activity ($P < 0.001$) than the common genotype.

Conclusions: Polymorphisms in the HNMT gene appear to confer susceptibility to atopic dermatitis in Korean children.

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Circadian Regulation of Scratching Behavior in NC/TND Mice, a Mouse Model for Human Atopic Dermatitis

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Background: Scratching behavior is a pivotal clinical sign and a therapeutic target of atopic dermatitis; however, due to the lack of an appropriate animal model, circadian regulation of this behavior remains unclear.

Methods: NC/Tnd mice, a mouse model for human atopic dermatitis, have been shown to exhibit severe scratching behavior together with the development of spontaneous atopic dermatitis when they are raised under air-uncontrolled environment. In this study, scratching behavior of the mice was measured by a SCLABA-Real system, a newly developed equipment that provides us with the real-time, long-term, quick and accurate quantification of murine scratching behavior by analyzing images with the high-speed camera and the invisible near-infrared light.

Results: Analysis by a SCLABA-Real system demonstrated that the frequency and duration of scratching behavior significantly correlated with the exacerbation of dermatitis in the mice, indicating that this system was able to measure scratching behavior without putting stress upon the mice. Twenty-four hours analysis revealed that the frequency and duration of scratching behavior increased in from the afternoon to the midnight and decreased in the morning. In addition to scratching behavior, transepidermal water loss (TEWL) also changed during a day in the mice. TEWL increased in the midnight and decreased in the morning.

Conclusions: These results indicate that scratching behavior and skin barrier function in atopic dermatitis exhibited circadian rhythm. In addition, NC/Tnd mice are considered to be an appropriate mouse model to investigate circadian rhythm of scratching behavior associated with atopic dermatitis.

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Metallic Soap Aggravates Skin Conditions in Patients With Atopic Dermatitis and a Mouse Model for Human Atopic Dermatitis, NC/TND Mice

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Background: Hardness in water is consisted with mineral salts, including calcium (Ca^{++}) and magnesium (Mg^{++}). The mineral salts react with soap to form an insoluble precipitate known as metallic soap (soap scum). Since metallic soap remains tightly on the skin and is hard to rinse off, it may become one of irritants that exacerbate dermatitis. In this study, we used cation-exchange resin to prepare ultra-pure soft water (UPSW) excluding both Ca^{++} and Mg^{++}, and investigated effect of UPSW rinsing on skin conditions in subjects with atopic dermatitis. Furthermore, antigenic activity of metallic soap was investigated by in vivo experiments.

Methods: Stratum corneum was collected from arms of healthy volunteers who rinsed soap in tap water or UPSW, and the quantity of remained soap scum was determined with a gas chromatography. After 4 weeks of bathing in UPSW, the water content of the stratum corneum and transepidermal water loss (TEWL) of volunteers with mild atopic dermatitis were measured. With atopic NC/Tnd mice, a model for atopic dermatitis, we attempted to confirm results obtained from atopic volunteers. Plasma total IgE was measured by an ELISA after immunization of mice with metallic soap.

Results: On skins rinsed in UPSW, soap was disappeared immediately and remained metallic soap was significantly reduced when compared to that on skins rinsed in tap water. In skins of atopic volunteers who used UPSW for bath, the water content in stratum corneum was increased and TEWL was

decreased. Skin dryness and itch scores were reduced in most volunteers. After washed with soap and rinsed in UPSW for 2 weeks, severe dermatitis of NC/Tnd mice were reduced as well as TEWL. On the other hand, dermatitis in NC/Tnd mice rinsed in tap water became worse. Plasma total IgE was increased in mice that were immunized with metallic soap.

Conclusions: UPSW protected skins from residue of metallic soap. Metallic soap has antigenic activity and increased plasma IgE levels. Clinical symptoms and the skin barrier function were improved by the use of soap with UPSW. UPSW is beneficial for the skin of patients with atopic dermatitis.

CHILDHOOD ASTHMA AND ALLERGIES

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The Allergic March Resolved at Allergen Component Level

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Background: The allergic march is well known at the level of pattern of sensitisation, but there is no information of its evolution in term of sensitzation to single allergenic molecules. We investigated the evolution of the IgE repertoire by means of a microarray allergen assay.

Methods: Serum samples from allergic patients of a wide age range were analyzed by a micorarray chip, which allow to identify in a single assay the presence of specific IgE towards 103 allergenic molecules. Total IgE were also evaluated as an internal control. Patients were stratified in 6 groups according to their age (0–2; 3–5; 6–9; 10–13; 14–17 and >17 years).

Results: Samples from 609 patients were analysed. The behaviour of total IgE according to age strictly paralleled that of the sum of specific IgE. Food-related components were the more frequently recognized in the first ages, whereas specific IgE to plant allergens appeared later. Nonetheless, mite-specific IgE were the most represented in all age classes. Specific IgE against cross-reacting allergens were virtually absent in the first years and tended to appear after the age of 6.

Conclusions: The molecular pattern of allergen recognition according to age well reflects the clinical characteristics of the allergic march.

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Prevalence of Wheezing and Risk Factors Associated to Wheezing in Infants in the First Year of Life, Cuibá, MT, Brazil

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Background: The purpose of this study was to evaluate the prevalence of wheezing and risk factors related to wheezing in infants (12–15 month-old) in the city of Cuiabá, Mato Grosso State, Brazil.

Methods: Cross-sectional study by applying a standardized written questionnaire from "*Estudio Internacional de sibilancia en lactentes*" (EISL) phase III. Parents and/or guardians of infants were interviewed at a primary health care clinic or at home from August 2009 to November 2010. Signed written informe consent was obtained from parents and/or guardians of all subjects. Factors associated to wheezing were studied using bivariate and multivariate analysis (SPSS v.18.0) and expressed as odds ratio (OR) and confidence interval 95% (95% CI).

Results: One thousand sixty parents were interviewed (N = 1060), 27.7% (N = 294) infants had at least one wheezing episode in their first year of life, with onset at 5.8 ± 3.0 months (mean ± standard deviation), and 45.9% (N = 135) had had 3 or more episodes (recurrent wheezing). The use of inhaled β2-agonists, oral corticosteroids or leukotriene receptor antagonist, nocturnal symptoms, respiratory distress, hospitalization and medical diagnose of asthma were significantly more frequent in the group with recurrent wheezing ($P < 0.05$). Independent risk factors associated with wheezing in the first year of life were: history of previous pneumonia (OR = 10.80; 95% CI, 4.52-25.77); to have more than 6 upper respiratory infections (URI) (OR = 2.95; 95% CI, 2.11-4.14); asthma in sibling (OR = 2.13; 95% CI, 1.18-3.87); asthma in father (OR = 1.98; 95% CI, 1.22-3.23); asthma in mother (OR = 1.62; 95% CI, 1.07-2.43); exposure to paracetamol in the first year of life for URI (OR = 2.13; 95% CI, 1.54-2.95); exposure to moderate air pollution from traffic (OR = 1.59; 95% CI, 1.08-2.33); and a first URI before of third month of age (OR = 1.50; 95% CI, 1.04-2.17).

Conclusions: The prevalence of wheezing episodes among one year-old infants living in Cuiabá was high and early in life. Risk factors for wheezing are similar to risk factors for asthma. Exposure to paracetamol was associated with wheezing but more researches are required to clarify this potential association.

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Risk Factors Associated to Wheezing in Mexican Children. A Multicentric Isaac-based Survey Study

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Background: Asthma affects around 300 million people around the world, and is expected to increase 100 million more in the next 15 years. Multiple risk factors had been associated with its prevalence, though little is known about the regional variations of these risk factors.

Objective: Identify the main risk factors associated to the presence of wheezing in the last 12 months in Mexican children aged 6 to 7 years old.

Methods: Multicentric, cross-sectional survey. The standardized Spanish-version ISAAC questionnaire was applied to tutors of children aged 6 to 7 years old in 8 cities of the Mexican Republic. Sample was randomly selected through public and private schools of each city, and a sample of 3000 children per center was advisable. Risk analysis was made through multivariate logistical regression, central tendency and dispersion measures were obtained with respective 95% confidence intervals.

Results: Nine centers of 8 cities participated, data of 24,504 questionnaires were analyzed with an answer rate of 90.7%. Grouping the 9 participating centers, a prevalence of 8.4% (95% CI, 8.1-8.8%) for wheezing in the last 12 months was found, with the next distribution: Monterrey 8.6% (95% CI, 7.6-9.6%), Mexicali 9.6% (95% CI, 8.4-10.7%), Ciudad Victoria 8.6% (95% CI, 7.5-9.7%), Villahermosa 10.2% (95% CI, 9.1-11.4%), Northern Distrito Federal 7.3% (95% CI, 6.5-8.2%),

Southeast Distrito Federal 9.9% (95% CI, 8.5-11.3%), Toluca 5.9% (95% CI, 5.1-6.7%), Tijuana 8.2% (95% CI, 7.2-9.2%), Veracruz 9.7% (95% CI, 8.4-10.9%).Identified risk factors for the presence of wheezing in the last 12 months were: nasal symptoms accompanied with ocular symptoms (itching and tearing) in the last 12 months, OR 2.31 (95% CI, 2.01-2.66; $P \leq 0.0001$). Nasal symptoms (blocked nose, runny nose, and/or itching) in the last 12 months, OR 2.2 (95% CI, 1.66-2.92; $P \leq 0.0001$). Hay fever diagnosis by medical staff OR 2.02 (95% CI, 1.72-2.37; $P \leq 0.0001$). Atopic dermatitis symptoms (classic morphology and distribution) in the last 12 months, OR 1.65 (95% CI, 1.39-1.96; $P \leq 0.0001$). Use of antibiotics in the first 12 months of life, OR 1.68 (95% CI, 1.48-1.90; $P \leq 0.0001$). Use of acetaminophen in the last 12 months, OR 1.49 (95% CI, 1.35-1.65; $P \leq 0.0001$).

Conclusions: The presence of allergic rhinoconjuntivitis symptoms in the last 12 months doubles the risk for the presence of wheezing in Mexican children.

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Association Between Eosinophil Apoptosis in Induced Sputum and Asthma Severity in Children

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Background: There is increasing evidence that the disorder of eosinophil apoptosis contributes to the mechanism of prominent airway inflammation in asthma. However the relationship between dysregulation of eosinophil apoptosis and severity of childhood asthma is still unclear.

Objective: Investigate the relationship between eosinophil apoptosis in induced sputum and severity of asthma in children.

Methods: Eighty-six children aged 6 to 12 years with asthma and 32 age-matched healthy controls were observed. Diagnosis of asthma was made using a clinical questionnaire, physical examination and skin prick tests (SPTs). Lung function, and induced sputum analysis were measured in all patients. Total and antigen specific IgE levels were assessesed by ELISA. Eosonophils apoptosis was determined by staining nuclei with propidium iodide, and analyzed with a FACScan. Expression Apo-1/Fas antigen (CD95) in sputum eosinophils was assessed by immunohistochemical staining techniques.

Results: Diagnosis of asthma was confirmed by positive SPT and increased total and specific IgE levels. Asthma severity (assessed by FEV1, peak expiratory flow (PEF) variability and daily symptom scores) complied with mild and moderate asthma. The percentage sputum eosinophils was expressively increased (threshold of <3%) in all asthmatic children (compared to control group) and directly correlated with peripheral blood eosinophilia, skin sensitization, increased level of total and specific IgE and clinical symptoms of asthma and all of these markers were more significant in children with moderate asthma ($P < 0.05$). Asthma children showed decreased eosinophils apoptosis ("apoptotic ratio"-AR) in induced sputum as compared to controls ($P < 0.001$), which directly correlated with predicted value of FEV1, PEF variability and inversely with symptoms score ($P = 0.005$), and was significantly lower in patients with moderate asthma than those in patients with mild ($P = 0.001$). More of that, these parameters also correlated with decreased expression of Apo-1/Fas antigen (CD95), especially in moderate asthmatic children ($P < 0.05$).

Conclusions: Our investigation: 1. Confirms that reduced eosinophil apoptosis in induced sputum associated with increased clinical severity of asthma in children. 2. Provides additional evidence that eosinophil apoptosis may be important in the resolution of eosinophilic airway inflammation in asthma, because of their prolonged survival that maintains inflammation.

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Antibiotics but not Paracetamol Reduce the Risk for Recurrent Wheezing in Infants

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Background: Paracetamol (PCM) and antibiotic (ATB) use have been associated with risk for wheezing and asthma in children. The aim of this study was to verify the association of recurrent wheezing (≥3 episodes) in infancy and use of ATB or PCM in the first year of life.

Methods: Cross-sectional study using a standardized and validated questionnaire (EISL: *Estudio Internacional sobre Sibilancias en Lactantes*) with questions: Has your baby had wheezing or whistling in the chest area or bronchitis in the first 12 months of life? Has your baby had 3 or more wheezing episodes in the first year of life? How often has your baby used antibiotics in the first year of life? How often has your baby used paracetamol in the first year of life? Parents of infants, ages 12 to 15 months that attended to Health Centers for routine immunization were interviewed between September 2009 to September 2010 (EISL Phase III). Risk was demonstrated using Odds ratio and 95% CI.

Results: One thousand and 3 parents participated in the survey and 19.8% of infants had recurrent wheezing starting at 6.1 ± 3 months. The use of PCM was not related to the presence of recurrent wheezing [No PCM (OR = 0.91; 95% CI, 0.38-2.19; $P = 0.83$), PCM 1–3 times (OR = 1.21; 95% CI, 0.77-1.91; $P = 0.4$), PCM 4–6 times (OR = 1.21; 95% CI, 0.77-1.9; $P = 0.41$) and PCM ≥7 times (OR = 0.76; 95% CI, 0.51-1.13; $P = 0.17$)], while more frequent use of ATB reduced the risk of recurrent wheezing in the first year of life [No ATB (OR = 2.18; 95% CI, 1.35-3.51; $P = 0.001$), ATB 1–3 times (OR = 1.39; 95% CI, 0.93-2.07; $P = 0.1$), ATB 4–6 times (OR = 0.37; 95% CI, 0.22-0.62; $P = 0.001$) and PCM≥7 times (OR = 0.22; 95% CI, 0.07-0.66; $P = 0.001$)].

Conclusions: The frequent use of ATB reduced the risk of recurrent wheezing in the first year of life unlike PCM that was not associated with recurrent wheezing in this study population.

CONJUNCTIVITIS

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Ocular Signs and Symptoms Elicited by a Naturalistic Allergen Challenge in an Environmental Exposure Chamber Model Versus a Direct Allergen Instillation Model

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Background: Direct-instillation ocular models are well established for eliciting allergic responses in research and clinical testing. This study compared direct ocular instillation of allergen to a more naturalistic airborne allergen exposure.

Methods: Thirteen subjects with histories of ragweed allergy and positive skin prick responses attended screening, dose-finding, dose-confirmation, and analysis study visits. For conjunctival allergen provocation testing (CAPT), 1 drop of ragweed allergen was administered to each eye, at the lowest possible subject-specific concentration between 1.6 and 100 protein nitrogen units per 25 μl drop. For environmental exposure chamber (EEC) testing, subjects were exposed to continual airborne ragweed pollen at 3500 ± 500 particles/m^3. Symptoms of itching and tearing were self-assessed on diary cards by subjects. Signs of hyperemia, swelling, and mucous discharge were assessed by clinicians. Assessment time points started at 30 minutes before exposure and continued through 180 minutes after exposure.

Results: At baseline, there were minimal signs and symptoms. Maximum mean hyperemia with CAPT was 2.3 ± 0.6 units (between moderate and severe) and with EEC was 1.9 ± 0.5 units (approximately moderate); these maxima occurred after 30 minutes with CAPT (rapid spike) and after 180 minutes with EEC (gradual increase). Mean swelling was <1 unit out of 4 units at all times (CAPT and EEC), and mucous discharge was observed in only 1 subject during the study (with CAPT). Maximum mean itching with both CAPT and EEC was 2.8 ± 1.0 units (approximately severe), but this maximum occurred after 20 minutes with CAPT (rapid spike) and after 180 minutes with EEC (gradual increase). Maximum mean tearing with CAPT was 1.2 ± 0.7 units (approximately mild) and with EEC was 1.6 ± 0.6 units (between mild and moderate); these maxima occurred after 15 minutes with EEC (rapid spike) and after 120 minutes with EEC (gradual increase).
Conclusions: The time courses of allergic signs and symptoms differed between CAPT and EEC models; however, both models evoked similar maximum response levels. This demonstrates that the EEC model is a useful challenge model for mimicking natural airborne ocular allergen exposure.

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Increased Frequency of CD4+ CD25+ FOXP3- in Allergic Conjunctivitis Patients

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Background: Allergic conjunctivitis (AC) is one of the most common eye disorders in clinical practice. It has been shown that AC is a disorder mediated by Th2 lymphocytes producing IL-4 and IL-5, where the eye damage is caused by a type I hypersensitivity. It has been suggested in asthma and rhinitis that T regulatory cells (Tregs) $CD4^+$ $CD25^+$ $FOXP3^+$ have been involved in control allergic status, favoring an optimal microenvironment with immunosuppressive cytokines (IL-10, TGF-β). However is unknown if Tregs have a role in human allergic conjunctivitis, thus it was the aim of this study.
Methods: Peripheral blood mononuclear cells (PBMC) were isolated from blood samples of healthy donors (HD) and AC-patients, and then PBMC were labeled with mAbs against CD4, CD25 and FOXP3. Labeled cells were analyzed by flow cytometry. Statistical analysis was performed with GraphPad v.5.
Results: AC-patients showed 55-times more $CD4^+$ $CD25^+$ cells than HD ($P = 0.02$). Most of $CD4^+$ $CD25^+$ were $FOXP3^-$ (90 ± 5.4), when we compared MFI of FOXP3 in $CD4^+$ $CD25^+$ cells, we observed a decreased expression in AC-patients than HD (28.5 vs 85.36, $P = 0.02$).
Conclusions: Despite we observed higher frequency of $CD4^+$ $CD25^+$ in AC-patients, these cells were $FOXP3^-$, more interesting, the few cells $FOXP3^+$ showed a diminished MFI. These data suggest that allergic conjunctivitis status could be related with a regulatory dysfunction, as has been suggested in asthma and rhinitis.

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Increased Frequency of CD4+ CCR4+ CCR9+ Cells in Patients With Allergic Conjunctivitis

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Background: Allergic conjunctivitis is one of the most common diseases affecting the ocular surface, it has been suggested that T CD4+ cells regulate immune response in allergic diseases such as asthma and rhinitis, in a predominant Th2 response. In animal models, it has been observed a selective migration of CD4+ T cells to conjunctiva directed by chemokines; however molecules involved in CD4+ T cell migration in humans is unknown, thus it was the aim of this study.
Methods: Peripheral blood mononuclear cells (PBMC) were isolated from blood samples of healthy donors (HD) and AC-patients. PBMC were labeled with mAbs against CD4, CCR4, CCR5, and CRR9, and then labeled cells were analyzed by flow cytometry. *T* test was used to perform statistical analysis, $P < 0.05$ were considered statistically significant.
Results: We observed increased frequency of CCR4+ and CCR9+ on PBMC cells; interestingly, expression of CCR4+ was 1.46 times increased on CD4+ T cells of AC-patients compared to CD4+ T cells of HD ($P = 0.01$). Similarly, we observed higher frequency of CCR9 expression on CD4+ cells of AC-patients than on CD4+ T cells of HD ($P = 0.01$). On the other hand, CCR5 expression was diminished on PBMC from AC-patients than in HD ($P = 0.0002$).
Conclusions: Increased frequency of CD4+ CCR4+ CCR9+ was observed in AC patients with diminished frequency of CCR5 expression on PBMC. CCR4 and CCR9 have been involved in inflammatory process such arthritis and asthma, both could be related to inflammatory reaction at conjunctiva. CCR5 expression is mainly on Th1 cells, diminished frequency on PBMC in allergic conjunctivitis patients could be related with imbalance of immune response favoring a Th2 chronic inflammation.

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Long-term IFN-γ Treatment Alters Allergic Inflammation-Associated Gene Expression in Conjunctival Fibroblasts

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Background: Interferon-γ (IFN-γ) is a T helper type 1 (Th1) cytokine which has antiviral, anti-proliferative, and immunomodulatory properties. Despite the presence of IFN-γ in the conjunctiva or tear fluid of patients with severe allergic conjunctivitis, the role of IFN-γ in allergic conjunctivitis is controversial and enigmatic. In this study, we assess the effect of long-term treatment of IFN-γ on human conjuctival fibroblasts.
Methods: Primary cultured fibroblasts derived from human conjunctiva specimens were established. Cultured fibroblasts were incubated with or without IFN-γ (10 ng/mL) for up to 14 days. After IFN-γ treatment, cells were washed out and were re-stimulated with combinations of IL-4 (10 ng/mL) and TNFα (10 ng/mL) for 6 hours. Then, total mRNAs were isolated and mRNA expression levels were measured using a microarray and real time-PCR.
Results: In IFN-γ treated fibroblasts in short-term (6 hours), we confirmed the increased expression levels of well-known interferon induced genes, such as MHC class II, IRF1 and CXCL10. Increased expression of CCL11 stimulated by IL-4 + TNFα was suppressed by short-term IFN-γ treatment as described previously. In long-term (14 days) IFN-γ treated cells, the expression of CCL11 and several proinflammatory chemokines, which were associated with Th2 cell and eosinophil migration, was slightly but significantly increased without any other stimulations. Interestingly, IL-4 + TNFα stimulation greatly enhanced the expression levels of these chemokines, suggesting that long-term IFN-γ treatment alters the competency of gene expression potential on these gene loci in contrast to the situation for short term treatment. Time-course analysis of IFN-γ

treatment revealed that the treatment of IFN-γ up to 24 hours suppressed the IL-4 + TNFα-induced CCL11 expression, whereas the CCL11 expression was enhanced 3 days after the treatment.
Conclusions: These results uncovered previously unsuspected contribution of IFN-γ to the fibroblasts in allergic inflammatory milieu in terms of the change in production of certain chemokines. In other words, the antagonistic function of IFN-γ to Th2 cells at the early phase may represent only a small part. The intracellular signaling and IFN-γ-dependent secondary events are needed to be explored to explain the long-term effect or the late phase phenomenon after IFN-γ administration.

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Hyperosmolar Conjunctival Provocation Test (HCPT) in the Evaluation of Ocular Symptoms

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Background: Non-allergic environmental factors may cause ocular symptoms in atopic and non atopic subjects, which are known as nonspecific conjunctival hyperreactivity (CHR). This study aims to investigate the presence of CHR to the HCPT in subjects with ocular symptoms.
Methods: 63 adults with ocular symptoms (itching, red eyes or tearing) were selected and tested for allergy to house dust mites and grass pollen by skin prick tests (ALK Abelló) and serum specific IgE (Immunocap-Phadia). They were considered atopic if these tests were positive to at least one allergen and non atopic if tests were negative. HCPT with 10-fold serial diluted glucose solutions was performed in all subjects until it produced conjunctival redness. Digital images were analyzed by 2 investigators (MD and technician) registering redness of the challenged eyes in red and the total area of contra-lateral eyes in blue using the fine brush tool (software GIMP 2.6.5). The number of red dots of the affected eye (%) was compared to the number of blue dots of the control eye.
Results: TPCH was positive in 33/38 atopic subjects (87%) and in 4/25 non atopic (16%). Most reactions occurred at the 40% glucose solution. Sensitivity was 87% and specificity 84% ($P < 0.0001$). There was a significant correlation (96.5%, Pearson, $P < 0.0001$) between the number of red dots reported by investigators in 23 digitalized images.
Conclusions: TPCH identifies CHR in both atopic and non atopic subjects. Atopic subjects exhibit CHR more frequently than non-atopic subjects. Digital images may be useful for grading ocular hyperemia in TPCH.

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Tear IFN-G is Increased After Sublingual Immunotherapy in Allergic Conjunctivitis Patients and Correlates With Clinical Improvement

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Background: Despite success of sublingual immunotherapy (SLIT) in the treatment of allergy diseases, more research is needed related to ocular allergy. Thus, the aim of this work was to analyze the ocular microenvironment provided by tear cytokines in allergic conjunctivitis (AC) patients treated with SLIT and to correlate tear and serum cytokines with ocular findings.
Methods: 19 AC-patients were included in this study. AC diagnosis was based on a clinical history and full ophthalmologic examination according to the diagnosis standards of the American Academy of Ophthalmology. Routine immunological studies were performed to corroborate allergic status Negative coproparasitoscopic results were documented. This study was approved by Scientific and Ethics Committees if Institute of Ophthalmology "Conde de la Valenciana," Mexico City an all subjects gave their informed consent to obtain samples. Tear and serum samples were collected to determine cytokines IL2, IL-4, IL-5, IFN-g, TNF-a, IL-10 by cytometric bead arrays (CBA), following manufacturer's instructions.
Results: After 6 months of treatment with SLIT we observed significant higher IFN-g concentration, without significant changes in IL2, IL4, IL5, TNFa or IL10. We observed significant clinical improvement since 3 months of treatment and it was maintained until the end of 6 months. Clinical improvement correlated with IFN-g concentration.
Conclusions: Clinical outcome in AC-patients treated with SLIT could be tear IFN-g dependent.

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CYTOKINES AND CHEMOKINES

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Hypoxia-Inducible Factor 1 (HIF-1) Transcription is a "Signalling Driver" for Allergic Inflammation, Host Innate Immune Defence and Leukaemia Progression

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Background: Hypoxia-inducible factor 1 is a transcription complex that plays a pivotal role in cellular adaptation to low oxygen availability, which occurs during allergic responses, host immune defence and leukaemia progression. We investigated the role of HIF-1 in cellular adaptation to stress associated with different types of pathological reactions of immune cells. We studied IgE-dependent responses of human mast cells and basophils, Toll-like receptor (TLR)-mediated innate immune reactions of human myeloid cells and stem cell factor (SCF)-mediated responses of hematopoietic cells of myeloid lineage.
Methods: LAD2 human mast cells[1], primary human basophils, and THP-1 human myeloid cells were used for investigations of FcεRI, TLR ligand and SCF-induced responses. Quantitative real-time PCR, Western blot analysis, ELISA, fluorometry, luminometry and fluorescence microscopy were employed to run the assays.
Results: We observed that HIF-1 activation is differentially regulated in the cases of pro-allergic, TLR-dependent and SCF-induced cellular responses. While PI3K/mTOR and MAP kinase pathways were the major contributors to HIF-1 activation during allergic/SCF-dependent responses, TLR-mediated processes occurred mostly via redox-dependent mechanisms. Experiments with HIF-1α (the inducible subunit regulating HIF-1 transactivation) knockdown cells demonstrated that HIF-1 plays a crucial role in the expression of the primary angiogenic cytokine VEGF and controls intracellular energy metabolism by regulating glycolytic metabolic activity.
Conclusions: The HIF-1 transcription complex supports not only the survival of immune cells (mast cells, basophils, myeloid cells) in pathological environments but also determines their abilities to generate pro-allergic, pro-inflammatory as well as pro-angiogenic cytokines over sustained periods.

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Keratinocytic Thymic Stromal Lymphopoietin Plays an Important Role in Epicutaneous Sensitization and the Atopic March

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Background: Atopic dermatitis (AD or eczema) often precedes the development of asthma and allergic rhinitis in atopic subjects, a phenomenon known as atopic march. An important role of epicutaneous (*e.c.*) sensitization has been recognized in the atopic march; however, the factors involved in e.c. sensitization remain poorly understood. Our previous studies using mouse models have shown that induced overexpression of Thymic Stromal Lymphopoietin (TSLP) in keratinocytes not only triggers an AD [Li, M. et al. *Proc Natl Acad Sci U S A*. 2006;103:11736–11741] but also aggravates experimental asthma induced by systemic sensitization and airway challenge of ovalbumin (OVA) [Zhang Z, et al. *Proc Natl Acad Sci U S A*. 2009;106:1536–1541], suggesting that TSLP represents an important factor linking AD to asthma. However, whether keratinocytic TSLP is essentially required for developing e.c. sensitization and triggering the atopic march remained to be determined.

Methods: We develop a mouse model in which e.c. sensitization of OVA through tape-stripped skin is followed by intranasal challenge to induce an allergic asthma. $TSLP^{ep-/-}$mice (in which TSLP is selectively ablated in epidermal keratinocytes at adult stage) or $TSLP^{over}$ mice (in which keratinocytic TSLP overexpression is induced by topical application of MC903, a low-calcemic vitamin D analog) are subjected to this mouse model.

Results: Upon OVA e.c. treatment, $TSLP^{ep-/-}$ mice develop a defective allergen sensitization evidenced by decreased production of OVA-specific IgE and IgG1 and a reduction of the secretion of Th2 and Th17 (but not Th1) cytokines by in vitro OVA stimulated splenocytes. $TSLP^{ep-/-}$ mice also exhibit a decreased OVA-induced skin inflammation. Finally, upon intranasal challenge, $TSLP^{ep-/-}$ mice develop a less severe airway allergic inflammation and a reduced airway hyperresponsiveness. In contrast, overproduction of keratinocytic TSLP boosts the e.c. sensitization and triggers an aggravated asthma.

Conclusions: Our results demonstrate an important role of keratinocytic TSLP in developing epicutaneous sensitization, generating allergic skin inflammation and triggering the atopic march. Thus, blocking the expression or activity of keratinocytic TSLP could be helpful to limit epicutaneous sensitization and prevent the atopic march.

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Pivotal Role of Intestinal Interleukin-17-Producing Gammadeltat Cells in the Food Allergy

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Background: Food allergy is a serious health problem, which affect 5% of children in westernized countries and evoke life-threatening hypersensitivity, termed anaphylaxis shock. Type 2 helper T cell (Th2) response and immunoglobulin E (IgE) has been implicated in the progression of food allergy, but the roles of specific lymphocyte subpopulations and cytokines remain to be clarified.

Methods: The mucosal adjuvant, cholera toxin (CT) and ovalbumin (OVA) were co-administered orally into mice, while OVA alone could induce oral tolerance. To evaluate the contribution of various cytokines, we used interleukin-17 (IL-17) or IL-23 knockout (KO) and wild type (WT) mice as control.

Results: Here we demonstrate that gamma delta T cells in the intestinal mucosa, as well as the cytokines interleukin-23 (IL-23) and IL-17, have pivotal roles to suppress the induction of serum OVA specific immunoglobulins and anaphylaxis in the food allergy model. The expression of IL-23, which was derived mostly from mucosal macrophages, and IL-17 levels were elevated after CT and OVA sensitization, and this induction of IL-17 was dependent on IL-23.

Conclusions: These data, together with analysis of mice genetically disrupted for IL-17 and IL-23, suggest that IL-23 suppress the food allergy, whereas IL-17 has an important role in the anaphylaxis shock. Moreover, depletion of gamma delta T cells exacerbates the food allergy. We propose that T lymphocytes, including gamma delta T cells, could be a therapeutic target for mitigating the allergic response that evokes the anaphylaxis shock.

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Effect of Formoterol on Eosinophil Trans-Basement Migration Induced by Interleukin-8-Stimulated Neutrophils

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Background: Neutrophils are often increased in the airways of either chronic severe disease or acute exacerbation of asthma. Neutrophils migrated in response to interleukin-8 (IL-8) may lead eosinophils to accumulate in the airways of asthma and possibly aggravate this disease. In this study, we investigated whether formoterol modify the trans-basement membrane migration (TBM) of eosinophils stimulated with neutrophils and IL-8.

Methods: Neutrophils and eosinophils were isolated from peripheral blood obtained from healthy donors. The TBM of eosinophils was examined using a modified Boyden's chamber technique. Neutrophils were preincubated with or without formoterol (0.1 μM) at 37°C for 30 minutes. Eosinophils were added to the upper compartment of a chamber with a Matrigel-coated transwell insert. Medium that contained preincubated neutrophils and IL-8 was added to the lower compartment of the chamber. After 90 minute incubation, migrated eosinophils in the lower chamber were calculated using eosinophil peroxidase assays.

Results: A combination of neutrophils and IL-8 significantly induced TBM of eosinophils. Formoterol by itself did not modify the TBM of eosinophils. However, formoterol significantly attenuated TBM of eosinophils stimulated with neutrophils and IL-8.

Conclusions: These results suggest that formoterol may act as a therapeutic agent on enhanced eosinophilic inflammation in acute exacerbation or persistent severe disease of asthma. This effect of formoterol likely involves inhibition of activation of neutrophils.

DRUG ALLERGY

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Characteristics of Liver Injury in Drug-induced Systemic Hypersensitivity Reactions

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Background: Liver is the second most commonly involved organ in drug-induced systemic hypersensitivity reactions (DiSH). Although liver function is very important indicator in the course of DiSH, there have been few studies about the characteristics of the liver injury. In present study, we investigated clinical characteristics of DiSH associated with liver injury (liver-DiSH)
Methods: We retrospectively reviewed medical records of 38 hospitalized patients who developed liver-DiSH (AST or ALT ≥80 IU/L) from January 2008 to February 2011 in a tertiary referral hospital. We analyzed culprit drugs, the type and degree of liver injury, and the effect of systemic corticosteroids. Fisher's exact test and Chi-square test and Mann-Whitney test were used for statistical analysis.
Results: Thirty-eight patients of liver-DiSH were enrolled, whose clinical phenotypes were Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) (n = 9, 24%), drug reaction with eosinophilia and systemic symptoms (DRESS) (n = 23, 60%), maculopapular rash (MP rash) (n = 5, 13%) and acute generalized exanthematous pustulosis (AGEP) (n = 1, 3%). Antibiotics (n = 16/38, 41%) was the most common cause of liver-DiSH. Culprit agents of liver-DiSH were allopurinol (n = 3/9, 33%) in SJS/TEN and antibiotics (n = 13/23, 57%) in DRESS. Mortality tended to be higher in SJS/TEN than in DRESS (22% (2/9) vs 17% (4/23), $P = 0.846$). Degree of liver injury was statistically more severe in DRESS than in SJS/TEN (mean peak AST [423 IU/L vs 144 IU/L, $P = 0.062$], mean peak ALT [428 IU/L vs 156 IU/L, $P = 0.013$], mean peak ALP (alkaline phosphatase) [252 IU/L vs 85 IU/L, $P = 0.002$], mean total bilirubin [7.7 mg/dL vs 1.3 mg/dL, $P = 0.064$], and time required for AST/ALT to drop below 80 IU/L [15.8 days vs 4.1 days, $P = 0.049$]). Seventy-six percents (29/38) of patients were treated with systemic corticosteroid. The use of corticosteroid did not significantly affect both recovery of liver injury and mortality.
Conclusions: Our results suggest that liver-DiSH has distinguished clinical characteristics according to the disease phenotypes. Further studies are needed to evaluate the role of systemic corticosteroid in liver injury in DiSH.

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Drug Reaction with Eosinophilia and Systemic Symptoms (Dress): What We Still Have to Learn?

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Background: Cases of drug induced hypersensitivity syndrome are reported under various names and case definition for this reaction pattern is regularly poorly applied. Our aim was to analyze series of cases of Drug Reaction with Eosinophilic Hypersensitivity Syndrome (DRESS) and their clinical and demographic data.
Methods: A prospective study was developed in Allergy Clinics of 2 Services in São Paulo, Brazil, from November 2008 to June 2011. The patients were studied based on history of DRESS based on standardized scoring systems and using an adapted ENDA (*European Network of Drug Allergy*) questionnaire. Clinical and demographic data were analysed.
Results: Twenty-nine cases were validated as probable or definitive DRESS, 20 females (69%) and the mean age was 43.6. The reactions generally started with fever and exanthema. All cases had exanthema, mucosal involvement was found in 4 patients (13%). Fever >38°C was present in 89% and lymphadenopathy in 55%. Involvement of a single internal organ (69%) or variable combination of 2 or more internal organs (17%) was common, predominantly related to liver (79%), kidney (17%) and lung (6.8%). Eighty percent of patients with renal involvement required dialysis. Eosinophilia was documented in 89% and atypical lymphocytes in 31%. Sixty-nine percent were related with antiepileptics, 10% with sulfonamides and 6.8% with allopurinol, 6.8% with β-lactams antibiotics and 6.8% with non-steroidal anti-inflammatory drugs. The mean interval between the intake of the suspected drug and the reaction was 27.6. In all patients the duration of the reaction was protracted (>15 days). Forty-eight patients reported the intake of more than 2 drugs at the same time of the reaction, but in all cases there was 01 drug suspected. No fatalities occurred.
Conclusions: This series confirmed the clinical variability of DRESS, highlighting skin, fever, lymphadenopathy, internal organs involvement and eosinophilia. There was severe internal organ involvement, but no fatalities occurred. Clinical characters and time of onset of the reactions differs from others non-immediate hypersensitivity reactions, it supports that DRESS is an original phenotype. Prospective long-term multicentric epidemiological studies may be important for better understanding of this syndrome.

FOOD & DRUG ALLERGY: LATE-BREAKERS

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Influence of Transglutaminase and the Reducing Agent Glutathione in the Gastric Digestion and Immunogenicity of Beta-Lactoglobulin

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Background: Among the milk whey proteins, β-lactoglobulin (β-Lg) is the main allergen. In native state, β-Lg is resistant to pepsin, which is considered an indicator of its allergenic potential. Protein antigenicity can be reduced by treatment with transglutaminase (TG), an enzyme which catalyses inter or intra crosslink between Lys and Gln residues. Reducing agents have been used to increase the access of TG to the Lys and Gln residues. This study aimed at investigating the antigenicity and digestibility by pepsin of β-Lg modified by TG in the presence of the reducing agent glutathione (GSH).
Methods and Results: The polymerization of β-Lg (Davisco, MN, USA) by microbial TG (WM, Ajinomoto Ltda, Brazil) was studied using a central-composite experimental design with 2 independent variables, GSH concentration [GSH] (0–0.2 mmol L^{-1}) and enzyme:substrate ratio (E/S) (0–44.1 U g^{-1}). The dependent variable was the response of specific IgE obtained from the serum of BALB/c mice sensitized with native β-Lg (IgE anti-β-Lg) against the modified protein. Polymerization was carried out at 50°C/180 minutes and stopped by heating at 80°C/5 min. Digestion was simulated using pepsin (E/S 1:20 w/w, pH 2, 37°C, 1 hour), and SDS-PAGE and the ELISA assay used to characterize and evaluate the antigenicity of the samples, respectively. The linear and quadratic factors of [GSH] and E/S, and their interaction, showed no significant effect on the response of IgE. No treatment resulted in a decrease in the response of IgE anti-β-Lg, but a significant ($P < 0.05$) increase was observed in the response of IgE against treatments 1, 7 and center point. Intact β-Lg was observed in the electrophoretic profile of the digested samples, indicating resistance to pepsin. After digestion, the samples not presented difference with respect to the digested native β-Lg sample (213.06 ± 9.59 ng mL^{-1}).
Conclusion: Polymerization of the β-Lg with TG in the presence of the GSH did not alter its digestibility by pepsin or decrease the antigenicity. Under some of the conditions studied the antigenicity of the β-Lg increased, indicating that the treatment could have created or exposed epitopes.

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Immediate and No Immediate Reactions Induced by Iodinated Contrast Medium Nonionic Among Hospitalized Patients: Incidence and Severity

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Background: Contrast media (CM) are among the most widely used medications in the world. Our objective was to estimate the severity and incidence of adverse reactions to MC, first administered in hospitalized patients.
Methods: We prospectively studied 99 patients requiring computed tomography (CT) enhanced with MC. Immediate adverse reactions were identified by direct questioning and/or physical examination after administration of iodinated CM nonionic low osmolarity. Additionally, blood pressure, heart rate, oxygen saturation, serum creatinine and total count of eosinophils were measured before and after the procedure.
Results: Mean age of patients was 50.4 ± 20.2 years, women were 52. The occurrence of immediate adverse reactions and no immediate observed were 26.3 and 10.1% respectively. Eighteen (69.2%) of the immediate reactions were mild, 6 (23.1%) moderate and 2 (7.7%) severe (both developed symptomatic arrhythmias). The most common manifestations were warmth, nausea and itching, nephrotoxicity was observed in 5.1% of patients and eosinophilia in 3.1%. No skin reactions documented. Median serum creatinine before and after the procedure not observed significant difference ($P = 0.130$), instead the total number of eosinophils did show difference ($P < 0.001$).
Conclusions: Our results demonstrate a high incidence of adverse reactions compared with previously published reports worldwide. Although most adverse reactions are mild, those of severe intensity, with increased mortality and morbidity, increased costs and hospital length of stay continue to occur despite the increased use of contrast media of low osmolarity. More prospective studies that share the same methodology are needed to determine the actual frequency.

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Severe Cutaneus Drug Reactions: Description of a Serie Cases

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Objective: To describe the cases of severe cutaneus drug reactions reported in patients admitted to a hospital in São Paulo, assisted by the Service of Allergy and Immunology.
Methods: A case serie study based on record's analysis of patients who were hospitalized from January 2002 to June 2011 evaluated by the allergist.
Results: We evaluated 25 cases of severe drug reactions, among which 13 (52%) were Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), 7 (29.4%) Stevens-Johnson syndrome (SJS), 4 (16) Toxic Epidermal Necrolysis (TEN) and 1 (4%) Acute Generalized Exanthematous Pustulosis (PEGA). The patients' ages ranged from 5 to 77 years (median = 37), 13 (52%) were male. The drug classes more closely related were antibiotics 18 (45%), non-steroidal anti-inflammatory 12 (30%) and anticonvulsants 9 (25%). The mean length of hospital stay was 15 days. Systemic involvement occurred in 15 (60%) patients, of whom 15 (100%) liver involvement, 5 (33%) kidney, 2 (13%) pancreatic and 1 (6%) thyroid. There was mucosal involvement in 12 (80%) cases. Three patients (12%) had septicemia, which led to mortality. All of them had TEN with extensive cutaneus involvement. Other patients presented sequelae in the skin (4–16%) and in the eyes (5–20%). Other complications observed were: cholestatic syndrome, immunodeficiency and autoimunidade, each of them in one patient.
Conclusion: In this serie of cases, DRESS was the most frequent disease and antibiotics were the drugs most commonly implicated. The average hospital stay was prolonged. Liver involvement was the main systemic commitment. TEN was responsible for the major mortality rate.

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Frequency of Sensitization for Food and Aero-Allergens in Patients Received in a Venezuelan Laboratory During 2010 to 2011 Period

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Background: Type I Allergy had been defined as an adverse immunologic reaction mediated by IgE that occurs after a repeated exposure to specific protein. The prevalence of the allergies has increased considerably in the past 20 years, thus increasing the need of study the response to several allergens. The objective was evaluate the frequency of foods and respiratory allergens sensitization in patients referred to Corpodiagnostica Laboratory (Caracas, Venezuela, ISO 9001:2008 certified laboratory) in the period that correspond from January 2010 and to July 2011.
Methods: There were a total of 2.445 patients with a request of specific IgE against some foods and aero-allergens. The sample was divided in groups according the age and sex. We measured the specific IgE to each patient by the in vitro RIDA Allergy-screen immunoblot method (r-biopharm, Germany).
Results: The frequency of sensitization to aeroallergens were 41, 48% in 2010 (the most frequent were dust mites in the fallowing order: Dermatophagoides pteronissinus, D. farinae and Blomia tropicalis), and 51, 20% in 2011, being the frequent: D. farinae, B. tropicalis and D. pteronissinus. In the case of food allergens the frequency of sensitization were 25, 99% in 2010 and 36, 47% in 2011.
Conclusions: In Venezuela the most frequent aero-allergens during the whole period were the dust mites, unlike other countries with established weather seasons, by another hand for food allergens the most frequent were milk and cheese. In most patients, the specific concentration of IgE type antibodies against the aero-allergens and food proteins were low, however, we observed that for some allergens such as dust mites and seafood the concentration achieved were higher. The food allergies could predisposes to a further respiratory complication, therefore it is important the diagnosis of this kind of reactions.

FOOD ALLERGY

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Glutathione Exposed Sequential Epitopes of Ovomucoid Are Relevant for Persistent Egg-Allergic Patients

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Background: The egg allergen ovomucoid (Gal d 1) is conformationally stabilized by 9 disulfide bonds. However, patients with persistent egg-allergy have more IgE against sequential than conformational epitopes of ovomucoid. We investigated whether natural or added food compounds may cause reduction of disulfide bonds and linearization of ovomucoid.
Methods: Reduced ovomucoid in raw eggwhite was detected using a fluorescence-labeled alkylation probe. The common anti-oxidants glutathione and cystein were used for in vitro linearization and effects were monitored by CD-spectrometry. Egg-allergic patients were tested serologically (n = 19) and by skin prick test (n = 9) for IgE against native and linearized ovomucoid and optionally its cooked state.
Results: Linearized ovomucoid could be detected in native eggwhite. Glutathione and cystein treatments, but not cooking linearized ovomucoid, as confirmed by CD-spectrometry. In Western Blot involving cooking more patients had IgE against reduced than native ovomucoid. In ELISA, most IgE was found against raw and native ovomucoid. Cooking of native ovomucoid significantly decreased, whereas cooking of previously linearized ovomucoid enhanced IgE-binding. In skin prick test 5/9 patients reacted with linearized ovomucoid.
Conclusions: Linearized ovomucoid is present in natural eggwhite. Glutathione which is occurring naturally but is also frequently used as structure improving additive in processed food is partly responsible. Additional cooking

of linearized ovomucoid increases IgE-reactivity in patients with persistent egg-allergy in vitro and in skin prick tests. Our data provide evidence that reduction is a novel principle which contributes to the allergenicity of food. This may be relevant for new allergies to modern processed food.

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The Choice of Hypoallergens for Fish and Peach to Develop Food Allergy Specific Immunotherapy (TheFAST Project)

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Background: Classical allergen-specific immunotherapy (SIT), using subcutaneous injections with food extracts, may be effective but dangerous due to anaphylactic side-effects. The FAST project (Food Allergy Specific Immunotherapy) aims at the development of safe and effective treatment of food allergies, targeting persistent and severe allergy to fish (cod) and fruit (peach). Both are caused by a single major allergen, parvalbumin (Cyp c 1) and lipid transfer protein (Pru p 3), respectively. FAST will apply hypo-allergenic recombinant major allergens for SIT.

Methods: Two approaches were evaluated for achieving hypo-allergenicity, i.e. site-directed mutagenesis and chemical modification. Wildtype (wt) natural and recombinant allergens and the hypo-allergens were extensively purified and characterized physico-chemically. Their stability was tested and allergenicity was compared by CAP-inhibition and histamine release experiments while immunogenicity was tested in T-cell proliferation experiments and rabbit and mice immunizations.

Results: For Cyp c 1, the mutant without calcium-binding site showed up to a 1000 times reduced allergenicity, while secondary fold and immunogenicity (tested in human PBMC stimulations and by immunization of laboratory animals) were retained. Chemically modified Cyp c 1 demonstrated a reduced capacity to stimulate T-cells and showed less immunogenicity in rabbits. The calcium-binding mutant has been produced under GMP conditions.For Pru p 3, 5 potential hypoallergens were compared. The allergenicity was reduced to a similar extent (~1000-fold) for both variants in which disulfide bridges were disrupted, i.e. either by mutagenesis or by reduction/alkylation. The modification resulted in loss of alpha-helical secondary structure. However, unexpectedly, the immunogenicity was also significantly lowered/absent.

Conclusions: For the Cyp c 1 calcium-binding mutant we are preparing to enter Phase I clinical trials. For Pru p 3, we need to evaluate new molecules to generate a hypoallergenic mutant that retains immunogenicity.

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IFN-ã Induces Milk Allergen-Specific IL-10-Producing Regulatory B Cells in Non-IGE Mediated Milk Allergy

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Background: Tolerance induction is one of the most important concerns in the treatment of allergies and autoimmune diseases. L-10-producing regulatory B cells (Br1s) seem to have a role in immune tolerance to food allergens. Oral immunotherapy using IFN-gamma has been successful for food allergy treatmen. We were to investigate the effects of IFN-gamma on allergen-specific Br1 responses in milk allergy patients and milk-tolerant subjects to evaluate the mmunomodulatory effects of IFN-gamma on Br1 cell responses.

Methods: The 6 milk allergy patients and 8 milk-tolerant subjects were selected by DBPCFC and clinical characteristics. The PBMCs were stimulated in vitro with casein only, IFN-gamma with casein, or without any stimulant. And the CD19(+) CD5(+) B cells were gated and the expression of IL-10 and Annexin V binding were subsequently analysed.

Results: In milk allergy group, the Br1 fraction decreased from 24.4 to 15.0% ($P = 0.002$) after casein stimulation and it was recovered to 22.6% in the presence of IFN-gamma ($P = 0.006$). In milk-tolerant group, the Br1 fraction increased from 9.4 to 17.1% after casein stimulation ($P = 0.014$) and to 15.7% after IFN-gamma were added ($P = 0.066$). The proportion of apoptotic Br1s among CD5 (+) B cells decreased from 16.5 to 8.1% with casein ($P = 0.003$) and to 11.8% with IFN-gamma and casein ($P = 0.141$) in milk allergy group, while in milk-tolerant group, the proportion of apoptotic Br1 increased from 8.2 to 15.0% after casein stimulation ($P = 0.014$), but was unchanged by casein with IFN-gamma.

Conclusions: Allergen-specific Br1 responses and the apoptotic Br1 fraction were induced by IFN-gamma in milk allergy patients, but were not changed in milk-tolerant subjects. Finally IFN-gamma induced allergen-specific Br1 responses and immune tolerance to specific allergens in milk allergy patients.

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Analysis of IGE, IGE Rast Value and Prick Test in Wheat or Hen's Egg-Allergy Infants Treated with Slow Specific Oral Tolerance Induction Therapy

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Background: Food allergy primarily causes anaphylaxis in children. Food such as egg, cow milk, wheat and peanut are common allergen in Japan.

Methods: In this study total IgE, IgE RAST value and prick test are evaluated to monitor the efficacy outcome in wheat or hen's egg-allergy infants treated with slow specific oral tolerance induction (sSOTI) therapy.

Results: The 3 infants suffered from IgE-mediated food allergy (wheat: 2 years 8 or 10 months old boy [threshold dose 25 g] and girl [0.7 g], hen's egg: 4 years 9 months old girl [1.8 g]), diagnosed, by food challenge, as allergy to wheat and egg. Then, the patients were treated with sSOTI either with hard-boiled egg or wheat noodle at home daily starting with 0.1 g, respectively, increased to a dose of 60 g egg or 100 g wheat, every one to 2 weeks in double dose of the weight, until tolerance was taken on. The daily maintenance dose was 10 g for each food. Four weeks later confirmed was evolution of tolerance by re-challenge. The safety and efficacy of the sSOTI therapy were confirmed in these infants. Total IgE levels were increased after SOTI therapy whereas IgE RAST value to causative antigen such as egg and wheat, contrastingly reduced. IgE RAST value to some other food as cow's milk, reduced coincidently by bystander inhibition. IgE RAST value to a food, negative in prick test, was increased again, whereas that to a food, positive in the test, was carried on.

Conclusions: The results indicates that sSOTI therapy induced causative antigen-specific IgE-mediated tolerance in children with wheat or egg allergy, and the set of total IgE increased, reduced IgE RAST value and positive prick test was of service to evaluate evolution of tolerance in slow SOTI therapy.

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Efficacy of Slow Oral Immunotherapy for Cow's Milk Allergy

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Background: Efficacy and safety of slow oral immunotherapy (SOIT) is not yet clear, especially regarding tolerance acquisition.

Methods: We recruited 32 cow's milk (CM) allergy confirmed by oral food challenge (OFC). Twenty-five subjects were enrolled as SOIT group, and remaining 7 were as control. The inclusion criteria were as follows; (1) CM allergy without anaphylaxis confirmed by OFC just before the trial, and (2) children >4 years. In SOIT group, they were asked to take small amount of CM at home after the OFC. The initial dose was about 1/4 of the threshold eliciting positive objective symptoms, and it was built up to 200 mL CM depends on the symptoms (build up phase). After reaching 200 mL, they were asked to take 200 mL CM daily until the asymptomatic duration lasting for more than 3m (maintenance phase). The subjects, who completed maintenance phase, underwent OFC to confirm the tolerance acquisition after the cessation of CM ingestion for 2w (confirm-OFC). In control group, they had eliminated CM completely and underwent the confirm-OFC after 9.8 ± 2.9 m (mean ± SD). We investigated the endpoints (adverse reactions, medical treatments, results of confirm-OFC, and laboratory findings), prospectively.

Results: In SOIT group (n = 25) and control group (n = 7), the average age was 6.6y and 4.7y, respectively. The average threshold was 52 mL and 17 mL, and the CM specific IgE was 17.6 Ua/mL/9.9 Ua/mL, respectively. The average period of build up and maintenance phases in SOIT group was 80d (n = 25) and 98d (n = 15), respectively. The frequency of adverse reactions in all of build up (1973d) and maintenance phases (2924d) were 13.5% (mild symptoms)/2.3% (moderate symptoms) and 1.7% (mild)/0.3% (moderate), respectively. No patient had administered adrenaline during SOIT. Fifteen subjects in SOIT and 7 in control underwent the confirm-OFC. In SOIT, 8 subjects (53.3%) passed the confirm-OFC, whereas 2 (28.6%) passed in control. There was no statistically significant difference regarding tolerance acquisition between these 2 groups ($P = 0.277$).

Conclusions: This study suggests that SOIT for about 1/2 year induces desensitization effectively for CM allergy without severe adverse reactions. Further and longer study would be required to prove accelerated tolerance acquisition by SOIT.

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Factors Associated with Development of Food Allergy in Liver-Transplanted Children

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Background: The development of food allergy (FA) after transplantation has been described mainly about liver transplantation in children (*Pediatr Allergy Immunol*. 2009; 20: 741–747). It has been becoming important issue in this population. Although tacrolimus immunosuppressive therapy has been considered a significant risk factor (*J Allergy Clin Immunol*. 2011; 127: 1296–1298), other risk factors are not identified yet. This study was undertaken to evaluate the risk factors other than tacrolimus immunosuppressive therapy.

Methods: This study was a retrospective analysis of pediatric liver transplant recipients in our hospital. We reviewed the medical records of all patients who underwent liver transplantation during study period. Data collected including preceding-hepatic diseases, the number of previous surgeries, age at liver transplantation and etc.

Results: Between November 2005 and May 2010, 106 children received liver transplantation. The most common indication for liver transplantation was biliary atresia (BA; 47 patiens, 44.3%). The other conditions were: congenital metabolic diseases in 27 patients, fulminant hepatic failure in 19, liver cirrhosis in 6, congenital absence of portal vein in 3, congenital hepatic fibrosis in 2 and hepatic tumor in 2 patients. After transplantation, all the patients received immunosuppressive therapy based on tacrolimus regimen. Fifteen patients (10 female and 5 male) developed new-onset FA (14.2%). The average age at transplantation was 10 months and FA has been developed within 2 years (median 11 months, IQR, 4.5–19.0). Eleven patients with BA (23.4%) and 4 patients with the other conditions (6.8%) developed new-onset FA ($P = 0.023$). Among the patients who developed FA, the number of previous surgeries was significantly higher in patients with BA ($P = 0.008$).

Conclusions: New-onset food allergy after liver transplantation is now becoming a significant problem. We observed a trend toward an excess of FA in patients with BA compared to patients with other indications for liver transplantation. Patients with BA received surgical operations in several times before liver transplantation. Frequent operations might add some stimulation to generate new-onset FA and should be considered as a susceptible subgroup that requires specific attention.

GLOBAL ASTHMA EPIDEMIOLOGY

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Recurrent Wheezing in Infancy: Epidemiological Changes Between EISL Phase i and iii

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Background: Prevalence of allergic diseases has increased in the last years. Data on recurrent wheezing (≥3 episodes) in infancy is scarce. The aim of this study was to verify changing in prevalence of recurrent wheezing infants in the south of Brazil.

Methods: Cross-sectional study using a standardized and validated questionnaire (EISL: *Estudio Internacional sobre Sibilancias en Lactantes*) with questions: Has your baby had wheezing or whistling in the chest area or bronchitis in the first 12 months of life? Has your baby had 3 or more wheezing episodes in the first year of life? Parents of infants, ages 12 to 15 months that attended to Health Centers for routine immunization were interviewed between August 2005 to December 2006 (EISL Phase I) and September 2009 to September 2010 (EISL Phase III). Categorical variables are shown as proportion and differences verified by chi-square test, and continuous variables were expressed as mean ± SD and analyzed by Student *t* test.

Results: Three thousand three parents of infants answered questionnaire in the EISL Phase I, and 45.4% had had at least one wheezing episode; 50.7% were male, and 22.6% had recurrent wheezing episode starting at 5.5 ± 3.1 months. Five years later, in the EISL Phase III, 1003 parents participated in the survey: 40.6% had at least one wheezing episode ($P = 0.46$), 51.1% were male, and 19.8% had recurrent wheezing ($P = 0.1$) starting at 6.1 ± 3 months ($P = 0.06$).

Conclusions: Recurrent wheezing in infancy is highly prevalent and starts early in life. In our population, recurrent wheezing rates did not modify in the time period of study.

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Asthma Admission Rates in Germany: An Analysis of the Nationwide DRG-Statistic of the Year 2009

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Background: Within the OECD Health Care Quality Indicators (HCQI) Project up to 21 countries participated in calculations of 6 indicators on care for chronic conditions. Those so-called Health Promotion, Prevention and Primary

Care Indicators originally had been introduced by the US Agency for Healthcare Research and Quality and rely on the principal diagnoses of an adult hospitalization stored in a hospital administrative database. 2007 age-sex standardized asthma admission rates varied considerably across the countries and ranged from 17 (Italy) to 120 (United States) admissions per 100,000 population (OECD mean: 51). It was concluded that asthma outpatient treatment was not optimal in countries reporting higher rates. Germany provided the third lowest asthma admission rate of 21 (Health at a Glance 2009 OECD Indicators. http://www.oecd.org/health/healthataglance). As data collections from various countries can differ in, e.g. coding responsibility, incentives for coding, and implementation of coding guidelines, international variations cannot exclusively be explained by differences in health system performance. This study aimed to calculate asthma admission rates separately for all 16 Federal States of Germany, assuming national comparisons are not biased by these factors.

Methods: Using the 2009 nationwide Diagnosis Related Groups statistic we calculated age-sex standardized asthma admission rates according to the OECD HCQI Data Collection Guidelines.

Results: Among all adult hospitalizations (15 years or older) we found 14,399 admissions with a principal diagnosis code of asthma. Related to the corresponding population of 70,779,623, the crude rate is 20.34 admissions per 100,000. Age and sex standardized rate is 20.20 (95% Confidence-Interval, 19.86-20.54). Among the 16 Federal States of Germany age-standardized rates ranges from 7.62 in Berlin (95% CI, 6.17-9.08) to 20.26 in North Rhine-Westphalia (95% CI, 19.13-21.39) among men and from 16.15 in Berlin (95% CI, 14.07-18.23) to 36.70 in Bremen (95% CI, 29.89-43.98) among women, respectively.

Conclusions: Prevention Quality Indicators calculated on national hospital administrative databases might be a useful tool to identify national variations of asthma admission rates reflecting areas with differences in outpatient care. Reasons for the differences found, e.g., a varying regional density of primary care providers or regional differences on asthma prevalence are in focus of further investigations.

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Prevalence and Classification of Asthma in Freshmen Students of a Guatemalan University and its Relationship With Aeroallegens Sensitization

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Background: Establish the prevalence and classification of asthma in young adults and determine the sensitization to common aeroallergens.

Methods: ISAAC modified questionnaire for asthma in first year students between the ages of 18 to 22 years old, who attend the morning hours at the Universidad Rafael Landivar of Guatemala. Between the months of July throw October of 2009 on the campus of Guatemala City. We selected the students who meet the criteria for asthma and request and informed consent for the participation. In 70 students who accepted. We performed: Peak flow with a hand held apparatus and used the GINA questionnaire parameters for classification. We performed prick test with a panel of 8 aeroallergens and its positive and as negative controls to determine sensitization.

Results: Prevalence of asthma was the 23% according to the ISAAC modified questionnaire. Of this group of 287 students, 70 accepted to participate in the study. According to GINA guideliness: 56% classify as mild intermittent, 5% mild persistent, 33% as moderate persistent and 6% as severe persistent. In accordance to control: 54% appear to be controlled, 42% partly controlled and 4% uncontrolled. In the prick test the results of positive sensitization were: *Canis familiaris* 35%, *Felis domesticus* 37%, *D. pteronyssinus* 76%, *D. Farinae* 77%, *Cynodon dactylon* 19%, *Zea mays* 26%, *Eucalyptus globulus* 17% and *Casuarina equisetifola* 16%.

Conclusions: Almost one quarter of population were classified as asthmatics using the ISSAC modified questionnaire. Dahl report, a prevalence of asthma in various countries of Europe between 16 and 37% in people 16 to 29 years old.[1] Most of the students who participate, classified in the category of mild intermittent asthma, but one third of the students belong to the moderate persistent category.We found that a large percentage of the students were sensitized to aeroallergens, most of them, to both of species of dust mites. Heinzerling, refer sensitization of 25 to 67% for mites in various countries of Europe.[2]

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Asthma Mortality in Brazil (1998–2006)

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Background: Some countries have virtually abolished asthma deaths, thus demonstrating asthma mortality is largely preventable.

Objectives: To evaluate the specific mortality due to asthma in Brazil (1998–2006) and its correlation with access to health services and social indicators.

Methods: Data were obtained from the National Mortality Database from The Ministry of Health of Brazil. Mortality rates for each state and region were evaluated for the period 1998 to 2006 using linear regression models with gamma distribution and log link function. The correlation between human development index (HDI), the Gini index, GDP per capita and number of hospital beds and mortality rates were performed using the Spearman test.

Results: We recorded 23,758 deaths from asthma from 1998 to 2006. The annual mortality rate per 100,000 inhabitants was 1.68, 1.38, and 1.67, in 1998, 2002 and 2006, respectively (1998–2006 average: 1.51). Comparing only the extremes, 1998 and 2006, mortality rates declined in most economically developed regions of the country: Midwest (−26.11), South (−23.58%), Southeast (−8.83%), and show up rising in the poorest regions in the North (+5.34%) and Northeast (+31.33%). GDP per capita was inversely correlated with asthma mortality rate (rho = −0.378, $P = 0.048$). In men and women, the asthma mortality rates were respectively, 1.98 and 1.37 in 1998 and 2.01 and 1.30 in 2006. Analysis by age groups, found the coefficients increased with age after adulthood. Individuals over the age of 75 years had the highest rates and greater tendency to increase in the period.

Conclusions: There was an overall stabilization of asthma mortality in Brazil during the study period. However, a trend toward increasing mortality rates was observed in socio-economically disadvantaged regions, where access to health care and medication is still a problem.

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Dose Response Relationship Between Ascaris Sensitisation and Atopy and Bronchial Hyper-Responsiveness but not Allergic Diseases in Black South Africans

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Background: The relationship between sensitisation to helminths and atopy, bronchial-hyperresponsiveness and allergic diseases may differ depending on many factors, including the genes of the population studied. We sought to examine this relationship in an African cohort.

Methods: Urban Xhosa children were tested for ascaris IgE levels, bronchial hyper-responsiveness (BHR) by methacholine challenge, atopic sensitisation (skin tests to aeroallergens) and allergic disease (asthma, eczema and rhinitis) assessed by questionnaire.

Results: Ascaris sensitisation was strongly associated with BHR but not with asthma, eczema or rhinitis. There was a dose-response relationship between increasing class of ascaris IgE and increased BHR (Prevalence ratio (PR) 1.75; CI 1.09-2.82). Higher levels of ascaris IgE were seen in those with BHR. Ascaris IgE was associated with atopic sensitisation to aeroallergens. There was a dose-response relationship between increasing class of ascaris IgE and sensitisation to one or more allergen (PR 1.65; CI, 1.27-2.13), sensitisation to house dust mites (HDM) (PR 1.79; CI, 1.29-2.46) and grass (PR 2.66; CI, 1.24-5.71) and number of positive skin prick tests (PR 1.78; CI, 1.27-2.49). Presence of any sensitisation to ascaris was associated with more than doubling the prevalence of HDM sensitisation (41.5 vs 18.5%) and almost quadrupling the prevalence of grass sensitisation (10.8 vs 2.8%).

Conclusions: Ascaris sensitisation was strongly associated with BHR and with atopy, but not with allergic diseases. Possible explanations might be that the type of ascaris infection that causes high levels of ascaris IgE in this genetic population may also favour the development of atopy or that atopics in Africa have upregulation of their defence system against parasitic infection. These hypotheses are not mutually exclusive.

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Association of Matrix Metalloproteinase-7 and -12 Genes polymorphisms With Asthma: A Case-Control Study of MMP-7 and -12 in a Japanese Population

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Background: Genetic variants influencing lung function or immune system may be involved in the development of asthma and/or its symptoms. Matrix metalloproteinases (MMPs) contribute to both normal and pathological tissue remodeling and also act as regulatory molecules by processing cytokines or adhesion molecules. In animal models, growing evidences suggest that MMPs play important roles in asthma phenotypes. Some *MMP* genes (e.g. *MMP-9* and *MMP-12*) have recently been shown to be associated with asthma in Caucasian populations. We investigated whether single nucleotide polymorphisms (SNPs) in *MMP-7* and MMP-*12* could affect the susceptibility to and clinical phenotypes of asthma in the Japanese population.

Methods: We conducted a case-control study between SNPs in *MMP-7* and MMP-*12* genes and asthma-related phenotypes using childhood and adult Japanese populations (653 childhood asthma patients and 423 controls, and 428 adult asthma patients and 646 controls, respectively). To investigate the effects of amino acid substitutions by SNPs on MMPs' enzymatic activity, MMP activity assays were performed using commercially available kits based on fluorescence resonance energy transfer (FRET) peptide. We also evaluated the effect of 3'UTR SNP in *MMP-7* on its mRNA stability and the effect of SNP in *MMP-12* on its antimicrobial activity.

Results: We found that, in the Japanese population, SNPs of MMP-7 (rs10502001, G/A, Arg77His; rs14983, C/T, 3'UTR) ($P = 0.006$; odds ratio (OR), 1.46; 95% confidential interval (CI), 1.126-1.903) and MMP-12 (rs652438, A/G, Asn357Ser) ($P = 0.015$; OR, 1.60; 95% CI, 1.002-2.556) showed significant association with adult and childhood asthma, respectively. We also found that the SNP (rs652438) in MMP-12 was associated with severity in adult asthma ($P = 0.010$). Using supernatant from cultured HEK293 cells stably transfected with the pcDNA3.1 (+)-MMP-7 or MMP-12 as MMP proteins, we evaluated activation kinetics, rate of proteolytic cleavage of FRET peptide, Michaelis constant, and substrate specificity of the enzyme. In this system, we couldn't detect the functional effects of amino acid substitutions by SNPs on the enzymatic activity.

Conclusions: Our association study suggested that genetic variants of MMP7 and MMP12 conferred risk for development of asthma in the Japanese population.

HEREDITARY ANGIOEDEMA

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Hereditary Angioedema and Normal C1-Inhibitor (HAE TYPE III): A Novel Mutation in the Coagulation Factor 12 Gene

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Background: Hereditary angioedema with normal C1-inhibitor and mutations in the coagulation factor 12 gene is a recently described disease entity that occurs predominantly in women. Up to date, 2 different missense mutations of codon p.Thr328* in the coagulation factor 12 gene have been reported, co-segregating with clinical signs. Aim of the study was to assess the clinical symptoms, mutations in the factor 12 gene, and plasma parameters of this disease in a family with hereditary angioedema with normal C1-inhibitor.

Methods: Six members of one family were studied, including 2 women with recurrent angioedema. Mutation analysis of the factor XII gene was performed.

Results: By sequencing the factor 12 gene, a hitherto unknown mutation, the deletion of 72 base pairs (c.971_1018+24del72*), was identified in a family of Turkish origin, in 2 women with recurrent skin swellings and abdominal pain attacks, and in their symptom-free father. The novel mutation c.971_1018+24del72* caused a loss of 48 base pairs of exon 9 (coding amino acids 324* to 340*) in addition to 24 base pairs of intron 9, including the authentic donor splice site of exon 9. All carriers of this mutation had normal plasma concentrations and activity of C1-inhibitor, C4, factor XII clotting activity, and activated partial thromboplastin times.

Conclusions: The novel deletion mutation in the factor 12 gene was located in the same F12 gene region as the missense mutations p.Thr328Lys* and

p.Thr328Arg* reported previously, suggesting the importance of the exon 9 to intron 9 DNA region for the development of hereditary angioedema with normal C1-inhibitor.

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Immuno-Safety of Recombinant Human C1 Inhibitor in Patients With Hereditary Angioedema: An Integrated Analysis

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Background: Recombinant C1 inhibitor (rhC1INH) is a novel therapeutic option for the treatment of acute angioedema attacks in patients with hereditary angioedema (HAE). The amino acid sequence of rhC1INH is identical to that of endogenous C1INH. However, any recombinant protein may elicit antibodies against the protein and/or host related impurities (HRI). Clinical consequences of these antibodies can theoretically range from no clinical symptoms to allergic reactions and reduced C1INH activity due to neutralizing antibodies.

Objective: To analyze the immuno-safety of rhC1INH in symptomatic patients with HAE.

Methods: Plasma samples were collected pre-treatment and 22 and 90 days post-treatment of an acute angioedema attack. Plasma samples were tested for the presence of antibodies against plasma-derived C1INH and rhC1INH using 6 different, validated enzyme-linked immunosorbent assays (ELISAs), to detect IgM, IgG and IgA antibodies against plasma-derived C1INH or rhC1INH. Antibodies against HRI in plasma samples were measured in an ELISA testing for all antibody classes. Plasma samples from normal healthy controls and HAE patients, never exposed to rhC1INH, were used to estimate cut off levels of the assays. Plasma samples with antibody levels above the cut-off level in the screening assays were tested in confirmatory displacement assay in case of anti-HRI antibodies and in an assay for neutralizing antibodies in case of antibodies against C1INH.

Results: Data from 155 symptomatic HAE patients having received a total of 424 administrations of rhC1INH were analyzed. The frequency of anti-C1INH antibody levels above the assay cut-off was low and similar in pre- and post-exposure samples (1.7 and 1.8%, respectively). Results above the assay cut-off were sporadic and transient. Occurrence of anti-C1INH antibodies did not correlate with repeated treatment or time since last treatment. No neutralizing antibodies were detected. A total of 5/155 (3%) rhC1INH-treated patients had confirmed anti-HRI antibodies; these included 1 patient with presence of anti-HRI antibodies prior to exposure to rhC1INH. The presence of anti-C1INH and anti-HRI antibodies was not associated with clinical symptoms. The presence of anti-C1INH antibodies did not affect clinical efficacy.

Conclusions: rhC1INH used for the treatment of acute HAE attacks has a low potential to induce antibodies and has a reassuring immuno-safety profile.

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Clinical Efficacy of Recombinant Human C1 Inhibitor in Patients with Acute Hereditary Angioedema Attacks

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Background: Recombinant human C1 Inhibitor (rhC1INH) has been approved in Europe for the treatment of acute hereditary angioedema attacks. The efficacy of rhC1INH was demonstrated in 2 randomized-controlled trials. Open-label extension studies, where patients could be treated for subsequent HAE attacks, demonstrated continued efficacy for repeated rhC1INH treatments.

Objective: To review the integrated efficacy data of rhC1INH for treatment of acute HAE attacks.

Methods: Efficacy was assessed using patient-reported HAE-specific visual analog scales. The primary endpoint was time to onset of relief of symptoms (VAS decrease $\geq$20 mm), and the secondary efficacy endpoint was time to minimal symptoms (VAS $<$20 mm at all locations). Other endpoints included clinical response (relief achieved within 4 hours) and relapse (recurrence of symptoms within 24 hours following initial improvement). Subgroup analyses by attack location were also performed.

Results: The dataset included 141 HAE patients treated for 403 attacks. Median times to the onset of symptom relief for attacks treated with 100 U/kg, 50 U/kg and 2100 U rhC1INH were 66, 60, and 61 minutes, respectively, compared to 495 minutes in the placebo-treated group. Median times for time to minimal symptoms were 266, 240 and 241 minutes for the 100 U/kg, 50 U/kg, and 2100 U rhC1INH-treated attacks respectively compared to 1210 minutes for the placebo-treated attacks. High clinical response rates were observed for the rhC1INH-treated groups (93, 96 and 88% for the 100 U/kg, 50U/kg, and 2100 U respectively) compared to the placebo group (41%). None of the rhC1INH-treated attacks relapsed. Subgroup analysis by attack location showed that abdominal attacks had the fastest median time to onset of symptom relief (50, 36 and 60 minutes for 100 U/kg, 50 U/kg and 2100 U doses respectively), followed by oro-facial-pharyngeal-laryngeal attacks (70, 65 and 120 minutes), and peripheral attacks (75, 84 and 121 minutes). No drug-related serious adverse events or hypersensitivity reactions were observed.

Conclusions: RhC1INH has demonstrated efficacy for the treatment of repeated HAE attacks for all doses tested (100 U/kg, 50 U/kg and 2100 U). Controlled studies did not show additional benefit with doses greater than 50 U/kg. RhC1INH was generally safe and well tolerated.

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The Efficacy and Safety of Human Plasma-derived C1-Inhibitor Concentrate Administered for the Treatment of Attacks in Pediatric Patients with Hereditary Angioedema Due to C1-Inhibitor Deficiency

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Background: Hereditary angioedema due to C1-inhibitor deficiency (HAE-C1-INH) is a life-threatening, rare disease characterized by recurrent edematous attacks. In 50% of cases, the initial onset of symptoms occurs between 5 and 11 years of age. There are limited data on the emergency treatment of acute episodes in pediatric patients. Our aim was to analyze the efficacy and safety of human plasma-derived C1-INH concentrate in our pediatric patient population with HAE-C1-INH.

Methods: 50 pediatric patients (23 boys, 27 girls; 45 HAE type I, 5 HAE type II patients) were enrolled. The follow-up period began at the time of diagnosis and ended when the patient turned 18 years old. The indications for the use of

C1-INH concentrate were upper airway oedema of any severity; moderate-to-severe abdominal edema; edema of face, neck, or lips and severe edema of the extremities and trunk. Clinical and laboratory data were entered into the Hungarian HAE Registry.

Results: 152 attacks out of 1392 experienced by 42 patients were treated with C1-INH concentrate (28% of attacks at home and 72% at the clinic). The distribution of C1-INH-treated attacks by location was as follows: 38% subcutaneous, 32% abdominal, 30% upper airway. In all locations, the clinical symptoms were consistently relieved by 500 IU C1-INH concentrate. An additional 500 IU dose of C1-INH concentrate was required in 4 cases only. The symptoms improved within 15 to 60 minutes of drug administration. Time to complete resolution was 24 to 48 hours in subcutaneous edema, 12 to 24 hours in abdominal attacks, and less than 12 hours when the edema involved the upper airways. No progression or recurrence of the attack was observed. Repeated administration did not reduce therapeutic efficacy of the drug. Adverse events did not occur. Transmission of viral infections (HIV, HBV, HBC, Parvo virus B19) was not detected. Comparing the first and last year of follow-up, anti-C1-INH antibodies (IgA, IgG, IgM types) did not show any relationship with the administration of C1-INH concentrate.

Conclusions: Our prospective study demonstrated that the administration of C1-INH concentrate is highly effective and safe for the treatment of edematous attacks – regardless their location – in pediatric patients with HAE-C1-INH.

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Treatment of Idiopathic Nonhistaminergic Angiodema with Icatibant

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Background: Patients with Idiopathic nonhistaminergic angioedema appear to have similar clinical features and pathogenesis as those with hereditary angioedema. Icatibant, a selective bradykinin β2 receptor antagonist, licensed for use in acute attacks of hereditary angioedema could be also effective in treating other forms of angioedema. We report a patient with idiopathic angioedema who was successfully treated with icatibant.

Methods: A 77-year-old man with a history of arterial hypertension currently treated with hydrochlorothiazide and type II diabetes under insulin treatment. He had suffered from recurrent angioedema attacks located on his tongue without urticaria during the last 7 years. Serum levels of C1-INH, C4 and C1q and C1-INH activity were normal. In spite of cessation of treatment with ACE inhibitors and RAAS-blockers (he had been treated with enalapril and losartan previously) he continued with the angioedema attacks. As no cause of angioedema could be identified and the angioedema did not response to antihistamines, the patient was diagnosed of idiopathic nonhistaminergic angioedema. In one of the episodes he was admitted at the emergency room with a swollen tongue. The edema gradually progressed in spite of the treatment with antihistamines, corticosteroids and epinephrine. Tracheotomy was considered due to the severity of the angioedema that began to cause airway compromise. After consulting the Allergy Unit, treatment with icatibant was administered.

Results: Approximately 30 minutes after the subcutaneous administration of icatibant 30 mg the symptoms improved and the angioedema resolved completely within 6 hours. The only adverse effect following the icatibant administration was pain localized in the injection site. After 5 months the patient suffered a similar attack that was also successfully treated with icatibant sc.

Conclusions: Icatibant administered subcutaneously provided an effective and well-tolerated treatment option for acute angioedema attacks in a patient with idiopathic nonhistaminergic angioedema. This form of angioedema could have a pathogenic mechanism similar to the bradikinin mediated angioedema. We suggest the use of icatibant in the treatment of severe attacks of angioedema in patients that do not response to antihistamines, corticosteroids and epinephrine.

HYMENOPTERA ALLERGY

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Clinical Features and Diagnostic Value of Specific IGE to Component Allergen in Bee Venom Allergy in Korea

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Background: Although history taking is primary method in the diagnosis of bee venom allergy, serum specific IgE detection is critical to identify causative bee and assess the effect of immunotherapy. Component-resolved diagnosis (CRD) in allergy has been used for its high sensitivity and specificity in many allergy diseases caused by food, cat, birch, and grass pollens. The purposes of this study are to evaluate diagnostic value of serum specific IgE to 3 bee venom component allergens and observe the changes of allergen specific IgE during bee venom immunotherapy.

Methods: Fifty-six bee venom anaphylaxis patients receiving bee venom immunotherapy were recruited from Ajou University Hospital. Clinical manifestations and serum specific IgE levels to bee venoms and component allergen (rApi m1 of Apidae, rVes v5 and rPol d5 of Vespidae) measured by using ImmunoCAP (Phadia, Sweden) were analyzed retrospectively.

Results: Thirty-five (62.5%) patients were male and 33 (73.3%) were atopics. Their mean age was 44.9 ± 13.8 years ranged from 11 to 73 years. Local reactions were found in 13 (23.2%) patients, while systemic reactions, in 43 (76.8%) patients. The most frequent manifestation was anaphylaxis which were severe (37.5%) and moderate (39.3%) manifestations followed by urticaria and angioedema. Yellow Jacket (80.8%) was the most prevalent bee followed by yellow hornet, white faced hornet, honey bee and paper wasp at the time of diagnosis with concurrent sensitization in both Apidae and Vespidae at 70.9% patients. The positive predictive value (PPV) of serum specific IgE levels to rVes v5 and rPol d5 were 85.7 and 87.5%, and they significantly correlated with conventional serum specific IgE level ($r = 0.762$ and $r = 0.757$, respectively), however, PPV of rApi m1 was only 34.8% at the time of initial diagnosis. After 3 years of bee venom immunotherapy, all kinds of bee venom specific IgE levels tended to decline compared to those collected before allergen immunotherapy, especially in component specific IgE to Vespidae.

Conclusions: Yellow jacket sting and male gender may be risk factors for bee venom allergy in Korea. Component allergen specific IgE to Vespidae, not Apidae had a diagnostic and monitoring value comparable to conventional specific IgE in bee venom allergy.

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Is Basophil Specific Response to Hymenoptera Venom Related to T Regulatory Cells?

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Background: The exact mechanism of systemic hypersensitivity to venom is not exactly understood. It is suggested T cells with regulatory potential can downregulate other T cell subsets and effector cells, ex. mast cell or

basophils. We focused on relationship of specific basophil reactivity in relationship to proportion of regulatory T cells.
Methods: Forty-five patients with history of systemic symptoms of allergy to Hymenoptera venom were included. Basophil reactivity before the treatment and after one year of allergen immunotherapy (AIT) was measured by CD63 expression, CD203c marker used for basophil identification. Cells were stimulated by aqueous solution of allergen in concentration range 0.01 to 1 μg/mL. T regulatory cells were identified as CD4 positive, CD25 bright and CD127 negative at the same interval of treatment. Monoclonal antibodies conjugated with fluorochromes were used, measured by FACSCalibur. Paired t test and correlation analysis used for statistical evaluation.
Results: Median Treg proportion before therapy was 2.160, after IT 1.960, basophil specific response (proportion of CD63 positive cells) at the same interval were 3.65 and 4.11 at 0.01 μg/mL, 13.1 and 16.1 for 0.1 μg/mL and 33.85 and 40.8 for 1 μg/mL. All differences were not statistically significant. Differences of basophil activation were not significantly related to proportion of T regulatory cells.
Conclusions: In our group of patients with HV allergy, treated by AIT, we did not found any relationship between basophil specific activation during allergen immunotherapy and proportion of T regulatory cells.

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Improving the Diagnosis of Hymenoptera Venom Allergy: Component Resolved Diagnosis

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Background: Up to 3% of the general population suffers from potentially life-threatening systemic reactions after honeybee and wasp stings. Unfortunately, there are still individuals who have a convincing history of an anaphylactic event, but lack the necessary diagnostic, making difficult the decision for immunotherapy. Our aims were to evaluate the feasibility of using recombinant allergens in the Basophil activation test (BAT) for the diagnosis of Hymenoptera allergy and to develop a high-throughput diagnostic device combining the advantages of basophil activation tests with a panel of recombinant allergens: rVes v 1, rVes v 2, rVes v 3, rVes v 5, rApi m 1, rApi m 2, rApi m 3 and rApi m 5.
Methods: Basophil activation test (BAT) and measurement of specific IgE was performed on 47 wasp venom, 14 Honeybee venom allergic patients and 17 healthy controls. Specificity and sensitivity of BAT performed with recombinant His-tag purified wasp venom allergens Ves v 1, Ves v 2, Ves v 3 and Ves v 5, recombinant honeybee venom allergens Api m 1, Api m 2, Api m 3 and Api m 5 and commercial extracts have been compared. Each patient had a history of grade I or II anaphylaxis after an insect sting. All patient sera were collected before initiation of SIT.
Results: BAT performed with the panel of recombinant allergens markedly increased the specificity and the sensitivity in the detection of wasp venom allergic subjects.
Conclusions: Basophil activation test provides a valuable new in vitro method for the detection of allergy to wasp venom and may supplement routine tests for allergy diagnosis in problematic cases. Recombinant allergens might help to dissect relevant allergens for basophil degranulation.

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Efficacy of Venom Immunotherapy Given Every 3 or 4 Months. A Direct Prospective Comparison With the Conventional Regimen

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Background: The standard venom immunotherapy involves the administration of the maintenance dose every 4 to 6 weeks. This regimen may have compliance problem especially in the long term, thus extended intervals have been proposed. We prospectively compared the efficacy of 3- or 4-month extended maintenance dose and the conventional regimen.
Methods: Patients receiving immunotherapy of a single venom were offered the delayed maintenance dose, and were then followed-up for field re-stings. Only the re-stings by the insect for which the patients received immunotherapy were considered. A matched group of patients receiving the conventional maintenance were used for comparison, by univariate and multivariate analysis.
Results: Fifty-two patients (44 male, 8 female, mean age 52 years) were certainly re-stung on 113 occasions by the insect for which they were receiving immunotherapy. 90 re-stings occurred during the 3- month maintenance and 23 during the 4-month maintenance. The control group, on conventional protocol with one single venom, included 103 patients (79 male, 24 female, mean age 41 years) certainly re-stung on 160 occasions by the specific insect. The rate of re-sting without reaction was 97% in the delayed maintenance and 82% in the conventional group with a significant difference in favour of the former ($P = 0.01$). None of the variables considered resulted predictive for systemic reactions by logistic regression analysis
Conclusions: The delayed maintenance dose approach is al least as effective and safe as the conventional one. The 4-month maintenance seems to be the best option in term of convenience and economic save.

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Serum CTLA-4 AND IL-10 in Hymenoptera Venom Immunotherapy: Equivalence of Different Induction Regimens

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Background: Cytotoxic T lymphocyte associated gene-4 (CTLA-4) is involved in the activation pathways of T lymphocytes. It has been shown that the circulating form of CTLA-4 is elevated in patients with hymenoptera allergy and can be downregulated by immunotherapy. We assessed the effects on CTLA4 of venom immunotherapy given by different induction protocols (classic, rush or ultra rush).
Methods: Sera from patients with hymenoptera allergy were collected at baseline and at the end of the induction phase. In the classical regimen, the induction lasted 6 weeks, in the rush protocol it lasted 3 days, and in the ultra-rush maintenance was achieved in 24 hours. Soluble IL-10 was assayed in the same samples for comparison. CTLA-4 and IL10 were measured by commercial immuoassays.
Results: Seventy-six patients (52 male, mean age 35 years) were studied. Of them, 30 underwent the classic induction, 22 the rush and 24 the ultra rush. Soluble CTLA-4 was detectable in all patients at baseline, and significantly decreased at the end of the induction in all groups, thus irrespective of its duration. Of note, a significant decrease of sCTLA-4 could be seen already at 24 hours. In parallel, the same behaviour was observed with IL-10 that significantly increased at the end of the induction.

Conclusions: Soluble CTLA-4 is a useful immunological marker of the effect of immunotherapy for hymenoptera allergy. From an immunologic point of view, there is no difference among the various protocol of induction.

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Purification of the Allergenic Protein Hyaluronidase From the Venom of Social Wasp Polybia Paulista (Hymenoptera: Vespidae)

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Background: Between 9.3 and 28.5% of world population are estimated to be allergic to the protein components of Hymenoptera venom and among them, the hyaluronidase (HYAL) is one of the most important, although the nature of its IgE binding epitopes is unknown.

Methods: Enzyme was purified from *P. paulista* venom by cation exchange chromatography in AKTA-FPLC system with a Hiprep CM FF column. Fractions with HYAL activity were pooled, lyophilized, dialyzed against distilled water in presence of protease inhibitor (PMSF) and subjected to SDS-PAGE 15%. The only protein bands visualized were submitted to tryptic digestion and to MALDI-ToF/ToF mass spectrometry. Digested peptides produced were compared with partial/complete protein sequences from Data Bank including with the HYAL (Q9U6V9) of *Polistes annularis* venom used as model. Western blotting was performed with *Pp*-HYAL-specific antibody to test the identity of pure protein.

Results: All analysis performed identified the pure protein as an HYAL present in *P.paulista* venom, which also had its cDNA sequence (GI:302201582) cloned and determined in previous studies, being its high similarity with the *Polistes annularis* enzyme already confirmed. The mature allergenic protein has 338 amino acids and a molecular weight of 39 KDa. The same allergen is known in other insects, venoms and immunological cross reactivity may sometimes be observed among closely related species. Here, the immunoblotting assay revealed that the *Pp*-HYAL-specific antibody used recognized the correspondent protein in the purified fraction and in the crude venom of *P. paulista*, but not in the *Apis mellifera* and *Solenopsis invicta* venoms.

Conclusions: The methodology used was able to purify the allergen, which is a key step in the characterization of its binding epitopes. Such knowledge has direct implications in accuracy of diagnostic procedures and strategies for specific immunotherapy of allergic patients to the venom of this insect.

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High Immunogenicity of the Allergen PHL P 5 Expressed in Transgenic Mice as a Membrane-anchored Protein

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Background: Induction of long-term tolerance towards Phl p 5 was previously achieved by transplantation of hematopoetic stem cells (HSCs) genetically modified to express membrane-bound Phl p 5 allergen. To facilitate the further development of tolerogenic cell therapies for allergy, a transgenic mouse expressing Phl p 5 ubiquitously as membrane-anchored protein, was generated. Here we investigated the immunogenicity of the membrane-anchored version of Phl p 5.

Methods: The Phl p 5-transgenic mouse (Balb/c background) was generated by pronuclear injection integrating Phl p 5 fused to a leader peptide and a transmembrane domain under control of a CMV-promotor with a GFP-reporter. Splenocytes (2.5×10^6 per mouse), cell extracts containing mainly membrane proteins and recombinant (r) Phl p 5 [5 μg+/− $Al(OH)_3$ per mouse] were injected subcutaneously into naïve Balb/c mice (n = 8 per group). The amount of Phl p 5 of splenocytes and cell extracts was semi-quantitatively determined via western blotting. Furthermore skin of Phl p 5-transgenic mice was grafted onto naïve Balb/c (n = 13 in 2 independent experiments), a rejection model in allo-transplantation since skin is highly immunogenic and therefore readily rejected. Phl p 5-specific antibody response was determined in sera by ELISAs. For T-cell responses splenocyte-proliferation was assessed in vitro after stimulation with rPhl p 5.

Results: Surprisingly, a prompt rejection (within 8-10 days) was elicited, accompanied by a strong Phl p 5 specific antibody response including Phl p 5-specific IgE in wildtype Balb/c after skin rejection of Phl p 5-transgenic mice. Additionally to the skin grafted group, mice receiving splenocytes or rPhl p 5 plus adjuvant showed a comparable response in matters of Phl p 5-specific IgE- and IgG1-levels through the whole follow-up (week 1, 2, 3, 5, 7, 9, 11) suggesting an unusually strong immune response to cell or tissue-bound Phl p 5. Furthermore Phl p 5-specific IgG2a/2b/3, IgA and IgM were induced. Besides in vitro splenocyte-proliferation assays showed Phl p 5 specific T-cell responses in all groups of mice that showed strong humoral responses.

Conclusions: The high immunogenicity of tissue-bound Phl p 5 may represent a new mode of rendering antigens highly immunogenic.

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Specific Recognition of the Major Birch Pollen Allergen BET V 1 Programs Dendritic Cells to Induce Either th2 or Tolerogenic Responses

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Background: Only a limited number of proteins have the potential to induce Th2-polarized immune responses and specific IgE in genetically predisposed individuals. However, why the contact with an allergen results either in allergic sensitization or tolerance induction has remained unclear so far. Here, we focused on the in depth study of uptake, induction of signal transduction pathways, and gene regulation in monocyte-derived dendritic cells (MoDCs) of allergic and normal individuals in response to the major birch pollen (BP) allergen Bet v 1.0101 and its structural homolog from celery, Api g 1.0101.

Methods: Live cell fluorescence microscopy was used to analyze uptake kinetics, competitive binding, and internalization pathways of labeled allergens by iMoDCs. To delineate allergen-mediated gene activation, iMoDCs were incubated with the allergens, a control stimulus, or left untreated followed by real-time PCR-based gene expression profiling. Surface-bound IgE was detected by immunofluorescence microscopy and IgE-mediated gene activation by real-time PCR.

Results: Comparable kinetics of Bet v 1.0101 and Api g 1.0101 uptake were observed for both allergic and healthy donors. In competititve binding assays, however, Bet v 1.0101 outcompeted Api g 1.0101 for surface recognition in both donor groups. Pharmacological inhibition evidenced that Bet v 1.0101 internalization occurred in a receptor-mediated manner showing characteristics of lipid raft-dependent endocytosis. MoDCs of both donor groups were IgE positive and showed marked upregulation in NF-κB dependent genes after Fcε receptor activation by anti-IgE. Bet v 1.0101-stimulation, in contrast, exclusively triggered transcription of the Th2 cytokines IL-4 and IL-13

but not NF-κB related genes in MoDCs of BP allergic donors. Healthy donors were either unresponsive or showed elevated mRNA levels of the Th1-promoting chemokines CXCL10 and CXCL11.

Conclusions: This study supported by grant SFB-F1802 of the Austrian Science Fund shows for the first time that the allergen uptake is specific and similar in DCs from allergic and healthy individuals. More important, the ensuing signal cascade that is triggered by the allergen differs between DCs of the 2 donor groups and results in a Th2-polarized immune response in allergic individuals as compared to ignorance/tolerance in normal donor cells.

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Recombinant SCFV Antibodies for IGE Epitope Mapping and Detection of Parvalbumins

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Background: Parvalbumin, the major fish allergen, is responsible for IgE cross-reactivity among different fish species. We aimed to generate recombinant single chain antibody fragments (scFv) binding to epitopes responsible for IgE cross-reactivity among parvalbumins.

Methods: The parvalbumin-specific scFvs were selected from the human synthetic scFv phage library ETH-2 by alternating the parvalbumin from cod (Gad m 1), carp (Cyp c 1) and trout (Onc m 1) during 3 rounds of sequential biopanning. Based on their reactivity to parvalbumins by ELISA, 2 clones were expressed in *Escherichia coli*. The ability of the 2 scFv antibodies to inhibit the binding of parvalbumin-specific IgE from fish allergic patients' sera was showed by ELISA competition experiments and the rat basophilic leukemia mediator release assay.

Results: Based on ability to bind different parvalbumins and sequence analysis, phage clones scFv-gco9 and scFv-goo8 were selected for production of soluble scFv antibodies. We obtained 1 mg of scFv-gco9 and 1.3 mg of scFv-goo8 per litre of bacterial culture. The scFv-gco9 was able to detect all 3 parvalbumins at a concentration of 10 ng/mL. The scFv-goo8 bound to cod parvalbumin, but not to carp and trout parvalbumin. The detection limit for 1 μg/mL of the scFv-gco9 was 0.01 μg/mL of the Gad m 1 and 0.2 μg/mL of Onc m 1 or Cyp c 1. We found that scFv-gco9 dose-dependently blocked the binding of IgE to immobilized Gad m 1, Cyp c 1 and Onc m 1. At a concentration of 5 μg/mL of scFv-gco9 binding of IgE to the 3 parvalbumins was inhibited by approximately 40%, and at a concentration of 20 μg/mL the IgE binding was inhibited to ~70%. In the case of the scFv-goo8, inhibition of IgE binding to Gad m 1 was about 15%. The inhibition of degranulation of basophils was 55% in the presence of 2 μg/mL scFv-gco9.

Conclusions: This work, supported by grant SFB-F01802, revealed that the scFv antibodies can be used for the standardization of protein extracts used for allergy diagnosis and for IgE epitope mapping. Epitope characterization enables the engineering of parvalbumin molecules with reduced IgE binding for allergen-specific immunotherapy.

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Grass Pollen Allergen-induced Surface Expression of CD203C, CD63 and CD107A on CRTH2+ Basophils: Novel Biomarkers for Monitoring Efficacy of Allergen-specific Immunotherapy

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Background: Grass pollen immunotherapy is associated with reduction in symptoms, the need for rescue medication and improvement of quality of life in patients with severe seasonal pollinosis. Although, the suppression of the early allergic response following in vivo cutaneous allergen challenge is associated with inhibition of basophil histamine release, the effects of immunotherapy on basophil reactivity is yet to be fully determined. We hypothesized that basophil reactivity as measured by increased expression of surface activation markers CD203c, CD63 and CD107a on CRTH2+ basophils is increased in grass pollen allergic individuals following in vitro allergen stimulation. We further hypothesized that this hypereactivity is reduced in immunotherapy-treated patients.

Methods: Heparinized blood obtained from grass pollen allergics (n = 7), immunotherapy treated patients (n = 6) and non-atopic controls (n = 9) was incubated with 0, 0.1, 1, 10 and 100 ng/mL of *P. Pratense extract* at 37°C for 15 minutes. Cells were stained with anti-CD3, CRTh2, CD123, CD303, CD203c, CD63 and CD107a. Additionally, whole blood basophil histamine release was measured pre/post immunotherapy by ELISA (n = 6).

Results: A dose-dependent increase in the proportion of CD203c+, CD63+ and CD107a+ CRTH2+ basophils was observed following in vitro grass pollen stimulation in allergics but not in non-atopic controls. At 100 ng/mL of *P. Pratense extract*, CD203c+, CD63+ and CD107a+CRTH2+ basophils were significantly elevated in allergics compare to non-topics ($P < 0.001$, $P < 0.001$ and $P < 0.009$). This increase in CD203c+, CD63+CRTH2+ basophils in allergic individuals significantly correlated with timothy-specific IgE ($r = 0.84$, $P < 0.0001$; $r = 0.85$, $P < 0.0001$). Interestingly, 10- to 100-fold more allergen was required for CRTH2+ basophils to express CD203c, CD63 and CD107a in immunotherapy-treated patients compare to grass pollen allergics. At suboptimal allergen-concentration (10 ng/mL), CD203c+, CD63+ and CD107a+CRTH2+ basophils were significantly reduced in immunotherapy treated subjects compare to allergics ($P < 0.001$, $P < 0.001$ and $P < 0.002$). Basophil histamine release measured after treatment was significantly reduced compared to pre-treatment levels ($P < 0.03$).

Conclusions: Basophil reactivity and histamine release is significantly reduced following grass pollen immunotherapy. The use of surface activation markers CD203c, CD63 and CD107a on basophils for monitoring clinical efficacy requires further investigations.

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Specific IGE and IGG Binding to Allergoids of *Phleum pratense*

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Background: Allergoids were first used in the decades of the 60s and 70s of the last century as an effective treatment of allergic respiratory diseases. Allergoids can be modified with formaldehyde or glutaraldehyde. Modified allergens, or allergoids, decrease the risk of adverse reactions while administering higher allergen doses. The objective of this study was to analyse specific IgE and IgG binding to glutaraldehyde modified and non-modified allergen extracts of *Phleum pratense*.

Methods: The sera of 69 patients sensitized to *P. pratense* were tested. All these patients had signs and symptoms of rhinoconjunctivitis with, or without, asthma in May and June of 2011. All these patients had positive skin prick tests to a standardized extract of *P. pratense*, and other grass species. Most patients were also sensitized to olive pollen. Specific IgE and IgG binding were analysed by direct ELISA against *P. pratense* native (non-modified) and allergoid extracts. Relative potencies were evaluated through ELISA inhibition assays, and the protein composition of non-modified and allergoid samples was determined by Mass Spectrometry (MS/MS).

Results: Mean Specific IgE levels against the native extract was 16.68 ± 11.65 Units (U) and against the allergoid: 7.26 ± 8.24 U ($P < 0.0001$; Mann-Whitney). On the other hand, mean specific IgG binding against the

non-modified extract was 90.34 ± 75.57 U versus 76.19 ± 70.31 U against the allergoid ($P = 0.16$; Mann-Whitney). Linear regression coefficients obtained between immunoglobulin reactivity against both extracts were: $r^2 = 0.51$ for specific IgE and $r^2 = 0.83$ for specific IgG. An important decrease in the allergenic activity, measured by inhibition ELISA, was clearly observed. The MS/MS assay revealed the presence of the mayor allergen, and some isoforms, in non-modified and allergoid extracts.

Conclusions: Results obtained demonstrate that the glutaraldehyde polymerization process induces an important decrease in specific IgE binding to allergoids of *P. pratense* while there are no significant differences in specific IgG binding. The allergenic composition of the *P. pratense* allergoid was equivalent to the non-modified pollen extract.

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Anxiety and Depression in Patients With Variable Common Immunodeficiency in the Service of Allergy and Clinical Immunology - Centro Médico Nacional Siglo XXI

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Background: Depression and anxiety disorder are topics of interest, not only to psychiatrists. It comes in a 10 to 20% of cases, with the highest figures in people with chronic diseases. It has been shown that depressed patients have more mortality (not only attributable to suicide) than the general population. Depressive disorders in the community reach a lifetime prevalence of 15%. The average age of onset is situated close to 30 years, being similar in both sexes. The Variable Common Immunodeficiency (ICV) is a disorder characterized by low levels of immunoglobulins (Ig), these patients have an increased susceptibility to infection. The exact cause of low levels of serum Ig is not known and autoimmune diseases is complicated by up to 20%. It has a prevalence estimated at 1 in 25,000, is the most common primary immunodeficiencies, however, the diagnosis is not made until the third and fourth decade of life.

Objective: To evaluate the presence of anxiety disorders and depression in patients with ICV.

Methods: A cohort study, observational, cross-fifteen patients (11 female and 4 male) with ICV, aged between 17 and 71, diagnosed with ICV. Are individually applied assessment instruments and the preparation of tables and graphs. The data were expressed in absolute figures and percentages.

Results: 1) 13.3% had very severe, 6.6% had severe, 13.3% moderate and 66.6% mild depression. 2) 33.3% moderate-severe anxiety and 66.6% mild.

Conclusions: In this study, most patients are between the second and third decade of life, the moderate-severe anxiety was found in 5 patients and mild in 10 patients, a mild depression 10, a moderate 2, a severe 1 and 2 very severe. This allows to evaluate the ability of the patient with ICV to accept their illness and see the level of infection on the psychological, and offer a multidisciplinary therapy with counseling and/or psychiatric treatment for patients with moderate-severe anxiety and moderate depression to very severe and thus improve their quality of life. These patients have associated autoimmune disorders and family problems.

Sex		Age Groups					
Female	Male	<20	20–30	31–40	41–50	51–60	61–70
11	4	2	4	5	1	3	1

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Computed Tomography Findings Consistent With Rhinosinusitis, Clinical Correlation and Quality of Life in Patients With Common Variable Immunodeficiency. Original Article

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Background: Common Variable Immunodeficiency (CVID) is a clinical syndrome characterized by a reduction and/or absence of IgG, IgM and IgA to respiratory tract infections and/or gastrointestinal can be associated with lymphoproliferative and autoimmune processes. The infections found in paranasal sinuses are an important cause of morbidity and generate deterioration in the quality of life in this patient population. Multidetector Computed Tomography (MDCT) of the sinuses is the Gold standard for diagnosis of rhinosinusitis. The Rhinosinusitis disability index (RSDI) developed by Benninger and Senior, evaluates the quality of life in patients with nasal disease, including rhinosinusitis.

Methods: Fourteen patients were included with a definitive diagnosis of CVID according to the diagnostic criteria of the European Society for Immunodeficiencies in each of the patients were evaluated: (1) The diagnostic criteria according to the European Consensus on Rhinosinusitis and nasal polyposis (EPOS 2007) (2) MDCT of Sinuses. (3) Each patient answered the questionnaire of RSDI. Correlation was calculated using Spearman Ro (rs).

Results: Ten patients were female (71.4%) and 4 were male (28.5%). The average age was 34 years. In 8 patients (57%) received the diagnosis of rhinosinusitis. The maxillary sinus was affected in 5 patients find us (45%), followed by ethmoid sinus (36%), frontal sinus and sphenoid was affected in 9% of patients. The correlation between clinical symptoms and MDCT study was consistent with rhinosinusitis rs = 0.84. The correlation between the clinical diagnosis, CT and rhinosinusitis disability index was rs = 0.71. In 5 of the 14 patients studied showed no clinical symptoms of rinosinuistis, but in MDCT of the sinuses if they showed data compatible with the disease. Three of these patients showed bilateral location (69%) and in one patient the findings were found in 3 sinuses frontal, ethmoid and maxillary.

Conclusions: The sinus infection is a major cause of morbidity in patients with CVID. As in the initial study, should include a CT scan of paranasal sinuses for proper assessment and timely diagnosis.

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Case Report: Recurrent Mucocutaneous Candidiasis and Recurrent Diarrhea by Gram Negative Bacteria

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Background: Primary Immunodeficiencies (PID) are inherited disorders of immune system function that predispose affected individuals to increased rate and severity of infection, immune dysregulation with autoimmune disease, and malignancy.[1] In Peru there is a sub diagnosis and report of these diseases.

Methods: I present a case of a 7 month girl with recurrent mucocutaneous candidiasis and recurrent diarrhea by gram negative bacteria. Patient's current illness start at 3 days of age with macular anular lesions in skin and thrush, with poor response to topical antifungals and oral Itraconazole. Resolved with IV Amphotericin and then Posaconazole. Recurrence few days after treatment withdrawal. Culture of the lesions: Candida albicans. At 1 month of age she

starts with recurrent diarrhea. Stool culture: Escherichia coli, Klebsiella pneumoniae. Intermittent fever coincident with the worsening of diarrhea or thrush lesions. Sepsis in one opportunity. Poor weight gain. We requested some procedures.

Results: IgM (+) to CMV, positive viral load by PCR, asymptomatic, received ganciclovir. Chest CT: thymus with normal size. HIV: negative. Normal: WBC, glucose, creatinine, IgG, IgA, IgM, abdominal US, echocardiography. Flux cytometry (at 3 months of age): WBC = 13,040; Total lymphocytes = 4564; T CD4 = 1734; T CD8 = 1121; B cells = 913; NK cells = 574. GENETIC ANALYSIS: Gain-of-function human STAT1 mutation. Diagnosis: Chronic mucocutaneous candidiasis associated with STAT1 mutation.

Conclusions: Susceptibility to Candida sp has been described in combined immunodeficiency, phagocyte defects, or other immune defects resulting from mutations in AIRE, CARD9, dectin1, dectin2, NLRP3, STAT3 or MyD88.[2] As described in this case, the gain-of-function STAT1 mutation can also result in susceptibility to candida. There is a huge work to do in the field of PI in Peru. There has been until now a subdiagnosis and subreport of PI, but we have recently started working hard in purpose of giving affected patients a specific diagnosis and appropriate treatment.

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Bronchiectasis: Localization and Characteristics, Identified by Using a High Resolution CT Scan in Adults With Common Variable Immunodeficiency

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Background: The common variable Immunodeficiency (CVID) is the second cause of primary immunodeficiency. The bronchiectasis are the most frequent structural pulmonary alterations in CVID, which have been principally described in pediatric population, finding the presence of the same ones in 50% of the cases, nevertheless exists inssuficient information about the location and characteristics as type and distribution of the bronchiectasis; in adult population, less information exists still on this matter. High resolution CT scan is valuable for detection of bronchiectasis and may alter treatment of these patients.

Objective: The purpose of this study was to determine the presence of bronchiectasis, their characteristics and most frequent location using a high resolution CT scan in adults with diagnosis of CVID.

Methods: This was a cohort study whit 15 adult subjects whit the diagnosis of CVID, who underwent a chest high-resolution computed tomography scan, previous signature of a letter of informed consent and with the approval of the committee of ethics and investigation (F-2011-3601-21).

Results: We studied all the subjects (n = 15) whit CVID, finding the presence of bronquiectasias in 73% of the subjects with CVID, 82% was a women and 8% males. The most frequent location was in the left lung in 46% of the cases and 45 bilateral %, with only 9% of location in right lung. These were more frequent in the lower lobe in 42, 17% in top lobe and l6% diffuse, the rest of them were brought like diffuse, bibasal or parahiliar. In one patient we found the presence of a left apical cavitation and only one was brought by presence of pulmonary diffuse fibrosis.

Conclusions: There was realized a search of bronchiectasis and their characteristics in subjects with CVID disorders, the incidence of bronchiectasis is higher in our poblation (82%) than in the rest (50% described in other pubiclations). The most affected lung was the left in the lower lobe. The most frequent type of bronchiectasis was the cystic form.

IMMUNOMODULATORS

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Modulation of Human Basophilic Responses by a Fibroleukin-Allergen Fusion Protein

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Background: Fibroleukin or fibrinogen-like protein-2 is a immunomodulatory protein that was described to bind to Fcgamma-receptor-IIb and III. In the present study the effects of a fusion protein consisting of fibroleukin and the major allergen of shrimp, tropomyosin, on human basophilic responses were investigated in vitro.

Methods: The fusion molecule was generated by molecular cloning and expressed in *E. coli*. Receptor binding studies were performed by immunoblot, ELISA, and flow cytometry. Activation of basophils was studied by basophil activation test (BAT) with blood from shrimp allergic individuals.

Results: Tropomyosin and the C-terminal part of fibroleukin were fused by a short flexible linker consisting of the amino acids RADAAP. The fusion protein bound to the human Fcgamma-receptor-IIb in immunoblot and ELISA and binding of the fusion protein to human B-cells was shown by flow-cytometry. Shortening of the allergen into a peptide covering one-fifth of whole tropomyosin increased the binding to B-cells. Futhermore, a decrease in the activation of basophils to shrimp tropomyosin was observed in presence of the fusion protein.

Conclusions: Here we describe a novel fusion protein based on fibroleukin and shrimp tropomyosin that may have tolerizing effects on basophils and B-cells in shrimp allergic individuals.

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Immunogenicity and Safety Aspects of Adeno-Associated Virus–Like Particles (AAVLPS) as Carriers for B-Cell Vaccines

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Background: Adeno-associated viruses (AAV) are non-human pathogenic and replication defective ssDNA viruses. The surface of AAV consists of 60 capsomers, which can be exploited for high density display of recombinant peptides. AAV-like particles (AAVLP) can be generated via assembly of the recombinant capsid protein VP3. The aim of this study was to evaluate the uptake mechanism, immunogenicity and safety aspects of an AAVLP-displayed B-cell epitope, taking ovalbumin (OVA) as a model antigen/allergen.

Methods: An OVA derived linear B-cell epitope and for control purposes OVA-non related peptide TP18 (cholesterol-ester transfer protein 18) were inserted into capsid protein VP3 of AAVLPs.

Results: Life cell microscopy indicated that AAVLP internalized into HeLa epithelial cells and remained in intracellular vesicles up to 18 hours. When we immunized BALB/c subcutaneously, sera of AAVLP-OVA immunized mice showed similar titres of OVA-specific IgG1 compared to mice immunized with OVA protein. However, in OVA immunized mice high OVA-specific

IgE levels could be recorded, whereas immunizations with OVA-AAVLP rendered background IgE levels only. In accordance, sera of OVA mice which permitted mast cell degranulation upon OVA trigger in a specific β-hexosaminidase release assay, whereas sera of OVA-AAVLP mice did not contain anaphylactogenic antibodies. In an in vivo anaphylaxis experiment, upon intravenous OVA challenge OVA-immunized mice presented significant drop of body temperature, whereas AAVLP-OVA mice remained unaffected.
Conclusions: Our study demonstrates the immunogenicity, safety and efficacy of AAVLP as display system of B-cell epitopes for vaccination.

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M-Cell Targeting by Neuraminidase Functionalized Microparticles for Future Application in Oral Immunotherapy

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Background: Recently, we demonstrated in an experimental mouse study that mucosal M-cell targeting with Aleuria aurantia lectin (AAL) coated Poly (D,L-lactide-co-glycolide) (PLGA) microspheres represents a promising oral treatment approach in IgE mediated allergy. Due to its structural similarities with AAL we aimed to assess Neuraminidase (NA) from *Vibrio cholerae* as a novel M-cell specific targeters and compared its properties to AAL and wheat germ agglutinin (WGA) representing 2 plant lectins, which target either M-cells or epithelial cells, respectively.
Methods: The resistance against gastric digestion of NA, AAL and WGA was analyzed in simulated gastric fluid (SGF) experiments. Intestinal epithelial binding was determined using the colon carcinoma cell line Caco2, which represents a well established model for the human intestinal epithelium. Binding specificity was evaluated by inhibition experiments by incubating Caco2 cells with Biotin-labeled NA, AAL or WGA, after preincubation with a-L fucose, monoganglioside (GM1) or N,N′,N′′-triacetyl-chitotriose (TCT). The stimulatory effects of the targeting substances on the intestinal microenvironment were investigated by cytokine read-out experiments in real-time PCR. Further, the transeptihelial uptake of NA-, AAL- or WGA-functionalized fluospheres was evaluated in a human M-cell co-culture model.
Results: All 3 targeters were stable up to 180 minutes in SGF, indicating their suitability for oral application. The binding partners were a-L fucose for AAL and TCT for WGA, whereas NA interacts with intestinal epithelial cells via a-L fucose and additionally GM1. NA skewed the cytokine production by inducing a 2-fold increase of the Th1 cytokine IFNg after 60 minutes, whereas AAL decreased the overall cytokine expression. In a human M-cell co-culture model, a higher transepithelial transport rate of fluospheres coated with NA and AAL was observed as compared to WGA and plain particles.
Conclusions: NA specifically targets M-cells via a-L fucose and additionally GM1 and, thus, increases the transepithelial transport of NA coated particles. Due to the immunomodulatory capacity on intestinal epithelial cells, NA functionalized microspheres may represent a promising M-cell specific targeting approach for oral immunotherapy.

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Neisseria Meningitidis Derived Proteoliposome as an Adjuvant for Allergen Vaccines

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Background: In recent years one important trend of Allergen-specific immunotherapy is to investigate new adjuvants with immunomodulatory properties. The outer membrane vesicle or proteoliposome (PL) from *Neisseria meningitidis* serogroup B has been reported as a potent adjuvant inducing a Th1-skewed response. The aim of this work was to assess the immunogenicity of a novel anti-allergic vaccine candidate based on purified allergens from *Dermatophagoides siboney* mite and PL as adjuvant, both components adsorbed onto Aluminum hydroxide.
Methods: In a preventative experimental setting BALB/c mice were administered with 3 doses containing 5 μg of Der s 1 allergen at one week intervals by subcutaneous route. Further, mice were subjected to allergen challenge by aerosol inhalation. In another experiment, mice were administered first with 2 doses of PL + Alum and later with the whole vaccines formulation, including the allergen. The allergen-specific antibody response was assessed determining serum levels of IgE, IgG1, and IgG2a by ELISA. The local allergic inflammatory response was evaluated by measuring cytokine levels (IL-4, IL-5, IFNg and IL-10) in broncho-alveolar lavage (BAL) by ELISA.
Results: The formulation consistently induced IgG2a, as well as IgG1 antibodies with a potential anti-IgE blocking effect. The induction of IgG2a was clearly PL dependent while IgG1 was dependent mostly of Alum. Prior administration of the proteoliposome with alum without allergen showed to enhance this allergen-specific immunogenic effect. The vaccine prevented the development of systemic (IgE) and local allergic response in mice subjected to allergen exposure by inhalant route. Vaccinated mice showed lower levels of serum IgE, Th2 cytokines (IL-4, IL-5) in BAL and lower eosinophil counting in blood as compared to controls. Histological examination of lungs showed also a diminished allergic inflammatory response in vaccinated mice in contrast with mice which were administered with the conventional formulation of Alum-adsorbed allergen.
Conclusions: The antiallergic protective effect was proven in a preventative setting, showing to decrease the inflammatory response in the lungs of mice exposed to allergen aerosol, as well as, a Th2-antagonistic immune response with few injections.

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Immunomodulatory Effects of Manumycin-type Antibiotics on Human Macrophages

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Background: Polyketide-derived antibiotics including macrolides are known to exert potent anti-inflammatory and immunomodulatory effects beyond their purely antibacterial action. The mechanisms of their biological activities are still being investigated but the effect on signalling pathways of transcription factors which regulate a number of pro-inflammatory and/or pro-fibrotic genes might be preferentially involved. The aim of our study was to assess the effect of manumycin and structurally related compounds asukamycin and collabomycin on a release of proinflammatory cytokines IL-1beta and IL-18 from THP-1 monocyte/macrophage cell line. Furthermore, the level of mRNA expression of multiple genes associated with immune regulation has been studied.
Methods: The THP-1 cells were cultured in RPMI1640 with 5% fetal calf serum and then stimulated with TNF alpha (20 ng/mL) under serum free conditions in the presence or absence of manumycin and asukamycin (both at 0.3 μg/mL). The concentrations of cytokines in culture supernatants were measured by ELISA (IL-18, MBL) or Luminex (IL-1 beta, R&D). Quantitative RT-PCR (SABiosciences) was used for the evaluation of 84 different gene expressions in TNF alpha and manumycin stimulated cultures.

Results: IL-1 beta was not detectable in culture supernatants of unstimulated THP-1 cells but appeared in response to TNF alpha (4.96 + 0.59 pg/mL). Both manumycin (0.34 + 0.48 pg/mL) and asukamycin (1.06 + 0.81) inhibited IL-1 beta release induced by TNF alpha. IL-18 was found to be constitutively produced (14.68 + 7.83 pg/mL) and the release was doubled by TNF alpha (30.98 + 2.21 pg/mL) and inhibited to basal values by both manumycin (18.04 + 10.21 pg/mL) and asukamycin (12.96 + 2.32 pg/mL). Manumycin inhibited mRNA expression of several genes associated with proinflammatory responses including IL-1 beta, IL-6, and TLR8. Among the genes upregulated in response to manumycin, HMOX1, gene for heme oxigenase 1, showed the highest mRNA induction.
Conclusions: We assume from our study that manumycin and asukamycin represent potent inhibitors of IL-1 beta and IL-18 release from human macrophages. Some of the potentially proinflammatory genes are regulated on the level of transcription.
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INDOOR RISK FACTORS FOR ASTHMA

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The Relationship of Pets, Vitamin D and IGE Concentrations to Upper Respiratory Infections in the First Year of Life

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Background: The childhood origins of asthma are highly complex but viral respiratory infections during the first year of life may be associated with wheezing and later asthma risk. Recent studies have shown that both exposure to household pets and higher serum vitamin D concentrations may reduce wheezing illness in children.
Methods: To investigate potential relationships between household pet exposure, cord blood (CB) vitamin D and IgE concentrations and the number of upper respiratory infections (URIs) in the first year of life, we analyzed information from a geographically-based, prospective, non-high-risk, birth cohort. Household pets were assessed during pregnancy and medical records were abstracted for doctor visits of URIs. Because of large differences in vitamin D concentrations between Blacks and Whites racial stratification was done for some analyses.
Results: The cohort consisted of 1055 children of whom 62.4% were Black and 49.4% were female. When all children were considered, a one natural log unit increase in CB vitamin D concentration was associated with a greater risk of a URI visit (RR = 1.27, 95% CI, 1.01-1.59, $P = 0.037$) which remained after adjusting for the season of birth (RR = 1.28, $P = 0.033$). Individually adjusting for the number of children in the family, CB IgE, child gender, family or maternal smoking and race did not substantially change the association of vitamin D to URIs (all RR's were 1.25-1.27), although the risks only remained statistically significant with CB IgE ($P = 0.035$) and gender ($P = 0.043$). When models stratified by race including pets, dogs only, or cats only, and CB IgE were fitted with the other variables, the relationship between CB vitamin D disappeared for whites but did not change in magnitude for blacks (RR = 1.31; 95% CI, 0.89-1.92; $P = 0.165$). Among Whites the only variable associated with URIs was a relationship with female gender (RR = 0.62, 95% CI, 0.41-0.94; $P = 0.025$) with being in daycare approaching significance (RR = 1.72, 95% CI, 0.94-3.14; $P = 0.08$).
Conclusions: In a large, prospective, non-high-risk birth cohort higher, CB vitamin D concentration, after adjusting for other potential confounding variables, was not associated with a decreased risk of physician diagnosed URIs in the first year of life.

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Prevalence of Cockroach and Mouse Sensitization Among Children Hospitalized for Wheezing and Asthma

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Background: The prevalence and demographic correlates of cockroach (CR) and mouse sensitization among children hospitalized for wheezing and asthma are not known. Objectives: (1) To describe the prevalence of CR and mouse sensitization in a population-based sample; (2) To examine factors potentially associated with allergic sensitization including sociodemographic factors and asthma history.
Methods: We examined baseline data of the first 416 children enrolled in a prospective study cohort between August 2010 and February 2011. Eligible children were aged 1 to 16 years, were admitted for bronchodilator-responsive wheezing or acute asthma to a single children's hospital that captures >90% of all asthma admissions in the county. Allergic sensitization was determined using specific Ig-E to CR and mouse. Caregivers were surveyed regarding sociodemographic characteristics and asthma history. Associations were assessed using chi-square statistics.
Results: The sample is 65% African-American, 76% publically insured. 78% report household income less than $60,000. 81% have a previous physician-diagnosis of asthma. 26% of children are sensitized to CR, 16% to mouse, and 34% are sensitized to either CR or mouse. 8% are sensitized to both. Patients younger than 4 years are less likely to be sensitized to CR (10 vs 34%, $P < 0.0001$) and mouse (8 vs 20%, $P = 0.002$) than older patients. Patients with a previous physician-diagnosis of asthma are more likely to be sensitized to CR (29 vs 13%, $P = 0.007$) and mouse (13 vs 9%, $P = 0.06$) than patients without a previous diagnosis. Compared to children in families with annual income >$90,000, those in families earning less than $15,000 were more likely to be CR sensitized (33 vs 18%, $P = 0.01$). The opposite trend exists for mouse sensitization: 13% of low income children are sensitized compared to 25% of high income children ($P = 0.02$).
Conclusions: In a population based sample, one-third of children admitted for bronchodilator-responsive wheezing or asthma are sensitized to either CR or mouse. Sensitization is associated with older age, a previous physician-diagnosis of asthma, and household income. Assessment of allergic sensitization during an inpatient admission may be an opportunity to target interventions for children at highest risk of allergy-related asthma morbidity.

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Is Pet Ownership Associated with Higher Vitamin D?

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Background: Pet keeping has been linked with decreased risk of allergic sensitization, which has been associated with the Hygiene Hypothesis; and more recently, by ourselves and others, to particular home microbiome

patterns. Another factor possibly associated with pet ownership is increased Vitamin D among family members as pet keeping may be correlated with lifestyles involving increased outdoor exposure, such as dog walking. Prenatal vitamin D inadequacy has been hypothesized as a risk factor for pediatric atopy and asthma.
Methods: To investigate potential relationships between household pet exposure and cord blood vitamin D concentrations, we analyzed information from a large, geographically-based, general risk birth cohort. Household pets were assessed during pregnancy and serum level of 25 (OH)D (25-hydroxyvitamin D) in cord blood was used as the measure of vitamin D and a marker of maternal level. Because of notable differences in vitamin D concentrations between African Americans and Whites, analyses were stratified by race.
Results: A total of 1055 newborns were included in the study: 62.4% were African Americans and 49.4% were female. For Whites, but not African Americans, having no pet compared to 1 or >1 pet during pregnancy was associated with lower cord blood vitamin D concentrations (37.7, 45.2, 47.0 nmol/L, respectively, $P = 0.001$). Considering type of pet, the relationship for no pet compared to 1 or >1 dog (37.7, 46.1, 49.9 nmol/L, respectively, $P = 0.001$) was similar to that for no pet versus 1 or >1 cat (37.7, 43.0, 46.5 nmol/L, respectively, $P = 0.065$).
Conclusions: In a large ethnically diverse cohort of newborns, the presence of a pet in the home during the prenatal time period was associated with higher cord blood vitamin D, but only among Whites. This racial difference may reflect an impact on pet owner behavior resulting in increased outdoor exposure that is limited to lighter skinned individuals. However, as the effect doesn't vary by cats versus dogs, differences by race in factors correlated with pet ownership or variations in pet keeping styles may be more important. Vitamin D should be considered in studies of pets and atopic conditions.

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Taxonomic Identification of the House Dust Mites Associated to Allergic Patients in 6 Locations From Mexico

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Background: Taxonomic research on house dust mites carried out by acarologists doesn't exist in Mexico since 1991. However, the allergologists should know the sources of allergens present in their country. A survey of dust samples from 6 locations was made in Mexico to determine the diversity of indoor acarofauna.
Methods: All the samples of dust (1 g each) were collected with vacuum cleaners from mattresses of allergic patients from 10 georeferenced houses in each of 6 localities (3 coastal and 3 continental) from Mexico during February 2010 and May 2011. The mites were isolated by the sedimentation flotation method Spieskma-Boezeman 1967. All the identified material was deposited in a Basic Collection from Rocel Laboratories in Puebla and in the National Collection of Acarology from the Institute of Biology, UNAM, Mexico.
Results: Eleven mite species were found of which the most important were house dust mites, specially: *Dermatophagoides pteronyssinus* (Trouessart, 1897) and *Dermatophagoides farinae* Hughes, 1961. Both species were reported for the first time for the 6 localities under study. *Dermatophagoides siboney* Dusbabek, Cuervo and Cruz, 1982 is a vicariant species of *D. farinae* and was registered for the first time for Mexico in Ciudad del Carmen, Campeche, but we consider this result should be corroborated in future studies. *Blomia tropicalis* (Bronswijk, Cook and Oshima, 1973) was also registered for the first time for Mexico in 3 of the 6 Mexican localities and it has a tropical distribution. This last species has been used in Mexico for skin tests and this result favours its use for diagnosis and inmunotherapy.
Conclusions: This survey revealed the existence of house dust mites in Mexico. It seems there are differences between the geographical distribution of the species because of the local conditions of temperature and humidity of each urban ecosystem. This knowledge may be useful in the field of allergy medicine.

INHALED CORTICOSTEROIDS FOR ASTHMA

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Comparison of the Use Ciclesonide Versus Fluticasone for the Treatment of Asthma in Children

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Background: The mainteinance treatment in patients with asthma is based in the use of inhaled corticosteroids as ciclesonide and fluticasone. The objective of this stutdy is to compare the utility between ciclesonide versus fluticasone for treatment of asthma in children.
Methods: A search was done in journals databases of PubMed, EMBASE, LILACS and Cochrane, from 1996 to 2009. We searched for studies comparing treatment with ciclesonide versus fluticasone in the treatment of children younger than 18 years diagnosed with persistent moderate and severe asthma. The outcomes measured were: FEV 1, peak expiratory flow improvement, absence of nocturnal symptoms, decrease the number of crisis compared to baseline and need to use beta 2 agonist rescue crisis.
Results: When making comparisons between ciclesonide and fluticasone in terms of effectiveness in reducing nocturnal symptoms use of beta 2 agonists, peak expiratory flow improvement and prevention of asthma attacks, the studies reported equal effectiveness for both corticosteroids. Studies provide equally effective in improving FEV1. In terms of local effects, it refers in 2 studies presented the same presentation with both steroids, but there are 2 others less concerned with ciclesonide local effects, but both without presenting conclusive results. With respect to adrenal suppression, there are 2 articles that refer to is less with the use of ciclesonide with fluticasone, one adult on the other hand more equal terms the presence of adrenal suppression with both steroids. However, in all studies to make the overall analysis refers without significant changes. Ciclesonide showed the advantage of not inhibiting cortisol secretion. There were studies that compared quality of life by the result of health-related quality of life (PAQLQ) symptom-free days, days without the use of beta 2 agonists and days without nocturnal awakenings, all refers to both corticosteroids as equivalent. By comparing ciclesonide versus placebo, by applying PAQLQ only one study refers improved quality of life with the steroid.
Conclusions: Ciclesonide is equally effective as fluticasone in the treatment of children with persistent moderate and severe asthma. Besides, bioavailability of ciclesonide allows administration once a day, with less adrenal supression.

MECHANISMS OF ALLERGIC INFLAMMATION

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Type I and III Interferon Are Attenuated in a Human In Vitro Model of Alternatively Activated Macrophages

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Background: The alternatively activated macrophages (AAM) are induced by IL-4 and IL-13 and are distinct from the IFN-gamma mediated pathway of classically activated macrophages (CAM). The AAM are implicated in a wide

range of physiologic and pathological processes including clearance of helminthic infections, and allergy. They are closely associated with recruiting and amplifying T helper 2 (Th2) lymphocyte response in contrast to Th1-asscoiated CAMs. Wide donor-to-donor variability of human primary monocytes and their limited life span in vitro is a current impediment to investigating human AAM biology and their contribution to enhancing Th2-mediated pathologic inflammation found in asthmatic lungs.

Methods: Using the human promonocytic cell line, THP1, we have successfully established a THP1-derived and committed CAM and AAM populations demonstrating typical macrophage-oriented morphological characteristics.

Results: Quantitative PCR and ELISA demonstrated that THP1-AAM cell model express classic pathogen neutralizing dectin receptors such as scavenger type mannose receptor (MRC1) and Th2-associated signature chemokines including CCL13, 17, 18 and 22, and are tolerant to TLR4 challenge by LPS treatment in contrast to THP1-CAM which expressed an LPS enhanced expression of pro-inflammatory mediators such as TNF-a, CXCL10 and -11. Furthermore, THP1-AAM cell model expressed 50- to 100-fold lower expression IFN-alpha 4, IFN-beta, and IFN-lambda1 compared to THP1-CAM. Quantitative PCR array revealed that a select group of interferon regulatory factors (IRFs), antiviral genes such as Mx1, and interferon stimulated genes such as ISG15 are down-regulated only in THP-1 AAM cell model upon differentiation or LPS treatment emphasizing its classic infection tolerant phenotype. In addition, IRF4 was found to be up-regulated only in the THP1-AAM model which may point towards its critical role in orchestrating the macrophage lineage commitment towards an alternatively activated phenotype as well as governing its unique cytokine and chemokines expression profile.

Conclusions: Compared to the donor variability of primary human monocytes, establishing THP1-AAM and CAM cell models will enable a more rapid and efficient investigation of a spectrum of molecular mechanisms governing innate, classic, and alternative phenotypes in macrophage populations and their role in pathologic processes, in particular allergic inflammation of the upper airways.

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A Highly Sensitive and Specific Universal Mirna Profiling Method

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Background: miRNAs can be used as robust biomarkers for diagnosis, staging, prognosis and the response to therapy in various diseases. Although a wide spectrum of miRNA detection techniques have been developed, none can accurately and sensitively perform genome-wide high-throughput miRNA profiling (Chen C, Ridzon DA, Broomer AJ, Zhou Z, Lee DH, Nguyen JT, Barbisin M, Xu NL, et al 2005. Real-time quantification of microRNAs by stem-loop RT-PCR. *Nucleic Acids Res*. 33:e179). This problem stems from that miRNAs are only ~22 bases, and multiple species of nucleic acids that contain the mature miRNA sequences are present in the total RNA samples that are usually used for miRNA detection.

Methods: A novel RT-qPCR miRNA assay (UQmiR, universally quantitating miRNA) was developed to overcome the difficulty. This assay requires only one RT reaction and one universal set of multiple hydrolysis probes to detect all miRNAs, using one universal RT primer, a common reverse primer, and individual miRNA-specific forward primers. A computer program (MSPPD, miRNA-specific primer and probe designer) was developed for the assay.

Results: The UQmiR has the advantages, but not the disadvantages, of the 2 mostly used miRNA assays. It has the specificity of hydrolysis probe assay and the universal detection of SYBR Green assay. This assay is more sensitive and specific than the commercially available hydrolysis probe assay and SYBR Green assay. Using this method, we have successfully detected 91 out of 96 miRNAs in 0.8 mL of plasma for each miRNA.

Conclusions: This approach affords a highly specific, sensitive, economical and convenient system to profile the expression of all known miRNAs.

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Caspase-4 Plays a Role in the Activation of the Cryopyrin/ NLRP3 Inflammasome

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Background: The inflammasome is a multi-protein complex which regulates the activation of caspase-1. This activation results in the cleavage and secretion of the IL-1β super family cytokines, IL-1β, IL-18, and IL-33. NLR family-pyrin domain containing- 3 (NLRP3) is a nucleotide binding domain-leucine rich repeat (NLR) family protein responsible for sensitization and oligomerization of the NLRP3 inflammasome complex. Although various damage and pathogen associated patterns have been implicated as stimuli, the exact mechanism of activation has yet to be elucidated. Capase-5, an inflammatory caspase with similar homology to caspase-1, is a key molecule activation of the NLRP1 inflammasome. Caspase-4, an evolutionary duplicate in humans to murine caspase 12 along with caspase 5, is important in IL-1β processing; its involvement with the NLRP3 inflammasome is unknown. We therefore investigated whether caspase-4 plays a role in the activation of the NLRP3 inflammasome.

Methods: Inflammasomes in THP-1 macrophages were activated using Nigericin (10 μg/mL), a bacterial pore causing toxin and NLRP3 inflammasome activator, in the presence or absence of various concentrations (0.1 μM, 1 μM, and 10 μM) of caspase-4 inhibitor, Z-YVAD-FMK. We analyzed the inflammasome activation, caspase-1 cleavage, and IL-1β release by western blot and ELISA analysis.

Results: Our results indicate that inhibition of caspase-4 leads to a dose dependant decrease in IL-1β secretion. In addition, our results show that caspase-4 contributes to IL-1β and caspase-1 cleavage, both of which are hall marks of inflammasome activation.

Conclusions: These findings suggest that caspase-4 is important to the activation of the NLRP3 inflammasome. In modulating the inflammasome, caspase-4 appears to be a druggable target for treatment of chronic inflammatory pulmonary conditions such as allergy and asthma.

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Genome-Wide Association Studies of Asthma Indicate Opposite Immunopathogenesis Direction From Autoimmune Diseases

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Background: Genome-wide association studies (GWAS) of asthma and asthma-related traits, including our previous TENOR study[1], have consistently identified *ORMDL3-GSDMB*, *IL33, IL1RL1-IL18R1*, *RAD50-IL13*, *TSLP-WDR36*, and *HLA-DR/DQ* regions.[2]

Methods: In this study, GWAS of asthma was performed in non-Hispanic white population from STAMPEED study (813 cases and 1564 controls). Our GWAS results were compared with the published GWAS of asthma and autoimmune diseases (AD).

Results: Multiple SNPs in *TNFAIP3* interacting protein 1 (*TNIP1*) on chromosome 5q32-q33.1 were associated with asthma in STAMPEED: rs1422673 ($P = 3.44 \times 10^{-7}$) and rs10036748 ($P = 1.41 \times 10^{-6}$). rs1422673 was weakly associated with asthma in the published GABRIEL study ($P = 0.018$ for meta-analysis)[2] but not in the TENOR study ($P = 0.18$ but same trend).[1] *TNIP1* may interact with *TNFAIP3* and inhibit *TNF*α-induced *NF*κ*B* inflammation pathway. Joint analyses were performed on 6 SNPs in *GSDMB* (rs2872507), *IL33* (rs3939286), *IL1RL1* (rs13431828), *IL13* (rs20541), *TSLP* (rs1837253), and *HLA-DRA* (rs2395185) in STAMPEED and TENOR populations, but only limited variance can be explained (percentage of deviance = 1.5–1.9%; the area under the receiver operating characteristic curve (AUC) = 0.58–0.59). Minor allele T of rs20541 in *IL13* is the risk allele for asthma but the protective allele for psoriasis. Minor allele A of rs2872507 in *GSDMB* is the protective allele for asthma but the risk allele for rheumatoid arthritis, Crohn's disease and ulcerative colitis. T allele of rs10036748 in *TNIP1* is the minor protective allele for asthma, but the minor or major risk allele for systemic lupus erythematosus in non-Hispanic white or Chinese population, respectively.

Conclusions: Our study provides genetic evidence that asthma and AD have opposite immunopathogenesis directions.

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Allergy is an Epithelial Barrier Disease

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Background: The purpose of this study is to explore the role of epithelium in acute allergic diseases.

Methods: Birch pollen allergic patients and healthy control subjects were recruited. In vivo nasal pollen challenges were performed and nasal epithelial specimens were collected. A systems biology approach using a wealth of methods, including several microscopy techniques (light, confocal, immuno transmission electron [TEM]), transcriptomics (chips and massive parallel sequencing), mass spectrometry, immunohistology, in silico analyses were used.

Results: Already 1 minute after the birch pollen perturbation Bet v 1 was found both on cell surfaces as well as within villae, in cytoplasm, in intracellular vesicles, and also in nuclei of epithelial cells in allergic patients, but not in the healthy individuals. Anti-Bet v 1 stainings in conjunctival biopsies supported a very rapid traffic through the epithelium in allergic patients, but not in healthy subjects. A striking specificity is observed when birch pollen allergic subjects were also challenged with timothy grass pollen and no entry of this pollen allergen Phl p 1 into epithelial cells was detected. While the specific transport mechanism for birch pollen remains unsolved the first hints of the role of caveolae in this have been obtained. In the double immunoTEM analyses caveolin 2, but not caveolin 1 or 3, was present on the conjunctival epithelial surface in the same clusters as Bet v 1. Transcriptomics indicated that the health epithelium displayed a strong immune response against pollen allergens while this response was absent in the epithelium of allergic patients.

Conclusions: Active transport of allergens through the epithelium might be incorporated to the pathogenesis of allergy. It is possible that the healthy epithelium displays a strong immune response against pollen allergens and thus escapes from becoming allergic. If allergy turns out to be, at least in part, a result of epithelial hyposensitivity, it could have major consequences in the strategies of prevention and treatment of these diseases. Towards this end, a national allergy program has been launched in Finland, which changes the basic idea of trying to avoid allergens to the concept of natural exposure and tolerance.

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EGCG Downregulates Mucin Gene Expression Through the Mapk Signaling Pathway in Asthma

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Background: Mucus plays an important role in protecting human airway from external environments. Highly glycosylated mucin proteins are the major components of mucus, responsible for its viscoelastic properties. Excessive mucus is major manifestation of inflammatory respiratory diseases. Epigallocatechin-3-gallate (EGCG) is major component of green tea extract and known to provide numerous functions, such as anti-oxidant effect, anti-tumor effect, anti-diabetic effect and anti-inflammatory effect. But precise mechanisms are still unclear.

Methods: Using NCI-H292 human airway epithelial cells, we measured phorbol 12-myrisate 13-acetate (PMA)-induced MUC5B mRNA expression with the treatment of indicated doses of EGCG. We also measured PMA-induced MUC5B protein secretion with the treatment of indicated doses of EGCG using ELISA technique in NCI-H292 cells. To test the brief signaling pathways, we performed activation study of mitogen-activated protein kinase (MAPK) pathways, which is well-known to signaling the PMA-induced mucin gene over-expression, using Western blot technique in NCI-H292 cells. And then we performed in vivo study using ovalbumin-induced asthmatic mice model and control mice group. In ovalbumin-sensitized asthmatic mice model, EGCG was treated with indicated dose. And then ovalbumin was challenged and we sacrificed the mice. Tissue samples from the mice were stained with PAS (periodic acid-Schiff) for mucin distribution in bronchioles of each group. Immunocytochemical stain was performed using MUC5B specific antibody. MUC5B mRNA and protein level was measured using extracted lung tissues.

Results: PMA-induced MUC5B mRNA and protein level was significantly decreased after treatment of EGCG at all doses in NCI-H292 cells. PMA-induced phosphorylation of p38 MAPK was significantly decreased after treatment of EGCG at all doses in NCI-H292 cells. Results from in vivo studies showed that decreased bronchiolar mucin distribution in the group of pretreated with EGCG in asthmatic mice. MUC5B mRNA and protein levels were significantly decreased in the group of pretreated with EGCG in asthmatic mice.

Conclusions: PMA-induced MUC5B mRNA and protein over-expression in both NCI-H292 cells and extracted tissues from asthmatic mice were significantly decreased with the treatment of EGCG. We demonstrated that

EGCG downregulates mucin gene expression through the MAPK signaling pathway in asthma.

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Enhancer of Zeste Homolog 2: A Pivotal Role in Pulmonary Artery Smooth Muscle Cell Proliferation

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Background: Pulmonary arterial hypertension (PAH) is a progressive and a devastating disease characterized by excessive proliferation of pulmonary artery smooth muscle cells (PASMCs). The pathogenesis of PAH is not fully understood and treatment options are limited. Studies suggest that PAH and cancers share apoptosis resistant state featuring excessive cell proliferation. Proliferation of cancer cells is mediated by increased expression of Enhancer of Zeste Homolog 2 (EZH2), a mammalian histone methyltransferase that contributes to the epigenetic silencing of target genes. However, the role of EZH2 in PAH has not been studied. In this study, we hypothesized that EZH2 could play a role in PASMCs proliferation.

Methods: In the present study the effects of EZH2 overexpression on human PASMCs proliferation were tested. PASMCs were transfected with wild type EZH2 cDNA or GFP using the Lonza 4D nucleofector system. After transfection, cells were incubated for 48 hours at 37°C. PASMCs proliferation and cell cycle analysis were performed by flow cytometry; PASMCs apoptosis was determined using annexin V staining, and cell migration was tested by the wound healing assay. Expression levels of EZH2 were confirmed by real time PCR.

Results: The overexpression of EZH2 in PASMCs enhances proliferation, migration, and decreases the rate of apoptosis when compared to GFP transfected cells. There was a 3.5-fold increase in proliferation and a 1.5-fold increase in the percentage of cells in the G2/M phase in the EZH2 transfected cells while there was a significant decrease in the rate of apoptosis in the PASMCs.

Conclusions: These findings suggest that EZH2 plays a role in the migration and proliferation of PASMCs .It also suggest that EZH2 could play a role in PAH development and serve as a potential target for new therapies for PAH.

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The Features of Airway Remodeling Are More Severe in Female Mice

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Background: Epidemiological studies have already shown that females are dominant in terms of the sex ratio of adult asthma prevalence and severe asthma. It has also been reported that female mice are more susceptible to the development of allergic airway inflammation and airway hyperresponsiveness (AHR) than males. However, there have been few reports of studies on sex difference in the pathogenesis of severe asthma, especially airway remodeling in an animal model. In this study, we investigated sex difference in formation of airway remodeling using a long-term antigen challenged asthma model.

Methods: Following ovalbumin (OVA)/alum intraperitoneal injection, male or female mice (BALB/c) were challenged with aerosolized 1% OVA on 3 days/week for 5 weeks, and we investigated the sex difference in AHR, airway inflammation, as well as airway remodeling.

Results: In OVA-sensitized and -challenged (OVA/OVA) female mice, AHR, the number of eosinophils and lymphocytes, as well as Th2 cytokines and growth factors in BAL fluid were increased compared with OVA/OVA male mice. On the other hand, there is no significant difference in the level of eotaxin in BAL fluid. The histological features of airway remodeling, including goblet cell hyperplasia, subepithelial fibrosis and myofibroblast hypertrophy, were also increased in OVA/OVA female mice. Moreover, serum total and OVA-specific IgE were significantly elevated in OVA/OVA female mice.

Conclusions: These results indicate that female mice are dominant in terms of forming airway remodeling as compared with male mice. The involvement of sex difference for sensitization and growth factor release in lung tissue based on inflammatory cell infiltration is indicated for the mechanism of sex difference of airway remodeling.

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Ovalbumin-induced Bronchial Asthma is Compromised in Apoptosis Signal-Regulating Kinase-Deficient Mice

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Background: Apoptosis signal-regulating kinase 1 (ASK1), a member of mitogen –activated protein (MAP) kinase kinase kinases (MAP3Ks) protein family, plays a crucial role in the induction of apoptosis and inflammation in some cell types. Allergic asthma is a chronic inflammatory airway disease characterized by airway hyperresponsiveness (AHR), inflammatory cell infiltration, and airway remodeling. In the present study, we examined whether ASK1 is involved in the induction of bronchial asthma using a mouse model of airway inflammation.

Methods: ASK1-deficient (ASK1−/−) and wild-type (WT) control mice were sensitized with ovalbumin (OVA) in saline intraperitoneally on consecutive 7 days. Eighteen days later, mice received intranasal administration of OVA aerosol and were assayed for AHR, cytokine production, cell proliferation, antibody (Ab) production, and lung tissue histopathology at 24 hours after the last serial OVA administration. Levels of Ab and cytokines were determined by enzyme-linked immunosorbent assay (ELISA).

Results: Control WT mice showed inflammatory infiltrates in airways in response to OVA to a greater extent than ASK1−/− mice. The number of cells, especially eosinophils accumulating in airways, was reduced in ASK1−/− mice relative to control mice. OVA-induced AHR is also compromised in ASK1−/− mice. Anti-OVA IgE Ab production in ASK1−/− mice was substantially reduced, although levels of other isotypes were comparable to those in control mice. Levels of some Th2 cytokines (IL-5 and IL-13) and pro-inflammatory cytokine TNF-a in BAL fluid from ASK1−/− mice were substantially diminished relative to control, although a comparable level of a typical Th2 cytokine IL-4 and anti-inflammatory cytokine IL-10 was produced. Although the BAL fluid TNF-a levels from ASK1−/− mice were severely diminished, lymph node cells from ASK1−/− mice produced comparable levels of TNF-a to WT in vitro. Intranasal administration of recombinant TNF-a caused a comparable increase in AHR between ASK1−/− and WT mice, whereas the TNF-a -induced accumulation of inflammatory cells was severely reduced in ASK1−/− mice.

Conclusions: ASK1 appears to be involved in the induction of OVA-induced bronchial asthma, probably through cytokine production such as TNF-a and IL-13. Moreover, TNF-a sensitivity in response to OVA is also regulated by ASK1.

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Role of the CC− Chemokine Receptor CCR9 in the Regulation of Inflammatory Process During Allergic Airway Inflammation

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Background: Airway eosinophilia and Th2 lymphocytes-recruitment to the lung are one of the main pathological features of asthma. It is clear now that the axis chemokine/chemokine receptors have a role in controlling leukocyte recruitment and development of the inflammatory process observed in asthma. Although it has been reported that CCR9 receptor is expressed in asthmatic patients, it is not known whether CCR9 may have a regulatory role of the development of this disease. Our aim was to analyze the expression of CCR9 in a murine model of allergic airway inflammation (WT) and compared to CCR9 deficient (KO) mice.

Methods: Four groups of 6 to 8 weeks female CCR9-deficient mice were sensitized by intraperitoneal injections of 10 micrograms of ovalbumin (OVA) in alum (ALOH3) diluted in PBS, on days 1 and 8 of the established sensitization protocol. Aerosolised OVA was administered (1% in PBS) on days 15, 20 and 34. 24 hours after last OVA exposure, mice were sacrificed and bronchoalveolar lavage (BAL) fluid and cells were obtained. Total and differential cell numbers were obtained and characterized cell subpopulations by FACS analysis. Cytokine/chemokine levels were quantified by ELISA and qRT-PCR respectively.

Results: Total cell numbers in BAL were no significantly different between WT and KO mice. Interestingly, reduction in the numbers of eosinophils was observed in CCR9 KO mice compared to WT mice. Histological analysis of lung tissue demonstrated a reduction in the granulocytic population (eosinophils) in CCR9 KO mice. Analysis of cell subpopulations by FACS demonstrated that CD4+ lymphocytes were significantly reduced but CD8+ and CD19+ lymphocytes numbers were not different between WT and CCR9-deficient mice. A population of CCR9+ Gr1+ was altered in KO mice and it correlated with cytological analysis. Furthermore, histological analysis demonstrated alteration in mucus production in allergic airway in CCR9 deficient mice, accompanied with a no-significant reduction of OVA-specific anti-IgE antibodies in serum at the time of analysis.

Conclusions: Altogether, these results suggest that CCR9 may be involved in recruitment of granulocytic cell subpopulation into the allergic airways and have an impact in the regulation of the chronic inflammatory process.

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Serum IL6 and Soluble IL6R Are Correlated With Lung Function in Non-Hispanic Whites with Asthma

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Background: Interleukin 6 (IL6) belongs to a family of cytokines with both pro- and anti-inflammatory properties. The functional relationship between IL6 signaling and airway disease has not be well characterized; however, IL6 expression is increased during lung inflammation and injury. In this study, serum IL6 and soluble IL6R levels were assessed in non-Hispanic whites with asthma from the Severe Asthma Research Program. Correlations between serum IL6 and IL6R levels, lung function, phenotypic asthma clusters, and asthma severity were evaluated.

Methods: Serum IL6 and soluble IL6R was measured in 149 subjects with mild to severe asthma. Serum sIL6R levels were measured using the sIL-6R DuoSet (R&D Systems, Minneapolis, MN) ELISA kit and reported as ng/ml. Serum IL6 measurements were determined using the IL-6 ELISA kit (R&D Systems, Minneapolis, MN) and reported as pg/ml. Serum IL6 and sIL6R measurements were transformed to normalize distribution. The continuous variables analyzed included: % predicted FEV_1 [ppFEV$_1$], % predicted FVC [ppFVC], and FEV_1/FVC. Serum samples were collected at Wake Forest. Phenotypic asthma clusters were derived as previously described (*Am J Respir Crit Care Med*. 2010;181:315–323).

Results: Elevated serum IL6 was associated with lower ppFEV$_1$ ($P = 0.02$) and lower ppFVC ($P = 0.003$), while elevated serum soluble IL6R was associated with lower ppFEV$_1$ ($P = 0.02$) and lower ppFVC ($P = 0.008$). Increasing trends in serum IL6 were observed in atopic asthma Clusters 2 and 4 and the later onset fixed airways obstruction Cluster 5. The highest IL6 serum levels were observed in Cluster 3 characterized has having late onset asthma and elevated BMI. Serum IL6 levels were elevated in subjects with severe asthma (log IL6 = 0.33; N = 25) compared to subjects with mild/moderate asthma (log IL6 = 0.16; N = 69).

Conclusions: Serum IL6 and sIL6R levels are elevated in non-Hispanic white asthma subjects with lower lung function. Serum IL6 and sIL6R are potentially important biomarkers that may distinguish between non-severe and severe asthma and between atopic asthma Clusters.

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Heterogeneity of Allergen Epitope-specific CD4+ T Cells Responses: Steps Toward Optimal Composition for Peptide-based Immunotherapy

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Background: Peptide-based allergen immunotherapy is a promising alternative to conventional allergy vaccine. However, the optimal composition of such vaccines, in terms of the choice of the appropriate peptides, has remained unclear. Knowledge of the epitope-specific T cell responses to allergens can give important information on the pathogenesis and regulation of allergic inflammation. In this study we sought to identify candidate allergen-epitopes that can be used to improve peptide-based allergen immunotherapy.

Methods: Tetramer Guided Epitope Mapping was first used to identify CD4+ T cell epitopes for group 1 and group 5 timothy grass pollen allergens. MHC class II tetramer technology was then used in an ex vivo approach to assess the grass pollen-specific CD4+ T cell responses in allergic and non-allergic individuals. The frequency, surface marker phenotype and cytokine profile of these cells were directly analysed by flow cytometry.

Results: CD4+ T cell responses to Timothy grass allergens are directed to a broad range of epitopes characterized by defined immunodominance hierarchy patterns. We observed heterogeneity of phenotype within the allergen-specific CD4+ T cells that depends on the epitope for which the cells are specific. T cell epitopes associated with production of IL-10 or IFN-g are recognized at low frequencies in both allergic and healthy individuals. In contrast, allergy-associated epitopes are only recognized in allergic individuals by high frequency, terminally differentiated allergen-specific CD4+ T cells, which are susceptible to deletion by repeated stimulation with high doses of antigen. Allergen-specific immunotherapy caused significant changes in the epitopes hierarchy of the grass pollen allergen-specific memory CD4 T cell pool.

Conclusions: The ability to evaluate epitope-specific T cell responses to allergens can give important information on the pathogenesis and regulation of allergic inflammation and could be of great use in designing peptide-based allergy vaccination strategies. Some epitopes may play a prominent role in

driving a protective response, while others may directly impair the pathogenic response.

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The Association between Mast Cells and Remodelling of the Small Airways in Chronic Asthma

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Background: Repeated airway challenges with House Dust Mite (HDM) allergen results in marked remodelling and mast cell hyperplasia in the small airways of allergic sheep. We now examine mast cell activation and its association with small airway function and remodelling in these sheep using a novel segmental allergen challenge approach.

Methods: Eight allergic sheep received weekly intra-lung challenges of HDM to the left caudal lung for 24 weeks. Eight separate sheep were used as controls. Baseline lung function was assessed in the left caudal segments of all sheep throughout the challenge regime using a wedged-bronchoscope technique. Airway tissue was collected from challenged segments from all sheep, 7 days following the final intra-lung challenge. The airway tissues were immunohistochemically labelled for chymase-mast cells and eosinophils. Collagen and airway smooth muscle content were assessed on Masson's Trichrome stained sections.

Results: Resting lung function in the left caudal segment is elevated in 4 out of 8 sheep at the end of the repeated allergen challenge regime. Chymase mast cell density was significantly increased in the small bronchial walls of the HDM-challenged group compared to the control group (52 ± 8 vs 8 ± 4; $P < 0.01$). There were significant increases in bronchial collagen deposition in HDM-exposed segments compared to control segments (0.17 ± 0.02 vs 0.11 ± 0.02 mm^2/BM, $P < 0.05$). A correlation analysis of individual sheep data showed that there was a trend for a direct association between the increases in bronchial collagen deposition and the density of chymase-labelled mast cells ($rs = 0.71$, $P = 0.088$). Eosinophil density in the small bronchial walls of HDM-challenged segments was also significantly increased compared to controls (65 ± 19 vs 11 ± 3 cells/mm^2, $P < 0.001$), but not associated with collagen content. The bronchial smooth muscle content was not different between HDM-challenged and unexposed control segments.

Conclusions: The results show that repeated exposure to allergen results in significant increases in density of chymase-labelled mast cells, together with increased levels of collagen content in the small airways. The segmental challenge protocol allows for a novel approach to characterise the progressive remodelling events occurring in the small airways in chronic asthma.

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Creation of a Humanized Model for Respiratory Allergy Using a Human Mugwort-specificT-Cell Receptor and HLA-DR1

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Background: Currently, T cell receptor (TCR) transgenic (tg) mice with a murine TCR specific for chicken ovalbumin in the context of a murine restriction element (I-A^d) are frequently used in allergy research to investigate T helper cell differentiation and allergy treatment in vivo.

Methods: We here aimed to generate double tg mice expressing a human TCR specific for the immuno-dominant epitope of the major mugwort (*Artemisia vulgaris)* pollen allergen Art v 1 in the context of the human restriction element HLA-DR1 to provide a valid model for studying allergy development and treatment in vivo. To obtain high expression levels the allergen-specific human TCR variable sequences were chimerized with murine TCR constant sequences. Resulting transgenes were cloned into the pT_{cass} vector system and thus put under the transcriptional control of the natural TCR alpha and beta promotor/enhancer elements. Allergen-specific TCR tg founder mice were cross-bread with HLA-DR1$^+$ B10.M-DR1$^{dlAb1\text{-}Ea}$ mice.

Results: Immunophenotyping of double tg TCR/HLA-DR1 mice revealed clear-cut expression of the Art v 1-specific TRBV18 chain on peripheral blood CD3$^+$ T lymphocytes and HLA-DR1 expression on CD14$^+$ monocytes and B220$^+$ B lymphocytes. In vitro, splenocytes from TCR/HLA-DR1 double tg mice but not of HLA-DR1 single tg mice or wt mice specifically proliferated upon incubation with the human-relevant immuno-dominant Art v $1_{25\ to\ 36}$ peptide or whole Art v 1 protein. No proliferation was observed upon incubation with control peptides or proteins. Allergen-specific cellular proliferation is accompanied by the production of a balanced cytokine milieu including IFN-gamma, IL-2, IL-4, IL-6, IL-13 and IL-17 (>50 pg/mL per 2×10^5 splenocytes). No cytokine secretion was evident upon incubation of splenocytes with a control peptide or medium alone. Importantly, double tg mice are proficient to mount both IgG2a and IgG1, IgE responses when i.p. immunized with antigen plus alum.

Conclusions: A fully humanized allergy model, in which all components of the allergen-specific synapse are well-defined enables to analyze the relevant T-cell dependent (and independent) pathways by which allergic diseases can be influenced in vivo and will provide important insights into the pathophysiology of allergic diseases and their possible cure in the future.

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Eosinophils Enhance Airway Smooth Muscle Cell Proliferation Via the Release of Cysteinyl Leukotrines

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Background: Asthma is a chronic inflammatory disorder of the lung airways that is associated with airway remodeling and hyperresponsiveness. Its is well documented that the smooth muscle mass in asthmatic airways is increased due to hypertrophy and hyperplasia of the ASM cells. Moreover, eosinophils have been proposed in different studies to play a major role in airway remodeling. Here, we hypothesized that eosinophils modulate the airways through enhancing ASM cell proliferation. The aim of this study is to examine the effect of eosinophils on ASM cell proliferation using eosinophils isolated from asthmatic and normal control subjects.

Methods: Eosinophils were isolated from peripheral blood of 6 mild asthmatics and 6 normal control subjects. ASM cells were incubated with eosinophils or eosinophil membranes and ASM proliferation was estimated using thymidine incorporation. The mRNA expression of extracellular matrix (ECM) in ASM cells was measured using quantitative real-time PCR. The effect of eosinophil-derived proliferative cytokines on ASM cells was determined using neutralizing antibodies. The role of eosinophil derived Cysteinyl Leukotrienes in enhancing ASM was also investigated.

Results: Co-culture with eosinophils significantly increased ASM cell proliferation. However, there was no significant difference in ASM proliferation following incubation with eosinophils from asthmatic versus normal control subjects. Co-culture with eosinophil membranes had no effect on ASM proliferation. Moreover, there was no significant change in the mRNA

expression of ECM proteins in ASM cells following co-culture with eosinophils when compared with medium alone. Interestingly, blocking the activity of cysteinyl Leukotries using antagonists inhibited eosinophil-derived ASM proliferation.
Conclusions: Eosinophils enhances the proliferation of ASM cells. This role of eosinophil does not seem to depend on ASM derived ECM proteins nor on Eosinophil derived TGF-β or TNF-α. Eosinophil seems to induce ASM proliferation via the secretion of Cysteinyl Leukotrienes.

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Colour Change in the Human Histamine Wheal; a Sign of Desensitized Histamine Vasoconstrictory Receptors

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Background: The aim was to find the cause and consequences of a colour change in histamine wheals found after ordinary histamine skin prick tests (SPTs) (10 mg/mL). A rapid change to a darker red colour from the 18th and to the 20th minute has been demonstrated by using a digital image-processing technique called LYYN and ImageJ to yield numerical values.[1]
Methods: Repeated histamine SPTs in the middle of the site for earlier performed histamine SPTs in humans. Calculations of the sizes of photographed wheals. Histamine solutions perfused in isolated rabbit ears.
Results: Histamine SPT performed 90 minutes or 6 hours apart from initial histamine SPTs evoked a ring of wheal peripherally around the site of the initial wheal or no wheal at all. The initial wheals had at those times disappeared. Histamine perfusion in isolated rabbit ears indicated first vasoconstriction and after a mean of 17 minutes vasodilatation in post-capillary vessels despite continued histamine perfusion.
Conclusions: The results indicate that total desensitization of histamine-1 receptors in the wheal is the cause of the colour change in human histamine SPTs and that such desensitization lasts long time. If histamine released at allergen provocations also evokes such a long-lasting desensitization and post-capillary vasodilatation it opens new aspects on vascular events in allergic reactions.

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Involvement of the Hypoxia-Inducible Factor-1 Transcription Complex in the Inflammatory Responses of Human Mast Cells and Basophils

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Background: We recently found that hypoxia-inducible factor 1 (HIF-1) plays a crucial role in the pro-allergic functions of human basophils by transcriptional control of energy metabolism via glycolysis as well as directly triggering the expression of the angiogenic cytokine vascular endothelial growth factor (VEGF). Here, we investigated whether there is an overarching principle of HIF-1 involvement in controlling the synthesis of angiogenic and inflammatory cytokines from various human effector cells stimulated by IgE-dependent or innate immune triggers.
Methods: LAD2 human mast cells,[1] primary human basophils, and THP-1 human myeloid cells were used for investigations of FcεRI and Toll-like receptor (TLR) ligand-induced responses. Quantitative real-time PCR, Western blot analysis, ELISA, fluorometry, luminometry and fluorescence microscopy were used to run the assays.
Results: In contrast to basophils, LAD2 mast cells expressed high background levels of HIF-1α, which was largely independent of the effects of stem cell factor (SCF).[2] Both mast cells and basophils expressed TLR2 and 4, albeit weakly compared to THP-1 cells. Cytokine production in mast cells following TLR ligand stimulation was markedly reduced by HIF-1α knock-down in LAD2 mast cells. In contrast, although HIF-1 is involved in IgE-mediated IL-4 secretion from basophils, it was not clearly induced by the TLR2 ligand PGN.
Conclusions: HIF-1α accumulation is fundamentally important for sustaining human allergic effector cell survival and function. This transcription complex facilitates the generation of both pro-angiogenic and inflammatory cytokines in mast cells but has a differential role in basophil stimulation comparing IgE-dependent triggering with innate immune stimuli.

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PATHO-BIOLOGY OF NASAL POLYPS

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Mutiplex Analyses of Cytokine and Chemokine Release From the Cultured Fibroblast of Nasal Polyp: the Effect of IL-17A

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Background: Nasal polyps of chronic rhinosinusitis (CRS) are characterized by epithelial damage, basement membrane thickness and subepithelial fibrosis. The fibroblast, one of the main cell types making up nasal polyps, is thought to be a target cell of various cytokines. The role of IL-17A in immunoresponse in the nasal poly fibroblast has not yet elucidated.
Methods: Subcultured fibroblasts were established from human polyp biopsy tissues in addition to normal mucosal membranes of sphenoid sinuses (controls).
Results: The IL-17A receptor was expressed at similar levels in all 3 groups. Simultaneous quantification of 27 kinds of cytokines and chemokines in culture supernatants was performed with a human multiplex cytokine assay system. In the eosinophilic group, basal secretion levels of IL-6 were significantly higher than those in the control and non-Eo groups. Basal secretion of MCP-1 in both the non-eosinophilic and eosinophilic groups was also higher than that of the control group. Both IL-9 and G-CSF secretion were remarkably enhanced by IL-17A stimulation in all 3 groups. The receptor-mediated response by IL-17A significantly upregulated IL-6 release alone in the non-eosinophilic and eosinophilic groups as compared with the control group. Only the basic FGF secretion was decreased by stimulation of IL-17A in all groups.
Conclusions: Our results demonstrate for the first time a potentially enhanced secretion of IL-6 and MCP-1 from nasal polyp fibroblasts, and a remarkable upregulation of IL-9 and G-CSF from nasal fibroblasts by IL-17A stimulation, which might contribute to nasal polyp formation and airway remodeling.

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Expression of Chemokine Receptors CCR1, CCR3, CCR4, CCR5, CCR8 and CXCR3 in Human Nasal Polyps (NP); Comparison With NP From Allergic Patients With Aspirin Intolerance

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Background: Inflammatory processes play an important role in development of nasal polyps (NP), but the etiology and to a great degree also the pathogenesis of NP is not known. Several cytokines and chemokines such as eotaxin, IL-3, IL-5, IL-6, IL-8, RANTES may influence development of NP

by regulation of migration, activation and survival of the chronic inflammatory cellular infiltrate.

Methods: In this study we investigated expression of selected chemokine receptors in human NP and non-affected human nasal mucosa and carried out a comparison with NP from allergic patients with aspirin intolerance. Biopsies of NP were obtained from 20 patients and 4 patients with NP and aspirin intolerance. Mucosal biopsy specimens of the inferior turbinate were obtained from 12 NP patients and 4 healthy controls. Using indirect imunohistochemistry, frozen tissue sections were stained for CCR1, CCR3, CCR4, CCR5, CCR8 and CXCR3.

Results: Numbers of infiltrating cells expressing CCR3, CCR8 and to a lesser extend also CCR1 were significantly higher in biopsies of NP compared to healthy nasal mucosa. Only a slight increase in CCR5 expressing cells was detected in NP compared to nasal mucosa. No differences in expression of CCR4 and CXCR3 were found in NP compared to nasal mucosa. There were no significant differences between NP of patients with or without aspirin intolerance.

Conclusions: We documented an increased expression of selected chemokine receptors within the cellular infiltrate of NP that may play an important part in the inflammatory pathogenesis of NP.

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Characterization of 2 Epithelial Cell Air-Liquid Interface (ALI) Culture Models for Human Healthy Nasal Mucosa and Nasal Polyps

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Background: Primary human airway epithelial cells, when submerged in culture, undergo a dedifferentiation with loss of many features of the in vivo airway epithelium. However, when cultured in an air-liquid interface (ALI), cells develop a well-differentiated, polarized, and pseudostratified epithelium. The aim of the current study was to characterize the mucociliary differentiation of human nasal mucosa and polyp epithelial cells cultured using an ALI system.

Methods: Nasal mucosa (NM, n = 3) and nasal polyps (NP, n = 3) were obtained from patients undergoing nasal corrective surgery and endoscopic sinus surgery, respectively. Epithelial cells were obtained from the explant method, and differentiated in ALI culture during 28 days. Cultures were studied at different time points (0, 7, 14, 21, and 28 days): tissue ultrastructure by scanning electron microscopy (SEM) and transmission electron microscopy (TEM); mucous (MUC5AC, MUC5B) and serous (lactoferrin) cell secretion by ELISA; and cytokeratin 18 (epithelial marker), β-tubulin IV (cilia marker), MUC5AC (goblet cell marker), and p63 (basal cell marker) expression by immunocytochemistry.

Results: In both NM and NP ALI cultures and at days 14 and 28, a pseudostratified epithelium with ciliated, mucus-secreting and basal cells was observed, and expression of cytokeratin 18, b-tubulin IV, MUC5AC and p63 was detected. In NP cultures, both MUC5AC (day 14: 2.2 ± 0.1-folds; day 28: 3.6-fold ± 0.7-fold) and MUC5B (day 14: 3.2-fold ± 0.6-fold; day 28: 3.1-fold ± 1-fold) increased over time compared to day 0 ($P < 0.05$). In NM cultures, only MUC5B (day 14: 3.9-fold ± 0.9-fold; day 28: 3.4-fold ± 0.4-fold; $P < 0.05$) but not MUC5AC increased over time compared to day 0 ($P < 0.05$). Secretion of lactoferrin was present but showed no changes over time in either NM or NP ALI cultures.

Conclusions: Epithelial cell ALI cultures provide a well-differentiated human nasal mucosa and polyp tissues that may be used as an in vitro model to study mucin regulation, inflammatory mechanisms of upper airways, and their regulation by antiinflammatory drugs.

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Corticosteroid Rreatment Reduces Tissue Eosinophilia and the Expression of Matrix Metalloproteinases (MMP-1, MMP-2, MMP-7, MMP-9) and Their Tissue Inhibitor (TIMP-1) in Nasal Polyps

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Background: Matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) may play an important role in both inflammation and remodeling of nasal polyposis. The aim of the current study was to compare the expression levels of MMPs and TIMP-1 between nasal mucosa and polyps, and to evaluate the effect of corticosteroid treatment in their expression in nasal polyps.

Methods: Nasal mucosa (NM, n = 12) were obtained from patients undergoing nasal corrective surgery while nasal polyp biopsies (NP, n = 33) were obtained from patients before (week 0) and after 2 (week 2) and 12 (week 12) weeks of corticoisteroid treatment (oral prednisone for 2 weeks and intranasal budesonide for 12 weeks). Matrix metalloproteases (MMP-1, MMP-2, MMP-7, MMP-9) and tissue inhibitor of metalloproteinases type 1 (TIMP-1) expression was evaluated by immunohistochemistry in tissue structural cells (epithelium, glands, vessels) and eosinophils.

Results: MMP and TIMP-1 expression were found in the epithelium, glands, vessels (in both NM and NP), and in eosinophils (only in NP). Expression of MMP-7 in epithelium (34% of tissues) and MMP-9 (19%) in glands was lower ($P < 0.05$) in NP than in NM (78 and 67%, respectively). Corticoisteroid treatment reduced tissue eosinophilia (Eos/5 fields) at week 2 (8.0 ± 2.9, $P = 0.001$) and week 12 (10.0 ± 2.3, $P < 0.003$) compared to week 0 (25.5 ± 8.4); and also decreased the expression of MMPs and TIMP-1 in eosinophils at week 2 and week 12 compared to week 0 ($P < 0.05$). In the epithelium, corticosteroids increased MMP-7 and TIMP-1 at week 2 and week 12, while decreased MMP-9 at week 12 ($P < 0.05$). In vessels, corticosteroids increased MMP-9 at week 2 and decreased MMP-1 at week 12 ($P < 0.05$). No effects were found in the glands.

Conclusions: Treatment of nasal polyposis with corticosteroids reduces both tissue eosinophilia and MMP expression in eosinophils while modifying the expression of remodeling markers in nasal polyp structural cells.

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Expression and Localization of CYSLT2 Receptor in Human Nasal Mucosa

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Background: We have previously reported the localization of CysLT1 receptor by using immunohistochemistry and in situ hybridization (Shirasaki H et al. *Clin Exp Allergy*. 2002;32:1007–1012).

Methods: To clarify the expression of CysLT2 receptor in human nasal mucosa, we investigated CysLT2 receptor mRNA expression and its protein

localization in human nasal mucosa, by polymerase chain reaction (PCR) and immunohistochemistry.Human turbinates were obtained after turbinectomy from 6 patients with nasal obstruction refractory to medical therapy. Total RNA was isolated from human nasal mucosa, and CysLT2 receptor mRNA was detected in these tissues by using reverse transcriptase-PCR analysis. To identify the cells expressing CysLT2 receptor protein, double immunostaining was performed using anti-CysLT2 receptor antibody and anti-CD31 (endothelial cell) antibody.

Results: Reverse transcriptase-PCR analysis of total nasal RNA demonstrated the expression of CysLT2 receptor mRNA. The immunohistochemical studies revealed that anti-CysLT2 receptor antibody mainly labeled blood vessels.

Conclusions: The results suggest a primary role for CysLT2 receptor as the vascular responses in upper respiratory tract.

PRIMARY IMMUNODEFICIENCY

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Mycobacterial Infections in cChildren With Chronic Granulomatous Disease

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Background: Chronic granulomatous disease (CGD) is a rare primary immunodeficiency caused by inborn errors of the phagocyte NADPH oxidase activity. Affected patients display severe, recurrent and multiple infections from the first year of life onwards, in particular caused by various pyogenic bacteria and fungi. Mycobacterial infections have more rarely been reported in these patients.

Methods: We examined the clinical features of mycobacterial disease in 59 CGD patients from 52 kindreds in 16 countries of 4 continents. Tuberculosis or BCG adverse reactions were identified by culture, staining, biopsy, polymerase chain reaction (PCR), and/or by a combination of clinical criteria with response to treatment. CGD was confirmed by NBT, DHR, cytochrome C reduction assay, or a combination of these. Genetic diagnosis was achieved by means of immunoblotting, flow cytometry, PCR and automated gene sequencing.

Results: We found that mycobacterial infections are fairly common in patients with CGD living in certain regions of the world. Twenty-four patients (45%) had tuberculosis, 43 (80%) presented with adverse effects shortly after Bacille Calmette-Guérin (BCG) vaccination; 12 of the patients (21%) had both tuberculosis infection and BCG adverse reactions. Most patients (93%) had also pyogenic and fungal infections; 7% of them, however, presented solely with mycobacterial disease. Most cases were one-time self-limited localized infections, but recurrence (13 patients, 20%), disseminated disease (18 patients, 30%) and even death (5 patients, 8%) were observed. A recurrent finding was early age of presentation for BCG reaction, with a median of 3 months of age; BCG disease was the first manifestation of immunodeficiency in 60% of these patients.

Conclusions: Our study offers compelling evidence for an important susceptibility to mycobacterial diseases in patients with CGD, more easily noticed in countries where tuberculosis is endemic and BCG vaccine mandatory. BCG adverse reactions should raise the suspicion of CGD.

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Increased Pro-Inflammatory Cytokine Production After Lipopolysaccharide Stimulation in Patients with X-linked Agammaglobulinemia

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Background: X-linked agammaglobulinemia (XLA) is characterized by impaired B-cell differentiation caused by mutations in Bruton's tyrosine kinase (Btk) gen. Btk is expressed in myeloid cells and recent evidence support that it participates in Toll like receptor signaling, but results regarding its rol in XLA patients are contradictories.

Objective: To evaluate lipopolysaccharide (LPS)-induced pro-inflammatory cytokine response in peripheral blood mononuclear cells (PBMC) from XLA patients.

Methods: Thirteen patients with XLA were included in the study. PBMC LPS-induced TNF-α, IL-1β, IL-6, and IL-10 production was determined by ELISA and compared with that obtained from matched healthy controls. Cytokine production was correlated with the severity of the mutation, affected domain and clinical characteristics.

Results: In response to LPS, PBMC from XLA patients produced significantly higher amounts of pro-inflammatory cytokines and IL-10 compared with controls and this production is not influenced by the neither severity of mutation or the affected domain. PBMC from patients with a history of more hospital admissions before diagnosis and patients with lower expression of Btk in monocytes produced higher levels of TNF-α and IL-1β, respectively. PBMC from patients with lower IgA levels showed a higher production of TNF-α and IL-1β. Less severe (punctual) mutations in Btk gene were associated with higher IgG levels at diagnosis.

Conclusions: Our results demonstrated a predominantly inflammatory response in XLA patients after LPS stimuli and suggest a TLR signaling dysregulation in absence of Btk. This response may be influenced by environmental factors.

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Hypogammaglobulinemia in a Boy: Consider Also X-linked Lymphoproliferative Disease

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Background: X-linked lymphoproliferative disease (XLP) is a primary immunodeficiency presenting with a variety of clinical manifestations, the most common being dysgammaglobulinemia and B-cell lymphoma. The first gene causing XLP, when defective, was termed *SH2D1A* or *SAP* for signaling lymphocyte activation molecule (SLAM)-associated protein. The absence of *SH2D1A* leads to an overwhelming and uncontrolled TH1- shifted cytotoxic immune response, which might, at least in part, explain the severe clinical picture. A second gene, XIAP (X-linked inhibitor of apoptosis), was later identified.

Methods: An 8 year old Mexican boy was admitted in June 2008 for bronchopneumonia, with no previous history of recurrent or severe infections. He had a family history of a brother deceased at 7 years from fulminate hepatitis, who was diagnosed with agammaglobulinemia. A laboratory evaluation for primary immunodeficiency was made, including serum immunoglobulins: IgG 30 mg/dL, IgA <5 mg/dL IgM 8.6 mg/dL; and flow

citometry for lymphocyte subpopulations: CD3+ 2590 mm^3 (56%) CD4+ 1004 mm^3 (42%), CD8+ 1267 mm^3(53%) CD16/56 171mm^3 (41%) CD19+ 1493 mm^3 (35%). The patient was started on monthly intravenous gammaglobulin (IVIG) therapy. He was admitted in December 2008 with fever and severe abdominal pain; an exploratory laparotomy revealed a rectal-sigmoid tumor. The biopsy reported an atypical Burkitt lymphoma (Immunophenotype "B": Bcl 2+, CD10+) with surgical margins negative for malignancy. Bone marrow aspirate and biopsy were negative for malignancy. In February 2009, management with chemotherapy was started with the diagnosis of Burkitt's lymphoma stage III. Patient received 6 courses of chemotherapy with complete response to induction; for consolidation, 4 doses of rituximab were given. PCR amplification and direct automated sequencing by the Sanger method was performed in both genes known to be responsible for XLP in chromosome X.

Results: A hemizygous splice-site deletion in *SAP* was found, in intron 2: c.187_201+10del25, which deletes exon 2 splice donor site, and is predicted to result in the skipping of exon 2, and thus in a truncated, nonfunctional protein. XIAP was also sequenced and no mutation was found.

Conclusions: Final diagnosis: XLP.The patient is currently in the program for hematopoietic stem-cell transplantation.

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Transmission Pattern and Carriers Identification in Male Patients with Chronic Granulomatous Disease

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Background: To identify the pattern of transmission in male CGD patients and the CGD X-linked carriers among their female relatives.

Methods: Through the 123 Dihydrorodamine assay in blood samples of the female relatives of CGD patients we identified a positive bimodal pattern in each woman. A positive bimodal pattern reveled 2 points, first, that the pattern of transmission in the patients was X-linked, second, that the woman was a carrier.

Results: We analyzed 59 female relatives of 18 male CGD patients. Among 14 CGD males we found 28 women whit a positive bimodal pattern; in 4 male CGD patients we did not find any relative with a positive bimodal pattern.

Conclusions: 123 DHR assay is an accessible and quickly technique to determinate the pattern of transmission and the carriers in X-CGD. However a negative finding of a bimodal pattern in the female relatives suggests an autosomal recessive pattern but it does not rule out an X-CDD because of a novo mutation or non-random (skewed) X-chromosome inactivation. Definitive diagnosis is based on candidate gene sequencing.

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Genetic Association Study of the IgE Immunodeficiency in Mexican Population

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Background: Primary immunodeficiencies (PID) are genetic diseases in which one or multiple components of the immune system, including cells (i.e. B cells, T cells, natural killer cells, phagocytes, complement components) or molecules (cytokines, chemokines, etc) are affected, leading to a low capacity to eliminate microorganisms and a high susceptibility to infection diseases. Most of the PID are multifactorial entities were the environmental and multiple genetic factor are involved. The single nucleotide polymorphisms (SNPs) analysis in case and control groups has been increasing the knowledge of the etiopathogenesis of several diseases and the opportunity to identify molecular markers useful in the clinical diagnosis.

Methods: We performed a case control study including 19 pediatric patients with IgE deficiency (5 U/mL), and 180 healthy controls. 25 SNPs distributed in the *IL-13*, *IL-10*, *IL-5*, *IL4*, *FCER1B*, *INF* γ, *GM-CSF*, *STAT* 3, *GATA* 3 and *TIK*-2 were analyzed. Genotyping was performed using sondas TaqMan. Hardy-Weinberg Equilibrium (HWE) and statistical significance were evaluated using FINETTI and STATCAL software.

Results: All genotypes, both in cases and controls were in HWE. We documented statistically significant differences in the distribution of the SNPs located in *IL-4* rs4986964, $P = 0.018$, OR = 14.74, *IL-4R*, rs18005010, $P = 0.018$, OR = 2.22, *FCER-1B*, *rs556917*, $P = 0.00001$, OR = 16.9, *GM-CSF, STAT-3* and *GATA-3* genes: *GMFCS-130* ($P = 4986964$, OR = 0.22), *STAT-3* rs2293152 ($P = 5.06 \times 10^{-9}$, OR = 6.18), *GATA-3* rs2229360 ($P = 0.005$, OR = 13.52). The highest difference was found in the T allele of rs556917, which was more frequent in cases than controls (42.1 and 1.5%, respectively, $P = 0.00001$ OR = 16.907, 95% CI, 5.02-54.93). Interestingly, the C allele of 4986964 (*IL-4*) increased significantly in homozygote genotype (C: OR = 14.74, 95% CI, 2.38-91.234, $P = 0.018$ to CC OR = 29.4, 95% CI, 1.154-749.32, $P = 0.002$).

Conclusions: Our results suggest that SNPs located in the genes involved in the IgE production are risk genetic factor to IgE immunodeficiency. Increasing of the sample size is currently to get solid conclusions.

RESPIRATORY INFECTIONS

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Inhibition of AKT Kinase Activity Decreases Replication of Human Respiratory Syncytial Virus

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Background: Human Respiratory Syncytial Virus (RSV) is a leading cause of pediatric pulmonary disease and severe RSV infection predisposes to wheezing later in life. RSV infection has also been shown to be an environmental trigger for asthma. We are investigating whether targeting host factors important for RSV infection is a viable antiviral strategy. Lowering viral burden through these therapies will result in decreased severity of infection and may also prevent the occurrence of pathologic sequelae.

Methods: Inhibition of AKT by chemical inhibitors, siRNA, or dominant-negative mutants, was tested for activity against RSV replication in cultured cells. We examined the effect of viral protein expression on Akt activation and downstream signal transduction by Western blot and promoter assay. In addition, we examined the effect of Akt on specific viral processes (entry, macromolecular synthesis, and assembly) and proteins both in vitro and in RSV-infected cells, using kinase assays, Western blotting, and qRT-PCR.

Results: We found that AKT inhibition decreases RSV protein expression and viral titers. Expression of RSV NS2 protein activates AKT, leading to NFkB-dependent transcription, and inhibition of AKT blocks this effect. Activated AKT also phosphorylates RSV P protein at a specific site. Interestingly, AKT inhibitors that target the pleckstrin homology (PH) domain of AKT showed decreased efficacy against RSV compared to those that target AKT kinase activity.

Conclusions: Inhibition of AKT can effectively decrease RSV replication in culture, likely by decreasing P phosphorylation and thus viral protein transcription and expression. Activation of AKT during RSV infection likely involves the NS2 protein and does not depend on the PH domain of AKT. AKT inhibitors have been found to be safe and efficacious in clinical trials for a number of different cancers; thus, AKT inhibition may be a potential therapeutic treatment for severe RSV infection.

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Abnormal Immune Response Against Respiratory Pathogens in Olympic Athletes

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Background: Viruses and bacteria are important contributors to asthma exacerbations. Exercise at competitive level is believed to increase susceptibility to respiratory infections. The study aimed at investigation of the anti-infectious immune response in athletes in the context of exercise intensity, atopy and allergic diseases.

Methods: Questionnaire data were obtained from 219 Polish athletes (median age 26 years) preparing for Beijing Olympic Games during the multicenter study within the GA^{2}LEN project (WP 2.8.2). Allergy Questionnaire for Athletes (AQUA) (Bonini et al 2009) was used to obtain data about symptoms and exercise pattern. Athletes were evaluated by allergist. Control group consisted of 77 healthy never-smokers (median age 29 years) not performing sport at competitive level. Serum IgG against parainfluenza virus 1,2 and 3 (PIV), respiratory syncytial virus (RSV), adenovirus and *Mycoplasma pneumoniae* were determined by ELISA.

Results: Percentage of athletes with positive serological testing was lower than percentage of HC in case of PIV ($P < 0.0003$), RSV ($P = 0.01$) and *M. pneumoniae* ($P = 0.01$). Analysis of IgG only in subjects with positive testing showed lower anti-PIV IgG levels in non-atopic athletes compared to HC ($P < 0.001$) and atopic athletes ($P < 0.01$) (median 66.0 vs 104.8 and 88.1 U/mL). In contrast, higher adenovirus IgG titres were found in atopic and non-atopic athletes as compared to HC (52.3 and 48.5 vs 36.6 EIU, $P < 0.001$). Positive anti-PIV serology test was most frequent in athletes with allergic rhinitis compared to asthmatic and healthy athletes (78.3 vs 50.0 and 46.8%; $P = 0.002$). For PIV and *M. pneumoniae* the difference was also seen when atopic and non-atopic athletes were compared separately with HC. Positive RSV serology was more frequent in atopic versus non-atopic athletes (76.3 vs 60.8%, $P = 0.03$) and in HC versus non-atopic athletes (84.4 vs 60.8%, $P = 0.001$) but no significant difference between atopic athletes and HC was seen. Positive RSV serology was associated with atopy (OR 2.89; 95% CI, 1.34-6.23; $P = 0.007$). No differences were observed with regard to exercise pattern (endurance vs non-endurance).

Conclusions: Competitive sport at Olympic level may be associated with altered immune response against respiratory pathogens. For some agents this response may be affected by the atopic status.

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The Immune Response Against Respiratory Pathogens in Patients with Chronic Rhinosinusitis/Nasal Polyps and Asthma with or without Sensitivity to Aspirin

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Background: Viral and bacterial infections can modulate the ongoing inflammation in both upper and lower airways of patients with chronic rhinosinusitis with nasal polyps (CRS/NP) and asthma. It was not clear if the protective immune response to pathogens may differ depending on the disease severity.Object: To compare serum IgG immune response against respiratory pathogens in patients with chronic airway disease (CRS/NP and asthma) with and without sensitivity to aspirin, and to refer the sensitization to severity of chronic rhinosinusitis.

Methods: We recruited 73 patients with CRS/NP and asthma with (43 patients) and without (30 patients) hypersensitivity to aspirin. The extent of mucosal hypertrophy in paranasal sinuses was assessed by CT scans and the sense of smell was valuated with "sniffing smell" test. Serum IgG immunoglobulin levels against respiratory pathogens: Respiratory Syncytial Virus (RSV), Adenowirus (ADV), Parainfluenza virus (PIV) and *Mycoplasma pneumoniae* were determined by ELISA.

Results: Patients with ASA-hypersensitivity had history of significantly more nasal polypectomies ($P = 0.002$), lower smell test score ($P = 0.03$) and higher mean paranasal CT score ($P = 0.03$) as compared to ASA-tolerant patients, reflecting higher severity of the upper airway disease. The percentage of positive serological testing to respiratory pathogens was very high in the whole group of patients with CRS/NP and asthma (RSV, 95.8%; ADV, 95.9%; PIV, 84.9% and *Mycoplasma pneumonieae*, 100% patients) without any difference between ASA-sensitive and ASA-tolerant subjects. Patients with ASA-sensitivity had significantly lower concentrations of PIV- specific IgG (mean 188.67 ± 34.46 U/mL versus 207.56 ± 30.036 U/mL; $P < 0.04$) as compared to ASA-tolerant subjects. There was a significant trend ($P < 0.048$) for lower PIV–specific IgG concentrations with increased number of polypectomies. No correlation of IgG immunoglobulin concentrations for other pathogens with the number of polypectomies, paranasal sinuses CT score or presences of smell were observed.

Conclusions: Patients with CRS/NP and asthma had high frequency of IgG immunoglobulin against common respiratory pathogens. Serum IgG immune response to paramyxoviruses may be related to the recurrence of nasal polyps and the presence of aspirin sensitivity.

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Immunologic and Clinical Characteristics of Pediatric Population with Human Influenza Virus H1N1 Infection in Federal Hospital of Mexico

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Mexico 2009 faced the H1N1VI influenza pandemic, a complex immunologic and clinical host response, whose defense mechanisms have yet to be identified. Lack of information on clinical an immunological features in pediatric population with H1N1VI, delay detection of patients at risk of contracting it. This study aims to identify specific immunologic and/or clinical features of pediatric patients with H1N1VI in a federal Hospital in Mexico City.

Methods: Single-center, observational, non-experimental, prospective trail from September to October 2009, for pediatric patients arriving to Emergency room of Juarez Hospital, with suspicion of H1N1VI, needing to be younger than 17 years, and agree and sign the consent form by tutor. Samples obtained were peripheral blood, and pharyngeal exudate. From blood LS, Cytokine levels, and routine measurements (CBC, BCH) were investigated; the pharyngeal sample underwent PCR study to viral genetic material. Complementary studies such as arterial blood gases or Torax radiography were realized as needed.

Results: 32 patients participated. PCR results confirmed 18 cases (56%), 1 patient resulted positive for SII. The average age was 9 years old; 12 (67%) were female, and 6 (33%) were male. The mean amount of days from symptom onset to receiving medical attention was 2.5 days. Main symptoms and signs were fever, malaise, cough, rhinorrhea, and headache. Associated risk factors included malnutrition and tobacco exposure. It was demonstrated

an elevation of IL-8, followed by IL-6, IL-12 and IL-10. Blood analysis proved no significant findings, though cases of neutrophilia and leukopenia were detected.
Conclusions: Limited resources, restricted participation from all the possible H1N1VI patients, thus biasing results due to small sample size; however, the obtained data is consistent with existing reports, nevertheless the information is not enough to establish standardized recommendations. Further collaboration among centers, is needed to identify features that can prompt H1N1VI early identification and prevention in pediatric population.
SII = Stational Influenza infection; LS = lymphocyte subpoulations; CBC = Complete blood count, BCH (blood chemistry) = Includes levels of glucose, urea, creatinine, ALT, AST, CPK CPK-MB, amylase and lipase.

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Evaluation of Various Forms of Sinusitis Using Bone Spect

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Background: Computed tomography (CT), a standard diagnostic technique used to evaluate the extent of the sinus disease, fails to show bone involvement in patients with sinusitis. Bone scintigraphy is the gold standard procedure for detecting the bone involvement. Osteitis may be one of the reasons for discrepancies between extent of the disease as evaluated by CT and symptom scores. The aim of the study was to determine whether or not nuclear scintigraphy is useful in the diagnosis and management of acute, complicated acute and chronic sinusitis.
Methods: Forty patients with sinusitis were involved (9 acute, 4 complicated acute, 27 chronic sinusitis). 20 of the chronic sinusitis patients were with nasal polyps. All patients were evaluated with CT and SPECT (Single-photon emission tomography). 99Technetium-methylenediphosphate (99Tc-MDP) was administered for scintigraphic examination of the skull. Abnormal patterns of increased radionuclide uptake were identified and subjectively described. The mucosal involvement of sinusitis graded on Lund-Mackay Scale (LMS) was compared to degree of bone involvement evaluated by SPECT.
Results: While, SPECT uptakes were negative (mean uptake index is less than about 2.5) in acute sinusitis, it's highly positive (mean uptake index is more than about 4) in complicated acute sinusitis. In group of chronic sinusitis, a positive correlation between the SPECT uptakes and LMS grade was found ($P < 0.05$).
Conclusions: In our view, the bone involvement as evaluated by SPECT correlates with the stage of chronic sinusitis. Poorer subjective response was observed in patients with positive SPECT. The clinical value of scintigraphy, is limited to special indications.

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Rhinitis: Where is the Biofilm?

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Background: Several ultramicroscopic studies have confirmed the presence of biofilms in ENT diseases, such as chronic rhinosinusitis, nasal polyposis or adenoid hypertrophy. Recently, it has been reported that light microscopy nasal cytology can identify biofilms, which appear as cyan-stained "Infectious Spots."
Methods: Subjects suffering from a wide spectrum of nasal disorders, after a detailed clinical history and ENT examination, underwent nasal fibroendoscopy, skin prick test, rhinomanometry and nasal cytology.
Results: 1410 subjects were studied. The infectious spot was present in 107 of them (7.6%) patients; this percentage reached 55.4% in 193 patients who had clear cytologic signs of infectious rhinitis. Biofilms were largely more frequent in patients with adenoid hypertrophy (57.4%), followed by nasal polyposis (24%), chronic rhinosinusitis (9.5%) and non-allergic "cellular" rhinitis (7.6%). Nasal cytology was normal in the remaining patients, with no infectous spot detectable. Statistical analysis showed that nasal resistances were significantly higher in presence of biofilms in patients affected by adenoid hypertrophy ($P = 0.003$), nasal polyposis ($P < 0.001$), chronic rhinosinusitis ($P = 0.018$) and septal deviation ($P = 0.001$).
Conclusions: The results demonstrate that biofilms are not present only in infectious rhinopathies, but also in inflammatory and/or immune-mediateddiseases. Biofilms were more frequent in patients with higher degree of nasal obstruction as assessed by nasal endoscopy (grade III and IV adenoids and stage-3 polyposis) and rhinomanometry. Nasal cytology, by allowing the identification of biofilms represents a useful diagnostic tool with promising research implications.

RHINITIS TREATMENT 1

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A 6-Week Study of the Efficacy and Safety of Ciclesonide Hydrofluoroalkane Nasal Aerosol in the Relief of Nasal Symptoms of Perennial Allergic Rhinitis

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Background: Ciclesonide hydrofluoroalkane nasal aerosol (CIC-HFA) is currently in development as a potential treatment for allergic rhinitis. The objective of this study was to determine the efficacy and safety of CIC-HFA compared to placebo in subjects with perennial allergic rhinitis (PAR).
Methods: Subjects ≥12 years of age with a ≥2 year history of PAR were randomized in a placebo-controlled, double-blind, parallel group, multicenter study to CIC-HFA 74 μg (N = 298), CIC-HFA 148 μg (N = 505), or placebo (N = 307) QD AM for 26 weeks. Subject-reported change from baseline in the average of AM and PM reflective total nasal symptom score (rTNSS) and instantaneous total nasal symptom score (iTNSS) averaged over the first 6 weeks of treatment period were key endpoints and were calculated as a sum of the 4 individual nasal symptoms of congestion, runny nose, sneezing, and nasal itching each on a scale of 0 (no signs/symptoms evident) to 3 (severe symptoms). Change from baseline in the individual reflective and instantaneous nasal symptom scores over the first 6 weeks of treatment period were also evaluated. Treatment-emergent adverse events (TEAEs) were assessed throughout the study.
Results: CIC-HFA 74 μg and CIC-HFA 148 μg doses demonstrated a statistically significant improvement in rTNSS (LS mean change 0.70 & 0.54 respectively, $P \leq 0.001$ for both), iTNSS (LS mean change 0.58 & 0.42 respectively, $P \leq 0.05$ for both) and improvements in individual reflective and instantaneous nasal symptoms ($P \leq 0.05$ for all, unadjusted for multiplicity) at 6 weeks from baseline. The overall incidence of TEAEs was low and comparable between the CIC treatment groups and placebo. The most frequently reported TEAEs (≥2% of subjects in any treatment group) were nausea, headache, sinus headache, cough, upper respiratory tract infection, instillation site discomfort, nasal discomfort, nasopharyngitis, sinusitis, oropharyngeal pain, and epistaxis.
Conclusions: In this study, once-daily treatment with CIC-HFA 74μg or CIC-HFA 148μg demonstrated statistically significant improvements in the nasal symptoms of PAR. Both active treatments were well tolerated.

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3-D Visualization of the Anti-Obstructive Effect of Levocetirizine

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Background: Our investigation aimed to visualize the 3-D spatial distribution of nasal cavity mucosal swelling under levocetirizine prophylactic treatment on exposure to allergens. This study made use of standard rhinologic diagnostics such as rhinomanometry and acoustic rhinometry, as well as 24 hours rhinometry and magnetic resonance imaging (MRI).

Methods: A suitable test subject with a history of allergic rhinitis was identified during the symptom-free interval after the pollen season when she showed signs of "minimal persistent inflammation," consisting of pronounced reaction to nasal challenge with allergens. Provocation with birch pollen caused moderate symptoms of allergic rhinitis. Nasal provocation tests were performed before and after 2 and 5 weeks of treatment with levocetirizine 5 mg OD. Long-term rhinometry was carried out to detect the progress of the nasal cycle and relative flow variances over 24 hours. Flexible air tubes required for this new procedure made it possible to quantify relative pressure changes. High resolution MRI was also used to capture, visualize, and process the geometrical data of the nasal cavity immediately before and after the challenge tests. Based upon the MRI data, we computed the nasal airflow using a computational fluid dynamics (CFD) nasal model to visualize intranasal pressure and flow. Rhinomanometry and acoustic rhinometry were performed to validate the results.

Results: After 36 days of treatment with levocetirizine, a 16% improvement in the nasal flow relative to baseline and an increase by 3.4 cm^3 of the total nasal baseline volume were documented as compared to the allergen challenge of the untreated case. 3-D images illustrated that treatment inhibited the allergen provocation effects on nasal airflow and normalised nasal flow velocity and pressure, including in the olfactory region.

Conclusions: Besides improving the nasal airflow to an almost normal pattern, levocetirizine also helps prevents the patient from having an allergic response, even 24 hours after last drug intake. Furthermore, it can improve olfaction by restoring airflow to the olfactory region.

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Levels of F VCAM and ICAM in Patients With Allergic Rhino-Conjunctivitis and H1 Antihistamines

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Background: Soluble intercellular adhesion molecule-1 (sICAM-1) and soluble vascular adhesion molecule-1 (sVCAM-1) play and important role in eosinophilic inflammation in allergic rhino-conjunctivitis (ARC). ICAM-1 and VCAM-1 have been identified as key molecules in allergic inflammatory diseases and in a few studies there was an increased value of those molecules in patients with allergic rhinitis. Treatment with H1 antihistamines is known to improve symptoms in allergic rhinitis and in vitro reduces the levels of adhesion molecules.

Object: To evaluate serum levels of sICAM-1 and sVCAM-1 in pts with ARC to grass pollen and the response to different antihistamines.

Methods: 50 pts with allergic rhino-conjunctivitis to grass pollen were evaluated regarding levels of sICAM-1 and sVCAM-1. The serum sICAM-1 and sVCAM-1 were evaluated during pollen season before and after antihistaminic terapy. Quantikine R&D System was used. Normal mean values in healthy volunteers were 208 ng/mL for sICAM and 557 ng/mL for sVCAM-1. 54% of pts were women and 88% from urban area.

Results: Mean levels of sICAM-1 and sVCAM-1 were elevated before therapy of the pts compared with mean values in healthy subjects (235 ng/mL vs 208 ng/mL for sICAM and 966 ng/mL vs 557 ng/mL for sVCAM. 42% of pts received desloratadine therapy and 58% of them received levocetirizine. In both treated groups' levels of sICAM-1 and sVCAM-1 increased after one month of antihistaminic therapy but no statistical significance. Was obtained: in desloratadine group sICAM-1 ($P = 0.066$) and sVCAM-1 ($P = 0.096$); in levocetirizine group sICAM-1 ($P = 0.681$) and sVCAM-1 ($P = 0.4060$. Patients with high levels of sICAM-1 and sVCAM-1 at the tended to have increased sICAM-1 and sVCAM-1 levels at one month ($P = 0.000$). No statistical difference was obtained between the 2 treated groups after one month regarding the levels of sICAM-1 and sVCAM-1.

Conclusions: In patients with allergic rhino-conjunctivitis to grass pollen levels of sICAM-1 and sVCAM-1 are higher than in healthy subjects. Levels of sICAM-1 and sVCAM-1 in serum tend to increase during pollen season despite antihistaminic therapy.

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Once Daily Intranasal Fluticasone Furoate Decreases Daytime Sleepiness and Improves Cognitive Performance in Symptomatic Seasonal Allergic Rhinitis

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Background: Seasonal Allergic Rhinitis (SAR) can cause Daytime Sleepiness (DS) and impair Cognitive Performance (CP); therapy of SAR can improve these symptoms.

Methods: We evaluated the effects of Fluticasone Furoate (FF) 110 mcg given in the morning on Nasal Symptons (NS), DS, an CP in adults with symptomatic SAR during an allergy season. 40 adults ages 18 to 55 with a history of SAR and positive allergy skin tests to seasonal allergens. After a 1 week placebo (PL) run in, they randomly received either FF (21) or identical appearing PL (19) for 2 weeks. They recorded nasal sympton score (NSS) and Eppworth daytime sleepiness score (EDDS) for the 21 days, performed a TOVA test (Computerized test of cognitive performance) at day 7 and 21, and completed a nocturnal rhinoconjunctivitis quality of life questionnaire (NRQLQ) at days 7, 14 and 21. Average daily weekly scores, comparing week 1 baseline to week 3 were used for evaluation of NSS, and EDSS/TOVA omissions, commissions and reaction times were compared, as was NRQLQ (day 7 and day 21).

Results: Mean total NSS (TNSS) instantaneous decreased from BL 12.88 to 10.84 in the FF group, and increased in PL group from 12.64 to 13.74 (P diff = .04). TNSS reflective decreased from 12.99 to 11.20 (FF group) and increased from 13.53 to 14.02 in PL. (P diff = NS). The mean EDSS decreased from 13.83 to 10.76 ($P = 0.03$) in FF group, and from 13.29 to 12.80 with PL (P dif = NS). TOVA commissin errors decreased by 7.13 (FF) vs 1.4 (PL) (P dif = 0.05). Omission increased in PL from 2.33 to 5.75, and 1.54 to 1.58 (FF) (P diff = NS). Reaction time increased in both groups 363 to 391 milliseconds (FF), 387 to 412 milliseconds (P = NS). The FF reported a minimally clinical importance difference of 0.5 or greater on all 16 questions of NRQLQ, the PL group only in 10. (Mean change 1.01 (FF) vs .63 (PL) $P = 0.004$).

Conclusions: Treatment of symptomatic SAR with intranasal FF decrease daytime sleepiness, less noturnal sleep disturbance, and improved cognitive performance.

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International Survey on the Management of Allergic Rhinitis by Physicians and Patients (ISMAR). Physicians' View

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Background: Allergic Rhinitis (AR) is a worldwide spread disease and has an important impact on social life, sleep quality (SQ), school and work productivity and huge direct costs. ISMAR was designed to identify attitudes and medical trends among physicians managing AR in different parts of the world. This study presents the physicians´ view and attitudes.

Methods: ISMAR is an international, multicenter, non-interventional and cross-sectional study conducted in adults and children (≥6 years) with physicians-diagnosed AR from 11 countries (Egypt, Mexico, Brazil, Colombia, Guatemala, Iran, Venezuela, Argentina, Israel, Kuwait, United Arab Emirates). Doctors from 4 specialties were required in each country: (i) GPs/Family doctors/internists, (ii) pediatricians, (iii) allergologists/pulmonologists, and (iv) ENT. They were invited to participate in the study from master lists of physicians attending patients with AR in their respective countries and answered the Doctor Questionnaire that included questions about guidelines awareness, relevant AR symptoms, and preference for prescribing medication, among others.

Results: Two hundred and thirty four physicians participated in the study. Most of them were awared about ARIA (82.5%), GINA (71.4%). They followed guidelines recommandations to classify patients severity (84.2%) and for choosing the treatment accordingly (84.6%). Key symptoms to make AR diagnosis were: congestion (84.8%), sneezing (79.1%), anterior watery rhinorrhea (75.9%). SQ and AR severity were assessed mainly by clinical history (97.1% and 98%). The main reasons to prescribe medication were: symptom severity/frequency (97.9%), drug efficacy (85.9%) and safety (76.5%). Other less relevant raisons were: personal experience (65%), cost (55.1%) and frequency of dosages (54.7%). The preferred medications were oral antihistamines (OH1A) and intranasal corticosteroids (INC) [5 in a 0–5 scale]. Other treatments (oral decongestants, leukotriene antagonists, SCIT/SLIT), among others were considered as second level in preference.

Conclusions: Guidelines are well known and useful to physicians. Clinical history was the main way to evaluate the patient's sleep quality, classification, severity and election of treatment. Objective measures for assessment were scarcely used. OH1A and INC were the most widely recommended treatment for AR and were considered effective and safe.

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International Survey on the Management of Allergic Rhinitis by Physicians and Patients (ISMAR): The Patients' View

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Background: Allergic Rhinitis (AR) is a worldwide spread illness and has an important impact on social life, sleep quality, school and work productivity and huge direct and indirect costs. Patient preference is becoming an important aspect in medical care. ISMAR was designed as the first-over global survey to identify differences in attitudes and preference in patients and physicians about AR. This study shows the patient's view.

Methods: ISMAR is an international, multicenter, non-interventional and cross-sectional study conducted in adults and children (≥ 6 years) with physician diagnosis- AR of at least 1 year of duration. Physicians recruited consecutive patients to whom the ISMAR questionnaire was administered. The study data collection was performed during a single visit. Other 2 additional documents (the investigator's questionnaire and Case Record Form) were also filled in.

Results: A total of 2776 patients from 11 countries were evaluated. Patient's demographics were the following: mean age 31 years, gender (F) 54%; urban residence (86.1%), suburban (6.6%) and rural (4.9%). The main co-morbidities were: sinusitis (50%), asthma (33%), conjunctivitis (36%), otitis (13%) and nasal polyps (11%). Nasal symptoms were associated to house-dust mites (84%), moulds (33%) animal dander (31%) and pollens (41%) exposure. At least one current treatment was received in 91%, and recommendation to avoid allergens or irritants in 93% of patients. 80% the patients had received oral anti-H1 antihistamines (OH1A), 66% intranasal corticosteroids (INC), 63% oral/intranasal decongestants and 14% sub-cutaneous specific immunotherapy (SCIT). The patients' preference was the following: oral route of administration, 51%; and intranasal route 28%. The patients' preference mediations were: OH1A, 76%; INC, 49%; and SCIT 12%. Main factors affecting treatment compliances were cost (32%), fear of Adverse Events reported (18%) and frequency of doses (34%). Taking into account patients' education, 85% of them received oral explanation on disease and only 51% written indications.

Conclusions: OH1A and INC were the most widely used treatments for rhinitis and were considered safe and effective. The majority of patients preferred the oral route. Written educational material given to patients is scarce. These might be taken into account to enhance treatment adherence and outcomes.

RHINITIS TREATMENT 2

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Patterns of Initiation and Adherence to de novo Allergen-Specific Immunotherapy Among Adults and Children with Newly-Diagnosed Allergic Rhinitis: Findings From Research Jointly Funded by the AAAAI AND ACAAI

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Background: Although allergen-specific immunotherapy (SIT) is the only disease-modifying treatment currently available for allergic rhinitis (AR), few potentially appropriate United States patients initiate or sufficiently adhere to treatment.[1,2] We compared SIT initiation and adherence between AR-diagnosed children and adults.

Methods: Selected were child (age <18 years) and adult (age ≥18 years) Florida Medicaid enrollees (1997–2009) with newly-diagnosed AR (no AR claim within 1 year preceding the first identified AR diagnosis) who received de novo SIT (no SIT preceding the first AR diagnosis), had ≥4 years of follow-up from first AR diagnosis, and 6 months of follow-up from first SIT administration. T tests, Wilcoxon signed-rank tests, and chi-squares compared differences between children and adults.

Results: Overall, 8% (330,993/4,193,986) of children and 3% (105,380/3,330,245) of adults received ≥1 AR diagnosis ($P < 0.0001$). Among these, 2,913 children and 1,332 adults met study criteria. Adults were 3.6 times more likely than children to immediately initiate SIT (ie on the date of their first AR diagnosis) (OR 3.6, 95 % CI, 3.1-4.2, $P < 0.0001$); children were twice as likely as adults to receive SIT ≥1 year from the first AR diagnosis (OR 2.2, 95 % CI, 1.9-2.6, $P < 0.0001$). The median number of SIT administrations was 13 for children and 5 for adults ($P < 0.0001$). Fourteen percent of children and 20% of adults discontinued SIT after 1 administration; 33% of children and 52% of adults discontinued after 5 administrations. Adults were 1.6 and 2.3 times more likely than children to discontinue SIT following 1 only administration (OR 1.6, 95% CI, 1.3-1.9, $P < 0.0001$) and 5 administrations (OR 2.3, 95% CI, 2.0-2.6, $P < 0.0001$), respectively.

Conclusions: Although adults were significantly more likely to immediately initiate SIT, they were also significantly more likely to discontinue treatment within the first 5 administrations. These preliminary findings may guide development of future patient-specific interventions to improve SIT access and continuity of care.

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Effect of Simvastatin on Transforming Growth Factor BETA-1-Induced Myofibroblast Differentiation and Collagen Production in Nasal Polyp-Derived Fibroblasts

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Background: Statins are the most commonly prescribed drugs for the treatment of hypercholesterolemia. Statins exert not only lipid-lowering but also other cellular effects, including anti-fibrotic properties. The purposes of this study were to determine the effect of simvastatin on Transforming growth factor (TGF)-β1-induced myofibroblast differentiation and collagen production in nasal polyp-derived fibroblasts (NPDFs) and to verify the mechanism of the effect of simvastatin in TGF-β1-induced myofibroblast differentiation in NPDFs.

Methods: NPDFs were pre-treated with simvastatin with or without mevalonate or Y-27643 for 2 hours prior to induction by TGF-β1. The expression of α-smooth muscle actin (SMA) and collagen type IV mRNA was determined by a reverse transcription-polymerase chain reaction, and the expression of α-SMA protein was determined by immunofluoescent cytochemical staining. Total soluble collagen production was analyzed by the SirCol collagen dye-binding assay. Phosphorylation of Smad 2/3 was evaluated by Western blot analysis.

Results: In TGF-β1-induced NPDFs, simvastatin significantly inhibited the expressions of α-SMA and collagen type IV mRNA and reduced α-SMA and collagen protein levels. Pre-treatment with mevalonate reversed the effect of simvastatin. The expression of α-SMA mRNA and protein was significantly decreased by pre-treatment with Y-27632. The TGF-β1-induced expression of pSmad 2/3 protein was notably decreased by pre-treatment with simvastatin.

Conclusions: We showed that simvastatin inhibits TGF-β1-induced myofibroblast differentiation (expression of α-SMA) and collagen production in NPDFs and Rho/Rock and TGF-β/Smad signaling is involved as an underlying mechanism. The results of our study suggest that simvastatin is a possible candidate for the suppression of nasal polyp formation.

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A 26-Week Study Evaluating the Safety and Efficacy of Ciclesonide Hydrofluoralkane Nasal Aerosol in Subjects With Perennial Allergic Rhinitis

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Background: Ciclesonide hydrofluoroalkane nasal aerosol (CIC-HFA) is currently in development as a potential treatment for allergic rhinitis. The objective of this study was to determine the long-term safety and efficacy of CIC-HFA compared to placebo in subjects with perennial allergic rhinitis (PAR).

Methods: Subjects ≥12 years of age with a ≥2 year history of PAR were randomized in a placebo-controlled, double-blind, parallel group, multicenter study to CIC-HFA 74 μg (N = 298), CIC-HFA 148 μg (N = 505), or placebo (N = 307) QD AM for 26 weeks. Subject-reported change from baseline in reflective total nasal symptom score (rTNSS) and instantaneous total nasal symptom score (iTNSS) averaged every 2 weeks over the 26 weeks of the treatment period were secondary endpoints and were calculated as a sum of the individual nasal symptoms of congestion, runny nose, sneezing, and nasal itching. Change from baseline in the individual reflective and instantaneous nasal symptom scores averaged every 2 weeks over the 26 weeks of treatment period were also evaluated. Treatment-emergent adverse events (TEAEs) were assessed throughout the study.

Results: CIC-HFA 74 μg and CIC-HFA 148 μg doses demonstrated improvement in rTNSS (LS mean change 0.65 & 0.52 respectively, $P \leq 0.01$ for both), iTNSS (LS mean change 0.51 & 0.42 respectively, $P \leq 0.05$ for both), and improvements in the individual reflective and instantaneous nasal symptoms ($P \leq 0.05$ for all except instantaneous sneezing for the CIC-HFA 74 μg dose) at 26 weeks from baseline. *P*-values were unadjusted for multiplicity. The overall incidence of TEAEs was comparable between the CIC-HFA treatment groups and placebo. The most frequently reported TEAEs (≥5% of subjects in any treatment group) were headache, nasopharyngitis, upper respiratory tract infections, viral upper respiratory tract infections, sinusitis, and epistaxis.

Conclusions: In this study, once-daily treatment with CIC-HFA 74 μg or CIC-HFA 148 μg demonstrated improvements in the nasal symptoms of PAR. Both active treatments were well tolerated.

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Omalizumab Improves Asthma but not Nasal Symptoms in Japanese Patients With Severe Allergic Asthma and Rhinitis

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Background: There is evidence that humanized monoclonal antibody against IgE (Omalizumab) is effective in severe allergic asthma. In this study, we examined the effectiveness of omalizumab on asthma and nasal symptoms in Japanese patients with severe allergic asthma and rhinitis.

Methods: An open-label study that enrolled 7 patients with both severe allergic asthma and rhinitis who visited Allergy Center, Saitama Medical University was performed. All patients presented uncontrolled asthma despite medication including high-dose inhalational corticosteroids, long-acting beta2-agonist, leukotriene receptor antagonist, theophylline, and oral predonisolone. Omalizumab was added on their treatments and symptoms score using Asthma Contol Test (ACT), peak expiratory flow rate (PEFR), exhaled nitric oxide (eNO), sputum eosinophils and nasal symptoms were evaluated before and 12 to 16 weeks after omalizumab.

Results: Omalizumab significantly improved ACT scores especially dose of rescue use of short-acting beta2-agonist ($P < 0.05$) and PEFR ($P < 0.05$). Furthermore, omalizumab significantly decreased exhaled both eNO ($P < 0.05$) and the percentage of eosinophils in induced sputum. On the other hand, nasal symptoms were not change following induction of omalizumab.

Conclusions: Clinical effectiveness of omalizumab was confirmed in Japanese population of severe allergic asthma, but not rhinitis. The therapeutic potency of omalizumab on asthma likely involves anti-inflammatory properties such as decreasing eNO or airway eosinophilia.

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Economic Evaluation of Grass Tablets for Immunotherapy (oralair) Compared to Placebo in Adults and Children in Italy

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Background: Specific immunotherapy is based on the regular administration over time of a maintenance dose of allergen extracts to allergic patients in order to modify the immune response, thus achieving a decrease in symptoms/drug intake and an improvement in quality of life, possibly on the long-term. Grass pollen tablet, Oralair (Stallergenes, Antony Cedex, France), were developed and registered for rhinoconjunctivitis allergy induced by grass pollen. There is sufficient evidence for the clinical efficacy of the product, but pharmaco-economy data are lacking.

Methods: An economic analysis, using a rescue medication adjusted score (AASS) was performed, based on the available registration trials—to assess the magnitude of Oralair effect if patients had not taken any rescue medication. In the present study the results of an adult and a pediatric study are pooled together with economic data in order to perform a cost–effectiveness analysis from the third party payer perspective. Medical visits, diagnostic exams, skin prick test, and drugs were valorized in euros according to the National tariffs and the standard drug prices in the Italian setting. The estimated ROC also enabled us to quantify the effectiveness in terms of Quality Adjusted Life Years (QALY). A decision tree was structured in order to model the possible outcomes and costs, according to a low, moderate and high AASS in adults and pediatric patients. A probabilistic sensitivity analysis was finally conducted to test the robustness of the results as well as the consistency with an assumed cost effectiveness threshold of euros 30.000/QALY.

Results: The results showed a relative difference of 1.84 in favor of the active treatment versus placebo in absolute value in adult study and of 1.64 in pediatric study. The results also show how the Oralair administration costs 1024 euro/QALY with high and moderate AASS. Including also the loss of productivity the incremental cost-effectiveness ratio (ICER) in adults is 700 euro/QALY. The 95% of the simulation performed by sensitivity analysis shows an ICER below the threshold of 30.000 euro/QALY.

Conclusions: In conclusion our results show that Oralair grass tablet is a cost effective strategy in adults and pediatric patients with moderate and severe AASS.

SUBLINGUAL IMMUNOTHERAPY 1

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The Post-Treatment Efficacy of House Dust Mite Sublingual Allergen Immunotherapy Tablets in Adults With Allergic Rhinitis

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Background: The efficacy and safety of 2 doses of sublingual allergen immunotherapy house dust mite (HDM) tablets administered for 12 months were demonstrated in a randomized, double-blind, placebo-controlled study of adults suffering from HDM-related allergic rhinitis. Here we report the efficacy during the 12-month, treatment-free, follow-up period.

Methods: Of the 509 patients randomized, 412 were included in the year 2 full analysis set (500 IR = 132, 300 IR = 134, Placebo = 146). The primary efficacy variable was the Average Adjusted Symptom Score (AAdSS, scale 0–12) an average of the daily score based on the severity of 4 rhinitis symptoms (sneezing, rhinorrhea, nasal pruritus and nasal congestion) and adjusted for rescue medication usage. The AAdSS was analyzed, at the end of the post-treatment period, using an ANCOVA and at 3, 6, 8 and 12 months after treatment cessation in a secondary analysis, using repeated measures ANCOVA.

Results: At the end of the post-treatment period, the 500 IR group showed a significant improvement in AAdSS vs. placebo ($P = 0.021$) with a LS Means difference of –0.70 (95% CI [–1.29, –0.11]), corresponding to –19.1%. The LS Means difference of –0.62 (95% CI [–1.20, –0.05]) between the 300 IR and placebo groups was also significant ($P = 0.034$), corresponding to –17.0%. The difference between the active treatment groups was not statistically significant. Eight months after treatment cessation, which corresponds to the autumn peak in HDM, the relative LS mean difference was –20.9% ($P = 0.0079$) for the 500 IR and was –25.5% ($P = 0.0011$) for the 300 IR group.

Conclusions: During the 12-month post-treatment period, house dust mite sublingual immunotherapy tablets at doses of 500 IR and 300 IR provided sustained symptom relief, demonstrating their efficacy after treatment cessation.

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Efficacy of Immnunotherapy with an Oral Bacterial Lysate and Vitamin C in the Primary Prevention of Acute Respiratory Tract Infections in Children

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Background: Airway infections are of great importance worldwide and nearly half of the pediatric consultations in industrialized countries are caused by respiratory tract infections (RTIs). Acute respiratory tract infections (ARTIs) are among the main causes of morbidity and mortality in children and recurrent infections of the respiratory tract are the most frequent cause of pharmacotherapy in pediatric practice. The aim of this study was to evaluate the efficacy and tolerability of immunotherapy with oral bacterial lysates + vitamin C in the prevention of ARTIs in children.

Methods: 109 children with ages between 4 and 16 years with frequent respiratory tract infections (2–5 infections the previous winter) were evaluated. Participants were randomly allocated in 2 groups: 52 patients (mean age 6.8 ± 2.9 years; 20 males 32 females) received no preventive therapy (NPT group) and 57 (mean age 9.0 ± 3.3 years; males 36 females 21) received immunotherapy with oral bacterial lysates + vitamin C (VC group) at the recommended dosage. Patients were followed up for 6 months, including the administration period. Primary end points were the type and number of ARTIs. Secondary end points (after the infection occured) included: time to clinical cure, severity of infection, absenteeism from school due to an ARTI, number of antibiotic courses or other drugs prescribed, and duration of concomitant drug treatment.

Results: There were significant differences between groups in the cumulative number of acute infectious episodes: 170 in NPT group (141 upper ARTIs, 29 lower ARTI, and 26 otitis episodes) vs 55 in VC group (50 upper ARTIs, 5 lower ARTI and 4 otitis episodes). Patients in the NPT group received 127 antibiotic courses compared to 28 in the VC group ($P < 0.0001$). Patients in the NPT group had 475 days of absenteeism from school compared to 100 days in the VC group ($P < 0.0001$). No adverse events related to the trial medications were reported.

Conclusions: Immunotherapy with oral bacterial lysates and vitamin C appears to be very effective in the prevention of infectious episodes in pediatric patients with frequent respiratory tract infections. Future studies are needed to further explore the role of oral bacteroial lysates in ARTIs prevention.

SUBLINGUAL IMMUNOTHERAPY 2

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Therapeutic Effect and Safety of the Sublingual Immunotherapy With Tropical House Dust Mite Allergen Vaccines in Asthmatic Cuban Adult Patients

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Background: Subcutaneous injection route (SCIT) is burdened with the risk of severe adverse events; therefore, sublingual immunotherapy (SLIT) is being increasingly investigated. The efficacy of SLIT in asthma has been reviewed in a Cochrane meta-analysis. Allergic sensitization to Dermatophagoides pteronyssinus (Dp), Dermatophagoides siboney (Ds) and Blomia tropicalis (Bt) is strongly linked to respiratory allergy and asthma in Cuba (3). These last 2 species are relevant in tropical countries or even only in the Caribbean region (4). Nevertheless, well conducted clinical studies of immunotherapy with standardized allergen vaccines of these particular species are very scarce.

Objective: This study was conducted to assess the therapeutic effect and safety of allergen therapeutic vaccines of Dermatophagoides pteronyssinus, Dermatophagoides siboney and Blomia tropicalis House-Dust mites (VALERGEN, BIOCEN, Cuba) by sublingual route, in asthmatic patients.

Methods: Three Double-Blind Placebo-Controlled clinical trials were performed in 40 patients each, showing asthmatic symptoms and positive predominant Skin Prick Test (SPT) to each mite, respectively. Half of subjects were randomized to active group. Treatment consisted of sublingual drops with increasing daily doses for 3 weeks and maintenance doses (2000 BU) twice a week until 12 months.

Results: Therapeutic effect was assessed after 6 and 12 months using symptoms/medication diary cards, peak expiratory flow (PEF) measures and skin sensitivity to investigated mites. Adverse reactions were classified using the World Allergy Organization scale. The treatment reduced significantly ($P < 0.01$) clinical symptoms (38%, 95% CI, 33-44) and medication intake (26%, 95% CI, 21-32) with respect to placebo. The skin sensitivity to the allergens decreased also significantly ($P < 0.01$). The allergen amount needed to induce a positive SPT increased 52-fold. PEF variability decreased also significantly ($P < 0.05$). The treatment was considered effective in 77% of patients. A major advantage as compared to subcutaneous route was a remarked lower frequency of adverse effects. Local reactions were noted only in 0.43% of administrations. No systemic reactions were observed.

Conclusions: The results indicate that sublingual immunotherapy using allergen vaccines of tropical mite species is effective and safe in mite-sensitive asthmatic patients.

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Candidate for Response Monitoring or Prognostic Biomarkers in Two-Year Sublingual Immunotherapy for Japanese Cedar Pollinosis

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Background: The aims of this study were to clarify the therapeutic effects and potential prognostic and response monitoring biomarkers of sublingual immunotherapy (SLIT) in a randomized, double-blind, placebo-controlled (DBPC) clinical trial for Japanese cedar (*Cryptomeria japonica*) pollinosis.

Methods: This trial was carried out for 2 pollinosis seasons in 2007 and 2008 in double-blind status. Carry-over therapeutic effects were analyzed in 2009 in single-blind manner. We recruited 130 participants diagnosed as Japanese cedar pollinosis based on clinical history and the presence of IgE specific to Japanese cedar pollen of at least class 2. Cytokine production from peripheral blood mononuclear cells and increase of iTregs were determined before and after 2008 pollen season. Clinical symptoms were estimated using a pollinosis-symptom diary and Quality-of-Life (QOL) questionnaire in 2007, 2008, and 2009 peak pollen seasons.

Results: The final sample size included 88 subjects for on-treat analysis (SLIT; N = 51, placebo; N = 37) for the DBPC study, and a total of 63 patients completed a pollinosis-symptom diary for the single-blind follow-up study (SLIT; N = 36, placebo; N = 27). The symptom-medication score (SMS) in the SLIT group did not differ from that in the placebo group in the 2007 peak pollen season. However, the average SMS in 2008 and 2009 peak pollen seasons were significantly ameliorated in the SLIT group compared with the placebo group (4.2 vs. 5.3, $P = 0.02$ in 2008; 3.5 vs. 4.5, $P = 0.03$ in 2009). The ratio of Japanese cedar pollen-specific IgE to total IgE before treatment correlated with the SMS in the SLIT group in 2008. The patients with increased Cry j 1-specific iTregs in the SLIT group showed a significant reduction of QOL and QOL-symptom scores compared with those in the placebo group.

Conclusions: SLIT can ameliorate the clinical symptoms after 2-year administration with standardized extract of Japanese cedar pollen and the amelioration was observed for at least one pollen season after the treatment. The ratio of specific IgE to total IgE can be used as a prognostic biomarker and the increase of Cry j 1-specific iTregs may serve as a biomarker to monitor the clinical response to SLIT.

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Efficacy and Safety of 300IR 5-Grass Pollen Sublingual Allergen Immunotherapy Tablets in us Adults With Grass-Pollen Allergic Rhinoconjunctivitis

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Background: Clinical trials in adult and pediatric populations in Europe have demonstrated the efficacy and safety of 300IR 5-grass pollen sublingual allergen immunotherapy (SLIT) tablets for the treatment of grass pollen-induced rhinoconjunctivitis. Here we present an assessment of this treatment in the US.

Methods: 473 grass pollen allergic adults with a Retrospective Rhinoconjunctivitis Total Symptom Score of >12 (scale 0–18) during the previous pollen season were randomized in a DBPC study to receive 300IR SLIT tablet or placebo, once-daily starting 4 months before and continuing through the 2009 grass pollen season. The primary efficacy variable was the daily Combined Score (CS, scale 0–3), which integrates symptoms and rescue medication use. Secondary efficacy assessments included the daily Rhinoconjunctivitis Total Symptom Score (RTSS), daily Adjusted Symptom Score

(AdSS, which adjusts the RTSS for rescue medication use) and daily individual rhinoconjunctivitis symptom scores. The primary efficacy endpoint, the daily CS during the pollen period while on treatment, was analyzed using a repeated measures ANCOVA model, as were the above secondary efficacy endpoints. The safety of the treatment was documented by means of adverse event reporting, laboratory data and physical examination findings.

Results: The 300IR group showed a relative improvement in daily CS versus placebo of -28.2% (relative difference in LS Means, 95%, CI [–43.4%; –13.0%], $P = 0.0003$). Significant improvements in RTSS and AdSS were consistent with previous European studies. There were also significant improvements in the individual symptoms: sneezing, rhinorrhea, nasal congestion, itchy eyes and watery eyes. The 300IR SLIT tablet was generally well tolerated. The most commonly reported treatment-emergent adverse events (TEAEs) in the 300IR group were application site-reactions: oral pruritus, throat irritation, and nasopharyngitis. No drug-related serious TEAEs were reported. The overall safety profile of 300 IR SLIT tablet was consistent with that observed in European studies.

Conclusions: The 300IR SLIT tablet showed clinically meaningful efficacy, with significant improvements on the primary and secondary endpoints. The treatment was well-tolerated. Overall, the results in United States are consistent with European observations.

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Establishing the Effectiveness, Cost-Effectiveness and Safety of Oral and Sublingual Immunotherapy for Food Allergy: A Systematic Review and Meta-Analysis of Intervention Studies

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Background: Oral and sublingual immunotherapy to food allergens aim to enable the safe consumption of the foods containing these allergens.

Methods: Systematic review of intervention studies, searching 11 international databases and contacting an international panel of experts. Studies were critically appraised using the Cochrane approach and meta-analysed.

Results: We identified 721 potentially relevant papers, from which we selected 16 reports of 14 eligible trials (12 randomised controlled trials and 2 controlled clinical trials). Eleven of these trials evaluated oral immunotherapy and the remaining 3 investigated sublingual immunotherapy.Meta-analysis revealed that immunotherapy substantially reduced the average risk of persisting food allergy in patients (RR = 0.24; 95% CI, 0.11-0.50). Pooling of the safety data however revealed an increased average risk of systemic adverse reactions in those receiving immunotherapy (RR = 1.13; 95% CI, 1.00-1.27); the average risk of local (minor oropharyngeal/gastro-intestinal) adverse reactions was also increased in those receiving immunotherapy (RR = 1.16; 95% CI, 1.04, 1.30). Meta-analysis of immunological data demonstrated that allergen skin prick test wheal diameter significantly decreased in experimental groups compared to controls (mean difference –2.96 mm; 95% CI, –4.48, –1.45), whilst specific-IgG4 increased by an average of 19.9 μg/mL (95% CI, 17.1, 22.6); however there was no change in specific IgE: –5.2 kU/L (95% CI, –12.39, 1.99).

Conclusions: Oral/sublingual immunotherapy substantially reduces the risk of food allergy, this effect being mediated by immunological mechanisms. However, because of the stringent exclusion criteria used in many of the reviewed studies and the increased risk of systemic adverse events, immunotherapy cannot yet be recommended for routine clinical practice. Future research needs to focus on larger randomised controlled trials investigating long-term clinical tolerance induction, impact on quality of life and estimating the cost-effectiveness of treatment. Overall, this appears to be a promising line of potentially disease-modifying treatment for people with a range of IgE-mediated food allergies.

URTICARIA AND ANGIOEDEMA

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The Efficacy of Human Plasma-Derived C1-Inhibitor Concentrate Used for Prophylactic Treatment in Patients With Hereditary Angioedema Due to C1-Inhibitor Deficiency

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Background: Management of hereditary angioedema (HAE) comprises the prophylaxis and emergency treatment of edematous attacks. Our aim was to appraise the wide variety of the prophylactic use of plasma-derived human C1-inhibitor concentrate in HAE type I and type II patients.

Methods: 125 patients with HAE (54 males, 71 females) were included in our study. Classical short-term prophylaxis (STP) was administered before surgical or diagnostic interventions in the head and neck region and other types of major surgery, as well as before endotracheal intubation. Alternatively, STP was introduced before the expected and unavoidable onset of triggering factors.

Results: Before diagnosis of HAE, 128 interventions performed on 43 out of 125 patients induced edema: dental procedures (99 interventions in forty patients), ENT interventions (13/9 patients), surgery in the head and neck region (2/2 patients), surgery under general anesthesia (3/3 patients), gastroduodenoscopy (2/2 patients), delivery (6/6 patients) and artificial abortion (3/2 patients). After diagnosis of HAE, 500 IU of C1-INH concentrate was administered for STP, one hour before dental intervention (to 14 patients in 26 cases), surgery on the head or neck (to 7 patients in 7 cases), surgery under ETN (to 11 patients in 12 cases), diagnostic procedures (1 colonoscopy, 2 bronchoscopy, 4 gastroduodenoscopy, 1 cardiovascular catheterization), artificial abortion (to 4 patients in 6 cases), or childbirth (to 11 patients in 11 cases). Thirty-three of the 125 patients received prophylactic treatment on 70 occasions altogether. The medical history was positive for oedema provoked by medical interventions in 20 of the 33 patients undergoing STP with C1-INH concentrate. Eight patients received alternative prophylaxis: 2 patients during airway infections, 5 others before stressful life events, and one patient on the first day of the menstrual cycle over 4 months. In all cases, C1-INH concentrate prevented the occurrence of attacks.

Conclusions: STP with C1-INH concentrate was effective in preventing angioedematous attacks in all cases. After interventions, during 48 hours observation period, edematous attacks did not occur. Repeated administration did not diminish its efficacy. C1-INH concentrate was well tolerated, and it was never associated with potentially treatment-related adverse effects.

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Treatment of Acquired Angioedema with the Bradykinin Receptor Antagonist Icatibant

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Background: Complement-mediated acquired angioedema (AAE) is a rare condition characterized by an increased degradation of C1-esterase inhibitor

(C1-INH) associated with lymphoproliferative disorders (AAE type I) or caused by autoantibodies against C1-INH (AAE type II). Reduced C1-INH activity leads to uncontrolled bradykinin formation and to angioedema symptoms. There is no established treatment for AAE. Replacement with plasma-derived C1-INH is effective in most patients with life-threatening attack; however, icatibant, a bradykinin B2 receptor antagonist, may represent an alternative treatment.

Methods: We describe 2 patients with AAE who were treated with icatibant during acute attacks. Patient 1 is an 86 year old male who reported cutaneous and abdominal attacks of angioedema beginning 2 years earlier with a frequency of 2 to 3 month. He had low C1-INH (antigenic and functional) C4 levels, normal C1q levels and detectable of anti-C1-INH IgM and anti-C1q IgA. Because of increased frequency, his attacks were treated with icatibant (30 mg s.c.). Patient 2 is a 64 year old female who reported angioedema of the tongue and upper limbs in the last 4 years. Her C4, C1-INH and C1q were low. Monoclonal gammopathy (6%) and IgA anti C1-INH were found. After the diagnosis she started icatibant for acute attacks.

Results: The first patient used icatibant consecutively for 20 attacks (mainly abdominal), with rapid resolutions of symptoms and no adverse events. Symptoms resolution began 30 minutes after administration of icatibant and resolution was complete in 3 to 4 hours. The second patient used icatibant for a tongue attack, a mixed cutaneous-tongue attack and a severe facial attack, with first symptom improvement in 25 minutes and complete resolution after 16 to 18 hours. The only adverse event was erythema at the injection site lasting few minutes.

Conclusions: Icatibant is an effective and well tolerated treatment of acute attacks in patients with AAE. Our data suggest that blocking bradykinin activity could be considered a good therapeutic strategy particularly in patients with anti-C1-INH antibodies.

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Early Versus Delayed Treatment of Swelling Attacks with Icatibant, a Bradykinin 2 Receptor Antagonist in Patients With Hereditary Angioedema due to C1-INH Deficiency

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Background: To compare the efficacy of icatibant in early versus late treated attacks of hereditary angioedema.

Methods: Thirty-one patients received 30 mg icatibant subcutaneously at various times for 121 swelling attacks. The time periods between onset of attacks and icatibant injection, icatibant injection and the first symptom relief, and icatibant injection and resolution of symptoms or, in some attacks, the start of a rebound attack were compared in 3 patient groups with different times to injection.

Results: Data are reported as mean ± SD. In 61 attacks treated at 2 or less hours after attack onset, the time to first relief was 1 ± 0.9 hours and the time to symptom resolution was 12.9 ± 11.5 hours. In 43 attacks treated at more than 2 to 5 hours, the time to first relief was 0.8 ± 1.2 hours and the time to resolution was 15.1 ± 15.3 hours. In 17 attacks treated later than 5 hours after attack onset, time to first relief was 0.6 ± 0.6 hours and time to resolution was 12.6 ± 10.3 hours. The percentages of attacks with first symptom relief within 30 minutes in the 3 groups were 59%, 70%, and 64.7%, respectively. There were no statistically significant differences between the groups. In a subgroup of 20 attacks treated within 1 hour after attack onset, the time to first relief was 0.6 ± 0.3 hours and the time to symptom resolution was 10 ± 12 hours. The only adverse events were injection site reactions that all resolved without intervention.

Conclusions: Icatibant is equally effective in early and delayed treatment of acute HAE attacks, with an early onset of relief.

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Assessment of Chronic Spontaneous Urticaria by Serum-Induced TNF & ALPHA; and MMP-9 Release

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Background: Previous studies from our group have demonstrated that IgE-mediated basophil activation leads to release of TNFα that in turn can induce matrix metallo-proteinase-9 (MMP-9) release from monocytes. We wished to investigate if serum from chronic spontaneous urticaria-patients with auto-antibodies against IgE/IgE-receptor could induce TNFα and MMP-9 release from donor PBMCs, and if release levels could be used to assess severity and activity of chronic spontaneous urticaria (CSU).

Methods: Peripheral blood mononuclear cells (PBMCs) were isolated from whole blood from healthy donors and basophils isolated with MACS Basophil Isolation Kit to 97 to 99% purity. Cells were pulsed 1 hour with or without anti-IgE or with sera from CSU-patients/healthy controls and incubated for a total of 21 h before protein analysis of supernatants. MMP-9 and TNFα in supernatants were measured with commercial ELISAs (R & D), and histamine release determined with HR-test from RefLab ApS.

Results: Stimulations with serum-pools demonstrated that CSU-serum, in contrast to healthy controls, was able to induce TNFα-release from isolated basophils. 10 sera from healthy controls and 22 sera from CSU-patients were tested for serum-induced histamine, TNFα and MMP-9 release. The CSU sera were grouped by reaction/no reaction in the autologous skin serum test (ASST), each group consisting of 11 sera. Nine of the 22 CSU-sera were found positive in the HR-test, 6 sera from ASST+ and 3 from ASST- patients. Sera from ASST+ and ASST- patients were observed to induce highly significant MMP-9 and TNFα release from donor PBMCs when compared to sera from healthy controls ($P < 0.001$). Urticaria assessment score (UAS) did not appear to correlate with release levels for histamine, TNFα or MMP-9 in either group but in the ASST+ group, the ASST score appeared to be positive correlated to histamine and TNFα release and to a smaller degree to MMP-9 release.

Conclusions: We have shown for the first time that serum from CSU-patients, in contrast to serum from healthy controls, can induce TNFα release from isolated basophils, as well as TNFα and MMP-9 from donor PBMCS. Release levels appeared to be positive correlated to ASST reaction in ASST+ patients but not to disease severity for CSU patients in general.

POSTER SYMPOSIUM
ALLERGIC RHINITIS

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Allergen Sensitization in Children with Allergic Rhinitis and Asthma in Guatemala

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Background: There are no previous studies published reporting allergen sensitizations in the population of most Central American countries, including Guatemala. There are many types of climates in different regions, with variable altitude, humidity, etc. The purpose of this study was to determine

the most common allergen sensitizations in children with Allergic Rhinitis and Asthma in 4 different regions.

Methods: The study was performed on 461 children aged 5 to 15 years, from 4 different regions in Guatemala. A questionnaire was given to record information regarding family history of atopic disease and symptoms of Rhinitis and Asthma. The diagnosis was made in the presence of at least 3 symptoms of each disease. Scratch testing was performed using a commercially available device and a panel of 8 allergen extracts: Cypress Arizona, Dog, Cat, Dermatophagoides farinae and pteronyssinus, Cockroach Mix, Mold Mix and Bermuda grass.

Results: Patient average age was 8.3 years, 55% male and 45% female. Patient distribution by region was 35% from Huehuetenango, 29% Chiquimula, 18% Mazatenango and 18% Quetzaltenango. Family history of allergic rhinitis was present in 46% of patients, asthma in 51% and atopic dermatitis in 33%. The most common diagnosis was rhinitis in 86% of patients, 52% had asthma and 43%, both rhinitis and asthma. 98% had a positive Histamine Control and all a Negative Saline Control. 36% of patients had no allergy sensitization to allergens tested and 64% showed positive skin tests. The most frequent allergic sensitization was to Dermatophagoides pteronyssinus (44%) and farinae (43%), followed by Cockroach (28%). We also found less frequently, positive skin tests to grass (14%), Cat (14%), Mold (10%), Dog (8%) and Cypress (6%). The regions with higher dust mite sensitization were Quetzaltenango (51–55%) and Huehuetenango (45–51%).

Conclusions: The most common allergen sensitizations in children with allergic rhinitis and asthma in Guatemala are dust mites and cockroach. Family history of either rhinitis or asthma is present in a significant amount of patients (46–51%) with atopic disease and allergic sensitization, showing that it is an important risk factor in Guatemala. In 36% of patients in this study, allergic sensitization does not seem to contribute to their rhinitis and asthma symptoms.

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The Impact of Breast-Feeding Duration and Mode of Delivery on Allergic Rhinitis in Korean Children: Cohort of Allergic Rhinitis in Korea (Coar-korea) Study

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Background: There is much interest in the possibility that environmental factors may influence the risk of allergic rhinitis in early life. We investigated simultaneously the effect of mode of delivery and breast-feeding duration on the development of allergic rhinitis in Korean children.

Methods: Data from 878 children of Cohort of Allergic Rhinitis in Korea (COAR-Korea) Study were analyzed. Children with rhinitis were recruited from 14 centers located in 6 provinces of South Korea between April 2008 and September 2010. All subjects were divided into allergic rhinitis (AR) group and nonallergic rhinitis (NAR) group according to skin prick test response. Data on environmental factors, including mode of delivery and breast-feeding duration, were collected using a questionnaire. Relationships were analyzed using logistic regression analyses.

Results: We found that 77% of the population with rhinitis had AR, whereas 23% had NAR. Compared with never breast-fed, breast-feeding for $\geq$ 12 month was significantly associated with a lower prevalence of AR (aOR, 0.64; 95% CI, 0.41-0.99). Children who were born by Cesarean section showed a higher prevalence of AR compared with those born by vaginal delivery (OR, 1.48; 95% CI, 1.05-2.09). However, after adjustment for confounders under study, this difference was lost (aOR, 1.40; 95% CI, 0.90-2.20). Children born by Cesarean section were shown significantly lower rates of breast-feeding initiation (70.5% vs. 78.9%, $P = 0.005$) and lower rates of longer (for $\geq$ 12 months) breast-feeding maintenance compared with those born by vaginal delivery (35.5% vs. 48.4%, $P = 0.005$).

Conclusions: Amongst environmental factors, longer duration (for >12 months) of breast-feeding seems to be the most powerful protective factor against the risk of developing AR in young children. However, breast-feeding behavior seemed to be affected by mode of delivery and must be considered as a strong confounding factor in evaluating the correlation between environmental risk factors and development of allergic diseases.

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The Efficacy of a Nasal Corticosteroid Ciclesonide for the Treatment of Serous Otitis Media in Atopic Children

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Background: Since chronic inflammation is the histopathologic landmark of otitis media with effusion, clinical observations led us to believe that the use of a Nasal Corticoteroid Ciclesonide may be more effective than an oral antibiotic in the treatment of serous otitis media in atopic children.

Methods: We studied forty pediatric patients (age 6–11 years) in a randomized open labeled 2-week trial to compare the efficacy of the nasal corticosteroid Ciclesonide 50 mcg/nostril 2 sprays per nostril once a day to an oral antibiotic Amoxicillin/Clavulanate potassium (90 mg/kg/day in 2 divided doses every 12 hours) for the treatment of otitis media with effusion. The efficacy of the treatment options was assessed using pneumatic otoscopy, impedance tympanometry and audiometry to monitor the clinical course of the middle ear effusion in both treatment groups.

Results: In the group nasal corticosteroid Ciclesonide a resolution of otitis media with effusion occurred at the 8th day. In contrast in the group treated with the oral antibiotic the resolution of otitis media with effusion occurred on the 14th day.

Conclusions: In conclusion, the nasal corticosteroid Ciclesonide is more effective than an oral antibiotic. The nasal corticosteroid Ciclesonide may be a safer and shorter therapy given the safety issues with long term use of systemic antibiotics in atopic children.

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Combination of a Nasal Antihistamine Olopatadine and A Leukotriene Receptor Antagonist Montelukast Sodium for the Treatment of Seasonal Allergic Patients not Currently Controlled on Monotherapy Intranasal Antihistamine or a Leukotriene Receptor Antagonist

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Background: For seasonal Allergic Rhinitis (SAR) patients that remain symptomatic on an intranasal antihistamine, Olopatadine or a leukotriene receptor antagonist Montelukast sodium, the combination of intranasal antihistamine with a leukotriene antagonist Montelukast sodium may provide additional efficacy in sub-optimally controlled Seasonal Allergic Rhinitis Patients.

Methods: In this open 8-week trial 40 patients with symptomatic SAR currently using Olopatadine 1330 mcg/nostril or Montelukast sodium, 10 mg p.o daily were randomized to receive the combination Olopatadine 1330 mcg/nostril BID + Montelukast sodium, 10 mg p.o QD. The end points of the trial include: rhinomanometry, nasal symptom score (composite score of nasal congestion, rhinorrhea, sneezing, post nasal drip, and nasal itching) and flexible rhinopharyngolaryngoscopy examination.

Results: Mean efficacy measurements at the end of the 8-week trial revealed significant improvements in all parameters examined in the combination treatment group compared to baseline measurements.

Conclusions: In conclusion, the combination nasal Olopatadine plus Montelukast orally is more effective than monotherapy nasal Olopatadine or Montelukast. It appears that in the combination treatment Olopatadine and Montelukast sodium, the primary end points (rhinomanometry and symptom scores) are significantly improved.

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Augmentation of cxcl10 Expression in Nasal Fibroblasts Derived from Patients With Recalcitrant Chronic Rhinosinusitis Associated With Bronchial Asthma

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Background: The prevalence of chronic rhinosinusitis (CRS) that is refractory to traditional therapy appears to be increasing, and CRS that is refractory to traditional therapy tends to be associated with bronchial asthma (BA), especially, aspirin-intolerant asthma (AIA). After viral infections, patients with CRS associated with BA usually experience exacerbations of their CRS symptoms, including nasal polyposis, in comparison with CRS patients without BA. Alternatively tissue fibroblasts as an important component of the epithelial mesenchymal trophic unit play a key role in maintaining tissue homeostasis and may also have the potential to contribute to disease pathogenesis through their contribution to inflammatory responses. On the basis of these findings, we hypothesized that CRS patients with BA are more susceptible to inflammation of the nasal and paranasal mucosa depending on the antiviral response of nasal fibroblasts.

Methods: Tissue specimens were obtained from the nasal polyps of 3 groups of CRS patients, a group that did not have BA (CRS-NA group), a group with aspirin-tolerant asthma (CRS-ATA group), and a group with AIA (CRS-AIA group). Nasal polyp fibroblasts (NPFs) were isolated from the specimens and stimulated with poly I: C. By using a DNA microarray and performing a hierarchical clustering analysis we were able to identify a cluster containing genes that were up-regulated after poly I: C stimulation. To confirm the results of the analysis data, we used quantitative real-time PCR (qRT-PCR) and an enzyme-linked immunoadsorbent assay (ELISA).

Results: Expression of *IFN-inducible protein 10 (IP-10)/CXCL10* transcript was higher in the NPFs of the CRS-AIA group and CRS-ATA group than in the CRS-NA group and control group. These findings were confirmed by qRT-PCR and ELISA.

Conclusions: The results of this study suggest that the increased poly I:C-induced CXCL10 expression in NPFs derived from the CRS patients with BA is involved in susceptible to T helper (Th)1-type immune response in the nasal and paranasal mucosa by viral infection compared with CRS patients without BA.

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Correlation between CU/ZN-SOD and Macrophages or MUC5AC in Eosinophilic Chronic Rhinosinusitis With Nasal Polyps

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Background: Recently, some researchers have reported that increases and decreases of infiltrating macrophages, a mucin gene or the antioxidant as well as infiltrating eosinoplils would be related to severe asthma. At present, eosinophilic chronic rhinosinusitis with nasal polyps (ECRS) has been considered intractable rhinosinusitis. From the point view of "one air way, one disease," we immunologically examined macrophages and mucin gene (MUC5AC), IL-17A with these promotive factors and Copper-and Zinc-containing superoxide dismutase (Cu/Zn-SOD). Furthermore, we discuss whether Cu/Zn-SOD would be associated with infiltrating macrophages, MUC5AC and IL-17A.

Methods: The patients were classified into ECRS and non-eosinophilic chronic rhinosinusitis with nasal polyps (non-ECRS) groups. In addition, normal mucosal membranes of the sphenoid sinus removed at operation for pituitary adenoma were used as control. Part of each specimen derived from the nasal polyps of ECRS and non-ECRS were divided and fixed in 10% phosphate buffered formalin, embedded in paraffin, processed routinely and then prepared as semi-thin sections (3.5 μm). We immunohistochemically observed Cu/Zn-SOD and macrophages by using CD68, IL-17A, and MUC5AC.

Results: Both the numbers of macrophages (CD 68 positive cells) and IL-17A-positive cells in the ECRS were significantly greater than in non-ECRS. Furthermore, there was a significant correlation between CD 68 and IL-17A positive cells. The rate of epithelial cells with MUC5AC-positive reaction was significant in the comparison of ECRS with non-ECRS. On contrast, the rate of Cu/Zn-SOD-positive epithelial cells in non-ECRS was significantly greater than that in ECRS. Cu/Zn-SOD was inversely and significantly correlated with macrophages, IL-17A, and MUC5AC.

Conclusions: The present study suggested that the decrease of Cu/Zn-SOD in ECRS could be increased by the infiltration of macrophages, the expression of IL-17A, and MUC5AC.

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Relationship Between Allergic Rhinitis and Dental-Facial Abnormalities

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Background: Allergic rhinitis (AR) affects 10 to 25% of the general population and is of great importance for the impact on quality of life and school performance.[1] Rhinitis has been associated with craniofacial abnormalities due to the high frequency of mouth breathing, oral breathing syndrome occurs when the child replaces the correct pattern of breathing caused by nasal obstruction resulting from allergic disease.[2]

Objective: To establish the type of relationship between allergic rhinitis and dental-facial abnormalities in the pediatric population of Veracruz ISSSTE Hospital General in 2009.

Methods: A case-control study, cases (25) were patients aged 6 to 18 years of age with allergic rhinitis. Controls (25) were entitled 6 to 18 years, informed consent, were referred to the dental service, where he underwent medical history and oral examination. For data analysis descriptive statistics were used, and chi-square test statistic (X2) and *t* test.

Results: The average age of cases was 12 ± 3.5 years, mean bodyweight 44.33 kg, age of controls was 12.6 ± 3.8 years, weight 48.23 kg. 16% of the cases has any oral habit (finger, tongue), in controls 36% assumed the habit. The predominant type of skull was normocéfalo controls (84%), where was dolichocephalic (63%). In dental abnormalities (dry lips, deep palate, malocclusion) 100% of cases had at least one, 90% have deep palate, in controls 32% had impaired and 24% with deep palate. We found a statistically significant difference $P = 0.007$, in the variable Inadequate Respirator Syndrome Nasal.

Conclusions: There is a partnership between the patient with allergic rhinitis and dental-facial abnormalities.

ALLIED HEALTH

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Reduction in Allergic Rhinitis Index by Decreasing Aero-Allergens and Malodor Causing Volatile Organic Compounds by Luna Air Purifiers Using Photo-Catalytic Oxidation (PCO) Technology

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Background: The quality of the environment within buildings is a topic of major importance for public health. Breathing pure and clean air allows us to think more clearly, sleep more soundly, and stay healthier. Studies show that we receive 56% of our energy from the air we breathe, more than from water and food combined. On average we breathe 37 pounds of air a day. It has been established that the use of negative ions in a purification system is an effective means of eradicating aeroallergens in room air.

Methods: The wall-mount, Inducts and Mobile Sanifier air purification units of Luna are designed to sanitize air, to kill surface mold, bacteria, and viruses in areas up to 26,000 cubic feet. Samples were collected from the clinic rooms to analyze the VOC concentrations using the Luna air purifiers to detect the efficiency in reducing the VOCs in the indoor air. We analyzed the aroallergens and VOCs prevalent in the indoor air in the clinics at the Coulter Animal Hospital, Amarillo, Texas. The data were correlated to the inhalant allergy index before and after running air purifiers that use PCO technology.

Results: Samples from the clinic rooms to analyze the VOC concentrations using the Luna air purifiers to detect the efficiency in reducing the VOCs in the indoor air. The SKC Pocket Pump and thermal desorption tubes were used to obtain the samples from the indoor air. Pumps were set on 200 mL/min as air flow to estimate the concentration of Acetic acid, Isobutyric acid, Butyric acid, Isovaleric acid, Valeric acid, Hexanoic acid, Phenol, p-cresol, 4-ethyl, 2-amino, Indole, and Skatole. All desorption tube samples were analyzed using a Markes UNITY and Markes Ultra automated thermal desorber (ATD) and a Varian 3800/Saturn 2000 GC with a MS. Slides with double sticky tape were exposed to room air stained with 2% safranin and were observed using a BX-40 Olympus microscope with DP-70 and Image Pro Plus software.

Conclusions: The data were correlated with the aeroallergen index and the frequency of inhalant allergy cases that showed reduction in allergic rhinitis index on using air purifiers.

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The Missing Link!! Specialist Nurse-Led Education for Parents of Children With Atopic Eczema

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Background: Australia's rate of children with food allergy is still on an upward trend. In infants the earliest manifestation is usually atopic eczema. Australian Bureau of Statistics National Health Survey (ABNHS, 2007–2008, p.305) reported hayfever, allergic rhinitis and asthma in the top 10 most commonly reported long-term conditions for children and young people. Early effective management of eczema is essential. Australia's medical model means long wait for allergy appointments with a specialist, limiting review appointment availability. Following diagnosis of atopic eczema and treatment recommendations by a clinical immunologist/allergist or dermatologist, parents report having many unanswered questions -contributing to anxiety and confusion. They feel overwhelmed that eczema is incurable and long-term management and constant vigilance is required. Many feel a lack of support and despair. Education, demonstration and support by a nurse specialist in eczema management at a Children's hospital in Adelaide has improved outcomes and reduced the psychosocial burden of the condition. Parents and children receive 30 minutes explanation, demonstration of required treatments and an individualised, written eczema action/care plan. The education sessions use a conceptual framework based on Social Cognitive Theory where active participation, goal setting and forward planning enhance understanding assisting the long-term behavioural changes needed to master eczema management effectively. The families are reviewed by the nurse several weeks later to review progress and answer questions that have arisen over the preceding weeks. The education sessions are tailored to the individual family needs, encourage self-management and aim for increased confidence to self-regulate the condition as it waxes and wanes.

Methods: Twenty-two families in a novel clinic at Children's Youth and Women's Health Service, Adelaide undertook a pre-post intervention questionnaire surveys.

Results: All 22 families (2009) reported that the service had assisted their understanding, enhanced management and compliance and called for expansion as soon as possible. A research project is scheduled in the near future to expand the service within the recommendations of the South Australian Chronic Diseases Action Plan 2009-2018.

Conclusions: Specialist nurse's support assists parents to gain the required practical skills, understanding increased confidence and compliance with their recommended treatments.

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Sublingual Immunotherapy for Grass Pollen Allergy in Children: A Systematic Review and Meta-Analysis

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Background: Sublingual immunotherapy (SLIT) using grass pollen extracts is an attractive treatment option compared with subcutaneous immunotherapy (SCIT) for children suffering with the symptoms of seasonal allergic rhinoconjunctivitis, with or without asthma. However, evidence for the efficacy of SLIT in children remains unclear. The objective was to undertake a systematic review of the available literature to identify high quality paediatric studies of SLIT for grass pollen allergy to assess the safety and benefits of SLIT compared with standard medication alone.

Methods: MEDLINE, EMBASE, CINAHL, NHSEED, DARE and Cochrane were searched from 1st Jan 2000 to June 2010. A pre-specified inclusion criteria was used to select studies, which were assessed for the risk of bias using the Jadad scale. The outcomes of interest were data from the studies including the reduction of nasal, eye and chest symptoms, use of symptom relieving medication and safety.

Results: Nine studies met the inclusion criteria. A narrative synthesis on the safety of SLIT found a high incidence of mild, adverse events. Outcomes were pooled using Rev Man 5 and the random effects model. Inter-study heterogeneity was measured using the I^2 statistic and was $<70\%$ in all meta-analyses. The reduction of total allergic rhino-conjunctivitis symptom scores indicated a small highly significant reduction with non-significant heterogeneity. (SMD –0.24, 95%, CI–0.38 to –0.11 $P = 0.0005$), (I^2 15% $P = 0.32$). The reduction in total relief medication use scores compared to placebo was non-significant. (SMD-0.25 CI -0.50, 0.01, $P = 0.06$). I^2 67% ($P = 0.006$).

Conclusions: SLIT has a small benefit on symptoms but does not demonstrate a significant reduction in medication use. This justifies current SLIT use in paediatric allergy in the UK where availability is limited to children who remain symptomatic despite having proven concordance using

optimised symptom relieving medication and children in whom SCIT is contra-indicated.

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Effect of EPA-DHA Supplementation on Forced Expiratory Volume in One Second (FEV1) and Triglycerides in Obese Adolescents With Hypertriglyceridemia

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Background: Evaluate the effect of supplementation of eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA) in FEV_1 and triglyceride levels in obese adolescents.

Methods: Single blinded, parallel, clinical trial in 2 groups of adolescents supplemented with an intake of 3 gm/d of EPA-DHA versus 3 gm of grenetin for 3 months. We included adolescents with exogenous obesity with Body Mass Index (BMI) CDC > 95%. All patients underwent anthropometry, lipid profile and spirometry at baseline and study end. They were divided into 2 groups: G1: EPA-DHE obese and G2: Grenetin obese. Samples analyzed by T Student (paired and independent).

Results: Adolescents were recruited with hypertriglyceridemia > 150 mg/dl, female 45.5%, male 54.5% mean and SD 12 ± 1.3 years. There were 34 patients in G1 and G2: 40 patients. The initial values averages the baseline IC 95% FEV_1 G1 102.27 (106.06–98.48), G2 102.18 (106.12–98.26), Tiffaneau Index G1: 0.87 (0.90–0.84), G2 0.85 (0.83–0.88) Triglycerides G1 221.71 (246.10–197.32), G2 190.91 (206.90–174.92), Cholesterol G1 169.29 (179.35–159.23), G2 157.09 (169.90–144.28), HDL G1 32.96 (35.58–30.36), G2 33.85 (36.55–31.06). After 3 months, FEV_1 G1 100.39 (104.99–95.79), G2 100.80 (105.88–95.74), Tiffaneau Index G1 0.83 (0.85–0.81), G2 0.86 (0.86–0.83) Triglycerides G1 101.00 (117.64–84.36), G2 127.09 (149.87–104.31), Cholesterol G1 169.88 (181.70–158.06), G2 163.32 (176.00–148.64), HDL G1 35.95 (40.25–31.66), G2 35.81 (38.93–32.71). Supplementation with EPA-DHA and grenetine for 3 months in triglyceride basal levels had only one significant value ($P < 0.05$), without a significant in FEV1.

Conclusions: Supplementation with EPA-DHA and grenetine for 3 months is helpful for reducing basal levels of triglycerides.

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A Pilot Study of Caregiver's Recall of Their Child's Skin Test Results and Environmental Remediation Education

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Background: Allergic asthma is common in urban minorities and evidence suggests that environmental remediation is an effective management strategy. However, remediation requires complex interventions. The purpose of this pilot study, therefore, was to examine caregiver's recall of their child's skin test results and the accuracy of planned remediation ~4 months after testing.

Methods: A Q-sort was used to determine caregiver's knowledge of the appropriate remediation for their child's allergic status. Using this method, caregivers sorted cards into piles: important for my child's asthma, not important or unsure. Each of the 52 cards represented one intervention for a common indoor allergen. Three of the 52 cards were specific to cat allergen, 3 for dog, 10 for mold and 23 for dustmite. Unlike typical Q-sorts, these cards used pictures and low-literary language. Caregivers were then instructed to place each card on a continuum of highest to lowest priority. At the conclusion of the Q-sort, caregivers received feedback on the accuracy of their prioritization in the context of their child's skin test results. Acceptability of this technique was assessed using qualitative interviews.

Results: Five African American women (mean age 33.6; 80% receiving public assistance) caring for 5 children (4 males; mean age 7.8) were enrolled. Caregivers recalled 4.6 positive results per child; only 4.2 positive results per child were noted. However, no caregiver recall of skin test results was concordant with actual results. Caregiver's accuracy in identifying trigger reduction strategies specific to their child's skin test results ranged from 33 to 100% for cat, 40 to 70% for molds, 70 to 87% for dust mites, and 100% for the 1 dog allergic child. No standard battery was performed; rather each test was specific to the child's history. Qualitative interviews showed Q-sort to be an acceptable way to learn about remediation.

Conclusions: Caregivers do not accurately recall skin test results and this may, in part, impede their ability to implement appropriate interventions. A low literacy game-style approach is a novel strategy to provide complex teaching that warrants further investigation.

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Evaluation and Comparison of Lung Function by Plethysmography in Adolescents with Morbid Obesity, not Morbid Obesity and Healthy Eutrophic Children

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Background: The objective was to measure and compare lung function by plethysmography in young healthy children, obese and morbidly obese.

Methods: Cross-sectional, prospective study in 150 adolescents from 11 to 17 years old, grouped according to their body mass index (BMI): group 1 (G1) healthy eutrophic (BMI percentile 10–84 of the boards of the CDC) Group 2 (G2) not morbidly obese (BMI 85–98) and group 3 (G3), morbidly obese (BMI> 99). Anthropometry was performed and plethysmography. Statistics: mean, standard deviation (SD), confidence interval 95%, CI 95%. ANOVA post hoc analysis.

Results: The mean age was 13.7 years, 46.7% women and 53.3% men. G1 had 40 children, G2 had 67 and G3 had 43. Mean values and CI 95% of vital capacity (VC) of G1 was 104.97% (100.12–109.82), G2 114.65% (111.36–117.94), G3 118.09% (112.71–123.47) [G1 with significant difference compared the G2 and G3 $P < 0.05$]. The total lung capacity (TLC) was 124.67% G1 (105.94–143.40), G2 145.61% (114.77–176.45), G3 132.27% (125.14–139.41) [no intergroup difference]. Functional residual capacity (FRC) of G1 was 145.95% (133.75–158.14), G2 122.41% (110.23–134.59), G3 115.74% (103.05–128.43) [G1 with significant difference compared with the G2 and G3 $P < 0.05$]. The expiratory reserve volume (ERV) of G1 was 113.15% (90.57 – 135.72), G2 68.64% (60.34 – 76.93), G3 67.33% (52.40 – 82.26) [In contrast to the G1 compared to G2 and G3 $P < 0.05$]. Inspiratory capacity (IC) in G1 was 76.90% (66.94–86.85), G2 102.04% (94.94–109 145), G3 115.72% (105.61–125.82) [G1 with significant difference compared with the G2 and G3 $P < 0.05$].

Conclusions: The morbidly obese have a lower FRC and ERV and increased IC and CV.

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Selecting Primal Therapy Appropriate for the Type of Pollinosis—Topic-J Study

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Background: In Japanese Guideline for Allergic Rhinitis, drugs for treatment after the start of pollen dispersal are recommended for each type of pollinosis, but drugs for primal therapy are not categorized by the type of pollinosis. We

examined the adequacy of different drugs for primal therapy on each type of pollinosis.
Methods: Patients with pollinosis attending 11 otorhinolaryngology clinics in Tokyo during part of pollen season (February 18–26) were enrolled and assigned to either an anti-leukotriene agent (pranlukast) or an antihistamine based on their symptoms in the previous year. During 3 months of treatment, symptoms and quality of life (QOL) were investigated by a mail questionnaire at 7 time points (at the start of treatment, and between March 1 and May 15).
Results: Of 150 patients with pollinosis who were registered, analysis was conducted on 144 patients (62 receiving anti-leukotriene therapy and 82 receiving antihistamine therapy), excluding those with incomplete questionnaires. In both groups, scores for symptoms of pollinosis and QOL were low, suggesting that both drugs were effective considering the high pollen levels season (5–9 times higher than the previous year). After defining types of pollinosis by the severity of symptoms (sneezing, rhinorrhea, or nasal blockage), stratified analysis was conducted. This showed that antihistamine therapy was effective for the sneezing/rhinorrhea type and anti-leukotriene therapy was effective for the nasal blockage type, with no difference between the 2 drugs the combined type. For the nasal blockage type, symptoms and QOL improved faster with anti-leukotriene than antihistamine therapy from the peak to the end of the pollen season. No adverse effects were observed.
Conclusions: When either an anti-leukotriene (pranlukast) or an antihistamine was used for primal therapy of pollinosis, both drugs improved pollinosis symptoms and QOL. Stratified analysis showed that the antihistamine was more effective for the sneezing/rhinorrhea type and the anti-leukotriene was more effective for the nasal blockage type, with no difference in effectiveness for the combined type. Therefore, appropriate drugs for the type of pollinosis should be selected for primal therapy.

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Olfactory Disfunctions in Patients with Chronic Rhinosinusitis

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Background: There are several factors that could produce olfactory dysfunction. The chronic inflammation of the upper air tract, especially allergic rhinitis is mentioned as a trigger factor. The aim of this study is assess the prevalence and identify clinical features associated with olfactory dysfunction in patients with chronic rhinosinusitis.
Methods: A prospective, analytical and observational study in adult patients (> 18 years) with chronic rhinosinusitis during the period May-October of 2010. We used the CCCRC (Connecticut Chemosensory Clinical Research Center smell test)
Results: A total of 33 patients were investigated. In the group of patients between 18 and 39 years, 73% of patients suffer from hyposmia and 18% anosmia; for the group of 40 to 64 years, 63% with hyposmia and 37% anosmia; patients older than 65 years, 67% hyposmia and 33% with anosmia. In the smokers group the 11% of patient presented hyposmia and 13% anosmia ($P < 0.05$); 5% in both cases had a history of nasal endoscopic surgery. In patients with chronic rhinosinusitis with nasal polyps have 18% with hyposmia and 19% with anosmia ($P < 0.05$). A 20% with allergic rhinitis had hyposmia while anosmia in 22% ($P < 0.05$). Septal deviation patients had 20% of hyposmia ($P < 0.001$) and 12% anosmia. Patients with turbinate hypertrophy had 22% hyposmia ($P < 0.001$) and 13% anosmia while in the group of patients with Asthma, the 4% had hyposmia and 16% anosmia ($P < 0.001$).
Conclusions: Nasal polyposis, septal deviation, turbinate hypertrophy, smoke, allergic rhinitis and asthma are negative predictors factors of olfactory dysfunction in patients with CRS. A previous endoscopic surgery, age and sex would not intervene in the olfactory loss.

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Perceptions of Caregivers of Patients with Cow Milk Allergy Regarding the Treatment

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Background: To understand the perceptions of caregivers of patients with cow milk allergy (CMA) regarding the disease and its treatment.
Methods: Qualitative study in which caregivers of children and adolescents with confirmed CMA followed, at least, for 1 year, were interviewed. They were recruited from outpatient clinic of Allergy and Immunology Division from a tertiary pediatric hospital in São Paulo, Brazil. The interviews were conducted under conditions of privacy and 2 opened questions were proposed: "Tell me about your experience with cow's milk allergy treatment" and "What do you expect from your child's disease treatment?" Data were audio-recorded, transcribed, analyzed using the content analysis method and categories and subcategories were generated based on their speeches.
Results: Nine interviews were done and 3 categories with subcategories emerged: A. Treatment and education of the patient and their caregivers (life experiences, bases of treatment, coping with the disease). B. Resolution of the disease (hope, gradual improvement). C. Quality of life (social inclusion, family daily activities, costs of dietary treatment). Caregivers experienced difficulties during the initial treatment but pointed out that the guidance given during follow-up made the adjustments easier. They also compared CMA with other chronic diseases and highlighted the importance of their children follow-up in this institution for adequate control. They commented on the difficulties about lack of cooperation from other family members regarding the restrictive diet, their experience coping with allergic reactions, doubts about the treatment and gaps on knowledge about the disease by other physicians and people. The majority of relatives was satisfied with the gradual improvement of patients, although there are no drugs or vaccines for treatment, and observed a reduction on the severity of symptoms and tolerance of milk traces. In addition, they commented on the efforts to give a normal life for their children, the changes in their daily lives and the difficulty to buy special products.
Conclusions: This qualitative study allowed us to understand how families cope with the disease, their histories and hopes about the treatment. They feel a great burden of the disease and need support and orientation from health professionals.

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Incidence of Systemic Reactions (SRS) to Prick (P) and Intradermal (ID) Tests, Response to Immediate ("STAT") Epinephrine IM (EPI IM) Dose versus BMI, Number of Delayed SRS, and WAO Systemic Reaction Grade

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Background: To determine the incidence of SRs to P and ID tests, the response to stat epi IM, number of delayed SRs, the dose of epi IM versus BMI and the World Allergy Organization (WAO) Grade (1-5) of the SRs.
Methods: SRs were compiled from 07/2010 to 06/2011 to P and ID tests for any combination of approximately 20 allergens (pollens, animal emanations, molds and Hymenoptera) in 1,332 subjects. Nurses administered stat epi IM (1:1000 v/v), 0.2 mg IM, into the arm or thigh for any signs or symptoms (SS) of a SR, including, but not limited to, itchy eyes, nose, pharynx, or palms; rhinorrhea, nasal congestion, sneezing; and generalized erythema, skin pruritus, or urticaria. SS (WAO Grade), total epi IM dose, and delayed SRs were recorded. Repeat doses of epi IM were given if SS persisted or worsened.
Results: 31 (2%) had SRs: 24 (77%) female, 7 (23%) male; 5 (16%) pediatric, 26 (84%) adult. Of the 31 SRs, 26 (84%) had Grade 1, 5 (16%) Grade 2 and Grades 3 to 5. 13 (42%) experienced SS during P and 18 (58%) during ID or at the completion of P and ID. All received stat epi IM with any SS. 2 BMIs were not available. 28 SRs, with a mean BMI of 28.5 (overweight range 25.0–29.9) received one epi IM, 0.2 mg, and one BMI 20.4 (normal range 18.5–24.9) received 2 epi IM (total 0.3 mg). There were no underweight (less than 18.5) or obese (30.0 or greater) subjects.
Conclusions: 31 (2%) had SRs to P and/or ID tests; 30 received one epi IM dose (0.2 mg) and one, 2 doses (0.3 mg total). There were no delayed SRs or relationship of epi IM dose to BMI and all but one were WAO Grade 1 reactions. Stat use of EPI IM may prevent more serious SRs and delayed reactions.

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The "Allergy Blog" and Lay Person Questions: An Interactive Educational Experience

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Background: Despite the increase of allergic diseases over the last decades, the population ignores the basic concepts, interfering in their prevention and treatment. The "Allergy Blog" (Blog da Alergia) has been using digital media resources to offer new forms of dialogue and patient's ethical enlightenment since 1996. This research objective to report the interactive educational experience, through the internet on "http://www.blogdalergia.com" and to find out, from the audience's questions, which are the main areas of interest about immune-allergic diseases.
Methods: Research on 1375 e-mails randomly selected, sent to the Blog home page, to know what were the main issues raised by the lay public. The e-mails were analyzed, considering the gender and age of the users and the topic searched.
Results: Since 1996, Allergy Blog answered 4,256 e-mails and 2,200 comments. Most of patients were female: 78.2%, compared with 19.9% male and 1.9% with no information. Many users (67.65%) did not reported their age, as there wasn't a mandatory item for this question. But, 25.38% of the users were parents or guardians of children with allergic disease. The frequency of the most popular topics searched were: Urticaria (14,55%), Doubts about drugs (12.51%), Allergic Rhinitis (10,98%), Pruritus (8,15%), Asthma (8, 87%), Contact dermatitis (5,60%), Atopic Dermatitis (4,58%), Drug Allergy (2,47%), Cough (3,86%), and Others (6,40%). Dermatologic manifestations of allergy bring more questions than the respiratory ones (32.9% versus 23.7%), and drug concerns responded for 14.9% of the doubts. Asthma, for which there are a lot of educative campaigns, represented only 8.9% of the questions. To clarify these questions, Allergy Blog published educational texts and interacted with the visitors through: a) Comments on Blog posted questions, 2) Answers to doubts sent via e-mail, 3) Chat intended for short answers.
Conclusions: The discoveConclusions: The discovery of the lay's greatest gaps and areas of interest can be a guideline to improve new educative actions in Allergy and Immunology. The use of digital media and social networks may be a prime tool for the education of allergic individuals, community dialogue and dissemination of correct information about the various aspects of immune-allergic diseases.

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Anaphylaxis after Anesthetic Reversal

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Background: Sugammadex is a new drug used for the reversal of neuromuscular blockade by rocuronium or vecuronium, a muscle relaxant used as fast acting.
Methods: We performed a review of a case of a patient scheduled for osteosynthesis of the ankle with a history of bronchial asthma and sensitization to Dermatophagoides pteronyssinus. After the surgery the patient suffered anaphylaxis, a minute after the use of sugammadex.
Results: We evaluated the drugs used during anesthesia Prick and intradermal, and we obtained positive results with Sugammadex at 1 month, 3 and 6 months. We performed the basophil activation test giving a positive result. Tests show IgE-mediated sensitization with positive skin tests and basophil activation test.
Conclusions: It is believed that prior sensitization may have occurred due to ingestion of cyclodextrins which is present in many foods. The atopic status of this patient may have had some awareness of cyclodextrins. This case has been published as the first documented case of anaphylaxis by sugammadex with normal doses. Our case raises clear that the underlying mechanism of this reaction was an IgE-mediated sensitization.

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Establishment of Reference Values for Differential Cell Counts in Nasal Lavage of Healthy Young Adults

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Background: Upper airway inflammation could be reflected by nasal lavage cytology test, which is characterized by advantages of non-invasive, simple, objective and costless. However, reference values nasal lavage cytology was not established. To establish reference values and positive standard for nasal lavage cytology through screening normal healthy subjects and patients with allergic rhinitis according to strict inclusion criteria.
Methods: To establish reference values and positive standard for nasal lavage cytology through screening normal healthy subjects and patients with allergic rhinitis according to strict inclusion criteria.
Results: There was no statistical significance in gender constitutional proportion, age, height and weight among each group. 95% CI of neutrophils, eosinophils was (0～12.61)/×200 and (0～1.70)/×200, respectively. The median (interquartile range) of neutrophils were 0(0.65)/×200 in AR group, which showed no statistical difference ($P > 0.05$) with that of normal group [0(0)/×200]. A significant difference was found in the median (interquartile range) of eosinophils [6.90(22.40)/×200] in AR group as compared with that of normal control group [0(0.10)/×200, $P < 0.001$].
Conclusions: Establishment of reference values of nasal lavage cytology test is helpful to discriminate normal individuals and patients with allergic

rhinitis, but also a non-invasive tool for objective reflection on upper airway inflammation, which is of great value for scientific and clinical purposes.

ASTHMA TREATMENT

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Reduction in Asthma Deteriorations in Subjects with Persistent Asthma not Well Controlled on Low-, Medium-, or High-Dose Inhaled Corticosteroids: A Pooled Analysis From Three Clinical Trials Using Combined Mometasone Furoate/Formoterol

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Background: We present a post hoc analysis from 3 phase III clinical trials examining the effects of mometasone furoate/formoterol (MF/F) combination therapy on asthma deterioration in subjects previously not well controlled on low-, medium-, or high-dose inhaled corticosteroids (ICS).

Methods: A 2- to 3-week run-in period with twice-daily (BID) MF 100 μg (MF/F 100/10 μg BID study), MF 200 μg (MF/F 200/10 μg BID study), or MF 400 μg (MF/F 400/10 μg BID study) was performed before subjects (aged ≥12 years) were randomized to BID: MF/F 100/10 μg, MF 100 μg, F 10 μg, or placebo for 26 weeks (n = 746; MF/F 100/10 μg BID study); MF/F 200/10 μg, MF 200 μg, F 10 μg, or placebo for 26 weeks (n = 781; MF/F 200/10 μg BID study); or MF/F 200/10 μg, MF/F 400/10 μg, or MF 400 μg for 12 weeks (n = 728; MF/F 400/10 μg BID study). Assessment of asthma deterioration (ie, 20% decrease in forced expiratory volume in 1 s [FEV_1], 30% decrease in peak expiratory flow [PEF] on ≥2 consecutive days, or clinically judged deterioration [ie, emergency treatment, hospitalization, or treatment with excluded medications]) was a coprimary endpoint for the MF/F 100/10 μg BID and 200/10 μg BID studies and a secondary endpoint for the MF/F 400/10 μg BID study. Post hoc pair-wise comparisons of pooled MF/F vs pooled MF, F, and placebo treatment groups were performed.

Results: Sample sizes in this pooled analysis were 861 for MF/F, 620 for MF, 390 for F, and 384 for placebo. There was a significantly lower incidence of asthma deterioration with MF/F (17.2%) versus MF (26.1%; $P = 0.002$), F (49.5%; $P < 0.001$), and placebo (50.8%; $P < 0.001$). Incidence of individual asthma deterioration criteria was 7.0% for MF/F, 10.0% for MF, 13.8% for F, and 17.7% for placebo for FEV_1 reduction; 7.5%, 12.6%, 27.2%, and 26.3%, respectively, for PEF reduction; and 2.1%, 2.6%, 6.7%, and 5.2% for clinically judged deterioration.

Conclusions: MF/F-treated subjects experienced a significantly lower rate of asthma deterioration compared with MF, F, and placebo in subjects previously not well controlled on low-, medium-, or high-dose ICS.

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Efficacy Comparison of Mometasone Furoate/Formoterol Versus Fluticasone Propionate/Salmeterol Combination Therapies in Subjects With Persistent Asthma: Noninferiority and Onset-of-Action Findings

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Background: Mometasone furoate/formoterol (MF/F) combination therapy is a new treatment recently approved by the US Food and Drug Administration for the treatment of persistent asthma and currently under regulatory review by Canadian authorities. We report findings from a noninferiority study that compared effects of MF/F and fluticasone propionate/salmeterol (FP/S) combination therapies on pulmonary function and onset of action in subjects with persistent asthma.

Methods: This randomized, active-controlled, multicenter, noninferiority trial enrolled subjects (aged ≥12 years) previously treated with medium-dose inhaled corticosteroid alone or combined with a long-acting β_2-agonist. Following a 2- to 4-week run-in treatment period with MF administered via a metered-dose inhaler (MDI) 200 μg twice daily (BID), eligible subjects were randomized to MF/F-MDI 200/10 μg BID or FP/S administered via a dry powder inhaler (DPI) 250/50 μg BID for 12 weeks. The primary endpoint of this trial was change from baseline in area under the curve (AUC) in forced expiratory volume in 1 second (FEV_1) measured serially for 0 to 12 hours postdose (FEV_1 AUC_{0-12h}). Key secondary endpoints included onset of action, defined as change from baseline in FEV_1 at 5 minutes postdose on day 1.

Results: 722 subjects were randomized to MF/F-MDI (n = 371) or FP/S-DPI (n = 351). The trial's primary endpoint was met, demonstrating that MF/F administered via an MDI was noninferior to FP/S administered via a DPI in the patient population investigated. Mean FEV_1 AUC_{0-12h} at endpoint for MF/F-MDI and FP/S-DPI was 3.43 versus 3.24 L × h, respectively (95%, CI, −0.40 to 0.76). Analysis of onset-of-action characteristics revealed that MF/F's effect on lung function occurred significantly faster than the effect observed with FP/S-DPI. MF/F-MDI was associated with a 200-mL mean increase from baseline in FEV_1 at 5 minutes postdose (first scheduled measurement) on the first day of treatment vs a 90-mL increase for FP/S-DPI ($P < 0.001$).

Conclusions: This trial demonstrated that MF/F 200/10 μg BID administered via an MDI was noninferior to FP/S 250/50 μg BID administered via a DPI in its effect to improve lung function as measured by FEV1 AUC0–12h. However, the onset of action for this effect was significantly faster with MF/F-MDI than with FP/S-DPI.

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Efficacy and Safety of Two Doses of Mometasone Furoate/Formoterol Combination Treatment in Subjects With Severe Asthma

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Background: Multiple strengths of mometasone furoate/formoterol (MF/F) metered-dose inhaler combination therapy have been investigated as new treatments for asthma. We report efficacy/safety findings from an MF/F study in subjects with severe asthma previously uncontrolled on high-dose inhaled corticosteroids (ICS) with or without a long-acting ß$_2$-agonist (LABA).

Methods: This was a 3-month, randomized, double-blind, parallel-group, multicenter study with a 2- to 3-week open-label run-in period during which subjects received mometasone furoate (MF) 400 μg twice daily (BID). Subjects (≥12 years) were randomized to MF/F 200/10 μg BID, MF/F 400/10 μg BID, or MF 400 μg BID. The primary endpoint was the area under the curve (AUC) of the change in serial (0−12 hours) forced expiratory volume in 1 second (FEV_1) for MF/F 400/10 μg vs MF 400 μg from baseline to week 12. Adverse events (AEs) and other clinical safety measures were recorded.

Results: 728 subjects were randomized (mean: age, 47.9 years; asthma duration, 14.0 years; FEV_1 % predicted, 66.3; reversibility, 22.9%; Asthma Control Questionnaire score, 1.93). Improvements in mean changes from baseline in FEV_1 AUC_{0-12h} at week 12 were: MF/F 200/10 μg = 3.59 L × h; MF/F 400/10 μg = 4.19 L × h; MF 400 μg = 2.04 L × h, with

both MF/F doses significantly better than MF ($P < 0.001$). These FEV_1 $AUC_{0–12h}$ values with MF/F 200/10 μg, MF/F 400/10 μg, and MF 400 μg correspond to average hourly increases of 0.30, 0.35, and 0.17 L, respectively. MF/F was associated with a rapid (<5 minutes) and sustained improvement in lung function. The percentages of subjects experiencing an asthma deterioration (ie, severe asthma exacerbation) were 12.4% (MF/F 200/10 μg), 12.2% (MF/F 400/10 μg), and 18.3% (MF 400 μg). There were no notable differences in AEs between the groups.

Conclusions: Both the 200/10 μg BID and 400/10 μg BID doses of MF/F combination therapy led to significantly greater improvements in lung function compared with 400 μg BID MF monotherapy in subjects with severe asthma previously treated with an ICS alone or in combination with LABA.

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Effect of Mometasone Furoate/Formoterol Combination Therapy on Nocturnal Awakenings in Subjects With Persistent Asthma

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Background: Asthmatics often report asthma-related nocturnal awakenings. These sleep interruptions may have a significant impact on patients' quality of life. We characterized the effect of mometasone furoate/formoterol (MF/F) administered via pressured metered-dose inhaler on incidence of nocturnal awakenings requiring short-acting β_2-agonists (SABAs).

Methods: MF/F's effect on nocturnal awakenings requiring SABA was characterized across 3 phase III efficacy trials (baseline = number of nights with awakenings in week before first dose; endpoint = number of nights/wk with awakenings averaged across the 26-week treatment period). Subjects were asthmatics previously treated with low- (n=746), medium- (n=781) or high-dose (n=728) inhaled corticosteroids at various doses. Subjects in the MF/F 100/10 μg BID study were randomized to 26 weeks of twice-daily (BID) treatment with MF/F 100/10 μg, MF 100 μg, F 10 μg, or placebo; subjects in the MF/F 200/10 μg BID study to 26 weeks of BID treatment with MF/F 200/10 μg, MF 200 μg, F 10 μg, or placebo; and subjects in the MF/F 400/10 μg BID study to 12 weeks of BID treatment with MF/F 400/10 μg, MF/F 200/10 μg, or MF 400 μg. All treatments were delivered via a metered dose inhaler.

Results: Baseline awakenings ranged from 0.84–1.05, 1.05–1.26, and 1.33–1.61 nights/wk in the MF/F 100/10 μg BID, MF/F 200/10 μg BID, and MF/F 400/10 μg BID studies, respectively. In the MF/F 100/10 μg BID study, nocturnal awakenings were reduced by MF/F = –0.42, MF = –0.21, F = –0.21, and placebo = 0.14 nights/wk; corresponding changes in the MF/F 200/10 μg BID study were –0.56, –0.35, +0.07 and 0.00 nights/wk, respectively. In each of these placebo-controlled studies, MF/F was superior to placebo ($P < .001$) and F ($P \leq .035$); MF was also superior to F and placebo. In the MF/F 400/10 μg BID study, awakenings were reduced by –0.70, –0.70 and –0.35 nights/wk by MF/F 200/10 μg, MF/F 400/10 μg, and MF 400 μg, respectively; both MF/F treatments were superior to MF ($P \leq 0.006$).

Conclusions: These results provide evidence that validates the role of MF/F in reducing nocturnal asthma symptoms in patients with moderate to severe persistent asthma and supports the efficacy of MF/F compared with that of placebo and F.

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Quality of Life Improvements in Persistent Asthma Subjects Receiving Combined Mometasone Furoate and Formoterol

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Background: A major goal of asthma treatment is to improve patients' health-related quality of life (QoL). Mometasone furoate/formoterol (MF/F) combination therapy was recently approved for the treatment of persistent asthma. The objective of this analysis was to examine the effect of MF/F on health-related QoL at the approved doses.

Methods: Data from 2 phase III studies investigating the effects of MF/F 200/10 μg (study P04334) and MF/F 400/10 μg (study P04431) were included. All subjects were ≥12 yeara and not well controlled on medium dose (P04334) or high-dose (P04431) inhaled corticosteroid (ICS). After 2 to 3 weeks of run-in on twice-daily (BID) MF 200 μg (P04334) or 400 μg (P04431), subjects were randomized to 26 weeks of BID MF/F 200/10 μg, MF 200 μg, F 10 μg, or placebo (PBO) in P04334; or 12 weeks of BID MF/F 200/10 μg, MF/F 400/10 μg, or MF 400 μg in P04431. The Asthma Quality of Life Questionnaire with Standardized Activities (AQLQ [S]), consisting of 4 domains (Symptoms, Activity Limitation, Emotional Function, and Environmental Stimuli), was used to assess QoL. AQLQ(S) score changes from baseline were assessed; a difference ≥0.5 was considered clinically meaningful. Study protocols were approved by IRBs; written informed consent was provided by all subjects or a parent/guardian.

Results: In P04334 (n = 781), subjects receiving MF/F 200/10μg experienced significant improvements in total score (13.1%) and the 4 domain scores of the AQLQ (S) at endpoint vs those receiving PBO ($P \leq 0.005$) or F 10 μg ($P \leq 0.024$). Clinically meaningful improvements in total AQLQ (S) from baseline to week 26 were observed in patients receiving MF/F 200/10 μg (0.61). In P04431 (n = 728), subjects receiving MF/F 200/10 μg experienced significant improvements in total score (12.8%) and the Symptoms and Activity Limitation domain scores of the AQLQ (S) at endpoint vs those who received MF 400 μg ($P \leq 0.017$). Clinically meaningful improvements in total AQLQ (S) from baseline to week 12 occurred in patients receiving MF/F 200/10 μg (0.61), MF/F 400/10 μg (0.51), or MF 400 μg (0.5).

Conclusions: Patients with persistent asthma receiving MF/F had statistically significant, clinically meaningful improvements in QoL in 2 phase III studies. These data suggest that MF/F combination therapy improves the health-related QoL of patients with persistent asthma who are inadequately controlled on medium- or high-dose ICS.

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Efficacy and Safety of Combined Mometasone Furoate/ Formoterol 100/10ìG Twice Daily in Subjects with Asthma Inadequately Controlled on Low-Dose Inhaled Corticosteroids

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Background: Asthma is a variable disease. Optimal control in clinical practice often requires the use of therapy at varying doses. Availability of treatments at multiple strengths is therefore essential. These are results from a 6-month trial of combined mometasone furoate/formoterol (MF/F) 100/10 μg administered via a metered-dose inhaler (MDI) as treatment for asthma deterioration (ie, severe asthma exacerbation) and bronchoconstriction in asthmatics previously treated with low-dose inhaled corticosteroids (ICS).

Methods: In a randomized, multicenter, double-blind, placebo-controlled study in asthma subjects (≥12 years) on ICS with/without a long-acting β_2-agonist (LABA), subjects were assigned to 2 to 3 weeks of open-label MF 100 twice daily (BID), followed by 26 weeks of MF/F 100/10 μg, MF 100 F 10 or placebo (all BID). Co-primary endpoints were time to first asthma deterioration across the 26-week treatment period (MF/F versus F) and change from baseline to week 12 in serial (0−12 hours) forced expiratory volume in 1 second (FEV_1) (MF/F vs MF). Adverse events (AEs) were monitored.

Results: 746 subjects (mean: age = 38.3 years, asthma duration = 14.77 years, FEV_1 % predicted = 75.08, reversibility = 18.69%, Asthma Control

Questionnaire = 1.31) were randomized to 1 of the 4 treatment groups. MF/F increased the time to first asthma deterioration thus decreasing the proportion of subjects experiencing asthma deterioration during the study (MF/F = 16.5%; versus MF = 28.2% [$P = 0.006$]; versus F = 44.7% [$P < 0.001$]; and vs placebo = 45.7% [$P < 0.001$]). Mean FEV_1 AUC_{0-12h} over baseline at week 12 were MF/F = 4.00 L × h; MF = 2.53 L × h; F = 3.83 L × h; and placebo = 1.11 L × h. Low rates of AEs were observed and were similar between treatment arms.

Conclusions: In asthmatics previously treated with low-dose ICS with or without a LABA, MF/F 100/10 μg BID was more effective than placebo, MF, or F (all administered by MDI) in reducing asthma deteriorations and improving lung function.

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Prevalence of Swallowing Dysfunction in Severe Asthma: Preliminary Results

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Background: The widespread use of inhaled corticosteroids (ICS) for the treatment of persistent asthma, although highly effective, may be associated with local side effects. The aim of this study was to evaluate swallowing function in patients with severe persistent asthma, by nasal fibroscopy.

Methods: Sixty-four patients with severe asthma with a mean age of 55 ± 11 years, using inhaled corticosteroids without spontaneous complaints related to swallowing, participated in the study. The participants were evaluated using nasal fibroscopy. Each participant was offered diet boluses (3, 5 and 10 ml) such as thin liquids, pasty and solids, and their swallowing function was determined according to the following criteria: (1) premature oral leakage to the pharynx; (2) laryngeal penetration; (3) tracheal aspiration; and (4) pharyngeal stasis.

Results: Nineteen (25,3%) of the patients with severe asthma presented premature oral leakage or pharyngeal stasis of the bolus after swallowing or laryngeal penetration.

Conclusions: Patients with persistent asthma presented subclinical manifestations of abnormal swallowing, when analyzed using nasal fibroscopy, possibly associated with neuromuscular dysfunction caused by inhaled corticosteroids.

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Influence of Montelukast on the State of Eosinophil Activation in Asthmatic Children

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Background: Eosinophils play an important role in inflammation asthma. In asthma, the leukotrienes are implicated in pathophysiological mechanisms. The antileukotriene montelukast inhibits proinflammatory cytokines and decreases half-life of eosinophils. However, the influence of montelukast on the activation of eosinophils is not clear yet. Therefore, the objective of this work was to evaluate the effect of montelukast on the state of activation of eosinophils in children with persistent asthma.

Methods: It was selected 83 asthmatic children, from 2 to 18 years old, that were randomly assigned to treatment with montelukast or placebo for 12 weeks and 10 healthy control children. Asthma severity was assessed by the criteria of Global Initiative for Asthma (GINA, 2010). Peripheral blood was taken from children after parent's informed consent. The activation of eosinophils was assessed by morphological parameters after adherence to slide, before and after 12 weeks of treatment with montelukast or placebo. The following morphological parameters were evaluated: normal eosinophils, spreading, rounding, presence of localized and generalized pseudopods, release of small, moderate and large quantity of granules, cytoplasmatic vacuoles, cluster of free eosinophils granules, cell degeneration and cell communication.

Results: The number of eosinophils with normal feature in peripheral blood showed an inverse correlation with the severity of asthma, while the emission of widespread pseudopods and isolated granules showed positive correlation with the severity of asthma ($P < 0.0001$; Spearman correlation test). Montelukast was able to reduce the number of eosinophils in peripheral blood from 513 cells/mm^3 to 485 cells/mm^3 ($P = 0.017$, paired t test) after treatment, and to increase the proportion of eosinophils with normal feature from 45% to 51% ($P = 0.03$; Wilcoxon test). The drug was also able to decrease the median of eosinophils with rounded feature (1.5 versus 0) and that releasing free eosinophil granules (2.25 versus 0.5) after 12 weeks of treatment compared to placebo, respectively ($P = 0.005$; Mann Whitney test).

Conclusions: Our data showed, for the first time, that montelukast is able to modify the activation of eosinophils correlated with clinical severity. Parameters of eosinophil activation could be used to the follow up of response to montelukast treatment of asthma individuals.

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The Impact of Administration of Leukotriene Receptor Antagonists, Pranlukast-EK to Infants with Bronchial Asthma

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Background: Bronchial asthma develops by the age of 3 years frequently in childhood in industrialized countries. Pranlukast hydrate, leukotriene receptor antagonists, has been shown to be clinically effective for the treatment of hypersensitivity and childhood asthma. The generic drugs for PLK were universally used in the market, and the effect of the drug also restrain the bronchial asthma onset of infants having an established allergic factor clinically, which necessitates the analysis of the mechanisms of allergic diseases and development of the effective treatment. Therefore we examined influence of administration of Pranlukast-EK (PLK-EK) on the symptom onset of a mild and moderate type of bronchial asthma.

Methods: The 116 patients, who accepted at least 2 to 3 times wheeze after birth, were enrolled ranging from 6 months to 6 years in age. They were treated with Pranlukast-EK (7-10 mg/kg) daily (71 cases, group A) or with suplatast tosilate as a reference (45 cases, group B). The severe and moderate type of patients, who were continuously treated with corticosteroids were excluded. The clinical evaluation was concerning frequency of coughing and wheeze, and that of the β2-receptor agonist inhalation consumption in every 4 months with an asthma diary. In addition, allergic tests; eosinophile count and IgE value were determined in every 4 months.

Results: The frequency of the coughing decreased significantly 12 months later (the last 4 months) as compared to the first 4 months in both groups. Concerning the wheeze, the significant change was also examined in both groups. As for the frequency of the β2-receptor agonist inhalation consumption, the significant decrease was observed in group A and B. The meaningful change of the peripheral blood eosinophile count was not watched in group A and B. The serum IgE value decreased 12 months later in the subgroup of group A, who showed the decreased frequency of symptoms, whereas such a meaningful decrease was never recognized in group B. PLK-EK likely restrains an increase of serum IgE value.
Conclusions: Pranlukast-EK modulates IgE production and eosinophile count in patients with the mild and moderate type of bronchial asthma, and has action to improve wheeze expression clinically.

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Effect of the Treatment With Montelukast in Asthmatic Patient

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Background: Asthma is chronic inflammatory illness of the air roads in which several cells playing an important rol in the development of the bronchial hiperreactivity. The leukotriens are mediators that participate in the inflammatory process being involved in the bronchoconstriction. To evaluate the effectiveness of the Montelukast in patient pediatric and adults with Moderate-Severe Persistent Asthma.
Methods: 201 patients were studied, 101 of 6 to 16 years of age and 100 of 17 or more years old with persistent moderate and severe asthma, without antecedents of illnesses hematológic, hepatic or renal, to those that were administered montelukast in dose from 5 mg of 6 to 14 years and 10 mg to those bigger than this age, once a day during 6 months. A monthly pursuit of its clinical evolution was taken, with control of the renal function and liverwort to the beginning, to the 3 months and when concluding the study; tests of breathing function were also made to the beginning and when finishing the treatment.
Results: Neither of the patients worsened, 81% of them passed to stay asymptomatics in this period and 18.9% they happened to fast. In 6 cases it was necessary to move away the treatment for different reasons for causes unaware to the medication.
Conclusions: The effectiveness of this medication was demonstrated and they were not problems of intolerance or important adverse effects.

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The Effectiveness of two Different Methods of Salbutamol Nebulization in Children with Asthma

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Background: Short acting beta-2 agonists (SABA) inhalation is commonly used in bronchodilatatory test, which is still an important research tool in the diagnosis of respiratory diseases with bronchial obstruction. Bronchodilatatory effect of SABA depends primarily on the degree of patency of the airway, the type and dose of SABA, as well as the type of inhaler and inhalation technique. The aim of the study was to evaluate the spirometric effectiveness of 2 different methods of salbutamol nebulization in asthmatic children.
Methods: The study group included 132 children aged 6 to 18 years (mean: 11.7), 91 (69%) boys and 41 (31%) girls with partly controlled asthma treated in the Allergy or Pulmonology Outpatient Clinics in Children's University Hospital in Lublin. The study was randomized and single blind design. Patients were randomly assigned to one of 2 groups. The first group used 2.2 mg of salbutamol (mean calculated dose) in the breath-actuated nebulizer (BAN) (Marine, Medbryt, Poland), while the second one–5 mg salbutamol (constans dose) in the constant-output nebulizer (CON) (Porta-Neb, MEDIC-AID, UK). Flow-volume curve (dynamic spirometry) was measured before and 20 minuts. after drug nebulization (bronchodilatatory test). FEV1 (expiratory volume in first second) and FEF25-75 (forced expiratory flow at 25 to 75% of forced vital capacity) values were analyzed. The change in FEV1 and FEF25-75 after treatment with respect to baseline was calculated.
Results: The mean baseline value of FEV1 was 67.4% in BAN and 70.5% in CON group and there was no statistical difference between these groups. The significant improvement of measured ventilatory parameters was observed. There was the significant difference in the bronchodilator response to salbutamol between 2 methods of nebulization. The value of FEV1 increased at 16.2% in BAN group and at 12.6% in CON group ($P = 0{,}026$). The value of FEF25-75 increased in both groups at 37.7% and 32.7% respectively and there was no statistical difference between these groups.
Conclusions: We observed greater bronchodilatatory effect of salbutamol inhaled via breath-actuated nebulizer while delivering a double lower dose. 2. Bronchodilatatory test using nebulized salbutamol in breath-actuated nebulizer should be recommended for children.

IMMUNOTHERAPY

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AAAAI Survey on Immunotherapy Practice Patterns Concerning Dosing, Dose-Adjustment after Missed Doses and Duration of Immunotherapy

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Background: Several practical issues dealing with the exact application of allergen immunotherapy (AIT) among European and US allergists are not well known. Guidelines on AIT give recommendations and suggestions for only some of them. We present this unique survey with worldwide response.
Methods: The AAAAI immunotherapy committee conducted a web-based practice patterns survey (program: Survey Monkey) among all members in&outside US on dosing, dose-adjustment after missed doses and duration of AIT.
Results: 1201 Returned questionnaires (almost 25% response rate). 21% were non-US-Canada members. Maintenance doses in USCan are (mean/median): *Dermatophagoides farinae* (Df) combined with *Dermatophagoides pteronyssinus* (Dpt): 2155/1000AU; Df solo 2484/1000AU. Dpt when combined with Df 1937/1000AU; Dpt solo: 2183/1000AU.Cat 3224/2000BAU. Grass 11,410/4000BAU. 57-65% of the dosing falls within the recommended Practice Parameters recommended ranges. Non-USCan allergists expressed maintenance doses in many different units making analysis impossible. Dose-adjustment after missed doses is based on 'time elapsed since the last applied dose' by 77% of USCan and 58% of non-USCan allergists and on 'time since missed scheduled dose' by the rest. Doses are adjusted when a patient comes in more than 14 d/5 wk after the last administration at build-up/maintenance by both USCan and non-USCan colleagues. The mostly followed dose-adjustment schedules after 1, 2, 3 missed doses are: Build-up: repeat last dose, reduce by one dose, reduce by 2 doses; maintenance: reduce by one dose, reduce by 2 doses, reduce by 3 doses. 26% uses a different approach reducing doses by a certain percentage or volume. AIT is restarted after a gap in build-up of >30 days and of >12 weeks during maintenance in both groups (median). Outside USCan AIT is prescribed for 3 years (Median). However, 75% of USCan allergists prescribes AIT for 5 years. Main reasons why to

continue AIT beyond 5 years: 'symptoms came back after stopping' or "patient afraid to relapse."
Conclusions: These results show regional differences on some points (especially AIT duration) and they suggest in which direction to plan further research in 2 areas to establish universal dose-adjustment plans for missed applications and define the usefulness (or lack of) of long-term AIT. Moreover, there is still room for improvement in the way AIT is dosed.

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Development of a National Guideline on Skin Testing and Immunotherapy

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Background: Several international guidelines exist on allergen immunotherapy (AIT) –eg American, European, British, Spanish, Italian- but local conditions that reign in each country limit their applicability. We present the steps we followed to develop a National Guideline on AIT, taking into account local legislation, extracts available, costs and patient preference.
Methods: Firstly a Nation-wide survey on the practice of skin testing and AIT was undertaken among all members of Mexican Allergist Societies. Secondly, based on the replies obtained with the survey clinical questions were formulated on critical points and issues susceptible for improvement, as diagnosed by the survey. Thirdly, all 6 Regional Allergist Societies were visited to obtain the opinion of their members on the clinical questions concerning how immunotherapy could best be practiced under local Mexican conditions. This led to the Consensed experience. Fourthly, 6 experts looked for the replies to the clinical questions reviewing the literature and assigning quality of evidence to the articles on the specific issues treated by each clinical question.
Results: To develop the final document the GRADE approach was used. For each clinical question both, knowledge from the local consensed experience and the evidence-based replies were taken into account, as well as cost, patient preference and safety to make a set of recommendations and suggestions on the most crucial aspects of skin testing and AIT. Forming centers of allergists in Mexico corrected the final draft. The final document came out as the January issue of *Revista Mexicana Alergia* and was presented by the authors in a National Course on Immunotherapy (May 2011), with—apart from the lectures—a more workshop-like part to allow for practical exercising and discussion. The updated questions on allergen immunotherapy for the final board exam are based on the Guideline. Allergy-residents developed a slide-show. In 2012 Regional Allergist Societies shall be visited again.
Conclusions: We present a democratic way of how a National Guideline can be developed, supported by evidence-based medicine and local experience in a country where little is legislated on this respect and quality improvement has to be stimulated by the professional community. We show how implementation can be enhanced.

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Efficacy of Mite Sublingual Immunotherapy in 130 Children with Atopic Dermatitis

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Background: Atopic dermatitis (AD) is a chrinic inflammatory skin disease with increasing prevalence. The aim of this study was to investigate the efficacy and safety of mite sublingual immunotherapy (SLIT) in children with atopic dermatitis (AD).
Methods: A total of 178 AD patients IgE-proved (class ≥3) Dermatophogoicles farinae sensitization. The treatment group (n = 130, 87 male and 43 female, age 2.5–14, SCORAD>7) were given sublingual drops of Dermatophogoicles farinae. They received increasing doses and concentration. Conventional treatment was added in the beginning. The 48 AD cases in the control group were treated with conventional drugs. The treatment time of SLIT is from 7 months to 2.5 years.
Results: In the 130 patients of treatment group, 18 cases were considered cured, 39 got a marked effect, 58 were effective and 15 got no effect, for a total effective rate of 88.46% (115/130). In the control group, 8 got a marked effect, 20 were effective and 20 got no effect, the total effective rate was 58.33% (28/48). There is a statistically significant difference between the treatment group and the control group (p©,0.05). The patients' status of asthma and / or allergic rhinitis were improved after their received the sublingual immunotherapy with no emergence of new allergic diseases or significant side effects.
Conclusions: SLIT appears to be an effective treatment of children with AD.

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Clinical Efficacy and Mucosal/Systemic Antibody Response Changes After Sublingual Immunotherapy in Mite-Allergic Children: A Randomized Double-Blind, Placebo-Controlled Study in Brazil

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Background: This study aimed to evaluate the clinical efficacy and mucosal/systemic antibody response changes after sublingual immunotherapy (SLIT) using *Dermatophagoides pteronyssinus* (Dpt) allergens with or without bacterial extracts in mite-allergic Brazilian children.
Methods: One-hundred and 2 patients presenting allergic rhinitis with or without asthma were selected for a randomized double-blind, placebo-controlled trial and distributed into 3 groups: DPT (Dpt allergen extract, n = 34), DPT + MRB (Dpt allergen plus mixed respiratory bacterial extracts, n = 36), and Placebo (n = 32). Clinical evaluation and immunological analyses were carried out before and after 12 and 18 months of treatment, including rhinitis/asthma symptom and medication scores, skin prick test (SPT) to Dpt extract, and measurements of Dpt-, Der p 1-, Der p 2-specific IgE, IgG4, and IgG1 in serum and -specific IgA in saliva and nasal lavage fluid.
Results: Clinical results showed a significant decline in rhinitis/asthma symptom scores in all groups, but medication use decreased only in active DPT group at 12 months. SPT results showed no significant changes and SLIT was generally safe, with no severe systemic reactions. SLIT using Dpt allergen alone induced increased serum IgG4 levels to Dpt, Der p 1 and Der p 2, and increased serum IgG1 and salivary IgA levels to Dpt and Der p 1. SLIT using DPT+MRB was able to decrease IgE levels, particularly to Der p 2, to increase salivary IgA levels to Der p 1, but had no changes on specific IgG4 and IgG1 levels.
Conclusions: Therefore, SLIT seems to be effective in ameliorating clinical symptoms, but only active SLIT was able to modulate the mucosal and systemic antibody responses. These findings support the role of specific serum IgG4 and IgG1, in addition to salivary IgA, as protective or blocking

antibodies as well as biomarkers of tolerance that may be useful for monitoring activation of tolerance-inducing mechanisms during allergen immunotherapy.

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Treatment Satisfaction with Sublingual Immunotherapy in a Real-Life Setting

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Background: By now, the efficacy and safety of sublingual immunotherapy (SLIT) have been well established, but as for all long-term treatments, adherence to the treatment is essential. Patient-related outcome measures, such as the patients' satisfaction with the treatment, have become more crucial for they may affect treatment adherence.

Methods: To evaluate patient satisfaction with SLIT treatment (Staloral, Stallergenes S.A., France) we designed a prospective, observational, multicenter study. Treatment satisfaction was measured using the QUARTIS questionnaire (= Questionnaire on Respiratory Allergies Treated by Sublingual Immunotherapy). As medical parameters effectiveness and adverse events were documented. Patients with allergic rhinitis and/or conjunctivitis due to tree pollen, grass pollen or house dust mites were included in the study.

Results: 226 patients (94 male, 132 female, median age 37 years) participated in this study. Treatment satisfaction: Compared to a period before treatment, patients reported improved nasal symptoms (13.03 vs. 9.70; $P < 0.0001$) and eye symptoms (6.11 versus 4.43; $P < 0.0001$). After treatment, the allergy was less bothersome in everyday life (9.62 versus. 7.27; $P < 0.0001$). 69.2% of treated patients experienced a better tolerability than they had expected. No relevant differences were observed between the different allergen groups. Effectiveness: The severity of nasal symptoms was reduced by 53.2% (2.35 versus 1.10; $P < 0.0001$). For eye symptoms the severity was reduced by 57.0% (2.14 versus 0.92; $P < 0.0001$). Only 36.1% of the patients needed symptomatic medication in the treatment period compared to 70.1% before treatment. 88.0% of the investigators assessed the patients' well-being as "much better" or "better" after treatment. Adverse events: The overall tolerability was assessed as "good" or "very good" in approximately 90% of the evaluable cases. Only 11.9% of patients experienced adverse events (AEs). The most common AEs were gastrointestinal disorders.

Conclusions: Patients treated with SLIT in a real-life setting were satisfied with the treatment: It was tolerated well, patients' symptoms improved and their allergy had less impact on daily life. The patients' high level of treatment satisfaction as well as the good tolerability and effectiveness of the extract are important factors for they may help to improve treatment adherence.

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Long-Term Clinical Efficacy of Immunotherapy in Rhino-Conjunctivitis with Pollen Extract

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Background: Evaluate long-term clinical efficacy 2 years after suspension of specific immunotherapy in patients with seasonal rhino-conjunctivitis.

Methods: During 5 years in a pre-seasonal period an extract of 7 grass pollens by sub cutaneous route (SCIT) was administered to a group of 16 patients with moderate and severe rhino-conjunctivitis, monosensitised to grass pollens. The mean age of the patients was 27.1 years, with homogeneous sex distribution. After the terminus of SCIT the group was followed during 2 more years to evaluate symptomatology and the use of rescue medication, during pollen season. We have compared this group with another group who did not perform SCIT. All patients received weekly information about forecasts and grass pollens count in their residential area. An informatics sheet was used to evaluate daily 4 degrees of 6 parameters including nasal and eye symptoms and any use of medication used to control the disease. As statistical method ANOVA test and t test was used for analyse mean differences between the 2 groups. For correlations the Spearman method was used.

Results: During the immediate 2 years after SCIT in the active group, a significant reduction on symptoms (42%) as well as a reduction on the use of rescue medication (59%) were observed ($P < 0.01$), compared with the control group. The eye symptoms had a higher reduction than nasal symptoms after the suspension of IT.

Conclusions: A significant efficacy of SCIT was verified even 2 years after the suspension of the treatment, with reduction on symptoms and on use of medication. The use of a daily score of symptoms and the use of rescue medication was very useful and confortable to the majority of the patients. Also providing regular information to patients regarding pollen count and climatic changes by electronic mail was considered useful to both groups.

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IGE/IGG4 Ratio as a Possible Surrogate Marker of Clinical Efficacy During Allergen-Specific Immunotherapy with House Dust Mite Vaccines

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Background: Allergen immunotherapy (AIT) induces IgG4 antibodies with blocking effect, and long-term reduction of IgE. The problem of finding suitable surrogate paraclinical markers during AIT is currently very relevant. The aim was to evaluate the allergen-specific IgE/IgG4 ratio as an immunological correlate to clinical efficacy during AIT with House Dust Mite (HDM) allergen vaccines in Cuban asthmatic patients.

Methods: Three separate Double-Blind Placebo-Controlled clinical trials of AIT were performed using standardized registered allergen extracts of 3 HDM species: *Dermatophagoides pteronyssinus*, and the tropical species *D. siboney* and *Blomia tropicalis*. Each clinical trial included 40 asthmatic patients, totalling 120 individuals. Half of them received placebo. Allergen-specific IgE and IgG4 antibodies were measured by ELISA. Antibody titres were normalized and averaged between the 3 trials. Size effect was calculated as the Standard Mean Difference (SMD) between the active and placebo groups, using meta-analysis tools.

Results: There was a significant increase of IgG4 antibodies ($P < 0.05$) after 6 months of treatment. At 12 months, the IgG4 increase was even greater and the IgE decrease achieved also significance ($P < 0.05$). Thus, IgG4 induction appeared to precede IgE changes, in agreement with the possible role of the Treg/IL-10 response induction at the initial AIT phase. Moreover, 83% of patients showed a decrease of the IgE/IgG4 ratio in the active groups, whereas only 32% showed reduction in placebo groups. The IgE/IgG4 ratio was the immunological variable with the greatest size effect value (SMD = 0.81 95% CI, 0.71-0.91), as compared to changes in IgE or IgG4 levels, alone. The size effect value was close to the clinical effect (symptom-medication score SMD = 1.2 95% CI, 0.7-1.7). Per-patient changes in IgG4 levels, as well as, in the IgE/IgG4 ratio, were significantly correlated to the symptom-medication variable ($r = 0.23$, $P = 0.04$).

Conclusions: These results support the use of the IgE/IgG4 ratio as an easily measurable marker for monitoring the allergen-specific immunity during AIT with HDM in asthmatic patients, and possibly, for predicting patient's clinical improvement after 1 year of treatment.

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Allergy Training and Immunotherapy in Latin America: How Survey-Results Lead to a Regional Overview

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Background: In April 2011 a group of Latin American (LA) allergy experts, leaders in their countries in the area of immunotherapy, met in Cordoba, Argentina, to discuss how allergy and allergen-specific immunotherapy (ASIT) can be improved in the region. The need for a situational sketch was expressed.

Methods: A questionnaire on allergy training (AT), ASIT, extracts and legislation was sent out to 22 leaders in the field of nine LA countries to obtain an overview of the LA situation.

Results: Results are presented with descriptive statistics. All 22 questionnaires were returned (9 countries). AT in 56% of the surveyed LA countries is at the third-level of medical care, after a core-training of 2 to 3 years internal medicine or pediatrics; in 3 countries it is a second-level career and in one country there is no AT. Board certification with exam is only mandatory in a third of the countries; recertification being obtained without exam. Mostly, training is in general allergy; pediatric AT only exists in 2 countries. Both sublingual (SLIT, only in the form of drops) and subcutaneous (SCIT) immunotherapy are practiced in all countries, from the age of 3 years (mean, range 1–5 years) onward. As no strict legislation exists IT can be managed by non-allergists in 7/9 countries. Mixed extracts are used with mostly 3 to 5 allergens/vial (range 2 to 6-10 allergens/vial) and all countries have bacterial vaccine. SCIT extracts come from US and European (89%) and 56% local providers. SLIT extracts are almost exclusively from Europe (Spain), but in Argentine, Brazil, and Mexico also local SLIT extracts exist. There is rudimentary regulation concerning extract potency in 2 countries. IT is generally paid for by private patients. Insurance companies reimburse IT in 56% of the countries, the social security system in 33% and in one country selected third level governmental hospitals supply IT. Publications on adverse events with IT are starting to appear (3 countries) and 3 countries have their own guidelines on IT (one only in pediatrics).

Conclusions: A clearer picture where and how to improve AT and ASIT in LA has been obtained; however, unmet needs on ASIT are still pending.

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Clinical Effects of Immunotherapy in Patients with Allergic Disease in the National Institute of Respiratory Diseases

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Background: Previous studies have shown that after the treatment with immunotherapy there is a reduction in the number of visits to emergency services for asthma crisis, a significant improvement in pulmonary function tests: forced vital capacity (FVC), forced expiratory volume percentage in 1 second (FEV1%) and in the percentage of peak expiratory flow (PEF%) and the dose and number of drugs. There is also evidence of decreased response to skin tests and IgE levels with immunotherapy specific to Dermatophagoides pteronyssinus (Dpt).

Methods: The objective of this study was to evaluate the clinical effects of immunotherapy in patients with allergic disease treated at the National Institute of Respiratory Diseases in Mexico City, Mexico. There was a random selection in a prospective study of 99 patients with positive skin tests and more than 18 months of treatment with subcutaneous immunotherapy specific to epithelia, pollens from trees, grasses and weeds; at the beginning and the end of the immunotherapy there was an evaluation of the scale of rhinitis symptoms and asthma control; pulmonary function tests were performed as well (spirometry).

Results: At the initial evaluation, 97% of patients presented moderate to severe persistent rhinitis, 80% of patients with asthma was uncontrolled; after 18 months with specific immunotherapy 80% of patients presented moderate intermittent rhinitis and asthma control was achieved in 85% of the patients. The FEV1 average increased from 78% at the beginning to 89% ($P < 0.001$). The average bump at the beginning of the specific immunotherapy was 12 cm for Dpt, for trees 10 cm, for weeds 8 cm and for grasses 8 cm; at the end of the SIT the average bump for Dpt was 10 cm, trees 2 cm, weeds 1cm and grass 0 cm (P value < 0.01).

Conclusions: The specific subcutaneous immunotherapy had beneficial clinical effects in patients with allergic disease, with significant improvement in pulmonary function tests and reduced positivity in skin tests, specifically for patients who were sensitive to pollens from trees, weeds and grasses.

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Approach of Paediatric Allergists to Allergen Immunotherapy in Severe Persistent Allergic Rhinitis

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Background: Hospital-based allergists manage children with allergic rhinitis (AR) in Lombardy (paediatric population 900,000 ca). These specialists' perception of severity in referrals was assessed by questionnaire.

Methods: During May 2011, a spreadsheet was e-mailed to 51 paediatric allergy units, followed up by telephone interviews by trained volunteers providing online assistance for compilation. Data were collected in preschoolers (group I), school-age (group II) and adolescents (group III).

Results: Overall response was 66.6%. AR estimates among these referrals were 75.6% (70.6% in group I, 75.5% in group II and 82.9% in group III). AR alone occurred in 18.7% (21.4%, 17.2%, and 19.1%) of cases. Co-morbidities included asthma in 18.1% (30.1%, 14.1%, and 13.4%), conjunctivitis in 25.5% (13.8%, 27.8%, and 34.6%), or both in 13.4% (5.3%, 16.4%, and 15.7%). Specialists report intermittent AR in 51.4% (52.9%, 49.5%, and 54.7%), persistent disease in 48.6% (47.1%, 50.5%, and 45.3%), mild in 61.5% (53.6%, 64.1%, and 63.9%) and moderate/severe in 38.5% (48.4%, 35.9%, and 36.1%) of cases. In moderate/severe persistent rhinitis (18.4%), allergy was considered relevant for 42.2% (46.4%, 35.9%, and 36%) of cases. SIT was considered appropriate for mild persistent grass-induced rhinitis in 22.5% (10.1%, 29.2%, and 22.7%, respectively) and for 10.3% of moderate/severe persistent rhinitis (3.8%, 18.9%, and 15.8%).

Relevant allergens	Group I	Group II	Group III
Dust mites	45.9	46.2	57.3
Grass pollen	37.8	64.7	69.7
Ragweed	11.1	23.5	46.1
Tree pollen	17.1	20.2	27
Animal danders	13.3	19.7	16.8
Mould	15.6	23.5	13.5
Food allergens	5.8	2.1	0.8

Conclusions: Rhinitis was the most frequent symptom, though rarely alone. From the Italian ISAAC, AR affects 18.9% schoolchildren and 35.5% adolescents, while severe persistent rhinitis affects 30,700 (3.42%) in Lombardy. Some severe persistent rhinitis was considered indicative for SIT in Group I, and incidence was higher in other groups. SIT is likely to be considered particularly in the subset of patients not completely controlled by symptomatic drugs. In the absence of clinical surveys and given referral study limitations, epidemiological surveys are needed to quantify demand in the pediatric population.

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Compliance and Persistence to Grass Immunotherapy Treatment is Comparable for Allergy Immunotherapy Tablets and Subcutaneous Immunotherapy: A Swedish Registry Study

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Background: Allergy immunotherapy tablets (AITs) are administered by the patients in their homes and the medical compliance and persistence may therefore be poorer than for subcutaneous immunotherapy (SCIT) administered by physicians. Purpose: to compare medical compliance and persistence for AIT and SCIT treatments in Swedish patients with allergic rhinoconjunctivitis (ARC).

Methods: Two products for the treatment of grass pollen induced ARC were investigated: a SCIT treatment (Alutard SQ, *Phleum pratense*, 100,000 SQ-U/mL) and an AIT treatment (Grazax, *Phleum pratense* 75,000 SQ-T/2,800 BAU), ALK, Denmark). Data were drawn from the Prescribed Drug Registry 2007–2009, the National Board of Health and Welfare in Sweden. Data on patients treated and number of packages sold were used to calculate the compliance and persistence for each of the 2 products, for patients who started treatment in 2007.

Compliance: calculated as the duration of treatment estimated from the number of packages sold (assuming 100% compliance), divided by the actual duration of treatment (the time estimated from the first to the last observed prescription, plus the duration of the last package). *Persistence*: calculated as the percentage of patients who continued their treatment in 2009 with at least initiation of 1 treatment package or vial in 2009.

Results: Grass AIT treatment was started by 636 patients and the grass SCIT treatment by 354 patients in 2007. The persistence of treatment in 2009 was 55% for grass AIT treatment and 57% for grass SCIT treatment. The estimated average duration of treatment was 2.34 years for grass AIT and 2.47 for grass SCIT at cut-off 31 December 2009. The average number of tablets used per patient during this period was 770. For grass SCIT treatment the average number of up-dosing kits used was 1.07 and the average number of maintenance vials was 3.26 (5 injections per vial). This corresponded to a compliance of 90% for grass AIT and 82% for grass SCIT.

Conclusions: Compliance to treatment for grass ait and grass scit treatments were both high (>80%) and comparable. The persistence of swedish patients was comparable for grass AIT and grass SCIT treatments during the period 2007 to 2009.

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Fungal Sensitization and Its Relation to Asthma and Allergic Rhinitis in Children Aged 6 to 7 Years

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Background: The purpose of the study was to determine the skin sensitization to environmental fungi and its relation with the presence of asthma and allergic rhinitis in children aged 6 to 7 years.

Methods: A cross-sectional and analytical study was conducted in 100 school children aged 6 to 7 years in a primary school of San Antonio de los Baños, La Habana, Cuba, in February-March, 2007. The ISAAC (International Study of Asthma and Allergies in Childhood) questionnaire was applied to determine the presence of asthma and allergic rhinitis. The sensitization to environmental fungi *Penicillium, Cladosporium* and *Alternaria* was explored by skin prick tests. The statistical association between sensitization to each environmental fungi and the presence of asthma and allergic rhinitis was determine by chi-square tests.

Results: The 27% of the selected sample suffered from asthma, 40% from allergic rhinitis and 56% showed asthma, rhinitis or both, which was grouped in a term called allergic respiratory disease. From these 56 children, 18 had positive prick tests to one or more environmental fungi (32%); 9 showed cutaneous reactivity to *Cladosporium* (16%), 9 to *Penicillium* (16%) and 5 to *Alternaria* (9%). There was a significant statistically association between the cutaneous reactivity to *Penicillium* and the presence of allergic rhinitis ($X^2 = 5.46$ $P = 0.05$). There were no associations between any other fungal sensitization and the presence of asthma or allergic rhinitis.

Conclusions: Allergic sensitizations to environmental fungi were relevant in children with asthma, rhinitis or both; there was a significant statistically association between sensitization to *Penicillium* and the presence of allergic rhinitis.

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Study on the Sensitization Rates to Airbone Pollen and Mold in Children

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Background: Aeroallergens are important causative factors for allergies such as allergic rhinitis, allergic conjunctivitis and asthma. Previous studies for the sensitization rate to aeroallergen were based on those patient groups who had visited the pediatric allergy clinic. Compared to that, we inquired into the sensitization rates based on general school aged student population group in the city of Incheon, Jeju and Ulsan.

Methods: With informed consent, skin prick tests were performed on 5,094 students between April and June, 2010. Common 21 aeroallergens were used on elementary school student while middle and high school students were tested upon 28 allergens. 28 allergen list as positive control (1%Histamine), negative control (Normal saline), *D.pteronyssinus, D.farinae*, Citrus red mite, pollen (Birch, Alder, Oak, Japanese cedar, Pine, Willow, Elm, Maple, Bermuda grass, Timothy grass, Rye grass, Orchard, Meadow grass, Vernal grass, Mugwort, Japanese hop, Fat hen, Ragweed, Plantain), mold (*Penicillatum, Asperugillus, Cladosporium, Alternaria*) and 21 kinds of allergens that were used on elementary school students count as same as above except Elm, Rye grass, Orchard, Meadow grass, Vernal grass, Fat hen, Plantain.

Results: If arranged in rates of higher sensitization were *D. pteronyssinus* (25.79%), *D. farinae* (18.66%), Mugwort (6.20%), Willow (4.07%) in Incheon, *D. pteronyssinus* (33.35%), *D. farinae* (24.78%), Japanese cedar (15.36%), *Alternaria* (7.33%) in Jeju, *D. pteronyssinus* (32.79%), *D. farinae* (30.27%), Alder (10.13%), Birch (8.68%) in Ulsan respectively. The sensitization rate of Japanese cedar was statistically significantly higher in Jeju. The sensitization rate of Birch, Alder, Oak was higher in Ulsan. The sensitization rate of Ragweed was 0.99% in Incheon, 1.07% in Jeju, 0.81% in Ulsan. The sensitization rate of Mugwort in Incheon was 6.20% which was meaningfully

higher in comparison to 2.32% of Jeju and 2.73% of Ulsan. The sensitization rate of *Alternaria* was 2.98% in Incheon, 7.33% in Jeju, 2.39% in Ulsan and as we can see it was higher in Jeju. The sensitization rate of Dermatophagoides had an increasing tendency with increasing age.

Conclusions: Changes in exposure rate to allergens with increasing ages brings changes in sensitization rates. And because there are changes in sensitization rates due to different regional living environmental status and discrepancies of surrounding biologic species, this would leave us there lies needs for subsequent studies and nationwide researches.

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Influence of Degree of Specific Allergic Sensitivity on Severity of Rhinitis and Asthma in Chinese Allergic Patients

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Background: The associations between sensitizations and severity of allergic diseases are controversial. This study was to investigate the association between severity of asthma and rhinitis and degree of specific allergic sensitivity in allergic patients in China.

Methods: A cross-sectional survey was performed in 6,304 patients with asthma and/or rhinitis from 4 regions of China. Patients completed a standardized questionnaire related to the respiratory and allergic symptoms, their impact on sleep, daily activities, school and work. They also underwent skin prick tests with 13 common aeroallergens. 2,268 of them were taken blood for serum specific IgE (sIgE) measurements for 16 common aeroallergens.

Results: Significantly higher percentage of patients with moderate-severe intermittent rhinitis were sensitized to outdoor allergens while percentage of patients sensitized to indoor allergens was increased with increasing severity of asthma. Moderate-severe intermittent rhinitis was related to skin wheal size and sIgE to Artemisia vulgaris and Ambrosia artemisifolia ($P < 0.001$). Moderate-severe asthma was associated with increasing in skin and sIgE response to Dermatophagoides (D.) pteronyssinus and D. farinae ($P < 0.001$). Moderate-severe rhinitis and asthma were also associated with increasing in number of skin and sIgE sensitized allergens.

Conclusions: Outdoor allergen sensitizations are significantly associated with severity of intermittent rhinitis and indoor allergen sensitizations are significantly associated with severity of asthma in patients in China. Number of allergen sensitization is also related to severity of rhinitis and asthma.

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Allergic Sensitization to Domestic Mites in Santo Domingo, Dominican Republic

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Background: The objective of this study was to determine the prevalence of mites sensitization in Santo Domingo.

Methods: One hundred consecutive patients (52 males and 48 females, mean age 30.3 years; 4–68) with asthma and /or allergic rhinoconjunctivitis were skin tested with 9 commercial extracts of mites of the following species: Dermatophagoides pteronyssinus, D. farinae, Blomia tropicalis, B. kulagini, Acarus siro, Lepidoglyphus destructor, Tyrophagus putrescentiae, Glycyphagus domesticus and Chortoglyphus arcuatus. A skin test was considered positive when the wheal was > 3 mm with erythema. Conventional exclusion criteria were used, in order to avoid masking a skin reaction.

Results: A positive skin test to any of the mites tested was detected in 98% of the patients; Dermatophagoides spp. was positive in 89% of the patients; 15% were exclusively positive to Dermatophagoides spp; 87% reacted to Blomia spp. and 3% were exclusively positive to Blomia tropicalis spp; 80% were sensitized to 3 or more specie.

Conclusions: The allergy sensitization to domestic mites in Santo Domingo is high. Sensitization to several species is very common. B. tropicalis is an important species in this region. With these results we could extrapolate that immunotherapy with only Dermatophagoides species could not be enough achieve clinical improvement in mite allergic patients. Other species, such as B. tropicalis may be needed.

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Prevalence Sensitizing to Most Common Allergens in Elderly in Western Mexico

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Background: Allergic diseases affect a great proportion of seniors. Our objective was to determine the prevalences of allergen sensitization in this age group.

Methods: Retrolective study was performed during 3 years follow-up at Hospital School in Guadalajara city, Mexico. The allergen sensitization with a common allergen panel by a prick test was evaluated in seniors of first consultation in an Allergology Service.

Results: We included 60 subjects, with an average of 67.7 years old; 83.3were women. Diagnosis of allergic rhinitis was present in 60%, allergic rhinitis plus asthma in 30%, and asthma alone in 10%. Non atopic comorbidities were present in 56.7% of the cases. Median of serum IgE was 124.95 UI/mL, whereas for positive prick test was 4 (minimum-maximum, 1–21); 13.3% were sensitized to just 1 aeroallergen, and 55% were to more than 3 aeroallergens. Sensitization to pollens was predominant, even more to tree pollens. One by one, house-dust mite, Fraxinus sp and Amaranthus palmeri were the most common found. To have diabetes was associated to a minor positive prick test ($P = 0.021$).

Conclusions: It's recommendable to identify the allergen sensitization in seniors with allegic disease symptoms, as part of their evaluation. The most common sensitizing allergens are similar for other age groups proceeding from the same area. It's recommendable to search for more findings possibly associated between diabetes and number of positive prick tests.

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Cross Reactivity Between Cypress Pollen and Plant Food in Queretaro, Mexico

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Background: Food allergy prevalence is growing continuously. Reasons are unknown. It is suggested that environmental factors have a greater impact

than genetic. The hay may be responsible for developing food allergy to plants. The geographical and climatological condition of Querétaro city, and having a large industrial corridor are risk factors for development allergic problems. In Mexico there are no prevalence studies on food allergy and therefore the most common food allergens. The objectives of the study are to identify common allergen sensitization and to determine if there is cross-reactivity between cypress pollen and plants most commonly consumed in Queretaro.

Methods: We performed a correlation study in patients allergic to cypress pollen to determine if there is cross reactivity between it and plant food by spick prick test and specific IgE titers by inmunocap technique.

Results: Studied 45 patients, 23 (51,1%) males and 22 (48,8%) women, 43 patients had allergic rhinitis (95,5%), 23 had asthma (51,1) and 12 had atopic dermatitis (26,6%). As background, 16 patients (35,5%) had no first-degree relatives with atopy, in 17 (37,7%), the father had a history of allergy, the mother was allergic in 31,1%, and 24,4% (11) had at least one sibling with allergy. 51,1% (23) were born by eutosia, and 22 (48,8%) via cesarean section. 24 (53,3%) received mixed feeding, 17 (37,7%) were breastfeed and only 4 (8,8%) received only formula. The average time of breastfeeding was 5,3 months. Person correlation coefficients were found in descending order relationship with oregano (0.69), corn (0.65), wheat (0.63), oats (0.63), bean (0.597), melon (0.569), tomatoe (0.538), lentil (0.537), peanut (0.515), chickpea (0.480), soybean (0.479), carrot (0.474), avocado (0.457), apple (0.438), pepper (0.418), celery (0.187).

Conclusions: Although the literature reported association between cypress with tomato only, we found relationship with apple, wheat, celery, peanuts, melon, lentil, tomatoes, beans, avocados, soybeans, chickpeas, corn and pepper.

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Study of the Allergenic Crossreactivity and Allergenic Composition of *Dermatophagoides Pteronyssinus* and *Blomia Tropicalis*

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Background: *D. pteronyssinus* and *B. tropicalis* are the most common house dust mite species worldwide. *D. pteronyssinus* and *B. tropicalis* are the most prevalent species in the tropics. Twelve allergens have been described in *B. tropicalis* and fifteen in *D. pteronyssinus*. The objectives of this study were: 1) to analyze the prevalence of sensitization to *B. tropicalis* and *D. pteronyssinus* on the tropical Island of Martinique; 2) to evaluate the allergenic cross-reactivity *between D. pteronyssinus* and *B. tropicalis* and 3) to identify common, and species specific allergens, using mass spectrometry (MS). The serum of patients sensitized to a single, or to both species, was further analyzed by western blots.

Methods: The sera of 1,243 consecutive patients evaluated for allergic rhinitis and/or asthma were evaluated for specific IgE using direct ELISA. All patients resided on the tropical island of Martinique. Crossreactivity between both species was analyzed by ELISA Inhibitions. Proteins of both species were digested with trypsin and analyzed by MS/MS (MALDI TOF/TOF). Different databases were used for the identification of the proteins.

Results: Sensitization to *B. tropicalis* was detected in 868 sera and to *D. pteronyssinus* in 919 sera; 135 were sensitized exclusively to *B. tropicalis* and 177 to *D. pteronyssinus*. Specific IgE levels to *D. pteronyssinus* were significantly higher than to *B. tropicalis* (Mean 0.67 OD $\pm$ 0.89 vs. 0.86 $\pm$ 1.04; $P < 0.001$). The correlation coefficient between specific IgE levels to both species was 0.135. ELISA Inhibition studies demonstrated minimal cross-reactivity between both species. Western blots done with the serum of poly or monosensitized patients revealed specific IgE binding to similar proteins. Proteomic analysis revealed the presence of the following allergens: *B. tropicalis*: groups 2, 3, 4, 6, 9, 14 and groups 1, 2, 3, 4, 8, 11, 14, 15, 16 and 18 in *D. pteronyssinus*. Species specific, as well as common proteins were detected.

Conclusions: There is limited crossreactivity between *B. tropicalis* and *D. pteronyssinus*. Sensitization to their allergens seems to be a parallel phenomenon. Allergen extracts of both species are needed for the correct diagnosis and treatment of mite allergic individuals in the Caribbean.

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Ficus Benjamina Sensitization in Adult Patients with Rhinitis

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Background: In Monterrey there are a considerable number of *Ficus benjamina* trees, but the awareness-related information to this plant is scarce. The objective of this study is to determine the frequency of sensitization *to Ficus benjamina* in patients with rhinitis who were attended the Regional Centre of Allergy and Clinical Immunology of Monterrey, Mexico.

Methods: Observational, transversal and descriptive study. We included patients over 18 years old with chronic rhinitis, which completed a questionnaire to assess exposure to *Ficus benjamina.* Skin prick tests (SPT) to common aeroallergens in our region with extract of *Ficus benjamina* (*Allerstand* Company) had done in all subjects.

Results: A total of 177 patients were included, mean age was 38 years, 65% (115) were female, 135 (76%) reported contact with a *Ficus benjamina* tree in their home or neighbor. 12 (17%) patients had a positive skin test to *Ficus benjamina*, but up to 15% (26) had clinical manifestations when they were close to a tree of *Ficus benjamina*. Most patients with positive skin test to *Ficus benjamina* (76.9%, 9) had positive test more than one of the aeroallergen tested. The association between *Ficus benjamina* and sensitization to other aeroallergens, as well as the symptoms associated to the contact with the tree was not statistically significant.

Conclusions: Sensitization to *Ficus benjamina* is common and was similar to that reported in European countries. To demonstrate the association between sensitization to *Ficus benjamina* and symptoms should be made studies with nasal challenge test.

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Identification and Statistic Analysis Related with Climatic Variability and Transportation of the Most Abundant Spores in Mexicali, Mexico

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Background: The Mexicali valley with intense agricultural and industrial activities has among its community a high incidence of allergenic diseases and one of the causes could be suspended particles including pollen and spores. Unfortunately, there are not backgrounds for aerobiological analyses, being Mexicali a city where the levels of atmospheric contamination have exceeded the air quality standards (Reyna, 2006). This situation has led

studies to determine the impact of concentrations of air pollutants including spores as causal agents in allergies and respiratory diseases.
Method: Three periods of sampling have been carried out. The first sampling in 2005 with Rotorod equipment; the quantitative parameters were diversity, volume, and frequency of spores, as well as its relation with meteorological factors, like average temperature, relative humidity, and precipitation; a second study was performed in 2008, with same parameters and equipment. In 2011 new sampling is performed by using the Burkard sampler which includes same parameters as the first and second sampling.
Results: In 2005 the most abundant types were Alternaria 3,419/m^3 with greater representativeness in August (24.81%); the same to Bipolaris 1,846/m^3 (22%); Stemphylium 1197/m^3 with greater presence in February (15%); temperature and relative humidity were correlated with the presence of spores being an association linear loss; the correlation in annual tendency is smaller, related to the seasonal monthly correlation; correlation of cold season is greater than correlation of the warm season. A study carried out in 2008 showed, high incidence of Cladosporium, on April 57, 32%. Same month in the first sampling only 15.11%. In 2011 richness of Ascospora, Cladosporium and Periconia, showed very different results the same months but sampling in 2005 and 2008.
Conclusions: The studies show different data related with type and richness on same months. Data obtained in the first study correlated the relationship between air pollution caused by fungal spores and the incidence of childhood asthma in Mexicali (de la Fuente, 2009).

AEROBIOLOGY

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Thunderstorm-Related Asthma in Patients Sensitised to Olea Europaea Pollen: Twenty Emergency Department Visits for Asthmatic Symptoms in One Single Day

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Background: Asthma exacerbation associated with thunderstorms has been reported in several countries. Common to all epidemics of thunderstorm-related asthma is a significant increase in atmospheric allergen load during and immediately after a thunderstorm. Sensitization to Alternaria species or to grass and parietaria pollens has been suggested to play a key role in thunderstorm-related asthma. The only reported event of thunderstorm-related asthma in Mediterranean area was attributed to sensitization to parietaria pollen.
Methods: Here we describe a series of 20 patients who accessed to an Emergency Department in Puglia (Italy) for sudden and severe dispnoea between the 27th and the 28th of May 2010 (between 15:36 and 5:02), just after a violent thunderstorm which occurred after a very warm morning (mean atmospheric temperature: 29°C). All patients have been subsequently visited by an allergist and underwent a complete allergological work-up which included skin prick tests and a careful clinical history record. Data from atmospheric pollen count were recorded.
Results: In the months between 10th of May and 10th of June 2010, a total of 86 accesses to same Emergency Department were recorded for asthma exacerbations, 20 of them during the studied day. Patients' mean age was 44.25 ± 18.5 years (range: 9–81), 8/20 females, 2 smokers, 16 with a previous history of known respiratory allergy. All 20 patients were sensitized to Olea europaea pollen, 7 of which were monosensitized. Other sensitizations were: 10 patients to grass, 7 to parietaria, 5 to compositae, 5 to cypress, 5 to house dust mites, 3 to dog and 1 to cat danders. Mean atmospheric pollen count was 170 granules/m^3 for Olea europaea and 60 granules/m^3 for grass pollen.
Conclusions: This is, in our knowledge, the second thunderstorm-related asthma episode described in Mediterranean area and the first one in which sensitization to Olea europaea played a key-role. This result should focus the possibility that not only the increase of molds and grass pollen load after a thunderstorm may raise asthma exacerbations.

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The Revised Edition of Korean Calendar for Allergenic Pollens

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Background: The old version of pollen calendar was used until this year in South Korea. That calendar did not reflect current pollen distribution and concentrations that can be influenced by changes in weather and environment. A new pollen calendar of allergenic pollens was made based on the data on pollen concentrations obtained in 8 regions nationwide between 1997 and 2009 in South Korea.
Methods: The distribution of pollen grains was assessed every day at 8 areas (Seoul, Guri, Busan, Daegu, Jeonju, Kwangju, Kangneung, and Jeju) nationwide for 12 years between July 1, 1997 and June 30, 2009. Pollen were collected by using Burkard 7-day sampler (Burkard manufacturing Co Ltd, Hertfordshire, UK), and the collected pollens were sent every week to Hanyang Guri Hospital. Then pollens were strained with Calberla's fuchsin staining solution and were identified. The number of pollen grains per m^3 was calculated.
Results: Alder, birch and Japanese cedar started to appear in February. Japanese cedar showed a highest pollen concentration in Jeju. Pine became the highest pollen in May, and the pollen concentrations of oak and birch also became high. Common ragweed appeared in the middle of August and showed the highest pollen concentration in the middles of September. Japanese hop showed a high concentration between the middle of August and the end of September, and mugwort appeared in the middles of August and its concentration increased up until early September. Birch appeared earlier in Kangneung, and pine showed a higher pollen concentration than in the other areas. In Daegu, Oriental thuja, alder and juniper produced a large concentration of pollens. Pine produced a large concentration of pollens between the middle of April and the end of May. Weeds showed higher concentrations in September and mugwort appeared earlier than common ragweed. In Busan where is the southeast city, the time of flowering is relatively early, and alder and Oriental thuja appeared earliest among all areas. In Kwangju, Oriental thuja and hazelnut appeared in early February. In Jeju which is the end of southern island, Japanese cedar showed a higher pollen concentration than the other areas
Conclusions: New information on pollen distributions and concentrations should be provided for the general publics or allergic patients through the website in order to prevent the occurrence of pollinosis.

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Aerobiological Study of Anemophilous Pollens in the City of Toluca, Mexico

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Background: The pollen dispersal by wind is a natural event of great biological significance and an etiological factor in the genesis of allergic respiratory diseases. This is the first such study carried out in the city of Toluca, Mexico.

Objective: To present the data of collected pollen from September 2004 to September 2005.

Methods: The pollen was collected, using a Hirst type 7-day recording volumetric Spore Trap. According to the British Aerobiology Federation, we decided to read 12 sweeps in 24 hours in a transverse to have the mean pollen count. Standard equipment used for aerobiological sampling worldwide was used. Statistical analysis is a descriptive study using the SPSS Software.

Results: We found 14, 078.61 pollen grains, coming from 32 diferent pollinic types in the 12 Transverse traverses in the year analized. The 6 leading taxa, in order of abundance, were: Cupressaceae (49%), Oleaceae genus *Fraxinus sp* (17%), Betulaceae genus *Alnus* (14%), Pinaceae (11%), Gramineae (6%), Asteraceae or Compositae (3%). The most prevalent months regarding pollen counts were January and February 2005 in wich Cupressaceae and Oleaceae genus *Fraxinus* were accounted.

Conclusions: In aerobiological terms both Cupressaceae and *Fraxinus* seem to be a major risk for potential sensitized individuals due to its known allergenicity and its high atmospheric concentrations between late winter and early spring, followed by Alnus, Pinaceae, Gramineae, Asteraceae, Casuarinaceae, Schinus, Cheno/Amp and Moraceae. This is the first effort to create the Mexican Aerobiological Network (REMA), and further studies are needed to correlate clinical data.

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Allergenic Significance of Airborne Rhizopus Stolonifer (ehrenb.) Vuill, a Common Bread Mold

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Background: Airborne fungi, a significant constituent of atmospheric bioaerosol, are well-known source of allergens and can cause allergic rhinitis and bronchial asthma in sensitive subjects. *Rhizopus stolonifer*, the filamentous fungus is a widely distributed thread-like Mucoralean mold. Commonly found on bread surfaces, it takes food and nutrients from the bread and causes damage to the surface where it lives. Although a significant exposure risk is assumable in indoor environment, the role of this fungus in provoking allergic symptoms in pre-sensitized individuals, however, was poorly investigated. We conducted this study to monitor airborne *R. stolonifer* and to evaluate its potential as an aeroallergen causing nasobronchial allergy in sensitized individuals.

Methods: Seasonal periodicity of *R. stolonifer* was studied for 2 years (March, 2009-Feb.11) by Andersen air sampler. The relationships between meteorological parameters and airborne *R. stolonifer* concentration were explored by linear regression models. The allergic potential of *R. stolonifer* extract was studied on 389 respiratory allergic patients by performing skin prick tests (SPT) and measuring the allergen-specific IgE levels in SPT positive patient's sera by Enzyme-linked Immunosorbent Assay. SDS-PAGE and immunoblotting with pooled patient sera were performed to identify its IgE-binding components.

Results: Airborne *R. stolonifer* concentration range was 4 to 47 CFU/m^3 and reached the peak concentration in March. Relative humidity was found to be a significant predictor for occurrence of *R. stolonifer* in air. Positive skin reaction was observed in 105 patients (27%) including 10 (9.5%) showing markedly high (2+ to 3+) skin sensitization. Crude antigenic extract of *R. stolonifer* was resolved in 16 protein bands in the molecular weight range of 12 to 72 kDa on SDS-PAGE (12% gel). Three IgE-binding protein bands (17, 21and 67.12 kDa) were detected by immunoblot analysis.

Conclusions: Exposures to *R. stolonifer* in environments where it naturally occurs may confer risk of IgE-mediated sensitization in sensitive individuals.

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Aerobiological and Immunological Studies on Coconut Pollen Allergy

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Background: Pollen grains constitute a significant portion of the aerobiological flora. The plant *Coccos nucifera* (commonly known as coconut) is found in huge quantities in the tropical coastal areas of the world and is very common in Kolkata, India. A 2 years aerobiological survey was carried out using Burkard Volumetric Sampler to know the seasonal variation of Cocos nucifera pollen. The plant flower through out the year but maximum concentration was found in the month of August. Allergenicity of *Cocos nucifera* pollen has been reported from the Skin Prick Test, Lung function test, ELISA from a 400 susceptible patients in and around West Bengal in India. An immunobiological study was conducted to identify major allergens from *Coccos nucifera* pollen causing hay fever, skin allergy and allergic asthma in Kolkata population.

Methods: Proteins from pollen grains were obtained by initially defatting and then extracted with sodium phosphate buffer with 10 mM PMSF. Total protein was divided into 4 fractions by ammonium sulfate at 25%, 50 %, 75% and 100% respectively. SDS PAGE was done with the 25% fraction (result obtained from dot blotting) and subsequently western blotting was performed. Two dimensional gel electrophoresis and immunoblotting was also done from the crude protein.

Results: The total protein was separated on a SDS PAGE gel showed 21 prominent bands by Coomassie Blue staining. Dot -blotting the different fractions from ammonium sulfate cut, showed a positive result in the 25% fraction. Western blot with patient specific sera gave 3 bands out of which a major band was obtained at 60Kd. This result was obtained in more than 65% of the patients from whom Sera was isolated. 2D gel electrophoresis of the crude protein sample was performed which showed 120 protein spots in the PI range of 3 to 10 and molecular weight 14Kd to 97Kd. Immunoblotting the 2D gel with pooled patient specific sera showed 20 spots thus implying IgE reactivity.

Conclusions: It can thus be inferred that *Coccos nucifera* pollen grains are very common in the air and are important to cause allergy to susceptible persons. More over the 60 Kd protein is responsible for allergenicity.

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Patterns of Skin Prick Test Positivity in 519 Patients with Allergic Rhinitis and Asthma in Mexico City

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Background: There are studies in Mexico and worldwide about the patterns of positivity of skin prick test and the most frecuently allergens were: Dermatophagoides pteronyssinus (DPT), tree pollens (Ash/Oak in Mexico, Oak in U.S.A, Birch in Europe), grasses (Bermuda in Mexico, Timothy in U.S.A and Lolium in Europe) and thirdly cat ephitelium(CE). The reactivity to allergens was more common in males and the age groups in which there were positive skin test with the highest prevalence was from 5 to 15 years and 21 to 40 years.

Methods: The objective is to determine the pattern of skin prick test reactivity to aeroallergens in patients with rhinitis and asthma allergic in Mexico city, attending in the National Institute of Respiratory Disease (INER). This is a prospective, observational and longitudinal study based on data analysis of skin prick test results of individuals with clinical diagnosis of airway allergy (rhinitis/asthma). We use standardized allergens (alkalbello),

detailed clinic history was collected in all cases. The statistical analysis was performed with the program SPSS14.
Results: We obtained a total of 519 patients with positive skin prick test between January 2009 and March 2011. This group comprised 47% females and 53% male, with a mean age of 19 years between 3 to 79 years. We have 253patients with allergic rhinitis (AR) and asthma (A), 173 with RA and 93 with A. 55% of the patients reacted to one allergen extract (AE) and 45% of the patients reacted with 2 or more AE. The most frequently indoor allergenswith positive skin prick test were Dpt (65.1%), Dermatophagoides farinae (Df) in 32.3%, CE(31.7%), Cockroach (11.5%). Among the outdoor allergens ash was positive in 23.3%, Ligustrum (18.8%) oak (17.7%) birch (13.6%) Western Juniperus (9.6%), Ulm (8.6%).
Conclusions: The most frequently positivity skin prick test were Dpt, Df, CE, Ash, Privet, Oak. The reactivity to allergens was more common in males, and there are 3 peaks of age of positivity on prick test (7–12 years, 25–29 years and 36 years).

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Risk Factors and Their Impact on Development and Severity of Allergic Diseases in the CIS-Region

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Background: This paper presents the results of influence of risk factors (RF) on development and severity of allergic diseases (ADs) in the CIS-region (CIS-R).
Methods: ISAAC and ARIA studies results, data on atopic dermatitis, Republic Ministries of Health Statistical Reports as well as literature data has been analyzed.
Results: It has been established that in industrialized areas, ADs is 2 to 3 times higher than the incidence in rural areas. The highest incidence is noted in ecologically unfavorable regions of low mountains where suffering from ADs is more often met. In the medium mountains ADs appear with less intensity, in conditions of high mountains ADs are extremely rare. The maximum prevalence of ADs has been observed at the experience of working in hazardous conditions from 5 years and above. A high degree of contamination airpollutions (CO2, NO2, SO2 etc.) in the industrial cities correlated with the prevalence of respiratory allergies and other ADs were observed. Frequent cause and significant allergens, as identified in patients with different ADs in CIS-R were domestic, epidermal, pollen and fungous allergens. The main triggers which involved in the development or exacerbation of ADs in Azerbaijan, Armenia, Russia and Uzbekistan are: house dust mites, pollen of trees and plants, pet allergens. In Belarus, Kazakhstan, Turkmenistan, Ukraine, Moldova, the cause-important allergens are: pollen of trees, grasses and weeds. Among the most significant risk F for ADs should be noted: burdened by heredity (65,5–75,9%), high frequency of SARS in history (16,2–77%), passive smoking (43,1–62,5%), poor social conditions (17–42%) the presence of pets in the apartment (12,5–17%). Children (7–8 years) were more susceptible to environmental RF as compared with teens (13–14 years). In Tajikistan and Turkmenistan, ADs were closely related with poor social conditions, low household income and large-family.
Conclusions: Epidemiologic studies are of great theoretical and practical significance as they provide impartial evaluation and reliable data on ADs prevalence and the most important allergens. Climatic and geographical conditions of the environment and ecological situation in the region are significant RF, requiring consideration in determining the probability of a genetic predisposition to ADs.

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Monitoring of Air-Pollutants Concentration in Children with Allergic Diseases

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Background: All over the world, increases the incidence of allergy, asthma and autoimmune diseases. Both young and elderly people are at risk. Therefore, on time diagnostics of these changes and the improvement of patient's quality of life is the most important task for doctors worldwide.
Methods: Patients by random selection were interviewed and subsequently examined: 535 schoolchildren of Kutaisi, aged 7 to 14. Stepwise diagnostics of allergic factors included: 1. Questionnaire screening according to the international ISAAC questionnaire. 2. To identify the specific allergens in serum. 3. To define air pollutant concentration in the environment with the help of Burkard Trap (Burkhard Pollen Trap donated by the WAO).
Results: Investigation included questionnaire screening with the use of the international ISAAC questionnaire. The questionnaires for children aged 7 to 10 years were filled in by their parents; school children of 11 to 14 answered the questions themselves. Questionnaire screening allowed select the group of children with already diagnosed and with primarily diagnosed allergic diseases. From mentioned above 3 groups of children: I group 57 persons (10.7%) children with primarily diagnosed allergic diseases; II group-68 persons (12.7%) children with already diagnosed allergic diseases; III group-410 persons (77.6%) practically healthy children with no deviations according to ISAAC questionnaire. The next phase of the examination consisted of ImmunoCAP100 tests in II group 68 children with already diagnosed allergic diseases. There was determined the highest level of Phadiatop (inhaled environmental allergens) was positive in 35% of patient. We gave them the information and recommendation of air –pollens concentration according to Burkard Trap research. The use of allows accurately define the concentration of air pullutants in the environment including the pollen of trees, grass and weeds in particular geographical area in different seasons of the year.
Conclusions: Burkard Trap is committed to helping physicians identify the causative allergens in this complex mini environment, there are necessary condition for final verification of allergic diseases, which makes it posible to form successfully the basis of preventive therapy and appropriate undertake preventive measures.

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Analysis of an After-Care Questionnaire in Allergic People to Dust Mites Using Anti-Dust Mites Bed Covers

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Background: The goal of the study was to assess in a declarative way, the symptoms felt by the patients and the impact of micro-woven cotton (MWC) and a non woven polyester polyamide (NWP) anti-dust mites bed covers on allergic volunteers to dust mites.
Methods: This study is a descriptive survey based on an after-care questionnaire handed out to a group of 419 volunteers allergic to dust mites. 109 questionnaires have been used. Regarding the allergy, we asked questions in order to assess the most annoying symptoms. The discomfort level felt was assessed using scores that ranged from 0 (no discomfort) to 10 (severe discomfort). Values, expressed as mean ± SEM, were compared using 2-way ANOVA.
Results: The discomfort level felt by the allergic volunteers to dust mites has significantly decreased after the anti-dust mite's bed cover use (7.1 ± 0.2 versus 2.6 ± 0.2). After the anti-dust mites bed cover use, the discomfort level noticed decreased significantly and in a similar way no matter the age brackets. Thus, after the use of an anti-dust mites bed cover, it ranged between 2.1 and 2.3. The discomfort level felt after the anti-dust mites bed cover use was similar whatever the symptom. The reduction of the percentage of the discomfort level in volunteers having used MWC anti-dust mites bed covers was similar to the percentage of the volunteers having used NWP anti-dust mites bed covers (62.9 ± 3.1% vs. 60.7 ± 4.2%).

Conclusions: To conclude, the use of anti-dust mites bed cover permits to significantly reduce the symptoms felt by allergic patients to dust mites. Moreover, it underlines the fact that the use of MWC anti-dust mite's bed cover or NWP anti-dust mites bed cover had a similar efficiency on the reduction of symptoms felt.

POSTER SESSION

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Changing Scenario of Airborne Allergens in Bangalore, India

Anand Pendakur, MBBS, DLO[1] and Balaji Ramdas, MBBS[2]. *[1]Allergy Asthma ENT Clinic, Indian College of Allergy Asthma and Applied Immunology, Bangalore, India; [2]Community Medicine, Indian Academy of Allergy, Bangalore, India.* With phenomenal growth of Bangalore city and a distinct shift of its arboriculture in the last 2 decades, change in allergen profile has been suspected. Earlier studies reported the pollen of Partheenium, Albizia, Cassia, Ageratum and Ricinus, and dust mites D.pteronyssinus and D.farinae to be the commonest airborne allergens (Anand P and Agashe SN, Ind Journal Otolaryngol, Vol 36, no 2, 1984 and Channabasavanna GP, Final Report: Research Project H Dust Mites, DST, Gov Ind June 1983). Present study involved skin prick tests done on 134 patients of respiratory allergy with standard protocol. 82 male and 52 female patients with moderate–severe persistent allergic rhinitis, rhinoconjunctivitis and asthma were the study subjects with mean age of 30.2 ± 13.8 years. 30 were asthmatics and 64 were asthmatics with rhinitis. Cynodon dactylon (22.4%) and Pennisetum typhoides (5.9%) are the commonest grass pollen allergens. Artemesia scoparia (15.7%), Partheenium hysterophorus (8.9%), Ageratum conyzoides (8.2%) and Helianthus annuus (8.2%) are the commonest weed pollen allergens. Prosopis juliflora (14.2%), Cassia siamea (10.4%) and Ricinus communis (8.9%) are the commonest tree pollen allergens. D.pteronyssinus (58.9%) and D.farinae (47%) are the commonest indoor allergens. House dust mites have remained the predominant indoor allergens even now. Present study shows significant change in the type of pollen allergens. Cynodon, Artemesia and Prosopis have replaced Partheenium and Albizia as the predominant allergens in 2 decades. Helianthus annuus and Pennisetum typhoides, which were insignificant in the past, have emerged as significant allergens. Molds as airborne allergens have become very insignificant. Bangalore has grown enormously in the last 2 decades. Innumerable vacant lands and swampy areas covered by weeds like Partheenium, have become buildings. Helianthus is cultivated on a large scale all around as a commercial crop. Large outskirts around the city have become residential and, office and commercial hubs resulting in a considerable change in pollen allergen flora. This change in the pollen allergen profile is an important guideline for allergy diagnosis and immunotherapy. This evidence may have significant application to the management of allergy patients in other major cities of India like Hyderabad, Chennai, Delhi, Mumbai and Kolkata as well.

ALLERGIC RHINITIS

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PCR Analysis of Microorganisms in Chronic Rhinosinusitis with Nasal Polyps

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Background: Chronic rhinosinusitis (CRS) with nasal polyps is characterized by tissue eosinophilia, which is speculated to be related to Staphylococcus superantigen and fungus, in European and U.S patients. However, Japanese patients with CRS with nasal polyps showed 2 distinct phenotypes of eosinophilic and neutrophilic inflammation (Hirotsu et al 2011). We attempted to analyze the microorganisms from nasal polyps of Japanese patients by PCR method.

Methods: Eleven specimens of nasal polyps with CRS were collected for examination by endoscopic sinus surgery. All specimens were treated with 70% ethanol and physiologic saline to eliminate microorganisms outside of the nasal polyps. Bacterial and fungal culture was performed for 2 weeks using 5 different culture media. We detected 16S rRNA bacteria and 18S rDNA-ITS-26S rDNA fungus, and then identified species of microorganisms by direct-sequence. In addition, the number of eosinophils in the nasal polyps was counted.

Results: No bacteria or fungus were recovered from any of the nasal polyps by culture medium. By the PCR analysis, DNA for bacteria could not be detected, whereas 7 samples of the nasal polyps showed amplification of fungal DNA such as Candida parapsilosis, Candida glabrata, and Rhodotorula etc. Grocott dyeing for the nasal polyps, however, showed no intracellular presence of fungus. The number of the eosinophils in the nasal poly with the patients with the presence of fungal DNA (240 ± 191) was significantly ($P < 0.05$) higher than that in the absence (56 ± 40).

Conclusions: The present study suggests the participation of fungus in eosinophilic CRS with nasal polyps.

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Incidence of Allergy to Artemisia Vulgaris and Salsola Kali in Sabzevar cCty

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Background: Artemisia vulgaris and Salsola kali are common plants in North hemisphere (eg in Iran). The pollens of Artemisia vulgaris is major aeroallergen in late summer usually 10 to 14% patients that suffering from allergic rhinitis in summer have allergy to Artemisia vulgaris. The pollens of Salsola kali is major aeroallergen in early summer. Usually 53 to 76% patients that suffering from allergic rhinitis in summer have allergy to Salsola kali.

Methods: In one search in Sabzevar, we studied 47 patients with allergic rhinitis. They were tested with prick test.

Results: In this study, were known that 27 patients (58%) had allergy to Artemisia vulgaris and 43 patients (92%) had allergy to Salsola kali.

Conclusions: This study showed that incidence of allergy to Artemisia vulgaris and Salsola kali in Sabzevar is more common than usual.

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The Prevalence of Allergic Rhinitis in Adolescent in La Paz, Bolivia (3600 m.s.n.m.)

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Background: Allergic Rhinitis is the most prevalent illness in allergy. We didn't know the prevalence about it to 3600 m.s.n.m. It exist paper about prevalence at least altitude in 10 to 30% in different places. The purpose of this study is showing the prevalence of the allergic rhinitis in students in the city of La Paz, Bolivia.

Methods: We realize a question form with the methodology ISAAC in student into 13 to 18 years old in schools of the La Paz. We choose urban zones. We realize this study in February 2009.

Results: We get 250 questionnaires in adolescent and were completely right only 245. Of these 245 questionnaires 64% (157) were women and 36% (88) men. To the first question: Any time in your life have you had a problem with sneezing or a runny, or a blocked nose when you did not have a cold or the flu? They respond yes in the 60% (147 persons). To the second question: In

the past 12 months, have you had a problem with sneezing, or a runny, or a blocked nose when you did not have a cold or the flu? They respond yes in the 43% (108 persons). To the third question: in the past 12 months, has this nose problem been accompanied by itchy-watery eyes? They respond yes in the 56.5% (83 persons). The months more prevalent were February 11.5% (17 persons); June 18% (27 persons); July 16% (24 persons) and august 20% (29 persons). Interference in their quality of life: neither 11.5% (17 persons), little 66% (97 persons), moderately 6.5% (10 persons) and a lot of much 16% (23 persons).

Conclusions: The Allergic Rhinitis is high prevalent in citizen about 3600 m.s.n.m. 43% have Allergic Rhinitis with symptoms more prevalent in winter season, interfere with life in 22.5% and associated with ocular problems in 66% (97 persons). We must realize allergic test to discriminate allergic of non allergic rhinitis, because many people we had non allergic rhinitis associated to the cold temperature. We need to study more about this pathology in high altitude.

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Pattern of Positive Sensitization in Patient with Asthma and Rhinitis to 3600 MSNM (La Paz, Bolivia)

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Background: In the high altitude exists very few studies about allergies, we seek to give to know our sensitization in population with breathing problems (asthma and Allergic Rhinitis).

Methods: They were carried out allergy tests to 94 patients between 6 and 13 years with breathing symptoms predominantly allergic rhinitis and asthma. They were carried out allergy tests to foods like peanut, wheat, almond, tomato, milk, fish, soya, nuts, corn egg, chocolate, dog epithelia, cat, rabbit, feathers, horse, dermatophagoides spp, blatella, periplaneta pollens: lolium, poa, cynodon, festuca, ambrosia, artemisa, plantago, chenopodium, rumex, zea mays, populus, cupressus, platanus, fraxinus, schinus, dactylis, and mushrooms like it would alternate, aspergillus and cladosporium. They took positive all hives bigger than 3 mm of diameter.

Results: Of the 94 patients 9 gave negative to the tests, 88 positive%. In the foods, milk prevails (lactoglobuline 39%; casein 21%), tomato 33%, fish, almond and wheat; 23% peanut and nuts less than 10%. In the epithelia: cat 20%. Dermatophagoides 46%, pollens grasses lolium 13% and poa 14%, other pollens important festuca, chenopodium and dactylis with 21 to 23%, trees less than 15% and mushrooms with less than 15%. You begin handling predominantly according to these tests to dematophagoides, poa, lolium, festuca, dactylis, mushrooms and cat epithelium since their reactions were similar to the positive challenge of histamine. It is necessary to mention that the diagnoses were alone allergic Rinitis on the whole in 60%, asthma allergic single 10% and asthma and rinitis 30%.

Conclusions: Although this is a closed population, it guides us that to 3600 m.s.n.m. the allergen more frequent is dermatophagoides, and many articles refers that to high altitude we are liberated of the mites but it is not this way. Another important discovery is the positive to milk, tomato and very little to other foods that it is part of our population's diet. They are data that deserve the attention and we will continue advancing in finding other factors of risk, clinic and prevalence.

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Epidemiology of Allergic Rhinitis Cases in the Allergy Service of a Third Level Medical Center. Six Year Experience

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Background: The purpose of this study is to report the cases of Allergic Rhinitis (AR) in the Allergy service from a Third level medical centre since its creation in July 2005.

Methods: This is a descriptive, retrospective, transversal study from July 2005 to February 2011. Selected medical records of patients apply for diagnostic criteria for an allergy disease were made. ARIA guide 2009 was used to make diagnosis of allergic rhinitis. Patients were classified by age and sex and find out how many skin prick test were made in such patients, and how many patients began immunotherapy.

Results: 13737 consultations were attended in the Allergy service between the period mentioned above. 2337 medical records of patients were selected, 1608 patients applied for a specific diagnosis for an allergy diseases as follows: Asthma 411, Atopic conjuctivitis 58, Atopic Dermatitis 180, Allergic Rhinitis 869, Urticaria 90. 869 patients completed criteria for Allergic Rhinitis. 433 (49.9%) patients were female, 436 (50.1%) patients were male. 490 (56.3%) patients were found to be in the range of 0 to 14 years. The mayority of allergic rhinitis patients were males in the range of 5 to 14 years, with 270 (42.5%) patients. There were an increase of AR cases in females in the range of 20 to 40 years, with 171 (39.4%) of total female cases. In 408 (47%) patients skin prick test were made, in 305 (35%) patients were positive and began treatment with immunotherapy.

Conclusions: In this study, AR represents the most frequent allergy disease among children, a good diagnosis of AR is mandatory because of the confusion of symptoms mainly related with upper respiratory tract infections, that implies a different management, increasing the risk of complications, such as asthma and therefore the cost of treatment, including immunotherapy. The results of this study are helpful to improve specialized medical attention not only in paediatric patients but also in adults.

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The Evaluation of Allergen Sensitivity in Allergic Rhinoconjunctivitis and Allergic Asthma Patients in Antalya, Turkey

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Background: Allergic rhinitis is a common health problem which has 2 forms; seasonal and perennial. The prevalence and etiology of allergic rhinitis varies from region to region and affect 10 to 20% of the population approximately. The prevalences of asthma, allergic rhinitis and allergic eye disease were detected as 8.2%, 10.8% and 7.5% respectively in Antalya, the south coast of Turkey.

Methods: The study was conducted in Antalya between 10th of November 2009 and 20th of September 2010. 866 of 2862 patients who had allergic rhinoconjunctivitis and asthma were enrolled in the study due to having high total IgE levels in blood conducted at the Allergy-Immunology Division of Antalya Research and Training Hospital. Allergen-spesific subcutaneous immunotherapy was given 626 of 866 patients.

Results: Of the 866 patients studied, 66.1 % were females. Most of the cases had declaired that the rhinitis symptomes were due to pollens and house dust the second most common irritant. Also the cases have said that their symptoms got worse with exposure to dust, smoke, heavy odors, perfumes, and detergents. Most of the patients have said that air pollution was the most important factor that exacerbated the symptoms of rhinitis and asthma. While there is a comparison between the age and SPT positivity, Aspergillus fumigatus and Dpteronyssinus sensitivity was statistically different in the mites and fungal mixture dermal test groups. As a result, in the study group of 866 allergic rhinitis patients, only the Plantagolanceolata, Corylusavellana, Aspergillus fumigatus, Dpteronyssinus and cockroach sensitivity was significantly varies with the age.

Conclusions: In allergic diseases; we all know that allergens may have regional variations. That's why; the allergen profiles of the regions must be determined and the dermal Prick tests must be prepared accordingly. Mostly grass and cereal mixtures and mites are responsible from the allergic rhinitis cases due to our observations in our clinic. The other important allergens that are linked to the flora and climate of the region are olive and the cockroaches. High asthma prevalence in people living in shanties and in housewives may be due to exposure to house dust mites.

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Allergic Disease Severity and Relations

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Background: Prevalence of allergic disease has increased in recent years all over the world. Asthma and rhinitis are the most prevalent in Portugal and, having them such a multi-factorial basis, atopy is the most important risk factor for its development. The authors aim to evaluate mono/polisensitization as risk factors for severity of allergic disease, if there is an impact in allergic disease manifestations number, the different treatment response, and if there is a relationship between VEMs, comorbilities and sensitization.

Methods: In a population of patients followed in asthma/allergology appointment were selected those with asthma and allergic rhinitis confirmed by cutaneous test and/or specific IgE. Clinical processes were reviewed and analyzed data related to the age of beginning, manifestations, atopic profile, severity, treatment, comorbilities and functional limitation. A descriptive analysis of the sample was made and used linear regression for variable correlations.

Results: 176 patients 30% men and 70% women, mean age 33,7 and mean age of early symptoms 12,7 Of these, 94% had asthma and 85% rhinitis. They were 53% monosensitized, 47% polisensisitized and 43% had comorbilities. 66,5% of patients has done specific immunotherapy (SIT). On linear regression analysis it was found that different sensitization has not been determinative for disease manifestations number neither of treatment response. It was observed that severity of asthma and rhinitis correlate with each other ($P < 0{,}001$), but no significant differences were verified in severity level between patients mono vs polisensitized. SIT demonstrate a positive and statistically significant correlation with treatment reduction ($P < 0{,}001$) and reduction on asthma and rhinitis severity ($P = 0{,}015$ and $P < 0{,}001$). SIT patients also demonstrate a decrease in asthma severity associated to the number of allergen sensitizations. It was found a positive correlation between the presence and number of comorbilities and asthma and rhinitis severity ($P = 0{,}001/P < 0{,}001$ and $P = 0{,}007/P = 0{,}001$), instead of individually, only nasal polyposis prove to be associated with statistical significance. Comorbilities were also related with a lower FEV1 ($P = 0{,}02$).

Conclusions: This study supports literature data, which says there is only one allergic disease and that severity of disease extends to its various manifestations. We confirmed that in atopic patients, SIT has benefit in the reduction on allergic disease severity and a better disease control with minor therapeutic use.

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Frequency of Patients With Clinical Manifestations of Allergic Rhinitis without Evidence of Systemic Atopy and Specific ige Sensitization

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Background: The diagnosis of allergic rhinitis (AR) is based on clinical manifestations and supported by a positive result for skin prick test (SPT) or serum specific immunoglobulin E (sIgE) antibodies to aeroallergens. Our objective was to investigate the frequency of patients with clinical manifestations of AR without evidence of specific IgE sensitization.

Methods: We evaluated patients with clinical manifestations suggestive of AR, other causes of rhinitis excluded, aged >5 years and who had total serum IgE and SPT or sIgE to aeroallergens measured. Skin tests were performed with extracts of *Dermatophagoides pteronyssinus, Dermatophagoides farinae, Blomia tropicalis* and *Aspergillus fumigatus* (FDA Allergenic) and total serum IgE and sIgE, for the same allergens, by ImmunoCAP (Phadia). Patients were subdivided into groups according to the results profile, and comparatively analyzed for association with asthma, severity of rhinitis and age.

Results: We evaluated 116 patients (64% female) aged between 5 and 79 years, including 34 children (29%) and 63 (54%) with bronchial asthma. The observed profiles and frequencies were: high IgE levels and positivity in the SPT or sIgE –55%; normal IgE levels and SPT or sIgE positivity –9%; high IgE levels and SPT and sIgE negativity –3 %; normal IgE levels and negativity in the SPT and sIgE –23%. Among patients with normal levels of total serum IgE and no evidence of specific IgE sensitization, 14% had asthma, while in the remainder the prevalence of asthma was 34% ($P = 0.0009$). There was no statistical significance in the influence of the rhinitis severity and age in the absence of markers of atopy and allergen sensitization.

Conclusions: We observed a significant number of patients with clinical manifestations of AR, without evidence of systemic atopy and specific IgE sensitization, indicating the importance of careful research of local allergic rhinitis, as well as other causes of chronic rhinitis. Local allergic rhinitis appears to be less frequent in patients with rhinitis and asthma. The observation of 13% of patients with elevated levels of total IgE without specific sensitization implies the possibility of sensitization to aeroallergens which were not investigated, such as occupational allergens.

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H1 Antihistamines Influence on Pro-inflammatory Cytokines Level in Patients With Allergic Rhinitis

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Background: The aim of the study is to evaluate the effect of H1 antihistamines on symptoms and pro-inflammatory cytokines plasmatic level in patients with persistent allergic rhinitis (PAR), after 4 weeks treatment, during continuous exposure to allergens.

Methods: 79 patients, mean age 30.44 ± 9.90 years, diagnosed with PAR were included in the study, divided into 2 groups: 39 patients were under treatment with Desloratadine 5 mg/day and 40 patients received Levocetirizine 5 mg/day for 4 weeks. The patients were evaluated before and after the treatment, regarding rhinitis symptoms (sneezing, rhinorrhea, nasal congestion, nasal and ocular itching), total symptoms score, type of sensitisation (indoor or outdoor allergens), plasmatic levels of IL-6 and IL-8. The obtained data were analised using SPSS 15 and GraphPad Prism 4 programs, using Wilcoxon Signed Rank and Mann Whitney test, with a significant P values < 0.05.

Results: Both Desloratadine and Levocetirizine reduce total symptoms score (8.35 versus 1.97, $P = 0.0001$, respectively 8.67 versus 1.97, $P = 0.0001$), especially nasal congestion in patients with allergic rhinitis (1.76 versus 1.02, $P = 0.001$ and 1.72 versus 0.87, $P = 0.0001$). IL-6 and IL-8 have no different

plasmatic level in patients with allergic rhinitis compared with the values obtained in healthy volunteers. Levocetirizine reduces plasmatic level of IL-6 (1.19 versus 1.006, $P = 0.0097$) and IL-8 (8.90 versus 6.90, $P = 0.0003$) after 4 weeks treatment, while Desloratadine has influence only IL-6 level (1.68 versus 1.36, $P = 0.0038$). The intergroup analysis revealed no significant difference between these 2 drugs regarding IL-6 ($P = 0.36$) and IL-8 ($P = 0.25$).

Conclusions: Both studied H1 antihistamines present anti-inflammatory effect in patients with PAR after 4 weeks treatment.

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International Survey on the Management of Allergic Rhinitis by Physicians and Patients (ISMAR)

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Background: Allergic Rhinitis (AR) is an underappreciated disease considered to be trivial. The small group of patients taking medications for AR are usually seen by specialists. AR is under-diagnosed and under-treated with frequent non-adherence to treatment. There are a gap and unmet needs regarding the management of AR at global level. ISMAR was designed as the first-ever global, quantitative survey to ask to patients and physicians the same questions to identify differences in attitudes and opinions about the treatment of AR at global level with the goal of identifying barriers to optimal management and revealing limitations of currently available treatments.

Methods: An international, multicenter, non–interventional, cross-sectional study was conducted in adults or children (≥ 6 years). Physicians were selected at random from a master list provided by country and combining private and public practices. ISMAR was designed according to the most accepted epidemiological recommendations based on the successful experience of the WAO-GAPP survey on asthma. A questionnaire addressing patient profiles, diagnostic assessment, therapeutic decisions, and real-life management was answered. The questionnaire also asked about national/local features, medications availability/cost, laboratory test facilities, traditions, geographical constraints, among others. The participating physicians recruited consecutive patients with AR. Study data collection was performed during a single visit with 3 types of documents: Investigator's questionnaire, Case Record Form, Patient's questionnaire.

Results: Two-hundred and thirty four physicians were surveyed with a mean age of 49 years (28–69), 180 of them were males (76.9%). The type of medical practice was public sector 16.7%, private practice 41.9% and mixed 41.4%. Regarding medical specialty is a follows: GPs/family practitioners/internists (22.2%), allergologists/pulmonologists (35.9%), pediatricians (11.1%) and ENT specialist (30.3%). Physicians recruited 2776 patients with AR (Egypt, n = 500; Mexico, n = 418; Brazil, n = 351; Colombia, n = 223; Guatemala, n = 216; Iran, n = 207; Venezuela, n = 201; Argentina, n = 200; Israel, n = 176; Kuwait, n = 150; UAE, n = 134).

Conclusions: ISMAR has made possible the participation of physicians from eleven countries in different regions of the world that see AR patients. The doctors surveyed and the patients they recruited will give us the opportunity to gain insight about different aspects of the management of AR at global level.

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Effectiveness of Sinus Surgery for Lower Airway Disease

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Background: Upper respiratory illness can adversely impact the lower airway. This study aimed to evaluate the relationship between clinical background and improvement in the lower airway after surgery for treatment of chronic rhinosinusitis.

Methods: A total of 22 patients with chronic rhinosinusitis surgically treated between January 2010 and February 2011 were included in the study. The presence or absence of asthma and peripheral blood eosinophils count were examined for all patients in addition to preoperative radioallergosorbent tests. Spirometry was conducted and fractional exhaled nitric oxide (NO) was measured at the preoperative, 1-month postoperative, and 3-month postoperative visits.

Results: The average level of NO in the exhaled air at the preoperative, 1-month postoperative, and 3-month postoperative visits was 51.5 ppb, 42.5 ppb, and 38.0 ppb, respectively. Although the average results of spirometry didn't show any improvement, forced expiratory volume in 1 second percentage improved in 2 of 4 cases with obstructive ventilatory disturbance. There were 10 improved cases, which were defined as those showing more than 1.2-fold difference in the ratio of preoperative NO level to the 3-month postoperative one. The remaining 12 cases, including 4 of 6 cases with asthma, 5 of 7cases with eosinophilia, and 4 of 4 cases with animal dander allergy were unimproved cases.

Conclusions: Chronic rhinosinusitis can cause latent lower respiratory disease. Endoscopic sinus surgery can improve the status of the lower airway. However, the effectiveness of surgery is significantly less in cases of animal dander allergy.

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Berberine Inhibits Myofibroblast Differentiation in Nasal Polyp-deroved Fibroblast via P-38 Pathway

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Background: The alkaloid has shown pharmacological activities and multiple biological functions such as antibiotic activity, anti-tumor, anti-inflammation and anti-fibrotic properties. The purposes of this study were to examine whether berberine has any effect on phenotype change and extracellular matrix production in nasal polyp-derived fibroblasts (NPDFs) and to investigate underlying molecular mechanism.

Methods: NPDFs were pre-treated with berberin for 2 hours prior to induction by transforming growth factor (TGF)-β1. The expression of α-*smooth muscle actin (SMA)* and *collagen type I* mRNA was determined by a reverse transcription-polymerase chain reaction, and the expression of α-SMA protein and collagen type I was determined by Westernblotting and/or immunofluoescent staining. Total soluble collagen production was analyzed by the SirCol collagen dye-binding assay. Expression of pSmad 2/3, pp38, pERK 1/2 and pJNK was evaluated by Western blot analysis.

Results: In TGF-β1-induced NPDFs, berberine significantly inhibited the expressions of α-*SMA* and *collagen type I* mRNA and reduced α-SMA and collagen protein levels. Berberine had no effect on the level of pSmad2/3, pERK1/2 and pJNK expression in TGF-β1-induced NPDFs. However, berberine suppressed the expression of phosphorylated p38 in TGF-β1-induced NPDFs. SB 203580 (a specific inhibitor of p38 kinase) markedly suppresse the increased expression of collagen type I and α-smooth muscle actin (α-SMA) protein in TGF-β1-induced NPDFs.

Conclusions: Berberine exerts suppressive effects on phenotype change and extracellular matrix production in NPDFs, through interfering of p38

signaling pathways. Our findings provide new therapeutic options for extracellular matrix production in nasal polyps.

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Mold Sensitization in Chronic Rhinosinusitis Patients

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Background: It is estimated that about 10% of the population have IgE antibodies to common inhalant molds. Exposure to fungal allergens could be linked to the presence and persistence of asthma, rhinitis and atopic dermatitis. Mold sensitization is a risk factor for development and deterioration of upper airway allergy, especially chronic rhinosinusitis. We addressed the incidence of mold allergy measured as specific IgE to molds and skin prick tests in chronic sinusitis patients. We assessed prevalence of allergic reactions to mould among surgery treated chronic sinusitis patients.

Methods: A group of 28 chronic sinusitis patients after surgery were included into the study. Routine medical examination, skin prick tests with common inhaled allergens and extended mold panel (*Alternaria alternate, Cladosporium herbarium, Aspergilus fumigatus, Candida albicans, Mucor mucedo, Botrytis cinerea, Rhisopus nigricans, Penicilliumi notatum*, Fusarum moniliforme *Pullularia pullulans* (Allergopharma, Germany), tIgE, asIgE measurement were performed (Phadia, Sweden). All investigated patients were consulted by laryngologist and mycological examination was performed.

Results: We found that sensitization to at least one allergen was present in 43.8(14/32) of sinusitis patients. The most prevalent was sensitization to house dust mite Dermatophagoides pt., found in 21.8 % (7/32) patients. Positive results of skin prick tests with Candida albicans we observed in 18.8% (6/32), with Alternaria alternate in 15,6% (5/32), Cladosporium herbarium in 6,3% (2/32), Aspergilus fumigatus in 3,13 % (1/32). None of investigated patients presented sensitization to other mold allergens. Microbiological methods demonstrated fungal infection only in 2 patients.

Conclusions: Almost half of chronic sinusitis patients presented sensitization to at least one allergen. Fungal allergy is relatively rare in chronic sinusitis patients.

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Nasal Cytology is Important in the Classification of Patients with Allergic and Non-Allergic Rhinitis

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Background: The purpose of the study is the classification and clinical characterization of patients with allergic rhinitis and non-allergic and differentiate the presence of eosinophils and neutrophils in nasal cytology.

Methods: Prospective study of 405 patients with chronic symptoms of sneezes, pruritus, nasal congestion and rhinorrhea were evaluated by clinical examination, skin prick test and nasal cytology. Patients with diseases and/or treatments that could alter the outcome of these tests were excluded.

Results: 405 patients from 3 to 80 years were evaluated; 248 female patients (61%) and 157 males (39%). The sample was divided into 2 groups according to skin prick tests: allergic 270 (67%), 135 non-allergic (33%). The mean age of onset of symptoms was 14.27 and 23.47 years in allergic and nonallergic respectively. Nasal symptoms (nasal congestion, sneezes/pruritus, rhinorrhea, postnasal secretion) and signs (turbinates color and edema, secretion and oropharynx redness) were accessed using scores from 0 to 3, ranging from 0 to 24. In the allergic group the mean total nasal symptoms and signs scores were 6.64 and 4.66, while in non-allergic were 5.67 and 3.52. Allergic patients had an average 27.82% of eosinophils and 64.09% of neutrophils in nasal smears, whereas non-allergic patients 8.38% and 85.30%. Using skin prick test and nasal cytology we were able to diagnose allergic rhinitis in 69.6% (208) of the patients. 20.7% (62) had neutrophilic non-allergic rhinitis (NARNA) and 9.7% (29) non-allergic rhinitis with eosinophilia syndrome (NARES). No idiopathic rhinitis patients were found.

Conclusions: The frequencies of the types of rhinitis were: allergic rhinitis 69.6%, RENA 9.7%, NARNA 20.7% and idiopathic rhinitis 0%. Despite the fact that each sub group of nonallergic rhinitis has particularities, in allergic rhinitis we found early onset of complaints, signs and symptoms more intense and a greater number of eosinophils, compared with the nonallergic patients.

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The Examination of the Association between the Chronic Rhinosinusitis and the Inflammation of the Lower Respiratory Airway by Using the Exhaled Nitric Oxide (NO) and the Respiratory Function Test

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Background: It is said that the chronic rhinosinusitis influences the lower respiratory airway and there is a report that a tendency to increase the eosinophilic rhinosinusitis later, but they are still unknown.

Methods: We divided the chronic rhinosinusitis patients with the adaptation of the operation into 4 groups and exaed whether there was a difference in the respiratory function, exhaled NO, and the number of the blood eosinophil.

Object: 29 patients with chronic rhinosinusitis who planned the endonasal sinus surgery.

Results: Comparing these 4 groups, it was the worst on the respiratory function (one second rate) in the group with nasal polyps and without nasal allergy. It was recognized the connection between the respiratory function and the presence of the nasal polyps. It was possible that the exhaled NO became the index to the lower airway inflammation.

Conclusions: We classified the chronic rhinosinusitis and evaluated the lower airway function. It helps the pathologic understanding of the chronic rhinosinusitis. And it leads to understand of the influence on the lower airway inflammation.

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Peak Inspiratory Flow Rate is More Sensitive Than Acoustic Rhinometry or Rhinomanometry in Detecting Nasal Obstruction Using the Allergen Challenge Chamber

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Background: We prepared an allergen challenge chamber (ACC) which facilitates quantitative pollen challenge at any time, and, so, the acquisition of objective data. The aim of this study was to evaluate peak nasal inspiratory flow rate (PIFR) as an endpoint during allergen challenge and compare this with rhinomanometry (Rhino) and acoustic rhinometry (AR).

Methods: The study was conducted in November, which is not in pollen season. Subjects were exposed to Japanese cedar pollen at a concentration of 50,000 counts/m3in ACC for 120 minutes each day for 2 days. Subject recorded nasal symptoms before challenge and every 15 minutes after challenge initiation. Nasal symptoms (sneezing frequency, nasal blowing

frequency, nasal obstruction) were recorded before challenge and every 15 minutes after challenge initiation. For the evaluation of nasal obstruction, we used visual analog scales (VASs); subjects marked a site on a 10-cm line corresponding to the symptom severity on which absence of symptoms was designated as 0 and worst imaginable symptom as 10. PIFR was measured using an In-check flow meter and nasal resistance was measured using Rhino. The cross-sectional area in the nasal cavity was also measured using AR before and after challenge as an indicator of nasal obstruction.

Results: When the volunteers with cedar pollinosis were exposed to cedar pollen in ACC, pollinosis symptoms were induced significantly. Changes in the 3 symptoms (sneezing frequency, nose-blowing frequency, nasal obstruction) were investigated before and after challenges on 2 consecutive days. No significant symptoms were induced on the first day of challenge in the non-pollen season. However, each of the 3 symptoms became more severe with second day of challenge, and a significant increase was seen in cumulative values by the second day. In terms of the allergen challenge test, we found a significant correlation between nasal obstruction symptom (VAS) and PIFR, but not AR and Rhino.

Conclusions: PIFR after allergen challenge is more sensitive than AR or Rhino in detecting nasal obstruction using the allergen challenge chamber.

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Nasal Poliposis and Allergic Disease. Dr. Salvador Allende Hospital

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Background: The edematous irritation of the corium of the pituitary mucosa wakes it suffers a degeneration that causes what is known as nasal polyposis, hypertrophy of the nasal mucosa as a result of a chronic inflamatory process. It is said that its formation is due to infectious processes, vascular changes as local disorders of the immunity of the nasal mucosa. However many concide in including the allergic factors as the cause of the nasal polypos and they give a special interest to the constitutional factor inside the genesis of them. The investigation had as objectives to know the relationship that there is between the nasal polyposis and the allergic diseases, as well as to study some parameters of the humoral and celular immunity in our patients.

Methods: 15 patients diagnosed wiht nasal polyposis were taken from the otorhinolaryngologists and they were sent to the allergic department to be evaluated. Patient's charts of all of thems were made and they were indicated some studies such as eosinophil global count, nasal exudate,sample radiographic study of paranasal sinus, serology, hemogram, glycemia and minimal clotting test, study of the humoral immunity and making determination of IgE, IgA, IgG, IgM. The celular immunity was also studied by making a determination of active and expontaneous Roseta test. And a life evaluation was made too by means of the hypersensitivity retard tests.

Results: High figures of elevated IgE were obtained in a 67 % of the patients studied. A control group was made for the Igs determination and the Roseta test. No significant difference was found in the Roseta test.

Conclusions: The elevation of the IgE in the patients studied makes us infer that there is an evident relation ship between these 2 pathologies. There is no evidence. That shows that there is an alteration of the celular immunity in the sample of the patients with nasal polyposis that were studied.

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Use of the CT Navigation in the Rhinology and Head Surgery

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Background: CT navigation is an assistant tool for identification and location of anatomical structures during surgery based on computer processed preoperative CT images followed by registration. CT navigation facilitates exact localization of particular anatomical points and at the same time also allows determination of the exact position of a respective instrument in 3D pictures and in 3 CT planes.

Methods: The optical CT navigation system Treon Plus (Medtronic-Xomed) is successfully being used at the ENT Department of the 3rd Medical Faculty Charles University and Central Military Clinic, Prague, Czech Republic. We studied the advantages of CT navigation use on 141 patients (257 procedures) operated from January, 1, 2007 till December, 31, 2009. The CT navigation was used for primary sinus endoscopic surgery (81 procedures), revision sinus endoscopic surgery (46), surgical treatment of injuries (7), and in tumors (7). We examined the use of optical CT navigation with MRI fusion for delimitation of extensive tumor of the tongue.

Results: In operated group of patients we observed no major per- or post-operative complications.

Conclusions: The primary benefit of the presented CT navigation is the feasibility of higher radicality, accuracy, together with delicacy towards the surrounding tissues.

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Assessment of the Quality of Methodological Rigour and Reporting of Clinical Practice Guidelines for the Management of Allergic Rhinitis—Qugar Study

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Background: To assess the methodological rigour and transparency of reporting in clinical practice guidelines for the management of allergic rhinitis (AR).

Methods: We systematically searched MEDLINE, TRIP database (including the National Guidelines Clearinghouse) and professional society websites for guidelines about the management of AR published after the year 2000. We assumed that older guidelines would no longer influence current clinical practice. If the guideline was updated after 2000 we assessed the most recent version. We included all guidelines published in English and endorsed by an international or national government agency or professional group, irrespective of country of origin or publication status. Two reviewers independently screened search results using predefined eligibility criteria and assessed the rigour of development and reporting of included guidelines using the AGREE II instrument (www.agreetrust.org).

Results: Our search revealed 432 records of which 34 full text articles were assessed for eligibility. Nine documents fulfilled our criteria–3 international and 6 national guidelines from Japan, Singapore, South Africa, UK and the USA. Overall methodological rigour and reporting of guidelines about the management of AR was variable—from fulfilling most AGREE II criteria to almost none. There was no association between the methodological rigour and time of publication or the target scope of the guideline (national versus international). Across all guidelines the most rigorously reported domain was "clarity of presentation" (median score 53%), mainly due to fair presentation of different management options (item 16), followed by "scope and purpose" (median score 42%). The least rigorously addressed was "applicability" domain with median score of 2% across all guidelines. Median scores for domains "stakeholder involvement", "rigour of development" and editorial independence" were 17%, 15% and 25%, respectively. The ARIA guidelines (2010 update) achieved the highest scores in 5 out of 6 domains and the lowest score on any domain was 60%.

Conclusions: Guideline users should be aware of the variability in quality of development and reporting of guidelines for the management of AR. They should choose higher quality guidelines to inform their practice. For many

guidelines there is much room for improvement, in particular in the domains of applicability and implementation.

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Health-Related Quality of Life and Prognostic Value of Acoustic Rhinometry in Patients With Perennial Allergic Rhinitis Treated with Fix Combination of Montelukast Plus Desloratadine

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Objective: To determine prognostic value of acoustic rhinometry in patients with perennial allergic rhinitis (PAR) treated with montelukast in fix combination with desloratidine and to assess effectiveness of this medication on health-related quality of life (HRQL).

Study design: A randomized, double-blind, prospective and multicentric clinical study.

Setting: Tertiary university hospitals.

Methods: Patients 20 years of age and older with PAR were assessed over 3 months of treatment with fix combination of montelukast 10 mg plus desloratidine 5 mg once daily (n = 40). Comparative acoustic rhinometric evaluation was used to compare nasal changes in before and after treatments. For evaluation of HRQL between before and after treatments at the first and third months, the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) was used.

Results: Nasal symptoms and findings including itching, sneezing, discharge, congestion and edema and color change of turbinates have been decreased after treatment. In acoustic rhinometry, minimum cross-sectional area (MCA) measurements and volume results were statistically higher than in before treatment ($P < 0.001$). Correlation was found that between the volume results and nasal discharged and/or congestion in right nasal passages. In left nasal passages, statistical relation was described between the MCA measurements and itching and/or change of turbinate color ($P < 0.05$). There was a larger decrease in the overall RQLQ score for the group using montelukast plus desloratidine compared with the pre-treatment scores ($P < 0.001$). The difference between scores at baseline versus the end of the first and third months for all domains was statically significant ($P < 0.001$). The treatment difference in change from first month to the end of the third month was statically significant, in favor of the third month, for eye, nose, and non- nose/eye symptoms, sleep, practical problems, emotions and activities that have been limited by nose or eye symptoms, and for overall score.

Conclusions: Significant reductions in signs and symptoms of PAR with montelukast plus desloratadine treatment were accompanied by improved disease-specific QOL measures. Montelukast in combination with desloratidine provides improvements in acoustic rhinometric values including volume and MCA in patients with PAR. Acoustic rhinometry should be use in diagnostic and prognostic process in patients with PAR.

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HLA-B58 Does not Increase Allopurinol Hypersensitivity among Patients with Hematologic Malignancy

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Background: HLA-B58 is a very strong marker of allopurinol-induced severe cutaneous adverse reactions (SCARs), especially in population with high frequency of HLA-B58, such as Chinese, Thai, and Korean. Although allopurinol is frequently prescribed to patients receiving chemotherapy for the prevention of tumor lysis syndrome, the risk of allopurinol-related SCARs in patients with hematologic malignancies is not evaluated. This study was conducted to find out the incidence of allopurinol-induced hypersensitivity in patients with hematologic malignancy during chemotherapy according to HLA-B58 and clinical usefulness of HLA-B58 as a risk marker for the development of allopurinol-induced hypersensitivity.

Methods: We retrospectively reviewed the medical records of patients with hematologic malignancy who ever took allopurinol and underwent serologic HLA typing for bone marrow transplantation from January 2000 to May 2010.

Results: Among total 463 patients, 13 (2.8%) patients experienced allopurinol hypersensitivity reactions which were simple maculopapular rash and none of those were compatible with SCARs. The mean duration of allopurinol exposure in total patients was 26.46 days (1∼2,173) and the mean duration until development of rash was 5.54 ± 1.20 days. Fifty patients (10.8%) had HLA-B58. However, the incidence of allopurinol induced rash was not different according to HLA-B58 (4% (2/50) and 2.66% (11/413) in B58 (+) and B58 (-) patients, respectively). Frequency of B58 was slightly higher in patients with rash (15.4%) compared with tolerant patients (10.7%) but the difference was statistically insignificant ($P > 0.05$).

Conclusions: The results of this study that HLA-B58 does not increase the risk of allopurinol induced SCARs as well as simple rash among patients with hematologic malignancy. Allopurinol can be used safely in most patients with hematologic malignancy during chemotherapy and HLA typing does not give additional advantage for clinical decision.

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Risk Factors Associated to Mortality in Pediatric Patients with Hemophagocytic Lymphohistiocytosis

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Objective: Identify risk factors associated to mortality in pediatric patients with hemophagocytic lymphohistiocytosis.

Methods: Retrospective cross-sectional study of medical records with discharge diagnosis of Hemophagocytic syndrome/Hemophagocytic lymphohistiocytosis (ICD-10; D76.1/D76.2) from Jan2004-May2011 in a pediatric-tertiary-care-center. Descriptive and risk analysis were made on SPSS Statistics V17.0.

Results: Thirty medical records were analyzed. Median-for-age: 2 years 8 months, (range: 2 months-to-15 years). Sex distribution: 14 girls (47%), 16 boys (53%). Median of symptoms duration: 1 month (range: 3 days-to-7 years). Reported symptoms and physical signs at hospital admission: fever n = 28 (93%), asthenia/adynamia n = 11 (37%), skin findings n = 10 (33%), epistaxis n = 5 (17%), gastrointestinal bleeding n = 4 (13%), hepatomegaly n = 27 (90%), splenomegaly n = 21 (70%), lymphadenopathies n = 14 (47%), paleness n = 14 (47%), purpura n = 5 (17%). Laboratory findings: anemia n = 29 (97%), LDH elevation n = 28 (93%), hypoalbuminemia n = 27 (90%), thrombocytopenia n = 26 (87%), hypertransaminasemia n = 25 (83%), haemophagocytosis n = 22 (73%), hypertrigliceridemia n = 21 (70%), hypofibrinogenemia n = 20 (67%), leucopenia n = 19 (63%), hyperferritinemia n = 15 (50%). In 18 patients (60%) active infection was evident at hospital admission: pneumonia n = 9(50%), gastroenteritis n = 2 (11%), meningitis n = 1 (5%), others n = 6 (33%). Epstein-Barr virus infection was diagnosed in 7 patients (23%). All patients were treated according to HLH-2004 guidelines.

Overall mortality 63% (n = 19), 9(47%) died from septic-shock, 7 (36%) haemorraghic-shock, and 1(5%) with acute liver failure. Differences between non-survivours and survivours by (x^2): hypofibrinogenemia (53%versus 13%; $P = 0.039$), epistaxis (17% versus 0%; $P = 0.023$), evident clinical infection (47%versus 13%; $P = 0.044$), elevated LDH levels (63% versus 30%; $P = 0.039$), hemophagocytosis (57% versus 17%; $P = 0.024$). Risk factors associated to mortality: history of epistaxis (OR = 1.78, 95% CI, 1.26-2.52; $P = 0.023$), evident clinical infection at hospital admission (OR = 2.41, 95% CI, 1.08-5.8; $P = 0.044$). Normal levels of LDH showed diminished mortality risk (OR = 0.32, 95%, CI, 0.18-0.55; $P = 0.039$).

Conclusions: The present study describes the most common clinical, physical and laboratory findings in patients with haemophagocytic lymphohistiocytosis attended in our hospital. We were able to identify risk factors associated to mortality, and 1 protective factor.

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The Clinical and Serological Findings in Patients with Toxocariasis in Korea

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Background: We performed this study to investigate the clinical and serological characteristics of human toxocariasis in Korea.

Methods: Total 152 patients with peripheral eosinophilia (>450 cells/μL) were enrolled and they were divided into 2 groups based on a Toxocara excretory-secretory IgG ELISA: 95 seropositive patients and 57 seronegative patients. We not only compared the clinical features including age, sex, tissue infiltration of eosinophil and presence of allergic asthma and rhinitis but also serologic markers such as serum total IgE, specific IgE to *Dermatophagoides pteronyssinus (Dp)* and *Dermatophagoides farine (Df)* by using immunoCAP between 2 groups.

Results: The seropositive rate of toxocara was 62.5% (95/152) in the patients with peripheral eosinophilia in whom seropositive patients were older than seronegative patients ($P = 0.043$), men were more than women ($P < 0.01$). The serum total eosinophils ($P = 0.048$), total IgE level ($P < 0.01$) and the Df seropositive (immunoCAP >0.35 KU/L) rate ($P < 0.01$) were significantly higher in sereopositive patients than seronegative patients. The eosinophilic tissue infiltration in liver ($P = 0.003$) or lung ($P < 0.01$) and ingestion of raw cow meat or liver ($P < 0.01$) were observed more frequently in seropositive patients but the presence of allergic asthma ($P < 0.01$) and rhinitis ($P < 0.01$) more frequnetly in seronegative patients. Among seropositive patients, there were positive correlations between the serum total IgE level, total eosinophils and the value of toxocara IgG ELISA OD ($r = 0.502$, $P < 0.01$; $r = 0.247$, $P = 0.016$, respectively) and the specific IgE to Df was significantly higher ($P < 0.01$) than that to Dp suggesting there might be cross reaction between the antigen of Df and toxocara antigen.

Conclusions: The ingestion of raw cow meat or liver was closely related to an increased risk of toxocariasis in Korea. We thought that the patients who had highly elevated serum total IgE level, peripheral eosinophilia and experience of ingestion of raw cow meat or liver but not allergic disease might have human toxocariasis so should be evaluated whether eosinophils were infiltrated in organs such as liver or lung.

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Interferon-Gamma Release Assay—Useful Tool for the Diagnosis of Pleural Tuberculosis

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Background: Pleural tuberculosis represents a big problem to diagnose despite of many diagnostic tools. CD4+T-lymphocytes play an imprortant role in immune response against Mycobacterium tuberculosis. They are accumulated in pleural space affected with Mycobacterium tuberculosis and release an inflammatory cytokines (interferon-γ, interleukin-2). These cytokines interact with macrophages to stimulate effective antimycobacterial actions. The pleural fluid lymphocytes and interferon-γ level are elevated in many cases such as viral infections, malignancy or tuberculosis. We decided to evaluate a benefit of utilization of antigen specific Interferon-gamma release assay (IGRA) in pleural effusion (PE) to the diagnostics of pleural tuberculosis.

Methods: We present results of 29 patients with lymphocytic PE of unknown cause. The total leukocytes count, lymfocyte subsets by flow cytometry with monoclonal antibodies directed against the T-lymphocyte antigens (CD3, CD4, CD8) and HLA DR antigen as a marker of T-lymphocyte activation were determined in PE. IGRA test was used to determine a level of specific interferon-gamma in PE and in whole blood too. Furthermore we analysed results of tuberculin skin test and Mycobacterium tuberculosis cultivation in the sputum and in PE.

Results: Of the 29 lymphocytic PE was IGRA test positive in 3 cases (10,3%). These patients had the pleural effusion with activated CD4 + T-lymphocytes predominance, elevated CD4/CD8 ratio. Mycobacterium tuberculosis cultivation was negative in both sputum and pleural fluid except 1 patient with positive sputum culture. The tuberculin skin test was higher than 15 mm of all 3 patients. The clinical diagnosis of active pleural tuberculosis was confirmed in these patients. AntiTB treatment was successful of all them. Lymphocytic PE with negative IGRA test was in 26 patients (89,7%): malignancy in 7, heart failure effusion in 3, parapneumonic effusion in 8 and other pathological causes was in 8 patients.

Conclusions: Our results acknowledge that IGRA test applied to pleural fluid is very helpful to the diagnostics of pleural tuberculosis because the pleural fluid interferon-γ level is measured after stimulation of T-lymphocytes by tuberculous specific antigens. We conclude that another important benefit of interferon-γ release assays is the differential diagnostics of CD4+T-lymphocytic pleural effusions.

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The Parasite Echinococcus Granulosus Promotes Allergic Response in Human

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Background: Helminth parasites are highly antigenic and some types favour the generation or exacerbation of allergic responses by inducing strong Th2-type responses (with the production of cytokines, particularly IL-4). Moreover, recent data suggest that Arginase is involved in the pathogenesis of multiple aspects of allergic disease. In the present work, our aim is to study whether the parasite *Echinococcus granulosus* induces Th2-type response and whether this is beneficial for the host or not. *Echinococcus g.* infection, which induces hydatidosis, remains a serious parasitic disease in Algeria. In human, the larval form develops into large cysts especially in the liver and lungs.

Methods: We have investigated the effect of laminated-layer (accelullar layer of hydatic cyst) extract (LLs) on IL-4, and IFN-γ production and Arginase activity in culture performed with mononuclear cells (PBMC). These cells are prepared from peripheral blood of hydatic patients (before and after surgery) and healthy donors. Of note, IFN-γ (Th1 cytokine) downregulates Th2-derived cytokines (like IL-4) which are the best inducer of Arginase pathway. Finally, we have investigated the effects of LLs and IL-4 on protoscoleces (larval form of parasite) viability in PBMC-protoscoleces coculture.

Results: We have found that LLs enhanced IL-4 production and Arginase activity and reduced IFN-γ production by PBMC. Furthermore, LLs and IL-4 also enhanced parasite survival in PBMC-Parasite cocultures. Moreover, we have purified by chromatography one of the major antigenic protein in LLs: the fraction 4 (F4, 12kDa). This fraction has the same effect as LLs on Th1/Th2 balance. Interestingly, similar findings are observed in cultures and

cocultures performed with PBMC of presurgical and postsurgical patient and healthy donors.
Conclusions: Taken together, our results suggest that the laminated layer of *Echinococcus g.* may promote allergic response in humans directly by inducting the Th2 pathway. Moreover, this response allows the parasite survival.

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Use of Transfer Factor in Patients with Persistent Genital Human Papillomavirus Infection

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Background: Human papillomavirus (HPV) is the most common sexually transmitted infection worldwide. About 75 to 80% of sexually active Americans will be infected with HPV at some point in their lifetime. The risk of HPV infection seems to be related with age at first intercourse, younger age and number of sexual partners. HPV infection is limited to the basal cells of stratified epithelium of the skin or mucous membranas. There is a wide latency period, from months to years, before squamous intraepithelial lesions develop. Most HPV infections are cleared within 2 years by the immune system. Only in 5% to 10% of infected women with "high risk" types the infection persists determining a high risk of developing intraepithelial neoplasias, as cervical cancer, vulvar cancer, penile cancer, and/or anal cancer. The gynecological evaluation and Papanicolau smear are the primary screening tools for detecting HPV infection. There is currently no specific treatment for HPV infection. The Transfer Factor (TF) or Dialyzable Leukocyte Extract is an immunomodulator that has been successfully used as an adjuvant in the treatment of intracelular infections such as recurrent herpes virus diseases. TF induces the expression of RNAm and IFN-γ and increases CD4+ cells. The IFN-γ activates macrophages, neutrophils, B lymphocytes, NK cells, and favours the differentiation of T cells into Th1 lymphocytes that are requiried for the control of intracellular patho gens.
Methods: We used TF in a group of patients with persistent genital human papillomavirus infection.
Results: We included 12 patients, aged 19 to 45 years old (mean 30), with 14 to 23 years at first intercourse and a mean of 3 sexual partners in their lifetime. All of them had persistent HPV that had been treated before with local and ablative therapeutic options (including cervical freezing, cauterizing loop, imiquimod, podophyllin and/or cervical conization). Transfer factor was administered daily for 5 days, and subsequently at 7-day intervals for 5 weeks. We found an important improvement in the gynecological evaluation of cervix and perineal lesions and a significant reduction in the frequency of relapses.
Conclusions: Transfer factor could be used as an adjuvant in patients with persistent genital human papillomavirus infection.

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Experimental Heterophyiasis: Histopathological & Immunological Study

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Background: The present study was conducted to evaluate the effect of immunosuppression on the course of infection, the extraintestinal pathological changes and the immune complexes deposits in kidneys and brain tissues with Heterophyes heterophyes infection in mice.
Methods: Seventy Swi-ss albino mice were divided into 4 groups; G (I) 30 immunocompetent infected mice, G (II) 30 immunosuppressed by cyclophosphamide, infected mice and G (III) 5 non-infected immunocompetent control mice and G (IV) 5 immunosuppresed non-infected. Groups I & II were infected with 300 metacercariae / mouse orally. Two weeks post infection (p.i.) 5 animals from each group were sacrificed at 14, 16, 18, 21, 25 and 28 days p.i., and the kidneys and brain were processed for tissue digestion with KOH and histopathological and immunofluorescence examination. The adult worms were counted by mucosal scraping of the intestines.
Results: The result of this study showed that the adult worm count was higher in G (II) and G (1). The kidneys of G (I) mice showed mild congestion of the glomeruli with lymphoid aggregates. While in G (II) mice, the glomeruli showed variation in size with mild thickening of their walls and the blood vessels showed moderate congestion with mild thickening of their walls. The brain in G (I) mice showed capillary haemorrhage with focal accumulation of endotheliocytes and histiocytes in a frame work of connective tissue. While in G (II) mice, the brain showed congestion, oedema and hypercellularity. In addition, gliosis accompanied with increased vascularity and endothelial hyperplasia was also observed. No adults or ova were detected by KOH digestion of the brains and kidneys. Mild immune complex deposits were detected from the 3rd week p.i. in G (I). The immunoflourescence reaction becomes moderate at the 4th week p.i. While in G (II) the immunoflourescence reaction was mild 2 weeks p.i. and became moderate at the 3rd week p.i.
Conclusions: These results proved that the H. Heterophyes antigen or immune complex deposits were detected in the kidneys and brain of infected mice. These deposits play an important role in the histopathological changes in the kidneys and brain of infected animals.

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Chronic Obstructive Pulmonary Disease and Lung Cancer Share Inflammation Pathways

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Background: The relationship between inflammation, air obstruction and lung cancer is complex and there is still great uncertainty regarding their underlying pathophysiology. Our aim was to investigate the inflammation pathways that are implicated in both chronic obstructive pulmonary disease (COPD) and lung cancer.
Methods: A literature search was performed in PubMed to identify relative studies published until June 2011.
Results: The pathophysiology of both COPD and lung cancer includes dysregulation of the inflammation process, but the cascade of signaling events is not yet fully understood. Both lung cancer and COPD are associated with cigarette smoking that induces a chronic inflammatory state in the lung by generating reactive oxidant species. It is considered that shared inflammatory pathways involve genetic and epigenetic changes due to chronic tissue injury and abnormal tumor immunity in susceptible hosts. The proposed role of chronic inflammation is based on the 2-stage model of carcinogenesis. According to this model, genotoxic injury is crucial in tumorigenesis, followed by promotional events that result in clonal growth of modulated cells. Research has shown that chronic inflammation creates the necessary environment for the development of lung cancer, acting as a tumor promoter. This environment, in combination with cigarette smoke, induces the upregulation of mediators of the inflammatory response, such as cyclooxygenase-2. This leads to the production of inflammatory cytokines through lymphocytes, such as IL-1, IL-6, IL-8 and IL-10, as well as to the increased formation of chemotactic factors. Some of the latter mediators may suppress cell mediated immune response and promote angiogenesis. They also impact cell growth, resulting in the inhibition of apoptosis. Inflammatory factors promote oxidative stress, contribute to the generation of reactive oxygen, and cause oxidative DNA base modification. COX-2 also plays an important role in promoting epithelial-to-mesenchymal transition, present in both lung cancer and COPD. Thus, chronic inflammation plays a pathogenic role in lung cancer by inducing preneoplastic mutations and cellular damage.

Conclusions: Additional research is required to understand the cellular and molecular mechanisms that link COPD and lung cancer, in an effort to discover new methods of prevention and treatment.

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Risk Factors of Recurrent Upper Respiratory Infections in Children under 5 Years. Habana Vieja

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Background: Upper Respiratory Infections are the most common diseases in childhood. It is possible to get even with no risk factors; although, if there are more factors, the higher it is the probability of illness.

Methods: It was carried out an analytic study of cases and controls to identify risk factors associated with Recurrent Upper Respiratory Infections (RURI) in children under 5 years old from Habana Vieja municipality between January and June of the 2008, 40 children with RURI were studied selected by convenience sampling and 40 controls. Surveys were relatives. The group of cases was compared with the group control and then it was analyzed if the exhibition factor was associated to the RURI by means of the test of square chi, for that which was considered as significant a $P < 0.05$ in which case the test of odds ratio was applied (OR) to determine if really the factor or characteristic is or not of risk.

Results: The most common was RURI was Adenoiditis with 18 cases (45%). All the cases had personal and family history of allergy, compared with 37.5% and 62,5% respectively in controls; (OR = 25.4 $P = 0.0001$ and OR = 16,3 $P = 0.001$). The adequate breastfeeding was more frequent in controls (OR = 2.5 $P = 0.048$). 70% of the cases were exposed to the smoke of the tobacco, and controls only 25% (OR = 8.2). 92.5% of the homes of the cases and 70% of the controls had animals, especially dogs. The cold (92.5%), temperature changes (80%) and humidity (80%) were considered environmental risk factors in this study (OR = 14.5 $P < 0.001$; OR = 16.5 $P < 0.001$, OR = 13.2 $P < 0.002$).

Conclusions: Risk factors affecting the RURI are: personal and family history of allergy, inadequate breastfeeding, exposure to the smoke of tobacco and the presence of domestic animals, cold, changing weather and humidity.

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Long Term Asbestos Exposure as a Cause of Eozinophilic Pleural Effusions

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Background: Exposure to asbestos can cause several different types of pleural disease: first diffuse malignant mezothelioma, plural plaques or calcification, loculated pleural abnormality called "rounded atelectasis" and benign pleural effusions (PE).

Objective: To determine the frequency of various pleural diseases related to asbestos exposure.

Methods: A retrospective analysis of 6 cases of PE related to the occupational asbestos exposure (AE) was made, after exclusion of other possible causes of PE. They were evaluated in the period of 7 years.

Results: All cases were male and almost all were more than 60 years old. All cases had more then 30 years from the first occupational AE (5 in building construction and sixt in mine). All of them reported pleuritic chest pain, or feeling heavy in their chest. The chest radiographs showed small to moderate-sized PE, which was bilateral by tree patients (pts) by the others with pleural califications in one of them. One of the pts had 3 episodes of PE and evidence of parenhimal asbestosis. PE was serous exudate and serosanguineous in 2 pts, with polymorphonuclear leucocytes, mononuclear cells and eosinophils (EO). We have evaluated the number of EO in the pleural fluid (PF), from the smear of PF colored by May-Grunwald-Giemsa. The PF differential WBC consisted predominately EO and mononuclear cells. At 4 pts more than 30% EO were found in the PF and 21% and 17% in other 2 pts respectively. During the follow up period of 3 years no other cause of PE has been found and there has been no evidence of mesothelioma in all the pts.

Conclusions: Exposure to asbestos can cause PE with predominant presence of Eo cells.

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A Novel Therapeutical Option in Resistant Ganglionar and Cutaneous Tuberculosis

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Background: Transfer factor was first described in 1955 and constitutes a Dialyzable Leukocyte Extract. It has been widely used in several infectious diseases and malignancies with satisfactory results. Although not yet fully clarified, among the mechanisms of action the most accepted is the enhancement of the cellular immunity.

Methods: We tested transfer factor in a 1 year old and 3 months patient diagnosed with Ganglionar Tuberculosis. 1 week after the administrarion of the Bacillus *Calmette-Guérin* vaccination, the present developed fever, cervical, submandibular, supraclavicular, inguinal and axillary lymphadenopathy. Later on the patient devoloped cutaneous clinical manifestations of tuberculosis such as scrofuloderma, fistulas, hypertrophic scars and ultimately, queloids. The patient had previously undergone short-term strictly supervised treatment for tuberculosis with very poor results. When the treatment was first administered, the patient had the following data: Total White Blood Count 12.9 Lymphocytes: 29% (12–46) CD3: 26.3% (59–90) T helper Cells (CD3/CD4) 21.6% (42–58) Cytotoxic T cells (CD3/CD8) 5.1% (17–33) Natural Killer Cells (CD56) 2.1% (3–7) B cells (CD19) 67.6 % (0–10).

Results: At the end of the treatment, the patientś immune system was enhanced in terms of cell count and improval of skin manifestations. Total White Blood Count 6.5 Lymphocytes: 51.3% CD3: 48.5% T helper cells (CD3/CD4) 31.2% Cytotoxic T Cells (CD3/CD8) 14.6% Natural Killer cells (CD56) 12.2% B cells (CD19) 985%. Cicatrization process was improved, with involution of skin lesions os scrofuloderma and fistulas. Lymphadenopathy was no longer encountered. We have followed the patient for a year and half and no relapses have been encountered.

Conclusions: We consider Transfer Factor a valuable option as adyuvant therapy in cases of ganglionar and cutaneous tuberculosis refractory to conventional treatments. To our knowledge, this is the first report of a case of the disease treated satisfactorily with transfer factor.

ALLERGY TO ANTIMICROBIALS

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Penicillin Allergy Evaluation: Experience from a Drug Allergy Clinic in Kuwait

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Background: To evaluate a cohort of patients with a suspected beta-lactam allergy history.
Methods: 42 patients with suspected beta-lactam hypersensitivity reactions were evaluated at a drug allergy clinic at a tertially allergy center. Skin prick tests (SPT) with major determinants (PPL), minor determinants (MDM), penicillin G, ampicillin, amoxicillin, intradermal tests (ID) and specific IgE determination were done. If all tests were negative, a drug challenge was performed.
Results: 42 patients were enrolled (mean age 39 years, 71.4% female and 28.6% males). History of atopy was present in 59.5%. The offending antibiotics were amoxicillin and amoxicillin/clavulanic acid in 28 (66.6%), penicillin in 10 (23.8%), and ampicillin in 4 (9.5%). Specific IgE to penicillin was negative in almost all patients with history of penicillin allergy (41 patients, 97.6%). SPT and ID tests were positive in 11 patients (26.1%) as follows: 3 patients (7.1%) had positive SPT to PPL, 1 patient (2.4%) SPT to MDM, 2 patients (4.8%) SPT to Penicillin G, 1 patient (2.4%) SPT to Ampicillin, 1 patient (2.4%) SPT to Amoxicillin, 8 patients (19%) ID to PPL, 3 patients (7.1%) ID to Penicillin G, 3 patients (7.1%) ID to Ampicillin. Only 1 patient had both positive specific IgE and skin tests. The remaining 31 patients (73.8%) underwent a drug challenge with the culprit antibiotic with no reported reactions.
Conclusions: One fourth of patients with history of beta-lactam hypersensitivity reactions were confirmed after testing. A combination of skin testing, specific IgE and drug challenge is necessary since none has sufficient sensitivity to be used alone.

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Association Between Genetic Polymorphisms of ABCC2 Transporter and the Susceptibility to Maculopapular Eruption Induced by Antituberculosis Drugs

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Background: ATP-binding cassette (ABC) transporter proteins play an important role in drug disposition. Polymorphisms of ABC transporter genes (*ABCC2 and ABCB1)* may be risk markers for maculopapular eruption (MPE) induced by unusual accumulation of antituberculosis drugs (ATD) itself or metabolites.
Methods: We compared genotype distributions of single nucleotide polymorphisms and haplotypes in *ABCC2 and ABCB1* genes between 62 ATD-induced MPE cases and 159 ATD-tolerant controls using multivariate logistic regression analysis.
Results: Among the 7 selected SNPs of *ABCC2*, -1549G>A in promoter and IVS3-49C>T in intron were associated with ATD-induced MPE ($P = 0.032$ and $P = 0.029$, respectively). *ABCC2* haplotype1 [G-C-C-G] was significantly associated with ATD-induced MPE ($P = 0.032$, OR = 0.35, 95% CI, 0.29-0.95). However, there was no significant association between other genetic polymorphisms in *ABCB1* and ATD-induced MPE.
Conclusions: These results suggest that genetic variations of *ABCC2* are a potential risk factor for ATD-induced MPE.

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The Real Use of Beta-Lactams after "Penicillin Allergic" Label Removal

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Background: The "penicillin allergic" label becomes very common, thus preventing from many patients the use of one of the most efficient antibiotic drugs, with the lowest cost and toxic effects. However, approximately 80% of patients with a history of penicillin allergy have negative results if they are skin tested and can actually use this drug class. We sought to determine whether in real life, removal of the label is implemented to the treatment of beta-lactams when it is required.
Methods: A retrospective study that includes all penicillin allergy history–positive/penicillin skin test–negative/oral amoxicillin challenge-non reactive individuals who had been tested in advance of need between the years 2000 toi 2009 at one medical center (n = 140). To uncover late reactions, they were offered after the test a 5 day course of amoxicillin. The study tool was a phone-questionnaire assessing the patients' confidence in their test results, and whether they have used penicillin since testing.
Results: 106 patients (76%) agreed to participate in the survey. Ninety-nine patients (93%) chose to take the 5 day course of amoxicillin. From this group of patients twenty-seven (27.2%) answered that they feel intermediate insecurity and fourteen (14.1%) that they feel complete insecurity to receive penicillin. Since having the test seventy 2 (72.7%) of the 99 needed penicillin. Sixty-two (86.1%) indeed took a beta-lactam while 10 patients (13.9%) chose to receive another antibiotic class due to their or their physician's disbelief in the test. All the patients (n = 7) who chose not to take the course of amoxicillin after the test stated that they feel complete insecurity to receive penicillin. Four (57.1%) of these patients had a disease that requires a beta-lactam antibiotic and actually, none of them agreed to take one ($P = 0.01$).
Conclusions: A negative penicillin test done in advance of need even when includes an oral challenge may not be enough to convince patients that they can use beta-lactams. Our study suggests that giving a 5 day course of amoxicillin after the test increases the patients' confidence in the results.

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Hypersensitivity to Beta-Lactam Antibiotics Evaluation Using the European Network Drug Allergy (ENDA) Algorithm

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Background: Hypersensitivity to beta-lactam antibiotics are usually defined only by the history of suspected previous reaction to these medicines. This definition, however, can erroneously restrict the use of these important therapeutic resources if not assessed by the proper tests. The objective was to assess the presence of hypersensitivity to beta-lactams through adequate testing.
Methods: Thirty-three patients were referred to our allergic clinic for testing of penicillin hypersensitivity in the period from 2008 to 2011: 22 (66.6%) females and 11 (33.4%) males, with ages ranging from 8 to 88 years. The first 24 (72.7%) patients were tested using only penicillin G, in the form of a prick test followed by an intradermal test with immediate reading, according to the Brazil Ministry of Health protocol (group I). The remaining 9 (27.3%) patients (group II) were subjected to the adaptations of standards-based assessment of hypersensitivity reactions to beta-lactam antibiotics, according to the algorithmic recommendations of the European Network Drug Allergy (ENDA), which includes a prick test and intradermal test with penicillin G, amoxicillin and the suspected beta-lactam, such as clavulanic acid or cephalosporins, with immediate and delayed readings. Patients who had negative skin tests results underwent a provocation test, which is considered the gold standard in determining drug hypersensitivity. In-vitro tests available in Brazil (specific IgE to penicillin and amoxicillin) were performed in patients with a history more suggestive of adverse reactions. It was respected the ENDA recommendation of not subjecting patients with severe reactions to this protocol.

Results: Of the 33 patients, 28 (84.8%) had negative results for the tests. One patient in group I showed inconclusive results. Four patients (12.2%) in group II had positive tests, including 3 for penicillin G and one for amoxicillin.
Conclusions: The results demonstrated that the clinical history collected by medical questionnaires is not the determining factor in confirming a patients' reaction to penicillin, and shouldn't be the only parameter used to exclude potential future prescriptions. In addition, the results denote that hypersensitivity to other beta-lactam antibiotics should be evaluated in a more proper way for a fuller understanding of each case.

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Clinical Features of Drug Rash with Eosinophilia and Systemic Symptoms Syndrome Caused by Antituberculous Medications

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Background: Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome is one of severe adverse drug reactions. Aromatic anticonvulsants and sulfonamides are the most common causes of DRESS syndrome. However, there have been only 2 case reports of DRESS syndrome induced by antituberculous medication. This study was aimed to observe the clinical features of patients with DRESS syndrome caused by antituberculous medications.
Methods: We retrospectively revealed the clinical and laboratory data of the patients from September 2006 to August 2010 at a University Hospital. Our patients were diagnosed as DRESS syndrome if 3 criteria were present: (1) cutaneous drug eruption, (2) peripheral eosinophilia >1,500/μL, (3) systemic involvement (lymphadenopathy, hepatitis or fever).
Results: Nine patients (5 men, 4 women; mean age 50.5 years) were enrolled DRESS syndrome induced by antituberculous medications. The most common causative agent was ethambutol which was identified as the cause in 8 of 9 patients (88.9%). In the other patient, streptomycin was considered as the causative agent. Two out of 8 patients with DRESS syndrome caused by ethambutol were induced by rifampicin as well. Drug eruption developed 6.9 weeks after antituberculous drugs were first used. Skin eruptions were involved on the whole body in 8 patients and on only upper trunk in 1 patient. Diffuse maculopapular eruption was the most common type of skin lesions that was observed in 8 of 9 patients. Other types of skin eruption were identified; 4 exfoliative eruptions, 3 facial edema and 1 urticaria. The mean value of peripheral eosinophil counts was 3,354/μL. The cervical, axillary or inguinal lymphadenopathy was observed in 7 patients and fever was detected in 6 patients. Hepatitis was developed in 3 patients. All patients with DRESS syndrome recovered after corticosteroid therapy and the elimination of the culprit drugs.
Conclusions: The most common cause of DRESS syndrome induced by antituberculous medications was ethambutol in our study. Diffuse maculopapular eruption on the whole body was the most common type of eruption and lymphadenopathy was the most common involvement of internal organ in patients with DRESS syndrome caused by antituberculous drugs.

ANAPHYLAXIS

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Basophil-Mediated Anaphylaxis Triggered by Drug-Activated Complement Alternative Pathway Without Mastocyte's nor Immunoglobulins Involvement

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Background: It's well known that drugs may induce complement alternative pathway's activation. On the other hand there is evidence that anaphylaxis may occur in absence of IgE and IgG antibodies (so-called non-immune anaphylaxis). We determined the tryptase, complement and circulating immune complexes (CIC) levels to understand the nature of anaphylaxis occurred in a woman during high rate infusion of high concentrated iron.
Methods: A 46 years-old woman was admitted to our department because of mixed anemia, iron and cobalamin deficiency-related, started after a surgical intervention (bilio-pancreatic derivation) for heavy obesity occurred 7 years ago (starting Hgb = 7g/dl). Ev. hydroxicobalamin and iron infusions were planned, but during high rate (100 gtt/m') infusion of high concentrated (0,5 mg/mL) iron, the patient suffered from discomfort, sweat and drop in blood pressure (BP 60/30). Blood samples were taken to evaluate tryptase, complement and CIC levels; standard treatment of anaphylaxis was started (im. epinephrine, inhaled O2 with steroids and beta-agonists, ev. electrolyte solution and vital parameters continuous evaluation). The shock resolution was gained in 3 hours.
Results: The level of tryptase was normal (4 mcg/mL; N.R.-Normal Range-= 1–20), while C3 and C4 were impaired (C3 = 65 mg/dl; N.R. = 75–165; C4 = 12 mg/dl; N.R. = 20–55). The search for CIC IgG, IgA, IgM was negative. Six months later the low rate (30 gtt/m') low concentration (0,25 mg/mL) iron infusion was well tolerated by the patient, so excluding any IgE sensitization.
Conclusions: We describe here for the first time a case of human anaphylaxis without mastocyte nor IgE involvement. The high infusion rate and hyperosmolality of hyperconcentrated drug caused complement alternative pathway's activation. The only cell type able to release anaphylaxis mediators other than mastocytes are the basophils, having anaphylotoxins receptors. So, we conclude that drug-induced complement alternative pathway's activation with consequent basophil's involvement was responsible for the patient's "non-immune" anaphylaxis.

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Wait at Least 60 Minutes After Eating

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Background: We will describe 2 unique cases of Food Dependent Exercise Induced Anaphylaxis.
Methods: Patients underwent a complete history, physical exam, and skin prick testing by classical method.
Results: Case 1: A 23 year old Asian Male presented with anaphylaxis following cashew ingestion and post prandial exercise. This was the first episode of anaphylaxis despite previous exposure to cashews and exercise independently. Patient ingested cashews and went for a jog 30 minutes later. His symptoms of anaphylaxis included urticaria and ocular swelling. Skin prick testing generated positive results to cashew, with measurements of 10 mm/30 mm (wheal/flare). Controls of histamine and saline measured were 10 mm/30 mm and 0 mm/0 mm, respectively. Case 2: A 42 year old Caucasian Male presented with anaphylaxis following shrimp ingestion and post prandial exertion. This was the first episode of anaphylaxis despite previous exposure to shrimp and exercise independently. Patient ingested shrimp and went for a brisk walk 30 minutes later. His symptoms of anaphylaxis included full body urticaria and shortness of breath. Skin prick testing generated negative results to shrimp and shellfish mix, with measurements of 0 mm/0 mm and 0 mm/0 mm (wheal/flare). Controls of histamine and saline measured were 10mm/30mm and 0mm/0mm, respectively.
Conclusions: The previous cases describe anaphylactic reactions after food ingestion followed by post prandial exercise. The precise pathophysiology of this rare syndrome is poorly understood, however it is believed that allergen absorption is increased in a post-exercise state. The contrast in our patients' results of their skin prick tests demonstrate that patients may or may not have food-specific IgE but still can experience food dependent exercise induced

anaphylaxis. Mainstay treatment for food dependent exercise induced anaphylaxis is recommending exercising only on an empty stomach. The consideration of food dependent exercise induced anaphylaxis in cases of unexplained anaphylaxis is important as reactions can be life threatening and clinicians should be reminded of the importance of thorough history taking.

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First Report of Anaphylactic Shock Caused by the Ingestion of Mite-Infested Flour in Panama

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Background: To report the first case of an anaphylactic shock, almost lethal, in the Republic of Panama, produced by ingestion of pancakes contaminated by mites.

Methods: A 21 year-old male patient was evaluated due to an anaphylactic shock after the ingestion of pancakes, eggs and milk. The patient had a background of a moderate allergic rhinitis. Not asthma. Skin prick test was performed on the patient with standardized extract of mites and food items, including, flour, milk and egg. After twenty minutes the results were read and considered positive since the wheal was 2 mm larger than the control (histamine 1 mg/mL). The Total IgE was determined by the chemiluminescence method. The determination of the specific IgE for mites and food was performed by the enzyme immunoassay technique. The counting and identification of the mites in the pancake samples that were eaten by the patient were placed in a microscopic slide using a Hoyer medium and analyzed in a stereomicroscope.

Results: The skin prick test performed was considered positive for Blomia tropicalis, Dermatophagoides pteronyssinus and negative for flour, milk and egg. The total IgE was increased and the specific IgE resulted positive for Dermatophagoides pteronyssinus and Blomia tropicalis, but negative for flour, egg and milk. The microscopic examination of the pancake wheat showed 3 different species of mites: Blomia tropicalis, Blomia sp. and Dermatophagoides pteronyssinus, the first one in major proportion.

Conclusions: The anaphylactic shock of the patient was produced by the ingestion of a commercial pancake contaminated by mites to which the patient was sensitized. Flour kept in open containers becomes a fertile ground for the growth of mites in tropical climates. Allergic patients should be warned of the danger of anaphylaxis in such conditions.

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Recurrent Aanaphylaxis in Cow Milk Allergy: What Is Wrong?

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Background: Food allergens are one of the most important triggers of anaphylaxis in pediatric population and all efforts must be done to avoid new episodes.

Objective: To determine some factors associated to recurrent anaphylaxis induced by cow's milk (CM) in pediatric patients with a previous anaphylactic episodes.

Methods: This is a retrospective study based on medical records from all CM anaphylactic patients, from a Brazilian reference center for food allergy. The anaphylaxis criterion used was based on the *Second symposium on the definition and management of anaphylaxis*. Patients and parents had received orientation regarding prevention of new episodes, including information about hidden allergens, label reading, and synonymous terms.

Results: It was included 53 patients (33M: 20F), median age of the first episode of anaphylaxis was 6 months (range 1–87 month) and in 56. 6% the first episode occurred until the age of 6 months. Fifty episodes were observed in 22 patients during the follow up. Twelve patients presented 2 or more episodes and 2 patients presented 6 episodes. It was not possible to detect the trigger food in 17 episodes and these situations were related to ingestion of: appetizers (4), margarine (3), bread (2), pizza (2), juice with casein (1), pasta (1), cake (1), chips (1), Italian sausage (1). Two episodes were challenged by accidentally skin contact and 2 by inhalation. Among the settings of episodes, the majority occurred at home. Other places included: school, restaurants and bakery.

Conclusions: This study showed that it is very difficult to reach success only with the orientations regarding anaphylaxis prevention. It is necessary to betake of other strategies to improve the measure to avoid new episodes of anaphylaxis such as: folders, visual midia and interactive activities. Furthermore, the continuous education is essential to reinforce the knowledge.

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Epidemiology of Anaphylaxis in Adults Treated in the Emergency Department, of the University Hospital of Monterrey n.l Mexico, During 2005–2010

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Background: The risk of anaphylaxis ranges from 0.2 to 0.7%. The objective of this study was to describe the causes, clinical features and complications of patients with anaphylaxis treated in the emergency department of our hospital.

Materials and Methods: A prospective, observational and descriptive survey was conducted for assessing adult patients with a diagnosis of anaphylaxis from March 2005 to 2010. Information was obtained from the medical records and from a questionnaire was that completed for the patients and a relative. The information included, triggers, demographics, allergy history and clinical characteristics of the current episode. All the cases were followed to their outcome.

Results: We documented 45 cases of anaphylaxis. 26 patients (58%) were male. The most common causes of anaphylaxis were: drug (49%) food (20%) and poison hymenoptera venom (16%). The most common clinical signs ando symptoms included: dyspnea (69%), nausea (58%) and hypotension (56%). 44% of patients came to emergency departments in the course of 30 minutes after onset of symptoms while the 29% took 30 minutes to 1 hour and 27% more than 1 hour. Among the associated diseases, hypertension was 13% and rhinitis (11%). In 85% of the cases, patients remained under observation for 3 to 12 hours were the most frequent discharged. 7 patients were hospitalized and 4 sent to intensive care later were discharged without complications.

Conclusions: Anaphylaxis is not uncommon in our environment. Drugs are the most common cause as reported in the literature. The most frequent clinical manifestations are respiratory and gastrointestinal.

ANTI-IGE

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Refractory Chronic Urticaria Treated with Omalizumab

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Background: Chronic urticaria (CU) is a common disorder characterized by recurrent episodes of urticaria pruritic erythematous lesions, associated with angioedema[1]. It affects 0.1% of the population, it is estimated that approximately 15 to 25% of the population will have hives at some point in their lives.[2] About 80% of UC patients are diagnosed as idiopathic chronic urticaria and that no cause is identified, 3 experiencing deterioration in their quality of life affecting your work, social relationships, schemes requiring multiple medications and doses higher than usual. This study proposes Omalizumab (anti-IgE humanized antibody) as a treatment for Refractory Chronic Urticaria (RCU)

Object: Demonstrate Omalizumab's effectiveness in the treatment of Refractory Chronic Urticaria.

Methods: A clinical study, was carried out to evaluate the effectiveness of the Omalizumab's treatment on RCU diagnosed patient, including male and female patients ages 12 to 50 diagnosed with RCU, with Scorad higher tan 30 points. We made a questionnaire to know about the patient's family background, skin symptoms beginning, administration of drugs such sistemic steroids, inmunosupresors, calceurine inhibitors, presence of inmunotherapy and age of start. Omalizumab was administered on doses according patient's weight and IgE levels, bimonthly or monthly according to treatment guides. Severeness level was calculated with scorad every 1 month, with IgE seric level measurement and life quality questionnaire.

Results: 5 patients diagnosed with RCU were included in the group of Omalizumab and 5 patients in the control group (placebo). All patients were female. A gradual decrease on the life quality score and in Score, with a significant P under 0.05 was observed on all patients treated with omalizumab compared with patient in the group with placebo.

Conclusions: Treatment with Omalizumab progressively decreases the severeness level on RCU, with a significant improvement on the patient's life quality.

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Clinical Experience in Allergic Asthma Patients: Omalizumab with Immunotherapy

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Background: To evaluate the therapeutic efficacy of omalizumab and specific subcutaneous immunotherapy (SCIT) as a treatment modality in patients with more than one allergic-type condition.

Methods: In the first group **(**Group A), 2 males and 7 females with severe persistent asthma and a mean age of 34.2 years received omalizumab and SCIT. In the second group (Group B), 4 males and 2 females with severe persistent asthma and a mean age of 52.7 years received omalizumab only. In the third group (Group C), 1 male and 3 females with severe persistent asthma and a mean age of 28.8 years received omalizumab followed by SCIT. All patients were followed for 2 years and comparisons were made using pulmonary function tests and asthma control tests.

Results: The patients studied had severe persistent asthma for periods ranging from 2 to 10 years, and in addition had been diagnosed as allergic asthmatics for 5 to 40 years. The mean IgE levels were as follows: Group A: 553.9 IU/mL; Group B: 422.3 IU/Ml; and Group C: 383.5 IU/mL. In all 3 groups results in the asthma control test increased by 2.5 fold over the period of study.

Conclusions: After the addition of SCIT to omalizumab therapy at 48 week of our study, no change was detected in urticarial attack rates. In another 17 year old male patient with moderate allergic rhinoconjunctivitis, asthma and atopic dermatitis, omalizumab administration with SCIT at the same time, increased the severity of atopic dermatitis. We stopped the immunotherapy than the skin lesions lost.omalizumab therapy is continued.

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Evaluation of Adverse Events Associated to Administration of Omalizumab

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Background: Anti IgE therapy is the ultimate therapeutic option for severe atopic conditions, not controlled by conventional treatment. Its efficacy and safety was described in several peer reviewed publications. Here we report on the events temporally related to the administration of almost 4 hundred doses of the only monoclonal Anti IgE antibody approved in our country for the treatment of severe asthma.

Methods: Descriptive retrospective analysis of clinical charts of patients receiving omalizumab because of Severe Uncontrolled Asthma, considering those events presented in the 72 hours after administration of it, which was not present before the procedure or as a concomitant condition of the patient. Vital signs, respiratory and cardiovascular evaluation, and dermatological inspection were performed in the hour after administration of corresponding doses. Patients having any kind of complaint were evaluated in unscheduled visits.

Results: 384 doses of 150 mg omalizumab were given to from April 2007 to June 2011, to nine severe asthmatic patients. One of them received treatment for over 4 years, and two for over 3 years.

Conclusions: Our records from patients receiving omalizumab have not registered severe adverse events in almost four hundred doses given. The moderate adverse events of nausea and tachycardia resulted in discontinuation

Events related to omalizumab administration

YES	NO
Local erythema and edema: 0.78%-mild	Muscle pain: 1%-moderate
Nausea: 0.26%-moderate	Bruises: 0.52%-mild
Sinusal Tachycardia: 0.26%-moderate	Headache: 0.26%-mild
	Ear pain: 0.26%-mild

of treatment in this unique patient. Overall, omalizumab demonstrated a very acceptable safety profile in our patients.
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Gender and Different Prevalence in Asthma Treatment With Anti-IGE (Omalizumab)

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Background: General opinion on pathogenesis and prevalence of bronchial asthma indicates that age and sex are the major risk factors. Detailed physiological mechanisms of the changing sex ratio are not fully known.
Aims and objectives: Investigate the influence the asthmatic patients treated with anti-IgE with different gender.
Methods: Here, we pooled data from ten published studies from 1999 with more of our unpublished data of patients with severe persistent asthma treated with omalizumab, an anti-immunoglobulin E (IgE) monoclonal antibody. Static analysis was used to find gender risk factors as the ratio of treatment effect (omalizumab: control) on the standardized exacerbation rate per year.
Results: The studies included 3270 patients (treated with omalizumab), whose had severe persistent asthma according to the Global Initiative for Asthma (GINA) classification. Analysis of 2 groups male versus female showed that the efficacy of omalizumab on asthma exacerbations was unaffected by patient age, gender, baseline serum IgE (split by median) or by 2- or 4-weekly dosing schedule, although a more large number of women were treated (1921/1349; 59 % women vs 41% men; $P < 0.001$) and benefit in absolute terms appeared to be greatest in women patients which had a more severe asthma, defined by a lower value of percentage predicted forced expiratory volume in 1 second (FEV1) at baseline, this subgroup showed odds of being a responder (composite definition) 1.25 times higher (95% CI, 1.18-3.01) than men.
Conclusions: These results suggest that in population of asthmatics treated with anti-IgE the number of women is shown higher than men, it confirms that asthma should be considered with different approach by the gender for being adequately controlled on current therapy.

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Fetal Loss in Severe Asthma and Posterior Healthy Pregnancy and Birth with the Use of Omalizumab—Case Report

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Background: Pregnancy may aggravate asthma and result in life-threatening for both mother and foetus. The humanized monoclonal antibody omalizumab has proven to be effective in controlling severe asthma. The purpose of this case report is to present the effectiveness and safety of this medicine during pregnancy.
Methods: Case report of a severe asthmatic pregnant woman who had a previous foetal loss due to asthmatic exacerbation, and obtained a subsequent successful pregnancy and delivery with omalizumab use.
Results: KRF, 35, female, housewife, presented bronchial asthma associated with allergic rhinosinusitis since childhood with periods of remission and exacerbations. Since 15 years old, she presented progressive worsening of the disease with increased intensity and frequency of the attacks. In 2005 she became pregnant, progressing with severe attacks, emergency visits and hospital admissions, and requiring courses of systemic corticosteroids, despite continued treatment including combined of long-acting beta agonist (LABA) and inhaled corticosteroids (IC), besides Montelucast and Bamiphylline. Nevertheless, the pregnancy was interrupted at 8 months, due to the fetal death. Despite using regularly Formoterol (24 mcg/day) and Ciclesonide (640 mcg/day), the exacerbations became frequent, requiring continuous oral prednisolone, 20 mg daily, to achieve asthma control. Other risk factors for severe asthma were ruled out through extensive investigation. Omalizumab, 300 mg monthly, was introduced in July 2006, resulting in important improvement of the asthma control, allowing the discontinuation of systemic corticosteroids in 2 months, and subsequent reduction of Ciclesonide and formoterol doses. Discontinuation in Omalizumab use resulted in asthma worsening, despite the increment in the other medications doses. When omalizumab administration was restored, 8 months later, the asthma control was achieved again. In November 2010, she became pregnant and the same treatment plan for asthma was maintained. Only one episode of a mild exacerbation of asthma occurred due to a respiratory infection. The pregnancy reached full-term with a cesarean section in May 2011 with mother and newborn presenting satisfactory health conditions.
Conclusions: Omalizumab has shown efficacy and safety in the control of severe asthma during pregnancy, reducing the risk of injury to health for both mother and newborn.

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Vasculitic Urticaria Treated with Omalizumab. Case Report

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Background: Vasculitic urticaria (UV) is a condition characterized by hives lasting more than 24 hours, itchy and burning with residual hyperpigmentation. Histopathology is characterized by leukocytoclastic vasculitis, perivascular infiltrate and fibrin deposits. The incidence is approximately 2%, prevalence in women (5:1). The treatment includes steroids, immunosuppressants, and has suggested the use of monoclonal antibodies. We report a patient treated with omalizumab.
Methods: Female 51 years old, his mother died of complications from Lupus Erythematosus (SLE). 10 years ago was diagnosed with SLE by criteria haematological and immunological joints treated with azathioprine, chloroquine and deflazacort, with control of lupus, immunosuppressive suspended and continuing low-dose steroids. Have hives as secondary reaction to netilmicin and penicillin. Two years ago shows like lesions papules and burning and itching rash on chest and limbs, with no peeling hyperpigmented macules, managed with systemic steroids (prednisone) and antihistamines, with a decrease of the same but has l month after similar injuries, and macula, adjust the dose of steroid 1 mg/kg with a decrease in events with exacerbations and remissions, until 3 months course again with increasing symptoms with erythematous, violaceous, painful to the touch did not disappear in extremities lower, upper abdomen and chest, with no improvement after systemic steroids, antihistamines, and immunosuppressants, laboratories report 4.600 leukocytes, eosinophils 100/mcl, 90.1 mgU/dl C3, C4 8.6 mg/dL of 169 I U IgE/mL, leukocytoclastic vasculitis biopsy reports, deciding Omalizumab use was calculated based on weight and IgE, showing significant improvement with disappearance of the lesions, without pain or itching with hives.
Results: Gradual decrease was observed of Score of 6 to 1 and score-related quality of of life with a 84.37 to 42.36 CUQ2oL after 3 applications, with a significant P by comparing the results and statistical analysis.
Conclusions: We conclude that Omalizumab may be useful in the treatment of vasculitic urticaria, although it requires clinical trials that include a greater number of patients and be compared with conventional treatment.

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Efficacy of Omalizumab in the Treatment of Urticaria-Vasculitis Associated to Churg-Strauss Syndrome: A Case Report

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PhD, and Massimo Triggiani, MD. *Division of Allergy and Clinical Immunology and Center for Basic and Clinical Immunology Research (CISI), University of Federico II, Naples, Naples, Italy.*

Background: Churg-Strauss Syndrome (CCS) is a rare systemic necrotizing small vessel vasculitis associated with bronchial asthma, peripheral blood eosinophilia and eosinophilic lung infiltration. Skin changes compatible with vasculitis are present in about 75% of patients. Previous reports suggest that patients with CSS can be treated with anti-IgE (omalizumab) in addition to conventional therapy to achieve asthma control. Here we report the efficacy of a 6-month treatment with omalizumab in a patient with CSS characterized by severe asthma and urticarial vasculitis.

Methods: A 44 year old Caucasian female with a 5 year history of severe asthma, chronic urticaria and mild eosinophilia (1100/μL) was evaluated for possible CSS. Total serum IgE was 662 KU/l with positive skin prick tests for dust mites. Bronchial asthma was not controlled and FEV1 was 60% despite treatment with budesonide (640 mcg/die) and formoterol (18 mcg/die). Diffuse and confluent urticarial rash occurred in the last 6 months before evaluation and responded neither to prednisone (10 mg/die) and rupatadin (10 mg/die) nor to immunosuppressive agents (cyclosporin 200 mg/die or azathioprin 100 mg/die). The patient was treated, as add-on therapy, with omalizumab (300 mg s.c. every 2 weeks) accordingly to total IgE and weight parameters reported in the drug information leaflet.

Results: After 6 months of treatment the patient reported a significant improvement in asthma control with 50% reduction of nocturnal awakenings and asthma exacerbations and a major FEV1 improvement (101% at 16 weeks and 103% at 24 weeks). Eosinophil count was reduced to 600/μL. A 75% reduction of oral prednisone was registered after 8 weeks of treatment. Importantly, urticarial lesions disappeared after the first injection of omalizumab. Omalizumab injections were well tolerated and no adverse event was recorded.

Conclusions: This case suggests that omalizumab can be beneficial and safe in patients affected by CSS with severe asthma and urticarial vasculitis. In addition to its effect on serum IgE, efficacy of omalizumab in CSS may be related to an inhibitory effect on blood eosinophilia.

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A 4-Year Follow-up in Children With Moderate/Severe Asthma after Withdrawal 1 Year Omalizumab Treatment

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Background: Asthma guidelines include omalizumab in the step up management in those patients with severe non-controlled asthma despite the use of the inhaled corticosteroids (ICS) at the highest dose recommended and/or oral corticosteroids (OCS) courses. This communication describes the 4 year follow up of children with moderate/severe allergic asthma treated for 1 year with add-on omalizumab after discontinuation.

Methods: 7 children (6 to <12 years) with moderate/severe uncontrolled asthma following strict inclusion/exclusion criteria. The patients completed a 1 year treatment with omalizumab according to the DBPC CIGE025 clinical study protocol. Four years follow up after discontinuation of the study medication was performed. It included clinical assessment, different asthma-related outcomes and lung function in outpatient hospital office

Results: All patients that received xolair during the study period achieved good asthma control and high dose ICS (mean dose fluticasone 500 mcg) were could be discontinued. Surprisingly, the 7 patients that received Xolair for one year were completely free of asthma symptoms during the first 3 years of follow up. They did not use any additional asthma medication. After the third year of follow up, only 2 out of 7 (28%) patients begun with persistent asthma symptoms and exacerbations. These patients have required rescue medication and then regular controller medication (budesonide 400 mcg). We could not identified any risk factor helping in predicting those who had symptoms relapsing. Lung function, number of exacerbation, number of hospitalization, eosinophilia, IgE levels or previous treatments with OCS

Conclusions: Most of these patients 5 out of 7 still remain asymptomatic 4 years after discontinuation Xolair without regular ICS treatment. They are still not using any controller medication only 2 patients had exacerbations and at present show persistent mild asthma controlled with medium ICS therapy. This follow up would generate the hypothesis that omalizumab could have a potential as a modifier of the natural history of asthma beyond the improvement of symptoms control in children with moderate/severe uncontrolled asthma. Further studies are needed to test this hypothesis.

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Serum Soluble Trail Levels in Patients With Severe Persistent Allergic Asthma: Its Relation to Omalizumab Treatment

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Background: The pathogenesis of allergic asthma and other allergic conditions are believed to be closely interrelated because of the similar dynamics of allergy-inducing cells and molecules, and the independent evidence for their clinical overlap. In this study we compare the diseases and the effect of Omalizumab treatment on the dynamics of cell apoptosis regulating molecules.

Methods: In the first group, 6 males and 8 females (a total of 14 patients) were selected with severe persistent asthma with a mean age of 42.4 years (Table I). All patients received omalizumab therapy for 4 months, with treatment administered every 2 weeks. Symptoms and severity of allergic reactions were recorded before and after treatment with omalizumab. Clinical changes and adverse effects were assessed and recorded at each patient visit. The second group consisted of 14 newly diagnosed allergic asthma patients with mean age was 43.8 years. All of these patients were followed up in the Immunology Allergy Clinic of the Antalya Education and Training Hospital, and were evaluated by clinical status. The third group consisted of 14 healthy volunteers, with no difference in age and sex (mean age was 43,3 years. Serum sTRAIL levels in all individuals (patients and healthy controls) were measured by a sandwich enzyme-linked immunosorbent assay (Diaclone, France).

Results: There were no differences between the healthy controls, newly diagnosed allergic asthma patients and non-treated severe persistent allergic asthma patients during the active phase ($P < 0.05$). Interestingly, the variance levels in patients who received omalizumab treatment were significantly lower than the healthy controls.

Conclusions: In summary, we speculate that the physiological functions of sTRAIL in allergic conditions, and the elucidation of the molecular mechanisms by which sTRAIL: TRAIL receptor signals cells, will be of significant interest to the scientific allergy community in the coming years. Our study provides a novel perspective on severe persistent allergic asthma and the effect of omalizumab treatment on cell apoptosis, using serum sTRAIL measurements.

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Total Antioxidant Capacity, Hydrogen Peroxide, Malondialdehyde and Total Nitric Oxide Concentrations in Patients With Severe Persistent Allergic Asthma: Its Relation to Omalizumab Treatment

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Background: There is no data available to adequately explain the alterations in total antioxidant capacity, hydrogen peroxide, malondialdehyde and total nitric oxide concentrations in severe persistent asthma and newly diagnosed allergic asthma patients. In the study below we have examined changes in total antioxidant capacity, hydrogen peroxide, malondialdehyde and total nitric oxide levels in severe persistent asthma and newly diagnosed allergic asthma patients and the association(s) between these variables.

Methods: The first group of patients included 6 male and 8 female subjects with severe persistent asthma, having a mean age of 42.4 years. A second group of subjects consisted of 14 newly diagnosed allergic asthma patients with a mean age of 43.8 years. All patients were followed in our clinic, and were evaluated by clinical status. A third group of 14 age-sex matched healthy controls were also included. Serum samples were collected and stored at –70 until use for the determination of total antioxidant capacity, hydrogen peroxide, malondialdehyde and total nitric oxide concentrations. Serum IgE levels, ANA, RF, hepatitis markers, C3, C4 and eosinophil levels were evaluated in all patients. All assays were carried out in duplicate.

Results: Total antioxidant capacity levels of Group IB, group II and group III were lower than the IA group. Total antioxidant capacity levels of groups II and III were higher than in group IB. Hydrogen peroxide concentrations in group IB were lower than in group IA, while concentrations in group II were higher than in group IB. The malondialdehyde concentration of group IB was lower than in all other groups. The malondialdehyde concentration of group III was higher than all other groups. The malondialdehyde concentration of group II was lower than in group III. The total nitric oxide level of group IB was lower than all other groups. The total nitric oxide level of group III was higher than all other groups, while that of group II was higher than for both groups IA/IB.

Conclusions: To monitor the omalizumab treatment efficacy in the severe allergic asthma patients; total antioxidant capacity, hydrogen peroxide, malondialdehyde and total nitric oxide concentrations might be new markers.

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Near-Fatal Asthma Treated with Omalizumab

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Background: Near-fatal asthma treated with Omalizumab. The near-fatal asthma is a severe form of asthma that threatens the life of patients and is associated with poorly controlled chronic asthma, accounting for limitations in the quality of life. Presents with ongoing chronic inflammation and irreversible changes in the airway. Treatment is difficult, however with the use of omalizumab can decrease the risk of mortality in these patients.

Objective: Evaluating clinical improvement, spirometric and income to the emergency hospitalization and intensive care unit, as well as near-fatal asthma episodes in patients with uncontrolled asthma in treatment with con Omalizumab.

Methods: We evaluated 4 patients with poorly controlled asthma and near-fatal episodes of asthma who were administered doses of omalizumab and IgE established according to weight, evaluating clinical, spirometric well as income to the emergency room and hospital intensive care unit.

Results: There was a significant clinical improvement in 4 patients after treatment with omalizumab with improved daytime symptoms by 75% and 68% nocturnal $P \leq 0.001$, as well as 100% improvement in revenue and hospitalizations to floor, well as income to the ICU with $P \leq 0.001$. No further episodes of near-fatal asthma. In addition to decreased use of systemic steroids 90% (P 0.003) and inhaled steroids 60% (P 0.005).

Conclusions: Omalizumab is a good treatment option in patients with poorly controlled asthma with near-fatal asthma episodes.

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Use of Omalizumab in Chronic Moderate to Severe Persistent Asthma-an Indian Experience

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Background: The worldwide prevalence of asthma is high and increasing. In India prevalence of asthma is variable from 4% to 20%. Despite ICS plus LABA therapy 72% of asthma patients were uncontrolled or not well controlled in INSPIRE study. Immunoglobulin-E plays a central role in inflammatory cascade. To study the efficacy of omalizumab in Indian patients with moderate to severe persistent asthma in terms of quality of life (QOL) improvement, reduction in severe exacerbation, ED visits and loss of working days.

Methods: 52 patients aged from 12+ years to 86 years (23.3 % females, avg age: 33.6, avg S.IgE: 283) fulfilling omalizumab indication criteria were given 150 mg subcutaneously once in 2 or 4 weeks for 16 to 24 weeks during March 2007 till date. QOL assessment 52 weeks after treatment in terms of following parameters were studied: Asthma symptoms (Cough, wheezing, tightness in the chest) Night Symptoms (frequent awakening, sleep disturbances) Rescue medication use Loss of working days/school days Emergency visits.

Results: 94% of patients were able to reduce or discontinue regular OCS use. 72% reduction in exacerbations, 76% reductions in emergency visits ICS/LABA dose was maintained/reduced in ~ 93 % patients. –54% improvement in working/school days in the age group of 12 to 40 years. 60% improvement in uninterrupted sleep hours best improvement in QOL was observed in 12 to 40 years age group.

Conclusions: Omalizumab is well tolerated and effective as an add-on therapy in patients of moderate to severe persistent Asthma and offers a therapeutic and economic benefit to patient. Its potential as disease modifier and early intervention in treatment guidelines needs further studies.

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Use of Monoclonal Antibody Omalizumab in the Treatment of Urticaria Chronic

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Background: The chronic Urticaria is a real problem of health and a frequent problem in the consultation of the allergist, which the treatment is not to satisfactory. Some Urticaria can be for autoimmunity where the antibody involved is IgE. Omalizumab is an monoclonal antibody against the C3 domain of the epsilon heavy chain of the antibody IgE (domain C3 of the IgE), involved, in allergic problems, which has proved a great utility in asthma off difficult control.

Method: Five patients of both genders were studied aged between 30 and 45 years, carriers of chronic Urticaria at least of ten years duration. Theirs control was not satisfactory, with the treatment habitual. They were not used glucocorticoids. The clinical evaluation and test of laboratory stated Chronic Urticaria idiopathic. The total IgE was below 100 U. I. The monoclonal antibody Omalizumab applying it for 6 month accorded to habitual schedule. According to dose schedule monoclonal antibody Omalizumab apply the antibody to them, calculating the dose habitual schedule applying for 6

month. According to dose schedule the monoclonal antibody Omalizumab apply to them, it applying for 6 month.
Results: All the patient improved their Urticaria between weeks 3 and fort of application of the drug, getting the control of the symptoms between the month 2 and 3 in the 5 patients, without requiring other drugs for their control, and remained asymptomatic for 3 and forth months discontinuity the product up to 6 months, not reactivity the Urticaria, the older case takes now 1 year without activity of his disease.
Conclusions: Omalizumab must be considered to be another therapeutic alternative in patients with idiopathic Urticaria.

ASPIRIN-EXACERBATED RESPIRATORY DISEASE

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Successful Treatment of Severe Nonallergic Asthma by Omalizumab. An Observation

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Background: Omalizumab (Oma) is used in Europe for treatment of severe allergic asthma we describe the use of anti-IgE for severe nonallergic aspirin-induced asthma.
Methods: A non-smoking woman with negative family anamnesis, negative skin prick test (28 allergens), no specific IgE antibody and IgE of 107 kU/l developed a chronic rhinitis with anosmia, sinusitis and severe asthma at the age of 31 years. She suffers from nasal polyps (7 operations) and intolerance to aspirin and ibuprofen as well as alcohol; both leading to severe breathlessness. She was treated over years without success with oral steroids, ICS, LABA's and montelukast. The asthma was not under control and unstable. Therefore, we decided to try Oma as an additional medication. Since 25.08.2010 she is receiving 150 mg Oma/month without any change in other medication. After only 2 months she reported a remarkable reduction in their bronchial and nasal symptoms including improved smell and that she can drink small amounts of alcohol and also stands aspirin. We performed appropriate provocation tests to prove this observation.
Results: The FEV1 increased from 1.4 L on the 25.08.2010 to 2.4 L after only 2 months of treatment with Oma and was stable at this normal level for the next 12 months (till October 2011). The severity of symptoms (night and day) were dramatic reduced and the quality of life increased significantly (asthma-control-test normalized from 11 to 21 points). A double-blind placebo-controlled (DBPC) test with 125, 250, and 500 mg aspirin (cumulative dose 875 mg) was negative (all-day well-being, no changes in lung function). The DBPC-test with 3 doses of alcohol (sum of 10 g) was also negative.
Conclusions: A severe, difficult-to treat nonallergic asthma with nasal polyposis, ASS, and alcohol-intolerance (Samter's syndrom) was successfully treated with additionally given Oma. The injection of 150 mg Oma per month induced a clearly improved quality of life, "an asthma under control", improved the lung function with respect to FEV1 and leads to an unexpected tolerance against ASS and alcohol. To our knowledge this is the first reported observation on successful treatment of a Samter's syndrome using Oma.

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Relationship between Aeroallergen Sensitization and Asthma Severity in Patients with Aspirin-Exacerbated Respiratory Disease

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Background: The pathogenesis of aspirin-exacerbated respiratory disease (AERD) is presumed to involve the aspirin/non steroidal anti-inflammatory drug (NSAID)-induced abnormal metabolism of arachidonic acid, resulting in the production of 5-lipoxygenase metabolites, particularly leukotriene C4. Aspirin intolerance occurs around the same time as asthma onset, and a few of the patients with AERD had suffered from pediatric asthma. Although atopy is not associated with the pathogenesis of AERD, some of the patients with AERD have aeroallergen sensitization. There are few studies in which the association between the pathogenesis of AERD and atopy has been clarified.
Methods: Ninety AERD patients, whose aspirin sensitivity was determined by the aspirin challenge test, and 100 aspirin-tolerant asthma (ATA) patients, whose age and sex were adjusted, participated in this study. Atopy was defined as a positive reaction in an intradermal test to one or more of 19 common aeroallergens, or a positive reaction above class one in Immuno CAP RAST. We analyzed the relationships between aeroallergen sensitization and clinical settings of AERD patients.
Results: The atopic and non atopic AERD groups showed median serum total IgE concentrations of 464 and 130 IU/l (P value = 0.004), respectively. The asthma of atopic patients with AERD was milder than that of non atopic patients with AERD. (P value = 0.05) The Lund-Mackay score of atopic patients with AERD was lower than that of non atopic patients with AERD. (P value = 0.02)
Conclusions: Two-thirds of the patients with AERD showed aeroallergen sensitization. The asthma and sinusitis in atopic patients with AERD were significantly milder than those in non atopic patients with AERD. Aeroallergen sensitization might prevent the worsening of asthma in patients with AERD.

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Persistence of Nasal and Bronchial Symptoms in Patients with Samter's Syndrome with Treatment Medical and Surgical in a 2 Year Period

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Background: Know the causes of nasal and bronchial symptoms persistence in patients with Samter's syndrome under treatment in a period of time.
Methods: Cohort study. Inclusion criteria: Patients with asthma diagnoses, hypersensitivity to aspirin and nasal polyps. Exclusion criteria: Other kind of asthma, COPD. Twelve patients were followed from June 2009 to June 2011. Nasal and bronchial symptoms were assessed every 6 months using the Visual Analogue Scale of severity (VAS) from EPOS guidelines and spirometry from GINA. All were treated with intranasal mometasone furoate 200 mcg at day, montelukast 10 mg at day, salmeterol plus fluticasone 50/100 powder 2 inhalation every 12 hours, fluticasone spray 150 mg every 12 hours, loratadine tablet 10 mg if was necessary, with modifications of doses every 3 months.Patients diagnosed at 6 months with sinusitis and nasal polyposis were administered amoxicillin plus clavulanate 1.5 g daily for 5 weeks. The patients without response at 6 and 18 months were prescribed clarithromycin 400 mg daily for 4 weeks. All patients underwent CT of the sinuses through the Lund-Mackay system, chest CT scan, skin prick test. Evaluated by otolaryngology at the 6, 12, and 18 months.
Results: In the 98, 2% had negative skin prick tests. At 6 months, 58.3% had nasal symptoms with VAS <7. At 33.3% reported bronchial relapses with FEV1 <80. At year nasal symptoms increased, with WAS> 7 in 66.6%. The bronchial relapse decreased to 16.6%. At year and a half it increased nasal

symptoms in 75% of patients, with VAS> 7. At 41.6% had obstruction of 100% and pansinusitis. They needed antibiotic scheme. At 2 years in 83.3% had a VAS>7. At 58.3% had pansinusitis. The bronchial relapse did not increase. We determined the presence of VAS> 7 and pansinusitis (OR = 4). The bronchial relapse did not influence with increasing VAS (OR = 1).
Conclusions: Nasal symptoms persistent were secondary to the nasal polyps and pansinusitis with higher levels of VAS. It was determinated a 4-fold risk over pansinusitis with a VAS> 7 (OR = 4). It should be stressed the palliative surgical treatment in earlier stages and desensitization protocols.

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Clinics and Laboratory Characteristics of Asthmatic Patients with Aspirin Exacerbated Respiratory Disease (AERD)

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Background: Clinics and laboratory characteristics of asthmatic patients with aspirin exacerbated respiratory disease (AERD): asthma, polyposis and aspirin hypersensitivity.
Methods: Asthmatic patients with AERD history were evaluated. They were evaluated about asthma severity, rhinitis severity, history of polypectomy, and atopy. Some complementary exams were performed: total and specific IgE, serum eosinophilia, spirometry and nasal fibroscopy.
Results: Forty-seven patients concluded the study. The mean age of the patients was 53.1 years old and eighty-five percent were women. All patients had nasal polyposis and 23 patients (49%) had performed polypectomy. Thirty-nine patients (83%) had moderate/ severe persistent rhinitis and thirty-6 patients (77%) had moderate or severe persistent asthma and all of them were in inhaled corticosteroid treatment. The spirometry was classified as mild obstructive ventilatory disturbed (FEV1 ^{3} 60%) in 31 patients (66%). The mean value of total IgE was 427 IU/mL. The mean number of eosinophils was 477 cell/mm^3. The specific IgE to inhaled allergens was present in 22 patients (47%), who also had family history of atopy.
Conclusions: AERD is clinic syndrome related to chronic and severe inflammation of superior and inferior respiratory tracts, and is complicated with chronic rhino sinusitis, recurrent polyposis and asthma. In this study, thirty-six patients (77%) had history of rhino sinusitis and 50% had moderate and severe asthma. Atopy was confirmed in 47% of the patients. Polypectomy was performed as therapeutic treatment in 23 patients (49%). The prevalence of AERD in asthmatic patients is around 40%, and therefore, an early diagnosis is essential.

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Association Analysis of Member RAS Oncogene Family Gene Polymorphisms with Aspirin Intolerance in Asthmatic Patients

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Background: Member RAS oncogene family (*RAB1A*) converts small G protein to rab1 protein, a inflammation of blood eosinophils. Thus, functional alterations of the *RAB1A* gene may contribute to Aspirin exacerbated respiratory disease (AERD).
Methods: Asthmatics (n = 1277) were categorized into Aspirin exacerbated respiratory disease (AERD) and aspirin-tolerant asthma (ATA). 8 SNPs were genotyped. Messenger RNA expression of the *RAB1A* gene by peripheral blood mononuclear cell is measured by Real time PCR and reverse transcriptase polymerase chain reaction (RT-PCR). Human PBMC culture supernatant expression of *11-dehydrothromboxane B2*. Protein expression of the RAB1A gene by PBMC is measured by *RNAi* (Knock down) analysis.
Results: The logistic regression analysis showed that the rare allele frequency of +41170 C>G on intron 5 was significantly lower in the AERD group (n = 261) than in the ATA group (n = 1016) ($P = 0.002$). The linear regression analysis revealed a strong association of +41170 C>G with the aspirin challenge induced-FEV$_1$ fall ($P = 0.00008$). RT-PCR and real time PCR revealed an exon-4-deleted variants. The level of full-length *RAB1A* mRNA did not differ, but the variants was significantly higher in *+41170 G* homozygotes than in *+41170 C* homozygotes ($P = 0.002$). Intron based PCR was was used to amplify transcripts of PBMC pre-mRNA in which intron-5 had been removed (mRNA) while another set of primers was used to amplify intron 5-containing pre-transcripts (pre-mRNA). Knock down analysis of RAB1A Transcripts level in hPBMC. Thromboxane B$_2$ were increased in the siRNA treated when compared those of scramble and control. After knock down analysis, the levels of thromboxane B$_2$ were significantly decreased in PBMC culture supernatant.
Conclusions: The rare allele of *+41170 C>G* may play a protective role against aspirin hypersensitivity via a lower catalytic activity of the *RAB1A* gene attributed to the increase of a non-functioning variants of *RAB1A*.

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Nasal Nitric Oxide Levels after Lysine Aspirin Nasal Challenge in Subjects with Aspirin Induced Asthma

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Background: Changes in nasal nitric oxide (nNO) levels after nasal lysine aspirin (lys-ASA) challenge have not been determined.
Methods: Fourteen patients with aspirin induced asthma (AIA) with or without nasal polyps with aspirin were included to the study. Hypersensitivity had to be confirmed by positive result of oral aspirin challenge Ten healthy subjects served as the control group. 12 mg of lys-ASA were applied unilaterally. Nasal symptoms were assessed using visual analogue scale (VAS) and nNO and peak nasal inspiratory flow (PNIF) measurements were performed before and 1, 2, 4 and 24 hours after the challenge. The result of the challenge was considered as positive when at least 20% fall of PNIF as well as 20% increase of total VAS score were observed.
Results: Ten patients (71.4%) had clinically positive result of the challenge. We observed significant fall in nNO levels in AIA patients after 1 and 2 hours after the challenge (653. 1 ± 420. 2 at baseline versus 490. 3 ± 456. 0; $P = 0.0029$ and 439. 9 ± 556. 4 ppb; $P = 0.0076$; respectively). The decrease in nNO level was more pronounced in patients with clinically positive result of the challenge (510. 1 ± 212. 5 at baseline versus 283. 3 ± 173. 4; $P = 0.005$; 159, 6 ± 166,1; $P = 0.005$ and 331. 0 ± 312.0 ppb; $P = 0.037$ after 1, 2 and 3 hours, respectively). In 4 subjects with clinically negative result of the challenge we noticed a trend towards higher nNO concentrations after lys-ASA challenge (1010. 8 ± 625. 2 at baseline vs 1341. 3 ± 670. 5 ppb after 4 hours). No significant changes in nNO levels after the challenge were observed in healthy controls.
Conclusions: NO levels decrease after lys-ASA nasal challenge in subjects with AIA and clinically positive nasal provocation. An unexpected trend towards increase in nNO levels was observed in subjects with AIA and clinically negative provocation Potential usefulness of nNO measurement in aspirin nasal provocation needs further evaluation.

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IL1B but not IL8 Polymorphisms Are Increased in Aspirin Exacerbated Respiratory Disease Patients Versus Aspirin Tolerant Asthmatics

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Background: Aspirin exacerbated respiratory disease (AERD) is a syndrome characterized by chronic hyperplastic rhinosinusitis, nasal polyposis, asthma and aspirin sensitivity. The mechanisms by which produce these manifestations of intolerance are not fully defined, the current research involve alterations in the metabolism of arachidonic acid, cyclooxygenase 1 (COX-1) inhibition and its deviation from substrate to the lipoxygenase (LO) pathway, inducing increased synthesis of leukotrienes (LT). Biological plausibility of this fact has led to the search for polymorphisms in genes responsible for LT synthesis however others factors such as genetics polymorphisms in pro-inflammatory cytokines like, IL1B and IL8 could be associated.

Methods: 78 patients with AERD, 135 aspirin-tolerant asthma (ATA) and 134 healthy control subjects participated. All participants who underwent a simple spirometry, methacholine challenge and nasal challenge with Lysine-aspirin (L-ASA), both tests performed according to international guidelines. Peripheral blood was drawn by venipuncture, genomic DNA was obtained using the commercial BDtract DNA isolation kit. We selected 2 polymorphisms in 2 genes related to chronic inflammation rs16944 in *IL1B*, and rs4073 in *IL8*, Allelic discrimination of SNPs was performed by Real Time PCR (PCR-RT) on a 7300 Real Time PCR Systems. Statistical analysis was performed between groups of cases (AERD and ATA) versus control group with Epi-info v.6.04 by $\chi 2$ test to identify the difference between the allele and genotype frequencies of each polymorphism made, considering a significant P value <0.05, in addition to the calculation of odds ratios and confidence intervals of 95%.

Results: We find no association between IL1B (rs16944) to GG and GA genotypes in ATA patients versus control group neither AERD versus control group. Interestingly, the AA genotype showed increased frequency in the AERD patients versus the ATA patients (FG = 0.19 versus 0.07), this association remained significant ($P = 0.018$, OR 2.98, CI, 1.17-7.82).

Conclusions: This is the first observation that IL1B polymorphisms are involved in AERD, suggest that patients carrying out the *IL1B*-511 polymorphism (rs16944 AA genotype) may show enhanced susceptibility to develop AERD.

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Fatty Acid Binding Protein 1 is Related with Development of Aspirin-Exacerbated Respiratory Disease

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Background: Aspirin-exacerbated respiratory disease (AERD) refers to the development of bronchoconstriction in asthmatics following the ingestion of aspirin. Although alterations in eicosanoid metabolites play a role in AERD, other immune or inflammatory mechanisms may be involved. We aimed to identify proteins that were differentially expressed in nasal polyps between patients with AERD and aspirin-tolerant asthma (ATA).

Methods: Two-dimensional electrophoresis was adopted for differential display proteomics. Proteins were identified by liquid chromatography-tandem mass spectrometry (LC-MS). Western blotting and immunohistochemical staining were performed to compare the amount of fatty acid-binding protein 1(FABP1) in the nasal polyps of patients with AERD and ATA.

Results: Fifteen proteins were significantly up-(7 spots) or down-regulated in the nasal polyps of patients with AERD (n = 5) compared to those with ATA (n = 8). LC-MS revealed an increase in 7 proteins expression and a decrease in 8 proteins expression in patients with AERD compared to those with ATA ($P = 0.003$-0.045). FABP1-expression based on immunoblotting and immunohistochemical analysis was significantly higher in the nasal polyps of patients with AERD compared to that in patients with ATA. FABP1 was observed in epithelial, eosinophils, macrophages, and the smooth-muscle cells of blood vessels in the polyps.

Conclusions: Our results indicate that alterations in 15 proteins, including FABP1, may be related to the development of AERD.

ASTHMA

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The Correlation of Cholesterol Lowering Statin Drugs and Worsening Asthma Control in Mild Persistent Asthmatics

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Background: To show that pharmacological agent statins use, adversely alter the immunomodulatory activities that promote the worsening of the clinical course of allergic diseases such as asthma.

Methods: Two groups of 20 asthmatics patients each were compared from baseline values. Twenty patients with extrinsic asthma (group A) were prescribed statins for their lowering of their cholesterol necessity, and 20 patients (group B) were controls who did not receive statins. Group A and group B were designed to compare FEV1, exacerbation asthma rates, beta agonists use, nocturnal awakenings, and daytime symptoms from baseline values.

Results: Statins treated asthmatic patients group A had significant worsening of FEV1 at 3 months, 6 months and 12 months, to almost no change in control asthmatic patients group B. Statins treatment patients group A were associated with more frequent use of rescue medication (albuterol inhaler), increased nocturnal awakenings, and increased daytime asthma symptoms, compared to group B.

Conclusions: Statin drugs may worsen asthma control in mild persistent asthmatics. Statins may cause possible immune alteration that promotes allergic diseases such as asthma.

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Studies on the Relationship between Airway Inflammatory Responses in Patients With Asthma or Not-yet Onset Asthma and Air Pollution

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Background: Substantial data have demonstrated that air pollution is associated with cardiopulmonary mortality and morbidity in the world. Among a variety of pollutants, particulate components, particularly PM2.5, are especially suggested to be harmful to our lung health. Diesel exhaust particles (DEPs) are the major component of PM2.5, and therefore the relationship between PM2.5 or PM10 and airway inflammatory responses of asthmatic and people of not-yet asthma onset is important to be investigated. Recent findings suggested that susceptibility to DEPs is dependent upon certain genetic variations of anti-oxidative stress enzymes such as GSTP1, which is largely regulated by a transcription factor Nrf2. By preliminary experiments, we found that exhaled breath condensates (EBC) are safely and repeatedly obtained from both disease and health persons, and that several biomarkers including growth factors, cytokines and oxidant stress markers could be measured.

Methods: In the present study, we attempted to study the airway inflammatory/fibrogenic responses from patients with asthma, and further, those from people who have suggestive, but not yet definite symptoms of asthma. Participants are asked to present exhaled breath condensates (EBC) by

R-tubes during spontaneous breathing for 5 minutes, which are processed to measure several inflammatory/fibrogenic markers.
Results: These molecules, including vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), basic fibroblast growth factor (FGF), IL-1 receptor antagonist, IL-8 and epidermal growth factor (EGF) tended to be increased in asthmatic group. These markers were significantly increased in severity step 4 patients as compared to mild asthmatics. There was a significant correlation between the PM10 concentration 1 month before the sampling of EBC and EBC EGF concentration. NO2 concentration and several markers in EBC in patients with asthma correlated with each other. EBC pH showed a significant relationship with the distance from main traffic roads.
Conclusions: These results suggested that mass screening using simple methods such as EBC and appropriate biomarkers might facilitate the progress in the prophylaxis against hazardous health effects of DE exposures in subjects with high susceptibility to DEPs.
This work was supported in part by a grant from Environmental Restoration and Conservation Agency of Japan.

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The Relationship Between Maternal Atopy and Childhood Asthma

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Background: The diagnostic difficulty of childhood asthma leads to widespread under-diagnosis, which negatively affects the quality of life of asthmatic children. The presence of atopy in children is often used as a clinical tool to assist in making the diagnosis. However, local studies have demonstrated that atopy occurs in fewer asthmatic children than previously thought. This brings into question the association between allergy and asthma. The purpose of this study was to determine if a family history of allergy is predictive of atopic asthma in children, by comparing allergy, history of asthma and allergic symptoms, in mothers of atopic versus non-atopic asthmatic children.
Methods: A random sample of children and their mothers attending the Children's Chest and Allergy Clinic at Steve Biko Academic Hospital were enrolled. Skin-prick testing or radioallergosorbent test results, of the children were obtained from the child's hospital records. Mothers completed a detailed questionnaire which included demographic details, a history of symptoms suggestive of 'atopy' and allergic diseases and a history of asthma. Skin prick testing was performed on the mothers.
Results: 100 children and their parents were enrolled. 64 mothers to atopic children were used as the study group and 36 mothers to non-atopic children were used as the control group. Of the 48 mothers with a positive skin prick test, 30 (64%) had atopic children ($P = 0.836$). Of the 16 mothers with asthma, 14 (88%) had atopic children ($P = 0.045$). Of the 70 mothers with a history of symptoms suggestive of an allergic disease, 45 (64%) had children with atopic asthma ($P = 1.0$). Of the 77 mothers who were considered to be allergic, 50 (65%) had children with atopic asthma ($P = 0.806$).
Conclusions: Both maternal skin prick positivity and a history of symptoms suggestive of allergic disease, are poor predictors of atopic asthma in children. This is true even in the mothers were considered to be allergic. However maternal asthma is a specific predictor of childhood atopic asthma with a good positive predictive and a high odds ratio. Further studies need to be conducted to compare the epidemiology of allergic asthma in different population groups.

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Sensitization of Severe Allergic Asthma Patients

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Background: The prevalence of asthma is high, the worldwide average being estimated at 10%, which makes it a public health problem. Many studies show a clear relationship between asthma and specific allergens. With sensitization to aeroallergens identified as a dominant risk factor for asthma.
Objective: The present study of asthma reports the allergic sensitization of patients with severe persistent asthma followed in the Division of Clinical Immunology and Allergy of University of São Paulo Medical School.
Methods: A total of 61 patients with severe persistent asthma defined according to the criteria of the Global Initiative for Asthma (GINA) were enrolled. Total IgE levels (IU/mL) were measured in serum and levels up to 120 IU/mL were considered within normal range. A battery of 7 aeroantigens (*Dermatophagoides pteronyssinus, Blomia tropicalis, Aspergillus fumigatus, Penicillium nonatum, Lolium perenne, Felis domesticus, Canis familiaris, Blatela germanica and Periplaneta americana*) was used in skin prick tests (SPTs), which were performed in each subject, on the volar side of the forearm. Histamine hydrochloride and normal saline solutions were used as positive and negative controls, respectively. The SPTs were read after 15 minutes and, a wheal at least 3 mm greater than the negative control was considered positive.
Results: The asthmatic patients had a mean age of 48 years and 75% were female. We found that mean total serum IgE levels were 518.4 IU/mL (between 17 and 4720 UI/mL). SPTs positivity was 91.8% for *D pteronyssinus*, 67.2% for *Blomia tropicalis*, 4.9% for *P nonatum* and *A fumigatus*, 6.5% *L perene* and *Felis domesticus*, 16.3% for *Canis familiaris*, 21.3% *Blatela germanica*, 13.1% for *Periplaneta americana*. Twelve patients were monosensitized and 23 patients were polysensitized to 3 or more allergens.
Conclusions: Most patients with severe allergic asthma were polysensitized, and dust mites, followed by cockroaches, were the main allergens.

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Reference Values and Influencing Factors of Exhaled Nitric Oxide in Healthy Korean Adults

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Background: Fractional exhaled nitric oxide (FeNO) is widely used as an inflammatory marker for asthma. However, reference values and influencing factors of FeNO using Niox Mino, which is the only device achieving US FDA approval, are not well described in healthy Asian adults. This study aimed to suggest the reference values and influencing factors of FeNO in healthy Korean adults.
Methods: Subjects who were over 19 years old and did not have any history of rhinitis, asthma or recent respiratory symptoms were enrolled. FeNO levels were measured using Niox Mino. Age, gender, body mass index (BMI), smoking status and lung function were also measured to analyze factors associated with FeNO levels.

Results: The mean value of FeNO was 16.14 ± 10.04 ppb. The reference value of FeNO, which was defined as the value of 95% in distribution curve, was same or less than 34 ppb. In a univariate analysis, FeNO levels were not associated with age, BMI and smoking history. However, atopy status (18.2 ± 11.8 for atopy and 15.1 ± 8.5 for nonatopy groups, $P = 0.008$) and gender (17.8 ± 10.2 for male and 14.8 ± 9.8 for female groups, $P < 0.001$) were positively associated with FeNO levels. In stratified analysis, the significance of both variables remained unchanged ($P < 0.001$).
Conclusions: Our data suggested that the reference value of FeNO in healthy Korean adults seemed to be same or less than 34 ppb. Reference values of FeNO in Korean adults are influenced by gender and atopy status. This study was supported by a grant of Korea HealthCare technology R&D project, Ministry of Health and Welfare, Republic of Korea (A092076).

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Association of Feno with IgE Levels in Patients with Allergic Asthma

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Background: Asthma is a chronic multifactorial disease characterized by inflammation with multiple triggers. Inflamation of the airways is the main pathologic pathway in asthma, and not only determines the diagnosis and severity of symptoms, but is also useful to establish treatment and predict potential complications. By measuring FeNO levels, an indirect level of pulmonary inflammation can be obtained since it is produced by alveolar macrophages in response cytokines. One of the main known causes of this inflammatory response is an allergic reaction. This allergic reaction sets off a cascade of biochemical events that leads to the expression of inflamatory mediators, preformed or de novo, and IgE being the principal of such mediators. The objective was to evaluate the relationship between levels of FeNO and IgE to inflammation and allergy severity.
Methods: 50 patients (72% female and 28% male) aged 12 to 50 years old, diagnosed with asthma were taken from the Allergy and Immunology department. A complete medical history was performed, and the diagnosis was confirmed through a clinical history and spirometric criteria, according to GINA 2010. All medications that could alter the inflammatory process were taken away for 15 days. Lastly, total serum IgE levels were measured with electrochemiluminescence technique and the FeNO with standard procedures. The data was further analyzed using a Pearson's correlation test.
Results: 21% of the participants showed normal IgE values (<100 UI/Ml) and 33% of the participants had normal FeNO measurements (<20 ppm). A 0.29 coefficient was measured using a Pearson's correlation test, which suggests a low positive correlation between the 2 observed variables.
Conclusions: The results showed a low correlation between the IgE and FeNO levels. This result does not allow for a correlation between both parameters; which leads to a conclusion that high levels of IgE from an allergic reaction is not necessarily going to lead to a high FeNO, thus a pulmonary inflammation. Additionally, it emphasizes the importance of the allergists and pneumonologists to work together when treating an asthma patient, given the multidisciplinary nature of this pathology.

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The Relationship of Fractional Exhaled Nitric Oxide (FeNO) and Acute Exacerbation of Childhood Asthma

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Background: Asthma is a chronic inflammatory disorder in the airways. Measurement of FeNO (fractional exhaled nitric oxide) is a non-invasive tool for measuring airway inflammation. The aim of this study was to investigate the relationship of FeNO and acute asthmatic exacerbation in children and to decide whether measurement of FeNO could predict acute exacerbation of asthma.
Methods: Thirty eight children with mild to moderate persistent asthma aged from 3 to 15 years were included. Patient's data were based on out-patient records. FeNO was measured thorough chemiluminescence analyzer. Prospectively, the patients were followed for 6 month. The FeNO levels of asthma exacerbation group and non-exacerbation groups were evaluated.
Results: Mean age of the patients is 5.4 years. There were no difference of peripheral blood total eosinophil count, serum IgE, age, sex between asthma exacerbation group and non-exacerbation group. In the range of abnormal FeNO level (more than 10 ppb), there was significant difference of FeNO level between exacerbation group and non-exacerbation group ($P = 0.004$). There was also significant correlation between FeNO level and acute asthma exacerbation ($P = 0.003$).
Conclusions: Measurement of FeNO can be a useful tool to predict asthma exacerbation in mild to moderate persistent asthmatic children.

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Relationship Between Exhaled Nitric Oxide and Levels of Asthma Control in Asthma Patients Treated with Inhaled Corticosteroid

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Background: While asthma control is defined as the extent to which the various manifestations of asthma are reduced by treatment, current guidelines of asthma recommend assessment of asthma control without consideration of airway inflammation. Our aim was to investigate the relationships between fractional exhaled nitric oxide (FeNO), a reliable marker of airway inflammation, and levels of asthma controls in patients treated with inhaled corticosteroid (ICS).
Methods: We enrolled 71 adult patients with asthma, who had been treated with ICS more than 4 months. Asthma control was assessed by the physician based on the Global Initiative for Asthma guidelines, and by the patients and by using Asthma Control Test (ACT). Statistical analyses were performed to analyze the relationships between FeNO and measures of asthma control and clinical indices for asthma manifestations.
Results: There was no significant difference in FeNO levels between 3 groups according to levels of asthma control (controlled, partly controlled and uncontrolled) determined by the physician ($P = 0.81$) and by the patients ($P = 0.81$). In addition, FeNO values were not correlated with the ACT scores ($r = 0.031$, $P = 0.807$), while FeNO showed peripheral blood eosinophil counts ($P < 0.001$).
Conclusions: These findings demonstrated that FeNO levels are not related with the measures of asthma control in patients treated with ICS. Information of airway inflammation from FeNO concentrations seems to be discrepant from levels of asthma control.

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Relationship between Aeroallergen Sensitization and Asthma Severity in Mexican Children

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Background: Asthma is the most common chronic disease in children. The aim of this study was to assess the association between asthma severity and skin test reactivity to common inhalant allergens.

Methods: With informed parenteral consent, we included children with asthma, who attended for the first time to Allergy Department and collected data on clinical history, respiratory function and allergic sensitization. Asthma severity was classified using the GINA guide. We integreted the data into regression models to identify allergen sensitization most strongly associated with asthma severity.
Results: We included 260 children with ages ranging from 3 to 18 years old (mean 11.5 ± 2.85). Male/female ratio: 1.4:1. 72.3% had mild asthma; 23.8% moderate asthma and 3.8% severe asthma. Skin prick testing with aeroallergens was performed. Most of the children were sensitized to at least one aeroallergen (89.6%). Male gender and the number of positive skin tests correlated to asthma severity. Among allergic children 72.1% had more than one allergic disease. Total serum IgE did not correlate with the number of sensitizing aeroallergens, neither with asthma severity. Dust mite was the most frequent sensitization. Cat and molds were associated with a greater risk of having moderate and severe asthma. We found a progressive sensitization with age.
Conclusions: Sensitization to some perennial indoor allergens, particularly cat and molds, were strongly associated with asthma severity.

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Association of Asthma and IGE Levels

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Background: Asthma is a multifactorial chronic inflammatory disease that presents with varying degrees of bronchospasm which can be triggered by multiple causes. One of the best known triggers is allergies, or contact with allergens that have different immunological mechanisms leading to activation of the inflammatory process characteristic of asthma. Immunoglobulin E is a protein that normally rises in the allergic process and used as a marker.
Objectives: To assess the prevalence of IgE as a key factor in asthma and to estimate the incidence of non IgE-mediated asthma.
Methods: 50 Patients (72% female and 28% male) aged 12 and 50 years old, diagnosed with asthma who met the inclusion and exclusion criteria, were taken from the Allergy and Immunology department. A complete medical history was performed, and the diagnosis was confirmed through a clinical history and spirometric criteria, according to GINA 2007. Subsequently, total IgE in serum were measured by electrochemiluminescence using the Cobascore equipment.
Results: 72% of the patients in the study, had an elevated total IgE which suggests that this group has an allergic cause as a trigger for their disease, meanwhile the cause for the remaining patients were due to other causes.
Conclusions: Evaluation of serum IgE levels should be considered in asthmatic patients in order to determine the specific etiologic treatment. Additionally, these results enhance the importance of a multidisciplinary working diagnosis, and management of this condition, considering that up to a quarter of asthma patients may have Non-IgE mediated etiology

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The Method of Antigen Specific Damage of Leucocytes by Food Additives in Patients with Bronchial Asthma

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Background: Diagnosis of adverse reactions to food additives is difficult due to a variety of mechanisms involved and the lack of sufficiently reliable methods for their determination. The diagnosis of intolerance to food additives is still based only on placebo-controlled oral provocation.
Methods: The aim of this study was to determine the incidence of intolerance to ponceau 4R (E124), indigo carmine (E132), azorubine (E122), tartrazine (E102), sunset yellow (E110) and sodium benzoate (E211) among patients with bronchial asthma. We studied 114 patients with bronchial asthma using clinical and laboratory methods. Also we used the method of antigen specific damage of leucocytes by food additives. After the incubation of leucocytes with solutions of food additives to leucocytes was added 0.05 mL of trypan blue and counted the percentage of stained (damaged) granulocytes with the food dye and in control tests. If damaging leucocytes were more than 20% in comparison with controls - the test considered positive.
Results: It was found that positive to ponceau 4R were 6 of 114 patients, to indigo carmine–3 of 73, to sodium benzoate–4 of 73, to azorubine–11 of 114, to tartrazine–7 of 114 and to sunset yellow–9 of 114. There was a correlation between the results obtained and data history. Between experienced and control group (the patients without allergic diseases) were the reliable differences ($P < 0.05$).
Conclusions: 1. Under influence of the food additives leukocytes of patients with bronchial asthma are damaged and painted by trypan blue. 2. The method of antigen specific damage of leucocytes by food additives can be used for diagnostics of the allergies to food dyes, sodium benzoate and other gaptens.

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Effect of Ascorbic Acid on Aiway Hyperresponsiveness in Bronchial Asthma

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Introduction: Ascorbic acid has been reported to have a role in the decrease of airway responsiveness in animal models. This data has been based on the regulation of airway tone and modulation of airway reactivity by ascorbic acid. Human studies show that ascorbic acid has a protective effect against the increase in bronchial responsiveness induced by ozone, and nitrogendioxide. We hypothesized that ascorbic acid may attenuate bronchial hyperresponsiveness in bronchial asthma.
Methods: We studied 15 mild asthma patients and 13 healthy non smoker controls. These patients were measured plasma ascorbic acid levels with 2, 4-DNPH (dinitrophenyhydrazine) method and checked methacholine challenge with Chi method before and 1 hour after ascorbic acid intake (3 gm). To assess chronic effect of ascorbic acid on airway responsiveness, these participants were checked again plasm ascorbic acid and methacholine challenge after daily intake of ascorbic acid (1 gm) for 2 weeks.
Results: There were no significant differences in plasma ascorbic acid levels in asthma patients and controls. Bronchial hyperresponsiveness was decreased after ascorbic acid intake (3 gm) in asthma patients, but not statistacally significant. This decrease was persisted with daily 1 g of ascorbic acid intake for 2 weeks. PC20FEV1 were not correlated to plasma ascorbic acid levels in asthma patients.
Conclusions: In mild bronchial asthma, Airway hyperresponsiveness may be ameliorated by ascorbic acid supplementations. But further studies are necessary to address the question of the effectiveness of ascorbic acid in bronchial asthma.

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Screening for Allergic Bronchopulmonary Aspergillosis in Patients with Aspergillus + Asthma From 2000 to 2010

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Background: Approximately 25% of patients with persistent asthma have immediate skin reactivity to Aspergillus species. The purpose of this study was to screen all patients with immediate hypersensitivity to Aspergillus for evidence of Allergic Bronchopulmonary Aspergillosis (ABPA).

Methods: All patients with asthma underwent immediate cutaneous testing including prick (epicutaneous) with a mix of Aspergillus species and if negative, intradermal at 1000 PNU/mL, Aspergillus fumigatus (Af). Sera were analyzed for total IgE (elevated is ≥417 kU/L) by Phadia ImmunoCap, anti-Af IgE and anti-Af IgG (ABPA range ≥ 2.0) ELISA, and precipitating antibodies. HRCT of the lungs was ordered next if serology was positive (diagnostic criteria for ABPA required total IgE ≥ 417 kU/L and both anti-Af IgE and IgG ≥ 2.0 compared to sera from skin test + patients with asthma without ABPA). To avoid bias from patients examined by the author, data were compared using screening from 5 other faculty in the same clinic.
Results: From 2000 to 2010, 864 skin test + patients underwent serologic testing for ABPA from which 81 (9.4%) were diagnostic for ABPA, and in this group, precipitins were positive in 42/81. To address referral bias in screened patients of the author, diagnostic criteria were positive in 49/208 (23.5%) patients of the author versus 32/656 (4.8%) of other allergy-immunology faculty. In addition, some 74/884 (8.6%) patients had total IgE ≥ 417 kU/L and either anti-Af IgE or IgG ≥ 2.0, implying an overall at risk for ABPA population of 155/864 (17.9%). The highest total IgE recorded in a non-ABPA patient with asthma was 192,100 kU/L.
Conclusions: Using total IgE and ELISA determinations to discriminate ABPA from skin test + asthma sera, 9.4% of patients had diagnostic evidence for APBA. Using data from faculty, presumably with less referral bias than the author, results in 4.8% patients with classic diagnostic criteria. This rate conservatively translates into a minimum of approximately 1.2% of patients with persistent asthma having APBA in the upper Midwestern US. The combination of elevated total IgE and precipitins but not elevated anti-Af IgE or IgG in this population has little/no value in diagnosis.

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Sleep-disordered Breathing in Obese and Eutrophic Adolescents, Asthmatics and not Asthmatics, in the Hospital Infantil of Mexico Federico Gómez

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Background: Sleep-disordered breathing (SDB) has been studied in obese adults but there are few studies on adolescents. This study analyzed the frequency of SDB in obese adolescents and controls with and without asthma.
Methods: A cross-sectional comparative study, 27 obese adolescents 10 to 18 years old with body mass index (BMI) ≥ 95th percentile, of whom 17 (43%) had mild intermittent asthma (MIA) according to GINA 2005 guidelines and 23 (57%) without asthma, plus a group of 20 eutrophics adolescents (BMI = percentile 50th–84th), 50% (n = 10) with MIA and 50% (n = 10) healthy. All patients underwent overnight polysomnography, primary snoring (PS) was diagnosed with recording of snoring and apnea/hypopnea index (AHI) <1 and sleep apnea /hypopnea syndrome (SAHS) with an AHI ≥ 1 plus oxygen desaturations >4% baseline, bradycardia or tachycardia. We obtained measures of central tendency, dispersion and t student test for different groups.
Results: In obese adolescents with and without asthma SAHS was found in 72.5% (n = 29), PS was diagnosed in 20% (n = 8) and the subgroup analysis of obese show that same number of asthmatic and non asthmatic had SAHS (70.5%, 74%, respectively). The subgroup analysis of asthmatics and healthy eutrophic had SAHS (60% (n = 6), 0% (n = 0) respectively. Globally AHI in the obese group was 2.05 ± 3.48 compared to healthy eutrophic (0.40 ± 0.26) with $P = 0.0016$, significant differences were obtained in the analysis of subgroups: the IAH in obese adolescents with asthma (3.41 ± 3.47) and obese without asthma (2.60 ± 2.55) with $P = 0.7017$. In the eutrophic group differences there were significant differences: eutrophic asthmatics (IAH: 2.15 ± 0.26) and 0.40 ± 0.26 healthy eutrophic $P = 0.0047$.
Conclusions: SDB is more common in obese adolescents. In eutrophic asthmatic adolescents SAHS was more frequent than in healthy, probably by the presence of co-morbidities such as rhinitis, hypertrophy of tonsils and all patients were classified as MIA. Adolescents who are obese have an increased risk of SDB compared with the group of healthy adolescents.

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Dyspnea in Chronic Fatigue Syndrome (CFS): Comparison of Two Prospective Cross-sectional Studies

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Background: Chronic Fatigue Syndrome (CFS) subjects have many systemic complaints including shortness of breath. Dyspnea was compared in two CFS and control cohorts to characterize potential pathophysiological mechanisms.
Methods: Cohort 1 of 257 CFS and 456 control subjects were compared using the Medical Research Council chronic Dyspnea Scale (MRC Score; range 0–5). Cohort 2 of 106 CFS and 90 controls answered a Dyspnea Severity Score (range 0–20) adapted from the MRC Score. Subsets of both cohorts completed CFS Severity Scores, fatigue, quality of life, and systemic complaints questionnaires. Cohort 2 also responded to other Dyspnea, affective and anxiety instruments. A subset had pulmonary function and total lung capacity (TLC) measurements.
Results: MRC Scores were equivalent for females and males in Cohort 1 CFS (1.92 [1.72-2.16]; mean [95% confidence interval]) and controls (0.31 [0.23-0.39]; $P < 0.0001$ by 2-tailed, unpaired Student's t tests with Bonferroni corrections). Receiver-operator curves identified 2 as the threshold for positive MRC Scores in Cohort 1. This indicated 54% of CFS, but only 3% of controls, had significant Dyspnea. In Cohort 2, the threshold Dyspnea Severity Score of 4 indicated shortness of breath in 67% of CFS and 23% of these controls. Cohort 2 Dyspnea Scores were higher for CFS (7.80 [6.60-9.00]) than controls (2.40 [1.60-3.20]; $P < 0.0001$). CFS had significantly worse fatigue, other CFS defining criteria and quality of life compared to controls. Although CFS had worse depressive affect and anxiety scores, only the controls showed correlations with Dyspnea Score. Pulmonary function was normal in CFS, but Borg scores and sensations of chest pain and dizziness were significantly greater during testing than controls. TLC was normal except for 2 of 16 CFS who had hyperinflation. A general linear model of Cohort 2 CFS responses linked Dyspnea Scores with rapid heart rate, chest pain and dizziness.
Conclusions: Sensory hypersensitivity without airflow limitation contributed to Dyspnea in CFS. Correlates of Dyspnea in controls were distinct from CFS suggesting different mechanisms.

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Incidence of Allergy in Patients With Benign Lesions of the Vocal Cords: Preliminary Report

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Background: Allergic inflammation commonly affects the upper and lower airways concurrently. Although allergic nasal and pulmonary effects have been well described, laryngeal effects are not well understood. In this study we investigated the incidence of allergy in patients with benign lesions of the vocal cords and types of allergens causing these reactions.
Methods: The study was approved by the local ethics committee, and written consent was obtained from all patients. A questionnaire made by the investigators taking the latest literature data into consideration were used during the study. Laryngeal examination was done with videolaryngostroboscopy and

the lesions of each patients was recorded. Serum IgE levels and eosinophil levels were evaluated in all patients. All assays were carried out in duplicate. Skin prick tests on the forearm were performed in all patients using standardized latex extract containing high ammonia natural rubber latex, and a full set of 35 common. In addition, venom SPT was performed on one patient based on the subject's clinical history. Positive tests were counted as wheals of 3 mm in diameter after 20 minutes. Commercial extracts used were manufactured by Alyostal ST-IR. None of intradermal tests were performed.

Results: The group of 30 patients included 10 male and 20 female subjects with vocal cord pathology, having a mean age of 39.87 years. Sixteen (53.3%) patients had vocal polyp, 10 (33.3%) had nodule, 4 (13.3%) had Reinke edema. The mean IgE levels was 133.73 IU/mL, and mean eosinophil levels was 10,728.3. Dermal prick tests were found to be positive in 66.7% of the patients): The most common allergen was mite (53.3%) and grass pollen (52.3%).

Conclusions: In conclusion skin Prick tests were found to be highy positive in patients with bening lesions of vocal cords compared to normal population. Thus we can speculate that allergy may play a role in pathopysiology of these lesions. Further research is needed to identify the underlying pathways mediating the laryngeal response to allergy so that improved diagnostic and therapeutic techniques can be developed.

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Eechocardiographic Findings in Obese Adolescents with and without Asthma

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Background: To detect echocardiographic alterations in the diameter of the aorta in relation to the diameter and ventricular volume in obese adolescents with or without intermittent asthma as well as in eutrophic adolescents with or without asthma.

Methods: Cross-sectional, prospective study in 10 to 17 year old adolescents. They were stratified into 4 groups based on the intermittent asthma diagnosis (GINA classification) and in the Body Mass Index [BMI] (Obesity: BMI higher than the percentile 95%; eutrophic: BMI percentile 10 to 85% according to CDC). Anthropometry and echocardiogram tests were done on all adolescents. Measures of central tendency were obtained (mean and 95% confidence interval [CI]) and data were analyzed through corrected ANOVA post HOC.

Results: One hundred and ninety-four subjects were studied and divided into 4 groups: obese with intermittent asthma (OA) [N = 72], obese without asthma (OnA) [N = 73], eutrophics with intermittent asthma (EA) [N = 22], eutrophics without asthma (EnA) [N = 27]. Expressing the mean values and the 95% CI, we obtained the relation of the aorta with the left ventricular diastolic diameter indexed to the body surface (millimeters [mm]) in OA = 1.105 (1.047–1.164), OnA = 1.130 (1.06–1.192), EA = 0.921 (0.885–0.988), EnA = 0.967 (0.873–1.061) [$P < 0.05$ EA vs OA y OnA]. For the aorta in relation to the left ventricular diastolic volume in mm/milliliters [mL] the values were: OA = 0.648, (0.624–0.673), OnA = 0.645 (0.623–0.666), EA = 0.649 (0.620–0.679), EnA = 0.650 (0.615–0.684) [$P > 0.05$]. The aorta values in relation to the stroke volume [mm/mL] were: AO = 0.573 (0.530–0.617), OnA = 0.553 (0.511–0.594), EA = 0.596 (0.526–0.666), EnA = 0.595 (0.525–0.665) [$P > 0.05$].

Conclusions: The diameter of the aorta in relation to the left ventricular diastolic diameter was lower in eutrophic adolescents with intermittent asthma. There was no difference in the diameter of the aorta of the obese adolescents with and without intermittent asthma.

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Asthma Prevalence and Body Mass Index in Children

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Background: Overweight seems to be a growing problem associated with diseases which are increase during the last decades. As an example both the BMI (Body Mass Index) and the asthma prevalence are increasing. The question is whether a link exists between these changes or whether the increase is independent of each other.

Methods: In the frame of a longitudinal repeated cross-sectional epidemiological study 4925 children in total have been medical checked up. A questionnaire was filled out by the parents. Among other things data were gathered concerning anamnesis, physical measurements, and physician diagnosed diseases, like asthma. Describing the overweight in children's age until 15 years the BMI was divided in percentiles <10%, 10 to 25%, 25 to 75%, 75 to 90%, >90% respectively >97%. The full data set was available for 3946 children (80.1% of all participants).

Results: Descriptive: The lifetime prevalence of asthma was 7.1% (age group until 15 years). The BMI was for the overweight group of 6/8/15 year old kids; 18.1/20.1/24.5 kg/m^2 and in the adiposity group 20.2/22.4/27.7 kg/m^2 respectively. Frequent air way infections and parental predisposition enhance the risk for asthma (4.1 vs 10.9%); boys are more affected than girls (8.1 vs 6.1%). Starting with the 10%-BMI-percentile the asthma prevalence increases using the above mentioned intervals from 3.6% up to 8.3% for children with overweight (>90%-BMI-percentile). Analytical: The logistic regression adjusted for relevant confounders (gender, smoking and passive smoking, parental predisposition, pets (like cats), duration of breastfeeding, socioeconomic status) confirms the descriptive results. The BMI dependent adjusted Odds Ratio (aOR) (range) for asthma was 1.6 (95% CI, 1.0-2.7; $P = 0.048$).

Conclusions: The results clearly show that within the group of higher BMI more asthma will detected. Contrary to other studies this study may not confirm that the dependence on asthma from the BMI is bimodal since no higher asthma prevalence was observed in the lower and lowest BMI classes. Up to now this pilot study does not answer the question about the underlying processes.

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Evaluation and Comparison of Lung Volumes and Capacities in a Group of Morbid Obese, Obese and Eutrophic Adolescents

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Background: Obesity is a major health issue in the world. It is associated with a range of adverse consequences and its prevalence appears to be increasing among children and adolescents. The effects of ventilatory function have been widely studied in adults but there are scarce studies in children and even more, in specific population as inmorbid obese adolescents. Knowledge of early complications on the lung by pulmonary function tests allow the development of new management strategies aimed at the sporting activity in patients with morbid obesity.

Objective: To measure and compare pulmonary function tests in morbid obese, obese and eutrophic.

Methods: Transversal prospective protocol, in a group of morbidly obese, obese and eutrophic adolescents, aged between 11 and 17 years, divided into 3 groups: 1) Eutrophic adolescents (BMI < p85); 2) obese adolescents (BMI > p95 and <99); and 3) Adolescents with morbid obesity (BMI > 35 or BMI > P99). All of them underwent complete medical history, measurements and pulmonary function tests (plethysmography) using a Sensor Medics VMAX plethysmograph.

Results: We used descriptive stadistics, measurement of standar deviation, standar error, confidence interval95%, we analized in groups using analysis of variance (ANOVA) with a Tukey post hoc analysis. Significance was taken as $P < 0.05$ for all tests. Funtional Residual Capacity (FRC) and Expiratory Reserve Volume (ERV) decrease sharply comparing the 3 groups: FRC $P <$ .032 eutrophic versus obese and $P <$ .031 eutrophic versus morbid obeses. ERV $P <$ .001 eutrophic versus obese and $P <$ .003 eutrophic versus morbid

obese. We also found a decrease in FEV1 comparing the 3 groups with a $P < .011$ morbid versus eutrophic and $P < .049$ morbid versus obese.
Conclusions: Our results confirm the findings of others, who have shown that lung volumes especially FRC and ERV decrease as body weight increases. Obese patients have a combination of mechanical and inflammatory effects that result in pulmonary disability.

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Difficult-to-treat Asthma with Idiopathic Chronic Eosinophilic Pneumonia

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Background: Idiopathic chronic eosinophilic pneumonia (ICEP) is a rare disorder of unknown cause characterised by subacute or chronic respiratory and general symptoms, alveolar and /or blood eosinophilia, and peripheral pulmonary infiltrates on chest imaging. Interestingly, some but not all patients diagnosed with ICEP have a history of asthma, whilst others may develop asthma after a dignosis of ICEP has been made.
Methods: We present this rare and interesting case, because ICEP is a rare complication of asthma, although it is seldom mentioned in reviews ant textbooks on asthma. Asthma in patients with ICEP is relatively severe and get worse after diagnosis of ICEP.
Results: A 70-year-old woman with a history of asthma and chronic rhinitis with polyps (diagnosed in 2003), nonsmoker, history of allergies negative. She suffered from frequent exacerbations of asthma (7 times a year with repeated courses of oral corticosteroids). In 2006 she had sudden fever, weight loss, malaise and impaired dyspnea with productive cough, mild chest pain on sternum and respiratory failure. A chest radiograph demonstrated bibasilar infiltrates. Peripheral blood smear showed a newly developed, marked eosinophilia, and a chest X-rays and HRCT scan revealed a diffuse patchy nodular infiltrate in all lung fields. Serum-precipitating antibodies against Aspergillus antigens negative, no cutaneous reactivity to Aspergillus antigen, negative findings for parasitic infections, no central bronchiectasis on previous HRCT, ANCA, ANA, ENA negative. She received an intensive course of corticosteroids with complete resolution of symptoms and the eosinophilia, as well as decreased infiltrates on chest radiograph. Doses of corticosteroids slowly reduced a maintained until June 2009. Her asthma often exacerbates so far and needs intermittent courses of corticosteroids, is difficult- to-treat, but without any relapses of ICEP.
Conclusions: Clinicians should consider pulmonary eosinophilia in the differential diagnosis of patients treated for asthma who develop pulmonary infiltrates with dyspnea.

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Diagnosis and Management of Post-radiation Pneumonitis in Patients with Asthma

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Background: Lung cancer remains the leading cause of cancer-related deaths among men and women in the civilized world. A notable number of patients undergo radiation in various stages of the treatment process and its main respiratory side effect is pneumonitis. Our aim was to investigate the diagnostic and treatment methods of post-radiation pneumonitis particularly in asthma patients.
Methods: A literature search was performed in Pubmed to identify relative studies published until June 2011. Lung cancer, post-radiation pneumonitis, therapy and asthma were the key words used for the search.
Results: Post-radiation pneumonitis is a clinical situation demanding early diagnosis in asthma patients, but the latter is often underestimated. Pneumonitis is clinically revealed by dyspnea, cough, fever and usually begins up to 12 weeks after the start of radiation treatment. Radiographically, it appears as diffuse or patchy consolidation and/or ground glass opacities. Pulmonary function decline is correlated to decreased values of forced expiratory volume in the 1st second (FEV1) and diffusing capacity of the lung for carbon monoxide (DLCO). The effects on normal tissue may mimic or hide tumor recurrence. Smoking cessation causes changes of total lung capacity and vital capacity and this may have consequences on lung volume results in dose volume histogram analysis, targeting precision, oxygenation changes, tumor biology (gene expression) and prognosis. NCI Common Toxicity Criteria (CTC) V3.0 assessments are usually preformed weekly during radiotherapy and at regular follow-up visits. Complication rates vary with dose, fractionation, schedule duration, technique, photons' energy, irradiated volume, dose escalation, accelerated fractionation schemes, fields, co-morbidities and concurrent chemo-radiotherapy.
Conclusions: The crucially deteriorating on therapy effect of pneumonitis leads to the realization that alertness and constant attention is not only strongly advised, but compulsory in asthma patients.

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Pathogenesis of Radiation-induced Pneumonitis in Patients with Chronic Obstructive Pulmonary Disease

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Background: Chest radiation is a common therapeutic approach in the management of lung cancer, as well as in other malignancies, rendering radiation-induced pneumonitis a rather commonly reported adverse event. A large proportion of patients undergoing radiation have underlying chronic obstructive pulmonary disease (COPD). We aim to elucidate the pathogenetic pathways implicated in radiation-induced pneumonitis particularly in this subgroup of patients.
Methods: A literature search was performed in PubMed to identify relative studies published until June 2011.
Results: The incidence of radiation-induced pneumonitis after conventional irradiation in COPD is about 7 to 10% in the moderate although symptomatic forms and about 1 to 3% in the severe forms. Radiation-induced pneumonitis seems to be an acute-phase reaction, taking primarily place in the most radiosensitive subunit of the lung, the alveolar/capillary complex. Reactive oxygen species, generated by radiation, initiate a cascade of molecular events that alter the cytokine milieu of the microenvironment, creating inflammation and chronic oxidative stress. COPD is characterized by a chronic inflammatory state in the lung, also generating reactive oxidant species. Biological markers intrinsic to the patient, such as early variations of certain cytokines (IL-6, IL-10, TGF-β) seem to be implicated and studies are under way to determine their role. The standard dose-volume metrics, such as V20, V13 and mean lung dose, are major factors influencing the clinical course of radiation-induced pneumonitis.
Conclusions: Understanding the underlying pathogenesis of radiation-induced pneumonitis may help improve optimal delivery of treatment plans, minimize the risks and increasing the therapeutic ratio in patients with COPD.

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Medication Responses in Chronic Fatigue Syndrome (CFS) and Non-CFS Subjects

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Background: There is a clinical perception that Chronic Fatigue Syndrome (CFS) subjects have greater drug sensitivity and "allergy" than the rest of the population. This perception was tested by assessing the symptoms associated with medication use in a group stratified by CFS status and gender.
Methods: 194 subjects answered a binary (yes-no) questionnaire (Simon GE et al, 1993) to determine if "medications" (not further subdivided by drug class) caused any of 25 symptoms from the neurological (6 symptoms); musculoskeletal (5); airways (7); gastrointestinal (5); and skin (2) systems. Subjects used our CFS Severity score to estimate the severity of fatigue and the 8 minor criteria for the previous 6 months.
Results: The subgroup of ALL CFS females had more frequent nausea (32% vs 13%; $P = 0.013$) and visual changes (19% vs 4%; $P = 0.018$) than ALL non-CFS females. ALL CFS males had nausea (26%; $P = 0.003$) and dizziness (23%; $P = 0.006$) compared to zero in ALL non-CFS males. However, these differences were misleading because many individuals had no symptoms, and so would not have adverse complaints or contact their physicians. Therefore, the 47% of CFS and 72% of non-CFS subjects with zero symptoms were removed.The remaining 65 CFS subjects had 5.6 symptoms (95% CI, 4.2- 7.0). The 20 non-CFS subjects had 3.5 symptoms (1.8 to 5.2; not significant by *t* test). Females in these subsets had no significant differences in symptoms frequencies. However, CFS males (n = 22) had more nausea (54.5% vs 0%; $P = 0.067$) and dizziness (50% vs 0%; $P = 0.091$) for non-CFS males (n = 4).
Conclusions: The apparent higher prevalence of medication-related symptoms in CFS than non-CFS was biased by the large number of subjects with zero symptoms. When subjects with no complaints were excluded, there was no difference between CFS and non-CFS females, but a trend for CFS males to have had more gastrointestinal and neurologic symptoms than the non-CFS males. Overall, the equivalence of symptoms in CFS and non-CFS suggests that Multiple Chemical Sensitivity (MCS) may be an independent syndrome. These methods will direct our analysis of other irritants in this multiple chemical sensitivity questionnaire.

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Psychogenic Intractable Sneezing. Case Report

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Background: Sneezing is a coordinated protective respiratory reflex which occurs due to stimulation of the upper respiratory tract, and frequently accompanies allergic or nonallergic rhinitis. Sneezing can also arise due to bright light or sun (ACHOO syndrome), physical stimulants of the trigeminal nerve, psychogenic or central nervous system pathologies, sexual ideation and psychogenic sneezing. There are few case reports in the literature of patients with psychogenic sneezing.
Methods: 14-year-old girl who had incessant sneezing for over 4 days. The patient was initially seen in a rural hospital, were it was prescribed prednisone and antihistamines but the patient did not show any improvement. She was refered to 3rd level Hospital and treated with nasal steroids, antihistamines, and isotonic sodium chloride solution nasal spray; sneezing remitted in 2 hours. During a follow up visit nasal endoscopy was normal. Had a similar episode a month after that, and was referred to our service. She didn't have either personal or family history of allergies.
Results: There were not abnormalities in physical examination but obesity; nasal cytology and skin tests to aeroallergens were negatives. Received the same management with isotonic sodium chloride solution nasal and the symptoms remitted. Consultation with psychiatry is requested by probable psychogenic sneezing. The interrogation relates to the loss of father 3 years also suffered from bullying for obesity. Combined treatment was initiated by psychiatry and psychology.
Conclusions: Psychogenic Sneezing is a rare disorder, but should be considered in the differential diagnosis of sneezing. May have suspect if inspiratory phase is quite short and the amount of nasal mucosal secretion expelled very low. Eyes may remain open during sneezing. It usually develops due to psychogenic factors and is refractory to medical treatment. It is important to assess the patient in a holistic manner through a medical history and physical examination. Psychosocial environmental conditions should be investigated, and once identified the trigger requires a multidisciplinary treatment.

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GERD Screening by the Use of F-Scale and Allergy Screening for Diagnosis and Treatment of Chronic Cough

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Background: Allergy and gastro-esophageal reflux (GERD) are main causes of chronic cough, and simple, easy and rapid screening is desired for diagnosis of these symptoms.We used F-scale (Frequency Scale for Symptoms of GERD: FSSG) for GERD screening, developed by Japanese gastro-enterologist, did general allergy screenings, and investigated clinical outcome after treatment retrospectively.
Methods: GERD was screened by F-scale questionnaire, composed in twelve questions concerned with reflux symptoms, and scored 5 grades in each symptom. General allergy screening was defined as asking history of allergy, serum immnogloblin E (IgE) test (total, fourteen kinds of specific allergens) and measuring fraction of exhaled nitric oxide (FeNO),its positive range was greater than or equal to 20 ppb. Allergy positive was defined as at least one positive finding of allergy screening test. GERD was treated with proton pump inhibitor (PPI), and allergy was treated with inhaled corticosteroid or histamine H1 receptor blocker or leukotriene receptor antagonist.
Results: Fifty-four consecutive chronic cough patients were screened in GERD and general allergy screening. Thirty-seven patients (69%) were F-scale positive and 43 patients (80%) were positive in general allergy screening. Thirty patients (56%) were positive in both F-scale and general allergy screening. All patients were treated with allergy medicine or PPI, or both medicines. In all patients screened and treated with both GERD and allergy concurrently, cough improved within 2 weeks, and in patients whose positive finding was either GERD or allergy, cough improved by treatment with PPI or allergy drugs similarly. Delayed screening or treatment of either GERD or allergy was related to delayed improvement of cough. Cough finally improved in all patients in visit within 3 times.
Conclusions: In examination of chronic cough, adding GERD screening by use of F-scale to general allergy screening is beneficial to proper diagnosis, treatment and rapid improvement of symptom.

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Diagnosis of Gastroesophageal Reflux Disease in Patients with Chronic Cough

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Background: A major cause of chronic cough is gastroesophageal reflux disease (GERD). Its diagnosis is based on symptoms and diagnostic tests, such as

upper gastrointestinal endoscopy (UGE), 24-hour pH monitoring and manometry. Many patients also present chronic posterior laryngitis in fibronasolaryngoscopy (FNL). The objective of the present study was to evaluate the diagnosis of esophagitis, by FNL and UGE in patients with chronic cough.
Methods: Patients followed up for chronic cough, over 18 years of age, were asked about the presence of GERD symptoms and submitted to the FNL and UGE, some of them with esophageal biopsy.
Results: Fifty-one patients participated in the study. The average age was 56.8 years (±13.2 years), 90.2% were female and the average duration of cough, 12.2 years (±14.9 years). Of these, 46 (90.2%) had dyspepsia, and partial or complete improvement of symptoms of cough with proton pump inhibitor. Of the 46 symptomatic patients, only 18 (39.1%) had esophagitis on UGE; however, 36 patients (78.3%) had posterior laryngitis on FNL. Seventeen patients also underwent esophageal biopsy, and 15 examinations identified esophagitis. Nine (60%) of these patients had only posterior laryngitis on the FNL (UGE without esophagitis).
Conclusions: Fibronasolaryngoscopy was more sensitivity than upper gastrointestinal endoscopy to confirm gastroesophageal reflux disease. Although the indication for biopsy of esophagus follows standardized criteria, this study suggests that in patients with chronic cough, if there is an indication for the performance of UGE, it would be interesting to complement with biopsy of the esophagus.

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Botox Injections in Larynx as a Treatment for Vocal Cord Dysfunction

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Background: Vocal Cord Dysfunction (VCD) is a respiratory condition in which vocal cords restrict airflow by closing during inspiration. Symptoms include shortness of breath, coughing, chest tightness and wheezing. These symptoms are commonly reduced with breathing exercises to relax the chest and throat. VCD is often misdiagnosed as asthma and treated as such. Studies have shown that steroids used to treat asthma are not beneficial in the treatment of VCD, and are therefore unnecessary. Recent studies suggest that Botox injections to relax the thyroarythenoid muscles surrounding vocal cords resulting in an improvement in the patient's airflow.
Methods: We followed a 56-year-old female patient over the course of a year who had a history of upper espiratory infections, sinusitis, allergic rhinitis and asthma reporting an increase in the severity of respiratory symptoms even though successfully undergoing immunotherapy treatment and following a regimen of asthma medication. Her symptoms included shortness of breath, wheezing and trouble sleeping.
Results: Pulmonary function testing done elsewhere revealed that the patient had a reduced lung capacity. After a consult with a speech pathologist, VCD and Spastic Dysphonia (SD) were diagnosed. The symptoms where initially treated with speech therapy. Four months later the patient noted a slight improvement in her symptoms, but also attributed this to the fact that she had developed behavioral ways to cope with symptoms. The possibility of Botox injections was mentioned and the patient agreed to follow with this treatment. Two 2.5 unit injections of Botox were administered in the thyroarythenoid muscles via an EMG guided needle, without any complications. The results from the procedure were very favorable. All her symptoms improved significantly. Lung function tests appeared normal, and she was able to reduce the use of most asthma control medications. She received another dose of Botox injections 6 months following the first, and continues to do very well.
Conclusions: Botox injections in the thyroarythenoid muscles are a successful treatment option for VCD patients with dysphonia. With this treatment patients are able to minimize respiratory symptoms and inhaled steroid use. A larger, randomized study with patients diagnosed with VCD alone should be considered.

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Myasthenia Gravis and Asthma, Relationship between Two Different Disorders of the Immune System

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Background: Myasthenia gravis is an autoimmune disease caused by absence of neuromuscular transmission due to antibodies directed against the nicotinic AChR located at the neuromuscular junction. The main symptoms include muscle weakness in the affected muscles, which is worse after its use. Diagnosis is made upon clinical manifestations and finding of IgG. Only 80 to 90% of patients with generalized disease are positive to these antibodies, and 30 to 50% with ophthalmologic manifestations. Other immunological alteration found in these patients is an overexpression of the low affinity IgE receptor (CD23). Asthma is characterized by shortness of breath, cough, wheezing and chest tightness caused by inflammation and a reversible contraction of bronchial smooth muscle. Immunologically is associated with a Th2 cytokine profile, mainly Il-4, Il-5, Il-13 and an increased IgE.
Methods: Allergic and autoimmune diseases represent an altered response of the immune system. Here we discuss the case of a patient who presented with an allergic disease at first then years later developed an autoimmune disease.
Results: Our patient had been diagnosed with persistent allergic rhinitis and asthma since 1992. He had been treated with inhaled corticosteroids, bronchodilators, intranasal corticosteroids, antihistamines and specific immunotherapy with control of symptoms. In June 2010 he noticed diplopia, palpebral ptosis and muscle weakness in upper extremities diagnosed with Myastenia gravis and started treatment with piridostigmine with adequate control of muscular symptoms. No thymoma was identified.
Conclusions: It has been noted the possible relationship between allergic and autoimmune diseases since in both there is an alteration in the regulatory mechanisms of the immune system. In this patient, we found the association between asthma and 19 years later the development of myasthenia gravis. Some of the explanations for this kind of association is the expression of CD23 in myasthenia gravis, which is a receptor found in B cells, among others, responsible of the increased production of IgE. Besides, autoimmune and allergic diseases share some pathogenic characteristics such as their influence by viral infections. They are one of the main factors associated with asthma exacerbations and it is suggested that they cause tissue damage, exposure to self-antigens and molecular mimicry.

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Immunological Characteristics of Patients with Bronchial Asthma and Obesity

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Background: The problem of obesity-related diseases is current and worldwide increasing. We aimed to estimate the relationship between obesity, it's biomarkers and immunological features of bronchial asthma (BA) in obese patients as compared to healthy people with different BMI.
Methods: Body mass index (BMI) was evaluated in 57 adult patients with atopic BA, 23 patients with allergic rhinitis (AR) and 25 healthy people. Spontaneous production of TNF-α and IL-4 from blood lymphocytes and levels of C reactive protein (CRP), total IgE and leptine were detected in serum samples using ELISA kits. Levels of IgE- autoAbs to keratin, III and VI collagen types and elastin that showed association with BA severity in our previous data were also measured by ELISA.
Results: Atopic patients with BMI > 30 kg/m(2) in groups with AR and with BA had elevated levels of C-reactive protein (744 ± 28 ng/mL) and high spontaneous production of TNF-α (45 ± 4 ng/mL) and IL-4 (9.5 ± 2.8 ng/mL) in comparison with normal-weight patients and healthy (7.3 ± 2.7

ng/mL, 3 ± 0.6 ng/mL and 1.7 ± 0.3 ng/mL accordingly). BMI was considerably associated with BA severity (R = 0.4) and IgE-autoreactivity only in obese asthmatics (R = 0.58; $P = 0.01$), which showed raised IgE-autoAbs to keratin (11.6 ± 2 IU/mL) and collagen III (1.03 ± 0.3 IU/mL) in comparison with preobese (6.7 ± 1.5 IU/mL, 0.3 ± 0.01 IU/mL) and nonobese patients. The levels of total IgE in all groups showed no association with BMI and serum leptine concentration. Leptine level correlated with CRP (R = 0.59) and BMI (R = 0.4) and appeared to be overproduced in obese (57 ± 7.1 ng/mL) via non-obese (23 ± 6 ng/mL) asthmatics, as compared with AR patients and healthy subjects independently from BMI (6.1 ± 0.3 ng/mL) and therefore was associated with BA but not atopy in overweight patients.

Conclusions: In obese patients with atopy the adipose mass represents an important source of inflammatory cytokines whereas it's mediators, such as leptine appears to impact especially in pathogenesis of BA in comparison with AR. Obesity is attended with higher generation of autoIgE-Abs, which elevated levels can indicate the disturbance of normal immune regulation. So asthmatics with higher BMI, show a special phenotype of disease which needs to be managed and treated distinctly.

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Bronchial Hyperresponsiveness in Obese Adolescents

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Background: Identify the frequency of bronchial hyperresponsiveness in the obese and morbid obese adolescent. Compare the results of the direct challenge with gender and BMI.

Methods: We analyzed 215 bronchoprovocation challenges of adolescents from 10 to 18 years old in the period 2006 to 2010. We classified them in 3 groups: eutrophic (BMI < p85), obese (BMI p90–99) and morbid obeses (BMI > p99) without smoking contact of pulmonar disease. A basal spirometry was performed according to the ATS guidelines. If the FEV_1 was above 80% for age and gender we performed the methacholine challenge. We use the dosimeter method with the following methacholine dilutions: 0.0625 mg, 0.25 mg, 1 mg, 4 mg and 16 mg. When a provocation concentration caused a 20% FEV_1 reduced was considered a positive challenge for bronchial hyperresponsiveness (BHR).

Results: Of the 215 adolescents in this study: 40 were eutrophic, 116 obese and 59 morbid obese. The methacholine challenges were positive in 12% of eutrophic, 22% of morbid obese and 25% of obese. But there were not a statistically significant difference. Gender was not associated as a risk factor for bronchial hyperresponsiveness. The positive bronchoprovation challege in women was observed in 27.6% of morbid obese, 23.7% of obese and 5% of eutrophic; in men 26.3% of obese, 20% of eutrophic and 16.7% of morbid obese. There was not a stadistically significant difference.

Conclusions: It is necessary a larger number of patients to concluded that BMI and gender are not associated with increased bronchial hyperresponsivess.

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Development of a Questionnaire for the Assessment of Bronchial Hyperresponsiveness in Korea

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Background: Bronchial hyperresponsiveness (BHR) is an important pathophysiological feature of asthma. In addition to the diagnostic significance, BHR is associated with the severity of airway inflammation and BHR- based treatment approaches has been shown to be effective. Nevertheless, challenge tests are time consuming, inconvenient to patients, and are not accessible in every primary care physicians. We aimed to develop a questionnaire for the assessment of BHR in Korean subjects.

Methods: From the 24 University-affiliated hospitals, we recruited 149 adults between age 20 and 40 years with more than one asthmatic symptom (cough, sputum or dyspnea) and who had bronchial provocation test. A list of 33 symptoms, past history of allergy or smoking and 10 provoking stimuli were selected for the BHR questionnaire. After a methacholine challenge test patients were asked to complete each questionnaire. For each item of questionnaire, diagnostic odds ratios for the presence of BHR were calculated and multiple logistic regression analysis was performed to select final questionnaire items. Receiver operating characteristic (ROC) curve analysis was used to evaluate the sensitivity and specificity of the selected questionnaire items.

Results: Methacholine challenge test was positive in 36 patients (24.2%). Eleven symptoms and 2 provoking stimuli items were statistically significant by the results of diagnostic odds ratio. According to the result of multiple logistic regression analysis, 4 items were finally selected for the significant BHR questionnaire: the presence of wheezing episode, past history of physician-diagnosed asthma, family history of asthma. The psychiatric stress was negatively associated provoking stimuli item for the presence of BHR. The area under the ROC curve was 0.80 (95% CI, 0.72-0.86). Sensitivity was 84.9% (95% CI, 68.1-94.9) and specificity was 65.5% (95% CI, 55.8-74.3).

Conclusions: Four BHR questionnaire items including wheezing episode, past history of physician-diagnosed asthma, family history of asthma and psyachiatric stress stimuli were able to assess the presence of BHR in Korean adults.

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Clinical Analysis of Salbutamol Responsiveness after Acetylcholine-induced Bronchoconstriction in Childhood Asthma

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Background: The bronchodilator is usually inhaled after the acethylcholine (Ach) inhalation test for asthmatic patients. We investigated clinical characteristics of asthma about the response to a inhalation of salbutamol after the Ach provocation test.

Methods: Asthmatic patients from 6 to 18 years old were examined. They inhaled aerosol with increased concentration of Ach to produce 20% or more decrease in FEV1.0 (RT-Ach point). After then they inhaled salbutamol, and respiratory function was examined after 0, 5, 10, and 15 minutes. We divided the patient into 4 groups (G0,G5,G10,G15) by the recovery time up to baseline FEV1.0 after inhalation of salbutamol.

Results: Pre-provocated baseline FEV1.0, the rate of actual FEV1.0 /predictive FEV1.0, RT-Ach and FEV1.0 at the point of RT-Ach were lower in the G0 than other groups significantly. Complication of exercise induced asthma (EIA) and increased rate of FVC after the inhalation of salbutamol were higher in the G0. Serum IgE, eosinophil count of peripheral blood was not different in these groups.

Conclusions: We investigated about the response to salbutamol after the provocation of Ach for childhood asthma. Bronchial constriction and

hyperresponsiveness exit prior to challenge Ach in the group of early response to β2-agonist after the provocation test.

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Preoperative Cardiopulmonary Exercise Testing (CPET) in Severe Asthma Patients

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Background: Lung resection is still the only potentially curative therapy for patients with localised non-small lung cancer (NSCLC). However, the presence of cardiovascular comorbities and pulmonary function impairment increase the risk of perioperative death and postoperative complications. Various studies have evaluated the use of different preoperative tests aiming to identify asthma patients at greater risk for complications.

Methods: A literature search was performed in Pubmed to identify relative studies published until June 2011.

Results: Postoperative complications are associated with prolonged hospital stays and excessive morbidity and mortality especially in this group of patients. According to the ACCP/BTS guidelines, patients without known underlying lung disease with a preoperative FEV1 in excess of 2 L, generally tolerate pneumonectomy whereas those with FEV1 greater that 1.5 L, tolerate lobectomy. Although spirometric values strongly correlate with the severity of obstruction, they do not provide direct information regarding the degree of gas exchange impairment or the status of cardiovascular function. Cardiopulmonary exercise testing (CPET) is a preoperative test suggested before lung resection in patients with known underlying cardiovascular or lung disease. It is based on the interactions among pulmonary function, cardiovascular function and oxygen absorption from the peripheral tissues. Patients with maximal oxygen consumption (VO_2 max) <10 mL/kg/min or those with VO_2 max < 15 mL/kg/min and both postoperative predicted FEV1 and DLCO $<40\%$ are considered to be at high risk of perioperative death and cardiopulmonary complications postoperatively. Studies have shown that oxygen uptake efficiency slope, oxygen pulse and heart rate at peak exercise are correlated with better postoperative outcome.

Conclusions: Further research is required to elucidate the role of CPET in the preoperative evaluation of this group of patients.

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Annual Change of Peak Expiratory Flow Rate in Asthma and COPD

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Background: Peak Expiratory Flow Rate (PEFR) is a useful measurement for the follow-up examination in a chronic airway disease because it has the advantage of simple measuring and repetitive examination. The aim of this study is to examine the annual decrease of PEFR in asthma and COPD patients and to confirm the factors which influence the annual decreasing rate of PEFR.

Methods: From May, 2003 to September, 2010, the annual decreasing rate of PEFR is obtained from the asthma and COPD patients attending an outpatient pulmonary clinic. PEFR was measured using Mini-Wright (Clement Clarke International Ltd. UK). We conducted an analysis of the factors to influence on the change of PEFR and the average of it.

Results: The result indicated decrease of 3.72 ± 12.55 L/min annually in the asthmatic patient and decrease of 8.69 ± 8.87 L/min annually in the COPD patient. In the asthma, age and FEV1 are the predictive factor to influence on the change, on the other hand, age, FEV1, smoking and the number of aggravation are the factors in the COPD.

Conclusions: We could confirm the annual decreasing rate in patients of chronic airway disease and similar factor with FEV1 to influence on the change.

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Evaluation of Chest Computed Tomography in Patients with Asthma

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Background: Asthma is an inflammatory disease of the airways. The pathophysiological effects of airway obstruction include air trapping and dynamic hyperinflation. The investigation of asthma is usually performed through pulmonary function tests. The assessment of asthma by radiological methods is required to rule out other causes of bronchospasm or out complications. The aim of this study was to evaluate the changes found in the chest computed tomography (CT) in patients with persistent asthma.

Methods: Sixty-nine patients of both genders and above 18 years of age, accompanied by persistent asthma, participated in the study. The charts were analyzed for severity and onset of symptoms of asthma, spirometry, search of specific IgE and chest tomography.

Results: The mean age was 55.7 years, 71% female. Asthma began in childhood in 55.8% of patients. All patients had persistent asthma, divided into 66.7% of severe asthma, 29% moderate and only 4.3% mild. Only 14.5% of spirometry was normal. Atopy, assessed by clinical history and research of specific IgE was observed in 75.8% of patients. Regarding CT scans of the chest, the primary findings were bronchial wall thickening in 70% of patients, nodules in 25%, and atelectasis in 25%. The bronchiectasis was present in 20% of CT scans of the chest, and signs of emphysema in 10% of them.

Conclusions: In this trial, the CT scans of the chest were primarily indicated for patients with severe persistent allergic asthma. Bronchiectasis was found in 20% of tests, suggesting that CT scan of the chest should be required for patients with partial response to conventional treatment, mainly in patients with severe asthma.

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Exercise-induced Airway Obstruction and Vitamin D Deficiency

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Background: Exercise-induced (EI) symptoms may be associated with bronchospasm (EI-B), or laryngospasm, that is a paradoxical VC adduction (VCD) mimicking asthma. We previously found that vitamin D deficiency (Ddef) favours the occurrence of VCD during hyperventilation test (HV), particularly in hypocapnic conditions. We evaluated the occurrence of EI-B and EI-VCD during HV in relationship with Ddef, in 37 non smoking young athletes (24 males, 13 females, age: 13–25 years).

Methods: Each subject underwent HV (5 runs of one minute) either in isocapnia (HViso, obtained breathing CO2 enriched air) or in hypocapnia (HVhypo, obtained breathing normal air) in randomized order, one week apart. Exhaled CO2 pressure was controlled breath by breath by a capnograph. A 10% decrease in FEV1 was used as EI-B marker, a 25% decrease in MIF50 as EI-VCD marker.

Results: Sixteen subjects (43%) were atopic, 6 (16%) reported past diagnosis of asthma. No subject was assuming drugs or had suffered from respiratory infections in the last month. All subjects had normal lung function tests. With HViso 10 subjects had EI-B and 12 had EI-VCD. With HVhypo 8 subjects had EI-B and 15 EI-VCD. Eighteen subiects (49%) had Ddef (serum 25-hydroxycholecalcipherol $<$ 25 ng/mL). Serum levels of vitamin D were significantly lower in athletes with than in those without EI-VCD, either with HViso (19.1 $\pm$ 1.8 vs 25.7 $\pm$ 1.5 ng/mL; $P = 0.013$) or with HVhypo (20.2 $\pm$ 1.9 vs 26.2 $\pm$ 1.8 ng/mL; $P = 0.029$). No influence of vitamin D on EI-B could be demonstrated. Vitamin D levels were significantly related to the decrease in MIF50 (as % of baseline) during the test (HViso: r = 0.41; $P < 0.015$ and HVipo: r = 0.42; $P = 0.017$).

Conclusions: Our young athletes had a high prevalence of paradoxical vocal cord adduction during HV, which was strongly associated to Ddef. The high prevalence of Ddef was expected, since the study was conducted during winter in a town located beyond 45° latitude. Vitamin D deficiency may favour laryngospasm by decreasing calcium availability, ATP production and Ca-ATPase pump activity in the striate muscle cell, with consequent tetanic contraction and delayed relaxation. The fact that alkalosis worsens hypocalcemia accounts for the higher prevalence of laryngospasm observed during HVhypo.

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Lung Age/Chronological Age Index as Indicator of Clinical Improvement or Severity in Asthma Patients

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Background: Spirometry is a very useful clinical test to evaluate pulmonary function in asthma. However pulmonary function could be affected by the sex, time of clinical evolution, lung age (LA) and chronological age (CA). The aim of this study was to evaluate LA/CA as index of clinical improvement or severity in asthma patients.

Methods: The tenets of the Declaration of Helsinki were followed, and all patients gave their informed consent to participate in this study. Asthma severity was evaluated according with GINA classification. Spirometry was performed at the beginning of this study, at 46 days, 96 days, 192 days and after 8 months. Statistical analysis was performed using *t* test, 2-way ANOVA test, correlation and multiple regression models as well as ROC curves were also performed, a $P < 0.05$ was considered as significant.

Results: 70 asthma patients were included (22 male and 48 female), mean CA was 35-years old; mean LA was 48-years with a LA/CA index = 1.4, time of clinical evolution was 13 years. A LA/CA index = 1 (range 0.5 to 0.9) was observed in asymptomatic patients. LA/CA index over 1 were related with airway inflammation, and a LA/CA index more than 2 correlated with GINA step 3. Interestingly when we analyzed CA and LA, we observed that in female group more than 10 years of difference between CA and LA, (GINA Step2 and 3); while in male we observed (GINA Step1, Step2 and Step3). LA/CA index $\leq$ 1 was considered as normal.

Conclusions: LA/CA index is a good as clinical indicator of clinical improvement or severity in asthma patients in with excellent correlation of pulmonary function and age.

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Transition from Cough Variant Asthma to Asthma With Reduced FEV1

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Background: Cough variant asthma (CVA) is one of the most common causes of chronic cough. It may have been thought to be as a pre-asthmatic condition. Some CVA patients show decreased lung function after diagnosed as a CVA. This study aimed to see differences of clinical characteristics between CVA with preserved FEV1 and CVA with reduced FEV1 after diagnosis of CVA.

Methods: We searched medical records from January 2007 to May 2011. Thousand six hundred sixty two patients were diagnosed as CVA. Among 1662 CVA patients, 284 patients were revisited to hospital with symptom of chest tightness.

Results: Among 284, fifty two (18.3%) patients showed reduced FEV1. Mean interval between diagnosis of CVA and reducing of FEV1 was 305.5 days. There was no significant difference of level of PC20 or other pulmonary functional values between FEV1-reduced group and -preserved group.

Conclusions: Only small portion of CVA patients was transformed to asthma with reduced FEV1, and most of CVA still preserved their lung function.

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Epidemiology of Asthma Cases in the Allergy Service of a Third Level Medical Center. Six Year Expirience

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Background: The creation of an Allergy service was required because of the high frequency of allergic diseases among paediatric population in the general consultation of a third level medical centre.

Objective: The purpose of this study is to report the cases of asthma diagnosed in the Allergy service from a Third level medical centre since its creation in July 2005.

Methods: This is a descriptive, retrospective, transversal study from July 2005 to February 2011. Selected medical records of patients apply for diagnostic criteria for an allergy disease. GINA guide 2009 was used to make diagnosis of asthma. Patients were classified by age and sex and find out how many of them skin prick test were made and also how many patients began treatment with immunotherapy.

Results: Thirteen thousand seven hundred thirty seven consultations were attended in the Allergy service between the time period mentioned above. Two thousand three hundred thirty seven medical records of patients were selected, 1608 patients applied for a specific diagnosis for an allergy disease as follows: Asthma 411, Atopic Conjunctivitis 58, Atopic Dermatitis 180, Allergic Rhinitis 869, Urticaria 90. Four hundred eleven patients completed criteria for Asthma. Two hundred thirteen (51.8%) patients were female, 198 (48.2%) patients were male. Two hundred twenty seven (55.2%) patients were found to be in the range of 0 to 9 years, 141 (62.1%) of them were between 5 to 9 years. The majority of asthma patients were males in the range of 5 to 9 years. Some increase in asthma cases were found in females between 30 and 40 years of age, 75 (35.2%) of total female cases, about 18% of total cases of asthma. Skin prick test were made in 164 (40%) asthma patients. In 134 were positive to a specific allergen and began immunotherapy.

Conclusions: Asthma represents the second highest incidence in allergy diseases among children. However, it is the main cause of hospitalization

among allergy diseases because of the presence of crises that increases the cost of medical attention. It is very important therefore to make a good diagnosis of asthma early on in order to bring adequate treatment, including immunotherapy. Education to these patients is also an important task, mainly in children.

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Latin America Asthma Insight and Management (LA AIM): A Survey of Asthma Patients in 5 Latin American Locales

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Background: In 2011, we conducted a comprehensive asthma survey in Latin America with a 3-fold purpose: to explore the realities of living with asthma, to identify the disconnect between expectations in asthma management and the patient experience, and to identify unmet needs in asthma management. The Latin America Asthma Insight and Management (LA AIM) survey was modeled on similar programs in the US, Europe and Canada, and the Asia-Pacific region.

Methods: Face-to-face interviews of approximately 35 minutes' duration were conducted with respondents drawn from a national probability sample. The survey was designed to include 2000 patients (400 patients/location) across countries in Latin America (Argentina, Brazil, Mexico, Venezuela) and the Commonwealth of Puerto Rico. Survey questions were organized under the topics of asthma burden; impact of asthma on patients' activities, lifestyles, and work productivity; emotional burden; defining and characterizing symptoms; seasonal influences on symptoms; triggers; most bothersome symptoms; and patient perceptions about current levels of control.

Results: The results from the LA AIM survey will become available in November 2011. In the 2009 US AIM survey,[1] 2500 asthma patients aged ≥12 years (adults, n = 2186, and parents of adolescent respondents) were interviewed by phone. Participants had a diagnosis of asthma, had taken asthma medication, or experienced an asthma attack within 12 months of the survey. Respondents in the patient sample were predominantly female (69%, n = 1732), aged ≥35 years (73%, n = 1819), and had "not well-controlled" or "very poorly controlled" asthma (71%), using National Asthma Education Prevention Program guideline criteria. One in 4 respondents experienced symptom worsening at least weekly over the past 12 months: 11% reported asthma exacerbations most days; another 14% reported them at least twice weekly.

Conclusions: The US AIM survey provides a comprehensive depiction of the current state of asthma burden and patient perceptions in the United States. The LA AIM survey provides a view of the state of asthma across 5 distinct Latin American cultures.

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Understanding of Asthma Terminology by Patients Interviewed in the Latin America Asthma Insight and Management (LA AIM) Survey

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Background: Patients often do not clearly understand the terminology regularly used by their physicians to describe asthma symptoms and their worsening, such as "attacks," "exacerbations," and "flare-ups", among others. The Latin America Asthma Insight and Management (LA AIM) survey, a large and comprehensive asthma survey being conducted in 2011, explores differences across regions in the understanding of terminology to describe asthma symptoms, asthma deteriorations, and other asthma-related concepts.

Methods: Adult participants aged ≥18 years with asthma responded to survey questions during 35-minute face-to-face interviews. The survey was conducted in 4 Latin American countries (Argentina, Brazil, Mexico, and Venezuela) and the Commonwealth of Puerto Rico. A sample size of 2000 patients (400 patients/location) was determined to provide an accurate national representation of the opinions and views of asthma patients. The survey question on asthma terminology was designed to reveal respondents' familiarity with and understanding of asthma terms, such as "exacerbation," "flare-up," and "attack."

Results: Results from the LA AIM survey will become available in November 2011. In the US AIM survey,[1] conducted via telephone with 2500 respondents (adults, n = 2186, and parents of adolescent respondents), only 24% of asthma patients participating in the US survey were familiar with the term "asthma exacerbation." In contrast, most asthma patients (97%) were familiar with the term "asthma attack," and 71% of them recognized the term "asthma flare-up." Perceptions of the meaning of "asthma flare-up" were less varied across groups.

Conclusions: Distinctions exist in patients' understanding of asthma flare-ups and asthma attacks; however, asthma exacerbations, the phrase used most regularly by physicians, may not be well enough understood by asthma patients for effective communication with them. The LA AIM survey was designed to determine whether physicians and patients currently communicate in a mutually understood terminology.

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Asthma Management in Latin America: Learnings from the Latin America Asthma Insight and Management (LA AIM) Survey of Patients

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Background: In 2003, the Asthma Insights and Reality in Latin America (AIRLA) survey assessed, in part, perception, knowledge, and attitudes related to asthma.[1] In 2011 the Latin America Asthma Insight and Management (LA AIM) survey was designed to ascertain the realities of living with asthma, disconnect between expectations in asthma management and patient experience, and unmet needs. Using results from our survey, we investigated the advances made in asthma care and the challenges that remain for Latin American patients with asthma.

Methods: Asthma patients aged ≥18 years from 4 Latin American countries (Argentina, Brazil, Mexico, Venezuela) and the Commonwealth of Puerto Rico responded to survey questions during 35-minute face-to-face interviews.

A sample size of 2000 patients (400 patients/location) provided an accurate national representation of the opinions of asthma patients. Questions probed respondents' views on topics such as patient-reported levels of asthma control, frequency and duration of exacerbations in the past year, and current and recent use of asthma medications. Participants in both surveys had a diagnosis of asthma, had taken asthma medication, or had an asthma attack within 12 months of the survey.

Results: Results from the LA AIM will be available November 2011. A total of 2184 adults or parents of children with asthma took part in AIRLA by phone or face-to-face interviews.[1] In AIRLA, 54.0% of respondents reported their disease as well- or completely controlled. However, only 2.4% met all guideline criteria for asthma control. Further, 6% of AIRLA respondents reported their asthma as severe; however, when guideline criteria were applied, 21% had severe asthma.

Conclusions: The responses in LA AIM shed light on whether there have been meaningful changes since the 2003 AIRLA survey in patient perception of their asthma control and that control as defined by guideline criteria. Because asthma morbidity is largely preventable, additional education is required to teach patients that by more closely following asthma management strategies outlined by current guidelines, more patients can achieve adequate asthma control.

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Project for Prevention & Control of Asthma and Allergic Diseases in Korea

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Background: The prevalence rate of allergic disease, one of chronic diseases, has been recently increased due to changes of life style and numerous environmental factors. In May 2007, the Ministry of Health and Welfare of Korea established the comprehensive countermeasures to prevent and control asthma and allergic disease in Korea and has pushed ahead with this project related associations and academic experts together.

Methods: To improve the quality of life, reduce social and economic burden through getting over allergic diseases, the evidence based healthcare policy should be established about prevention and control of allergic diseases ; 1) Campaign & education 2) Proper treatment & control 3) Construction of environment friendly living 4) Construction of investigation, monitoring and alert systems 5) Support the disadvantaged patients.

Results: This project has moved ahead according to each 5 major program ; 1) Establish and provide guideline for prevention & control, promote prevention & control measures by cooperating with the private sector, operate an education & information center for asthma and allergic disease, 2) Provide & educate standard treatment guidelines, program development for a patient's self-treatment & control, 3) Create asthma and allergic disease friendly school, improve the living environment to control the trigger of asthma and allergic disease, 4) Establish an surveillance and monitoring system for asthma and allergic disease, study on asthma & allergic diseases; cohort study, develop and forecast an asthma index, 5) Support the patients of the disadvantaged with treatment, improve the living environment of the disadvantaged patients

Conclusions: We expect that evidence based healthcare policy about prevention and control of allergic diseases would improve the quality of life by reduction inducing factor for allergic diseases, and minimize the recurrence and aggravation by realization of the proper treatment and control the trigger for asthma and allergic diseases.

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Asthma in the CIS-region: The Prevalence and Peculiarities of the Course

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Background: In this study there has been analyzed the data from epidemiological studies on the prevalence and peculiarities of the course of bronchial asthma (BA) among the adult (Ad), children (Ch) and teenagers (Tg) in the CIS-region (CIS-R) over the past 5 to 10 years.

Methods: There has been used the results of studies of ISAAC, Statistical Reports (SR) of the Republic Ministries of Health and Medical facilities; the literature data.

Results: It has been established that BA is dominated in the structure of allergic diseases (ADs) of the CIS-R. BA, on average, suffer from 7 to 48.3% Ad and from 4 to 31% Ch. The highest incidence of BA among the population, especially Ad is observed in Armenia, Belarus, Moldova, Ukraine, Kyrgyzstan, Russia, Tajikistan. The actual incidence among Ch and Tg was 21 to 40%, for the Ad-23 to 48%. In this case, the diagnosis of BA was recorded by the SR in only 2.3% of children (Tg-3.2%, Ch-1.5%), and Ad-less than 1%. In the structure of the severity of BA among Ch and Tg, and Ad are dominated by mild forms of the disease (60 to 90% and 35 to 55% respectively) as mild intermittent or mild persistent BA, which in most cases are not diagnosed and do not receive adequate, timely assessment. The share of severe and moderate BA according to the age accounted for between 2 and 48%. The structure of BA recorded by statistical morbidity, dominated the moderate or severe forms of BA.

Conclusions: Thus, an analysis of existing data revealed that the mild forms of BA were dominated. The true incidence is much higher, as the uptake to the doctor takes place only in cases of the disease formed, earlier symptoms often go undetected. Often BA has been diagnosed at later stages with severe disease and complications. Unified account of the early features of ADs in a particular region will not only develop a National Prevention Program of ADs in the CIS-R, identify the main ways of their implementation, but also will allow to plan Allergic service in each region, important element of which is education and training of primary care physicians to identify early symptoms of ADs.

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Asthma in the Elderly: A Mexican Point of View

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Background: Asthma has been considered as mainly a childhood disease, however, 4 to 8% of the aged population suffer from it. In the National Institute of Respiratory Diseases (Instituto Nacional de Enfermedades Respiratorias, INER) Asthma's Clinic, in the year 2010, 1056 medical attention appointments were attended for patients of this group of age, representing 12.7% of total medical consults for asthma.In this study we describing the characteristics of elderly patients with asthma of INER's Asthma Clinic.

Methods: Descriptive, transversal, retrospective research. One hundred sixty eight patients with asthma diagnosis were included, 60 years old and more, subjects with other respiratory diagnosis were excluded, as those with tobacco smoking of more than 10 packs, and those with exposure to other types of smoke.

Results: 86% of the study group were women average age of 68.7 years old, the Forced Expiratory Volume in the first second (FEV1) average was of 76%. The 8.8% of patients had asthma diagnosed since childhood, and the

rest onset with asthma symptoms at adulthood. Only 32% were submitted to skin prick tests; 4.5% suffered difficult asthma control; 56% of patients had overweight or obesity; 17.8% suffered Diabetes Mellitus type II, 37.5% had Arterial Systemic Hypertension and 3.75% had Ischemic Cardiopathy; 60% of patients had Gastroesophageal reflux symptoms, and 5% presented Obstructive sleep apnea. Most of the patients had a good control in Asthma Control Test (ACT).

Conclusions: Asthma can initiate at any age, the advanced age is not directly associated to certain changes in airway remodeling, or not major disease severity. There's a high persistence of co-morbilities. This study shows that it's necessary to study this age group further, a group that is gradually on the increase.

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Control of Asthma and Its Relationship to Quality of Life in Adolescents

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Background: Asthma in adolescence is an important cause of morbidity, affecting significantly the quality of life. In order to facilitate the management of asthma control and allow a better assessment of quality of life, symptoms can be evaluated with questionnaires that reflect the multifactorial nature of the disease.

Objective: Assessing asthma control and its impact on quality of life in adolescents followed up in specialized ambulatory.

Methods: A cross-sectional study included 120 patients from a center of reference, between 10 and 20 years, with a mean age of 13.8 years and 66% male. Asthma was classified according to the GINA (2009) and 8% of patients had intermittent asthma, 9% mild, 64% moderate and 19% severe persistent asthma. At the time of consultation were applied two questionnaires previously validated in Brazil: Asthma Control Test (ACT) and Pediatric Asthma Quality of Life Questionnaire Adapted (PAQLQ-A). The ACT included 5 items that assess asthma symptoms, use of rescue medication, influence of disease on daily activities and patient perception of control of the disease, giving a maximum score of 25. Patients with a score >18 were considered controlled. The PAQLQ-A is composed of 23 questions, divided into 3 areas: limitation of activities, symptoms and emotional function. The responses are evaluated using a 7-point scale, with higher value indicating the minimum commitment. In this study the data were statistically analyzed by Spearman correlation, with significant value < 0.05.

Results: Comparisons were made between the areas of PAQLQ-A versus results of the ACT. Thus, correlating ACT and the area of symptoms was found an $r = 0.7$. In the emotional function was found an $r = 0.55$ and in limitation of activities an $r = 0.49$. The 3 correlations were statistically significant with $P < 0.001$.

Conclusions: The use of questionnaires to assess quality of life and evaluation of disease control showed great potential to improve health care in chronic patients. Questionnaires are easy to apply and may allow a broader assessment of disease and better recognition of the patient's perception regarding their limitations and symptoms.

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The Leukotriene C4 Synthase (A-444C) Promoter Polymorphism in Venezuelan Individuals with Asthma

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Background: Asthma affects approximately 300 million individuals of all ages and ethnic groups worldwide. Previous studies have reported weak associations between leukotriene C4 synthase (*LTC4S)* promoter polymorphism with the asthma phenotype, bronchial responsiveness to methacholine, and the severity of asthma regardless of aspirin sensitivity. The aim of the present study was to study the association between leukotriene C4 synthase A–444C promoter polymorphism and susceptibility to asthma.

Methods: Whole blood was collected from 144 ethnically mixed Venezuelan subjects, classified in 2 groups: patients with asthma ($n = 90$) and healthy individuals ($n = 54$). The LTC4S A-444C polymorphism was analyzed by PCR-RFLP by using MspI restriction endonuclease. Frequencies were determined by direct counting and Fisher's exact test was applied to determine frequency differences between groups.

Results: No difference in the distribution of the frequencies *LTC4S* (A-444C) variants among control and patients was found. However, although no significant, the genotype AC of *LTC4S* was increased in control group (20%) compared with asthma patients (12%) ($P = 0.09$, OR = 0.54, 95% CI, 0.2181-1.3583).

Conclusions: These preliminary results suggest that *LTC4S* polymorphisms are not associated with the development of asthma and further studies are needed to determine the role of genetic factors in this disease.

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Allergic Disorders Prevented by Helicobacter Pylori Colonization

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Background: Previous studies suggest that an association exists between microbiological colonization and allergic disorders. The derived hygiene hypothesis postulates that the increase in atopic diseases may in part be due to diminished exposure to microorganisms. The study should contribute to clear up whether the association exists focused on chronic microbial colonization/infection and which type of infection does render the expected protection.

Methods: As part of a 3 times repeated cross-sectional epidemiological study 4925 children in total have been medical checked up. Gastrointestinal and respiratory types of infection where considered: (1) gastrointestinal colonization (*Helicobacter pylori* detection using in vivo [^{13}C] urea breath test) and (2) respiratory infections (physician-diagnosed lower (bronchitis) and upper (common cold) respiratory tract infections). Physician diagnosed allergic asthma, atopic eczema, rhinitis allergica and allergic symptoms were selected as allergic target variables.

Results: Descriptive: Whereas respiratory infections lead to higher prevalence of the allergic disorders (not infected/infected: asthma 3/10%, eczema 10/24%, hay fever 6/12%) *Helicobacter pylori* colonization protects against allergies (not infected/infected: asthma 6/3%, eczema 16/7%, hay fever 8/7%). Analytical: The descriptive results could be confirmed using a logistic regression adjusted for relevant confounders (gender, smoking and passive smoking, parental predisposition, pets (like cats), number of older siblings, duration of breastfeeding, socioeconomic status) except and not significant for rhinitis allergica. Related to asthma/eczema/hay fever the adjusted odds ratios (aOR) for *Helicobacter pylori* colonization were 0.58 ($P = 0.05$)/0.48 ($P < 0.01$)/1.07 ($P = 0.75$). Contrary respiratory tract infection shows an amplifying effect on asthma/eczema/hay fever of aOR 3.75 ($P < 0.01$)/1.96 ($P < 0.01$)/2.07 ($P < 0.01$).

Conclusions: *Helicobacter pylori* colonization seems to protect against allergic disorders in comparison with the effect of respiratory tract infections. The hygiene hypothesis may be better explained when this kind of gastrointestinal and respiratory tract infections are subtly differentiated.

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Early Clinical Differential Diagnosis between Infant Atopic Dermatitis and Seborrheic Eczema

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Background: Clinical differential diagnosis between atopic dermatitis and seborrheic eczema is sometimes difficult. Early differential diagnosis is important, since atopic dermatitis can be more difficult to treat and may be associated with asthma and allergic rhinitis.

Methods: In a cohort study, 96 infants with high risk for atopic dermatitis were followed up from the maternal ward until they completed one year of age. The infants were submitted to complete skin examination, monthly, for a 1 year period. A full skin examination was performed and any sign of eczema was registered. Therapy with hydrocortisone 1% cream was prescribed. Eczema onset time, skin distribution, response to therapy and the presence of pruritus were evaluated.

Results: 87 (96%) infants fulfilled the study criteria (physical examination at least 10 months). Fivty four (62%) infants had signs of eczema during one year follow up. Atopic dermatitis was diagnosed in 14 (16%) patients and seborrheic eczema in 30 (34.5%) infants, with 10 (11.5%) classified as: both eczemas. Atopic eczema onset was mainly between 2 and 4 months and seborrheic eczema between 1 week and 3 months, with an important coincident period. Facial eczema had similar onset and semiological aspect for both diseases in its beginning. Head eczema was present in 40 (74%) eczema infants, 33 (82.5%) with a posterior diagnosis of seborrheic eczema and 7 (17.5%) with atopic dermatitis. After 3 to 5 months, axillar and groin folds eczema were the main signs of seborrheic dermatitis diagnosis, while face, neck and limbs were the main eczema sites in atopic dermatitis. The 10 infants with dubious eczema just after 6 months could have a more accurate eczema diagnosis. Hanifin et Rajka diagnostic criteria for infants showed to be useful just after 6 months, since some of its criteria are evolutive. All patients improved with hydrocortisone cream, but seborrheic eczema infants had a better response and prognosis, with complete eczema resolution until 8 months. The presence of pruritus could be securely established just after 6 months of age.

Conclusions: Continuous follow up is indispensable for Infant atopic dermatitis differential diagnosis with seborrheic eczema. Eczema distribution and therapy response are the best predictors for differential diagnosis in infant eczema.

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Sensitization to Contactants in Patients with Atopic Dermatitis

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Background: Atopic dermatitis (AD) is a chronic inflammatory pruritic skin disease with extensive interindividual variation and multiple internal and external factors. In this study, we evaluated whether the atopic dermatitis severity (SCORAD index), gender, age, age onset or the presence of Allergic rhinitis (AR), Allergic conjunctivitis (AC) or Asthma has an influence on contact sensitization to common contactant allergens.

Methods: 30 AD patients were evaluated in the Division of Allergy of Federal University of São Paulo. AD was diagnosed according to the Hanifin and Rajka's criteria and all patients were currently under regular treatment. Questionnaire (age, gender, age at onset, presence of AR, Asthma or AC), clinical examination and skin patch tests were carried out on all patients at the beginning of the study. Patients in regular use of oral CE; topical CE and/or calcineurin inihibitor use or having active AD lesions in the back were excluded from the study. Patch test was applied onto the upper back with 8 mm chambers attached with hypoallergenic tape and removed after 48 hours. The interpretation of the test reactions was performed at 48th and 96th hour.

Results: Positive Patch-test reaction occurred in 14/30 (46.6%). Among those with positive patch-test, Nickel was responsible for 42.8% and Thimerosal for 28.5%. All patients finished the study and no adverse reactions occurred. Positive and negative Patch-test groups found no statistically significant difference ($P > 0.05$) when comparing: SCORAD index, sex, age, age of onset and presence of AC, AR or asthma.

Conclusions: According to our results, sensitization to common contact allergens in AD patients was more frequent than in normal subjects. Although we did not found an explanation to these findings, indiscriminate exposure to topic products should be avoided so that new sensitization or risk of deteriorating AD occurs. The benefits of avoidance to the contactants considered positive should be evaluated in the follow-up of these patients.

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Sensitization to Aeroallergens and Risk of Respiratory Allergy in Atopic Dermatitis Children

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Background: Infants and young children with atopic dermatitis (AD) are at grate risk of developing respiratory allergy later in life with rhinitis, eye symptoms, and sometimes asthma. The aim of our study was to describe the sensitization patterns to inhalants in our young patients with AD and to assess the relation between early sensitization to aeroallergens and the development of respiratory allergy.

Methods: 80 children diagnosed of AD, aged from 11 to 34 months, were included (51 male and 29 female). Seventy two of these 80 were followed up to 7 years of age. Except a clinical examination, total IgE level was investigated by ELISA, and analysis of specific IgE antibodies to aeroallergens was performed with MAST CLA Allergen specific IgE Assay. Nonparametric tests were used in comparative analysis.

Results: 79% of our infants with AD had increased level of total IgE (mean: 387 kU/L). Sensitization to inhalant allergens was determined in 52 atopic dermatitis children (65%). The most relevant results were: 39 patients (48.8%) were sensitized to pets, 36 patients (45.0%) were sensitized to house-dust mites, 25 patients (31.3%) were sensitized to pollen, 17 patients (21.5%) were sensitized to molds. During the follow up, 48% of patients developed asthma and 52% allergic rhinitis. The mean age of respiratory allergy onset was 29.8 ± 3.9 months. At the end of our study the cumulative prevalence of respiratory allergy symptoms was significantly higher in children with inhalant sensitization compared to children without sensitization to aeroallergens (71% vs 18%, $P < 0.001$). The risk of asthma in that group also was significantly higher (68% vs 14%, $P < 0.001$).

Conclusions: Early sensitization to aeroallergens in AD children is associated with increased risk of development of respiratory allergic symptoms later in life.

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Quality of Life in Pediatric Patients with Atopic Dermatitis

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Background: Atopic dermatitis (AD) is a common skin condition. The aim of this study was to evaluate the impact of AD on the quality of life of

children and their families establishing correlations with scores of disease severity.

Methods: It was carried out an observational study of the correlations between clinical indicators of severity and a questionnaire on quality of life: IDQOL. The study also included scoring of eczema severity – ISAAC. One hundred seventeen children with AD, fulfilling established diagnostic criteria, and 396 children with no dermatologic diseases were investigated for the effect of eczema on quality of life. Pearson's correlation was used for the correlation analysis and the comparison between the groups was carried out using the Mann-Whitney test.

Results: Data analysis demonstrated significant differences between the scores for the 2 groups. The mean score in the eczema group was 9.2 (range 1–19) for IDQOL. The highest scoring questions for IDQOL referred to itching and scratching, mood changes and problems caused by treatment. For the ISAAC, the highest impact domains were treatment-related expenditure and sleep disturbance affecting family members.

Conclusions: AD has a negative impact on the quality of life of pediatric patients and their families. The individuals dealing with AD and their families need more than just the physical treatment of symptoms. Educational and psychological support for patients and their families in addition to medical treatment of AD may improve their long-term physical outcomes.

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Epidemiology of Atopic Dermatitis in the Allergy Service of a Third Level Medical Center

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Background: The creation of an Allergy service was required because of the high frequency of allergic diseases among paediatric population in the general consultation of a third level medical centre.

Objective: The purpose of this study is to report the cases of Atopic Dermatitis (AD) in the Allergy service from a Third level medical centre since its creation in July 2005.

Methods: This is a descriptive, retrospective, transversal study from July 2005 to February 2011. Selected medical records of patients, some records supplied by the Dermatology service, applied for diagnostic criteria for an allergy disease. The EAACI/AAAI/PRACTALL/ 2006 guide was used to make diagnosis of AD. Patients were classified by age and sex and find out how many skin prick test were made in such patients, and how many patients began immunotherapy.

Results: Thirteen thousand seven hundred thirty seven consultations were attended in the Allergy service between the time period mentioned above. Two thousand three hundred thirty seven medical records of patients were selected, 1608 patients applied for a specific diagnosis for an allergy diseases as follows:

- Asthma 411; atopic conjuctivitis 58; atopic dermatitis 180; allergic rhinitis 869; and urticaria 90.869 patients completed criteria for allergic rhinitis.
- From 180 patients with diagnosis of AD, 111 (61.6%) patients were female, 69 (38.4%) patients were male. Ninety six (53.3%) patients were found to be in the range of 0 to 9 years. The mayority of atopic dermatitis patients were females in the range of 0 to 14 years, with 82 (45.5%) patients.
- There was an increase of atopic dermatitis cases in females in the range of 30 years compared with males (F 10/ M 3). In 111 patients with DA skin prick test were made, only in 76 (42%) patients were positive and began treatment with immunotherapy.

Conclusions: In this study, AD represents the third cause of allergy disease in frequency among children. AD requires interdisciplinary management because of dermatological and allergological aspects for treatment, including immunotherapy. Education of parents and patients is also an important task in the treatment of AD. The results of this study are helpful to improve specialized medical attention in paediatric patients and adults with AD.

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Gene-environment Interactions on the Development of Atopic Dermatitis in Preschool Children: Mold is the Main Environmental Factor

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Background: Genetic factor and environmental exposure are recognized risk factors for atopic dermatitis (AD) in children. It is known that fungus is the representative environmental factor of AD. However, the relative and the overall contributions of fungal exposure remain unexplored.

Methods: During July to August 2010 population-based cross-sectional survey, we investigate 986 preschool children from 16 kindergartens of Seoul and Gyeonggi-do province in Korea using a modified International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire. We investigated 5 mold exposure items (dampness stain, dampness damage, visible mold, mold odor, house repair) in this survey. Multivariate regression analysis was applied to determine impact of mold exposure as risk factor for AD.

Results: The prevalence of AD was as follows: lifetime symptoms, 28.0%; symptoms in the past 12 months, 28.7%; lifetime diagnosis by questionnaire, 35.1%; treatment in the past 12 months, 16.6%; current AD (which was defined as lifetime diagnosis by questionnaire together with symptoms in the past 12 months), 21.5%; and diagnosis by doctor's examination on the spot, 14.6%. A parental history of AD and mold exposure and environmental factors were independent risk factors for AD in preschool children. The co-existence of a parental history of AD and mold exposure together was synergistically related to AD prevalence. When children with a parental history of AD were exposed to mold (ex. mold odor), the risk for AD prevalence increased up to 7 times. (OR 6.956, 95% CI, 2.599-18.615)

Conclusions: This investigation provides a high prevalence of AD and a close relationship with mold. High prevalence of AD was detected by the combined effect parental history of AD and mold exposure at infancy. These findings suggest that early avoidance from mold exposure is important to prevent the development of AD especially in the susceptible children.

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FcRγ-mediated Immune Responses Modulate the Exacerbation of Clinical Symptoms in Atopic Dermatitis of NC/TND Mice

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Background: Although elevated specific IgG and IgE are observed in sera of patients with atopic dermatitis (AD), their involvement in the pathogenesis of AD remains to be determined. In this study, we investigated the contribution of the immunoglobulin in AD by using Fc receptor common γ-chain (FcRγ)-deficient NC/Tnd mice.

Methods: NC/Tnd mice spontaneously develop the AD skin lesion when they are raised in air-unregulated conventional circumstances, but not when maintained under air-regulated specific pathogen-free conditions. We established FcRγ - NC/Tnd mice; those mice lacked FcRγ-mediated immune responses initiated by specific IgG and IgE. The clinical skin severity score and scratching behavior were evaluated in FcRγ-deficient mice and wild-type (WT) littermates. To examine histological features and distribution of mast cells, tissue sections of the lesional skin were stained with hematoxylin-eosin and toluidine blue, respectively. With regard to inflammatory cytokine production, the mRNA expression was detected in the dorsal skin and the axillary lymph node by real-time RT-PCR.

Results: Although the absence of FcRγ did not affect production of the immunoglobulin, the clinical skin severity scores were lower in FcRγ$^{-/-}$ NC/Tnd mice by half than in conventional WT mice. On the other hand, there were no differences in both scratching behavior elicited by dermatitis and Th1/Th2 cytokine production between 2 groups of mice. In the skin lesion of FcRγ null mice, mild epidermal hyperplasia and immune cell infiltration were observed. Particularly, mast cell numbers and their degranulation were significantly decreased in the skin of FcRγ-deficient mice.
Conclusions: FcRγ was not critical to the onset of AD, because FcRγ-deficient mice exhibited moderate dermatitis and scratching behavior comparable to WT. On the other hand, although scratching behavior induced the mechanical destruction of skin barriers and mast cell activation, the absence of FcRγ markedly attenuated the skin severity, immune cell recruitment including lymphocytes, and mast cell degranulation. These results indicated that the FcRγ-mediated immune response by specific IgG and IgE regulate the exacerbation of clinical symptoms in AD.

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Autoimmune Diseases and Risk of Stroke

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Background: To determine the frequency of patients (pts) with autoimmune diseases who developed stroke and to analyse the associated risk factors.
Methods: We made a retrospective analysis of 251 pts with stroke, hospitalized during 1 year period at the Department for Urgent Neurology. Of them, we selected 7 pts with a history of autoimmune diseases.
Results: Three patients had systemic lupus erythematosus (SLE), 2 pts had M. Behcet, one patient was diagnosed with Sneddon sy and one patient had Vascullitis allergica leucocytoclastica. All pts were females, except one male pt with M. Behcet. The average age was 49 ± 11 years. Two patients with massive ischemic stroke had a lethal outcome. Hypertension was found as an independent risk factor for stroke in all pts ($P < 0.01$). Other risk factors included chronic renal failure, antiphospholipid antibodies, hypercoagulable state and symptomatic seizures.
Conclusions: The incidence of autoimmune diseases in patients with stroke was 2.7% in our material. Hypertension was an independent risk factor for subsequent stroke.

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Clinical Effects of Tocilizumab, a Humanized Anti-interleukin-6 Receptor Antibody, on Patients with Autoimmune and Allergic Diseases

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Background: A humanized anti-interleukin-6 receptor, tocilizumab, has been approved as a biological drug for the treatment of rheumatoid arthritis, systemic juvenile idiopathic arthritis and Castleman's disease. Since dysregulation of IL-6 production also plays a pathologic role in other various autoimmune and allergic diseases, we tested whether tocilizumab might have beneficial effect on refractory autoimmune or allergic diseases to conventional treatment regimens.
Methods: After informed consent by patients and approval by the Ethics Committee of Osaka University Hospital were obtained, patients were treated with tocilizumab at 8 mg/kg every 4 weeks.
Results: The diseases for which off-label use of tocililizumab was performed included amyloid A amyloidosis, relapsing polychondritis, systemic sclerosis, HLA-B27 positive spondyloarthritis such as reactive arthritis and psoriatic arthritis, polymyalgia rheumatica and polymyositis. After 3 injections of tocilizumab amyloid fibril deposits in the colon disappeared in a patient with gastrointestinal AA amyloidosis, who was resistant to anti-TNF drugs and disease-modifying antirheumatic drugs. In 2 patients with refractory relapsing polychondritis, the continuous tocilizumab treatment for more than 3 years could ameliorate clinical symptoms related to upper and lower airways and stabilize the disease activity. The skin sclerosis of 2 patients with systemic sclerosis became softened with reductions of 52 and 23% in the modified Rodnan total skin score by the tocilizumab treatment. Two administrations of tocilizumab led to the disappearance of joint swelling, pain and complete resolution of symptoms in a patient with refractory reactive arthritis to several therapeutic regimens for 4 years, whereas 2 patients with severe psoriatic arthritis did hardly respond to tocilizumab. In a patient with polymyalgia rheumatica, the tocilizumab treatment caused a reduction of the disease activity score (PMR-AS) from 22.14 to 0.74, indicating remission. Creatine phosphokinase normalized by 2 patients with polymyositis who had been resistant to corticosteroids and immunosuppressive drugs, in association with the disappearance of the high intensity zones in the thigh muscles on MR images.
Conclusions: These clinical effects of tocilizumab suggest that it may be an optional treatment for refractory autoimmune or allergic diseases although further clinical trails will be essential.

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Association between Autoimmune Reactions, Herpes Infection and Severity of Atopic Dermatitis in Children

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Background: Atopic dermatitis (AD) is a chronic skin disease predominately with the beginning in childhood. One hundred autoantigens and more are capable of binding with autoantibodies in AD patients, including autoantigens with common epitopes of EBV. Aim of study was to reveal IgE- and IgG-autoreactivity to some tissue proteins and IgG-abs to some herpes viruses and to compare the received dates with the severity of AD.
Methods: In the sera of 157 children with AD (from 1 to 17 years old) the levels of IgG- and IgE-abs to keratin, collagen III and VI, elastin, myosin and basic myelin protein were determined in adapted ELISA. The levels of IgG-abs to HSV, CMV and EBV were determined using commercial kit of ELISA. The level of total IgE and IgE-antibodies to allergens were detected using an autoanalyzer.
Results: In all age groups of patients (with light AD, middle AD and severe AD) elevated levels of total IgE were revealed, especially in children with severe AD (Me = 360 KU/L (80 – 1160); $P < 0.05$). An increased contents of IgE-abs to keratin (Me = 2.71 ME/mL (1.4–13.69); $P < 0.05$) and elastin (Me = 2.69 ME/mL (1.4–2.78); $P < 0.05$) and IgG-abs to keratin (Me = 296.21 μg/mL (127.88–342.01); $P < 0.05$) were revealed in children with severe AD in comparison with healthy children. Whereas in children with light AD the levels of these antibodies were not significantly increased ($P > 0.05$), but were being increased in proportion to a severity of AD. We revealed a correlation between the levels of total IgE and the levels of IgE-abs

to keratin in children with severe AD (r = 0.35; $P < 0.05$). In addition we revealed that the levels of IgG-abs to HSV were being increased in proportion to a severity of AD. Maximal increased level of IgG-abs to HSV was in children with severe AD (Me = 2.93 units of OD (0.14–3.15); $P < 0.05$).
Conclusions: The detection of the elevated levels of the autoantibodies, especially against the background of herpetic infection, amplifies the phenotypic and diagnostic criteria of severity of AD and allows the clinician to choose the most adequate and effective treatment of AD patients.

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Immunomodulatory Effects of Extracorporeal Photochemotherapy in Systemic Sclerosis

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Background: The aim of the present study was to evaluate the clinical and immunomodulatory effects of extracorporeal photochemotherapy (ECP) in systemic sclerosis (SSc).
Methods: In the study, we enrolled 16 patients with diffuse cutaneous SSc, who received 12 ECP treatments in total. Skin involvement was assessed by modified Rodnan skin score and high-resolution ultrasonography. Blood samples were taken prior to the first therapy and 6 weeks after each cycle. Samples were also obtained from 16 healthy controls. Lymphocyte subgroups were quantified by flow cytometry, autoantibodies were determined by ELISA technique, and levels of 17 circulating cytokines were measured by multiplex cytokine assay. We used in vitro test to assess the changes in suppressor capability of CD4+CD25+ Treg cells.
Results: After ECP treatments, the dermal thickness reduced and the mobility of the joints improved. Internal organ involvement did not deteriorate. Initially, patients had lower numbers and percentages of peripheral NKT, Th1, Tr1 and CD4+CD25+ Treg cells, compared to control values. Moreover, the suppressor activity of Treg cells was lower. During the therapy, the values of Tr1 and Treg cells elevated, and the suppressor capacity of Treg cells improved. Initially, patients had higher numbers and proportions of NK and Th17 cells, compared to control values. During the therapy, values of Th17 cells decreased. Levels of CCL2 and TGF-beta decreased, while the concentration of IL-1Ra, IL-10 and HGF increased during ECP.
Conclusions: ECP contributes to the restoration of the balance between regulatory and effector immune mechanisms, leading to the deceleration of disease progression.

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Detection of Anti-nucclear Antibodies (ana) Used for Diagnostic Approach of Systemic Autoimmune Diseases. Correlation with Double Stranded DNA (DSDNA) and Extractable Nuclear Antigen (ENA) Antibodies

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Background: To determine the correlation between the titer of ANA and anti-dsDNA and anti-ENA antibodies and the contribution of ANA detection to the diagnosis of connective tissue diseases (CTD).
Methods: Our samples consisted of 516 specimens, from Rheumatology Department, collected during January 2010 – July 2010. The detection of ANA was performed using indirect immunofluorescence (IFA) and the detection of anti-dsDNA and anti-ENA using ELISA.
Results: Of the 364 (70.54%) samples with negative ANA 4 (1%) had positive anti-ENA and 2 (0.5%) had positive anti-dsDNA while positive anti-ENA and anti-dsDNA were detected in the 44.73% (n = 68) and 21% (n = 32) of the specimens with positive ANA respectively. The probability of detecting positive anti-ENA and anti-dsDNA rises proportionately to the titer of ANA. Specifically, the correlation between the probability of detecting positive anti-ENA and the titer of ANA is 0.577 ($P < 0.001$) while the correlation between the probability of detecting positive anti-dsDNA and the titer of ANA is 0.18 ($P = 0.003$). Probability calculations on the basis of the ANA titer showed that samples with low titer ANAs (1:160 or less) had low probabilities for positive anti-ENA. The receiver operating (ROC) curves of the ANA titer for anti-ENA had a larger under the curve area compared to the ROC curve for anti-dsDNA, indicating that ANA titer is better for predicting anti-ENA than anti-dsDNA. The sensitivity of positive ANA in the prediction of the anti-ENA and anti-dsDNA was 94.40% and 94.10%, the specificity was 81% and 75.10%, the positive prognostic value was 44.70% and 21.10% and negative prognostic value was 98.90 and 99.50%.
Conclusions: The detection of ANA using indirect IFA has high sensitivity in predicting the presence of specialized antibodies and may be used as a screening method for the diagnosis of CTD. It is cost and time effective too. Our study also shows that the ANA titer is useful in predicting anti-ENA. Samples with low titer ANAs (1:160 or less) may not need a further test for anti-ENA unless an ANA-associated disease is highly suspected. However a test for anti-dsDNA should be considered in positive ANA samples at any titer including low titers.

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The Vasculitis Induced by the Cerebrovascular Coil

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Background: The treatment of a cerebrovascular coil is the popular treatment for the cerebral aneurysm. It is treatment to insert a metal coil in aneurysm. It is not reported the allergy of cerebrovascular coil. In Dec, 2019, a 57-year-old Japanese woman came to the neurosurgery hospital. The cerebral aneurysm was treated by coil embolization. Two days later, she was returned to hospital by left facial paralysis. Vasculitis was detected on the peripheral artery of the coil by MRI (magnetic resonance imaging). It was treated by prednisolone 60 mg/d, and paralysis was improved, although slightly remained sequelae.
Object: To understand of necessity of long term steroid therapy, we investigated metal allergy for coil.
Methods: The steroid was tapered and discontinued. The MRI was checked every 3 months. When vasculitis recurs, tapering is canceled. Three kinds of coils were used by embolization. Their coil consists of platinum and tungsten mainly, but it is unknown about the other component metal. After the steroid was discontinued, a patch test for 3 coil and LTT (lymphocyte transformation test) for the contrast medium was indicated. It was interpreted using ICDRG (INTERNATIONAL CONTACT DERMATITIS RESEARCH GROUP) criteria. It was given her informed consent to this study.
Results: After treatment of steroid, only Potassium bichromate was positive and other 17 metals, including the platinum was negative by the patch test. Two coils of the same type, was positive. The contrast medium was negative by LTT. One month later, new lesion of vasculitis was detected on the peripheral artery of the coil by MRI.

Conclusions: It is a metal coil at risk of causing vasculitis. When it was treated by coil embolization, the check of the allergy to metal is recommended, because it was possible to experience permanent sequelae.

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Prevalence of Thyroid Peroxidase Autoantibodies (ANTI-TPO) in Women with Autoimmune Connective Tissue Diseases (ACTD)

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Background: Chronic autoimmune thyroiditis, manifested by positive test for antithyroid antibodies, is common in the general population, occurring in 10 to 20 percent of women. The aim of the study was to determine whether Anti-TPO is more prevalent in women with ACTD, compared to the general population.

Methods: Anti-TPO was determined in 290 women diagnosed with ACTD based on ACR (American College of Rheumatology) criteria and in 50 healthy women (control group). Among ACTD patients, 121 were diagnosed with Rheumatoid Arthritis (RA), 44 Systemic Lupus Erythematosus (SLE), 43 Sjogren's Syndrome (SS), 42 Systemic Scleroderma (SScl) and 40 Psoriatic Arthritis (PsA). Anti-TPO was measured by Chemiluminescent Microparticle Immunoassay (CMIA) on Architect i2000SR (ABBOT Laboratories).

Results: The prevalence of Anti-TPO in separate groups of patients had as follow: RA 28.93%, SLE 29.55%, SS 27.91%, SScl 23.81%, PsA 30% and control group 12%.

Conclusions: ACTD and thyroid autoimmune diseases often overlap with each other. Increased Anti-TPO may be most common among women patients with ACTD. On the other hand, these systemic diseases are often present in Hasimoto's thyroiditis subjects. Therefore it is clinically important to screen women patients with ACTD for the co-existence of thyroid disorders.

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Anticardiolipin Antibodies in Patients with Acute Myeloid Leukemia: Prevalence and Clinical Significance

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Background: Leukemia in general is known to be associated with coagulopathies. The presence of antiphospholipid antibodies was associated with several medical problems, including recurrent spontaneous abortion, arterial and venous thromboses, and thrombocytopenia. A number of studies report the prevalence of anticardiolipin (ACL) antibodies in acute myeloid leukemia (AML). This study was designed to explore the prevalence and the clinical and prognostic significance of ACL antibodies in patients with acute myeloid leukemia (AML).

Material and Methods: The study includes 28 AML patients >15 years old and with no evidence of infection at the time of enrollment. The previous history of thromboembolism, recurrent abortion, and autoimmune disease was given from patients. Serum level of ACL antibodies was determined by indirect enzyme immunoassay.

Results: ACL antibodies were found in 9 patients (32.14%). None of the patients had high positive titers (>40 GPL). Two patients had moderately positive (20–40 GPL), while 7 patients had low positive (10–20 GPL) ACL antibody titers.

Conclusions: ACL antibody positivity was not correlated with the risk of thromboembolism, fetal loss, and autoimmune disease. These preliminary results demonstrate a prevalence of ACL antibodies in AML patients and suggest that serum ACL antibodies may have a role in some haematological malignancies. The correlation of ACL antibodies with predicting, relapse, and documenting disease activity is will be continue until 4 to 19 months of follow up.

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Alopecia as a Symptom of Neonatal Lupus: A Report of Case

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Background: Neonatal Lupus is a rare disease, described in 1954, which only occurs in children of mothers with antibodies to specific antigens of Systemic Lupus Erythematosus (SLE). Such antigens pass, transplacentally during gestation and is characterized by cutaneous manifestations such as rash, erythematous macules, papules or plaques which tend to coalesce; less frequent are blood disorders including aplastic anemia, neutropenia, thrombocytopenia, hemolytic anemia, pancytopenia; liver disorders with elevated liver enzymes and cholestasis; central nervous system disease such as mielopaias, convulsions; pulmonary as pneumonitis, and gastrointestinal tract such as bloody diarrhea. Alopecia is a common symptom in SLE but has not been reported in the literature in neonatal presentation.

Methods: Case report: A 1 month and 4 day old infant female, who presented 3 days after birth with a persistent bloody diarrhea, without mucus also presents dehydration and metabolic acidosis that warrant intravenous correction. An infectious etiology is discarded and is referred to an allergist for study of a possible lactose intolerance which is discarded initially. However, the physical finding of hair loss is evident with areas of alopecia which together with the persistence of the diarrhea and rash is suspect of a possible immunological etiology. Therefore, it was decided to test Anti-Ro autoimmunity in the infant and his mother; given a positive results.

Results: With the Anti-Ro test the presence of Neonatal Lupus is confirmed. A treatment with EV-dose methylprednisolone was initiated, which had little clinical response, meriting a treatment with azathioprine with a good clinical response, which improved and reduced Anti-Ro values.

Conclusions: The importance of clinical observation is evident when there are unusual features which allows for a rare diagnosis. This striking case, given the unusual presentation with alopecia which together with the clinical observations was indicative of this disease, and not of other syndromes characteristic of this age, like sepsis.

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Autoimmune Hepatitis Misdiagnosed as Hepatitis C Responding to Interferon/Ribavirine Therapy

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Background: Latent autoimmune hepatitis (AIH) triggered during interferon (IFN) treatment in patients with chronic hepatitis C (CHC) is well known. Here, we report for the first time improvement of AIH using IFN and ribavirin (RBV) in a patient initially incorrectly diagnosed as having CHC.

Methods: Case report

Results: 32 years old female was referred because of fluctuating elevations of aminotransferases (AT) (4- to 19-fold normal) known last 6 months. She had positive HCV-RNA by RT-PCR an untypable genotype. Liver biopsy revealed chronic active hepatitis grade 2, stage 2. She also had Hashimotoś thyroiditis with high titres of antithyroid antibodies. After 12 weeks of treatment with Intron A 3MU TIW and RBV 1000 mg/d, HCV RNA was negative and AT fluctuated between normal and 2-fold normal. One week after completing 48 weeks of treatment, AT showed 11-fold increase, but HCV remained negative. Indirect immunofluorescence became positive for ASMA (3+) and ANA (4+). A repeated liver biopsy showed no improvement. A therapeutic trial with RBV was started and within 11 weeks of this treatment her symptoms markedly improved and AT decreased to 2-fold. Unfortunately, cessation of RBV resulted in immediate reversion of symptoms and elevation of AT to its previous state. After restarting RBV therapy no response was observed within 2 weeks and the treatment was stopped. She was then put on prednisone 30 mg/d and azathioprine 50 mg/d. Within 6 weeks her symptoms resolved and AT and IgG became completely normal. The patient remains in remission with prednisone 5 mg and azathioprine 50 mg/d. A re-evaluation of the primary diagnosis of hepatitis C was warranted because of unusually high AT activity and repeatedly negative anti-HCV using a third generation assay.

Conclusions: This case may provide support for the hypothesis that RBV may dampen autoimmune reaction induced by IFN alpha and potentiate its anti-inflammatory effects.

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Ocular Muscles Myopathy Associated with Autoimmune Thyroiditis. Case Reports

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Background: Thyroid-associated orbitopathy is commonly associated with Graves' disease with lid retraction, exophthalmos, and periorbital swelling, but rarely with autoimmune thyroiditis or euthyroid state. We reviewed 3 cases from our hospital whose antibodies to anti-receptor of TSH were normal.

Methods: Case 1: 60 year-old non-diabetic woman with bilateral glaucoma in treatment, recurrent media otitis and euthyroidism, acute onset of painless diplopia, and lid ptosis in the left eye. MRI of orbit showed increased size of the III right cranial pair and high levels of thyroid autoantibodies (Tab) anti-tiroglobulin (ATG) 115.1, anti-thyroid peroxidase (ATPO) 1751 U/mL. She started oral deflazacort 30 mg each 3 days. Sixty days later, complete remission of eye symptoms correlated with lower auto-antibodies level (ATG 19 ATPO 117). Case 2: 10 year-old girl. At age 8, she had diplopia, lid ptosis and limitations of upper gaze in the left eye. The neurological study discarded ocular myasthenia; with thyroid goitier, and hypothyrodism, she started oral levothyroxin. At age 10 with normal IRM Botulinic toxin was injected, without change. High levels of Tab were found, ATG 2723, ATPO 10.7. She started oral deflazacort 30 mg each 3 days, azathioprin 100 mg, daily. Actually, Tab levels are almost normal, but she remains with ocular alterations. Case 3: 56 year-old woman, Gravés disease with exophtalmos in 1990, treated with I^{131} and immunosupression, with good outcome; obesity, hypertension and bilateral glaucoma in treatment. She suddenly presented diplopia and IV pair paresia of the right eye. A year later, ATb were found slightly elevated, ATG 100 years ATPO 227; despite prednisone 50 mg, each 3 days and azathioprin 150 mg/daily treatment, a surgical procedure was required for relieve the ocular symptoms.

Results: We found only 3 cases previously reported with this type of eye thyroid disease. Is important to note that awareness of this atypical form of orbitopathy

Conclusions: Early recognition facilitates successful treatment (Case 1) or persistent disease when diagnosis is delayed (Cases 2 and 3).

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Pulmonary Arterial Hypertension Associated to Antiphospholipid Syndrome in an Infant

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Background: Antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterized by a combination of arterial or venous thrombosis and recurrent fetal loss. It may be primary or in association with an underlying systemic disease, particularly systemic lupus erythemathosus.The diagnostic criteria include vascular thrombosis, complications during pregnancy with recurrent losses, positive titers of anticardiolipin and lupus anticoagulant antibodies.Vascular thrombosis can occur anywhere in the body, including lung vessels. The association of APS with pulmonary arterial hypertension has been estimated between 1.8% and 3.5%.

Methods: Case Presentation: We present an 18 month old male boy, who was admitted to our hospital with a history of 3 previous episodes of pneumonia, at arrival with pulse saturation of 69% without oxygen, improving to 100% with oxygen. Pulmonary arterial hypertension was documented with echocardiogram resulting in 100 mm Hg without structural abnormalities. An autoimmune etiology was suspected, resulting with high titers of anticardiolipin (IgG 34.6 mg/dL) and anti-b2 glicoprotein (IgG > 200 mg/dL, IgA 53 mg/dL).

Results: Treatment with acenocumarine, hydroxichloroquine and prednisone was initiated. Nowadays he has evolved with clinical improvement, on its last echocardiogram the pulmonary arterial tension resulted in 65 mm Hg, without evidence of thrombosis.

Conclusions: We report an infant with pulmonary arterial hypertension as the only manifestation of antiphospholipid syndrome, with clinical improvement with anticoagulant and steroid therapy.

CONJUNCTIVITIS

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Tear IL-4 is Decreased in Allergic Conjunctivitis Patients with Negative Skin Test After Dialyzable Leukocyte Extracts Treatment

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Background: It has been suggested that sublingual immunotherapy induces immune regulation, however in patients with clinical ophthalmological diagnosis as allergic conjunctivitis with negative skin test reactivity (ACNST) this treatment is not useful. Dialyzable leukocyte extracts (DLE) have been used in atopic dermatitis and asthma. The aim of this work was to evaluate treatment of ACNST with DLE and to analyze the microenvironment provided by tear and serum cytokines in patients before and after DLE treatment.

Methods: 10 ACNST-patients with negative skin test were included in this study. ACNST diagnosis was based on a clinical history and full ophthalmologic examination according to the diagnosis standards of the American Academy of Ophthalmology. Coproparasitoscopic negative for parasites was documented This study was approved by Scientific and Ethics Committees if

Institute of Ophthalmology "Conde de la Valenciana ", Mexico City an all subjects gave their informed consent to obtain samples. *Tear and Serum Samples* were collected to determine cytokines IL2, IL-4, IL-5, IFN-g, TNF-a, IL-10 by cytometric bead arrays (CBA), following manufacturer's instructions.
Results: Patients showed lower significant levels of L-4 after 6 months of treatment, without changes in IL2, IL5, TNFa and IL10. Significant Clinical improvement was also observed since 3 months of treatment and was maintained until the end of 6 months.
Conclusions: DLE could be an excellent therapeutic tool to improve the clinical outcome in ACNST patients; it is possible that clinical improvement could be Tear IL-4 dependent.

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Histochemical Study of Allergic Inflammation in Conjunctiva From Ovalbumin Sensitized Rabbits after Ocular or Nasal Challenge

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Background: We previously demonstrated that subcutaneous sensitization with ovalbumin (OVA) induce generation of specific IgE antibodies and quantitative modifications in immune cells populations from different mucosal sites in rabbit. The aim of the study is characterization of eosinophil infiltration in conjunctival mucosa from OVA sensitized and ocular and nasal challenged rabbits.
Methods: Animals were divided into 4 groups: G1 (n = 9): normal control; G2 (n = 10): subcutaneous sensitized with OVA; G3 (n = 10): subcutaneous sensitized and conjunctival challenged with OVA; G4 (n = 9): subcutaneous sensitized and nasal challenged with OVA. Four hours after challenge animals were sacrificed and obtained samples were processed for histochemistry with cromotrope 2R for eosinophil detection. Cells were counted in 200 high power fields per group.
Results: Data were expressed as positive cells per high power field. Conjunctival mucosa: G1: 2.3; G2: 3.4; G3: 12.2; G4: 3.3 (G3 vs G1, G2 y G4 $P < 0.001$). Specific anti-OVA-IgE levels were evaluated by positive passive cutaneous anaphylaxis test (PCA) at 160 fold dilutions.
Conclusions: We observed an increase in the number of eosinophils-positive cells after local challenge in conjunctiva as compared to normal controls and sensitized and nasal challenged animals. We conclude that systemic sensitization with soluble antigen and conjunctival challenge induces modifications in number of eosinophil populations in conjunctiva but not in nasal challenged rabbits.

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Prevalence of Allergic Conjunctivitis in Childhood

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Background: The prevalence of allergic conjunctivitis (AC) has not been established. Estimates suggest that ocular allergies affect 15 to 20% of the worldwide population yet most epidemiological studies encompasses nasal and ocular allergy symptoms together and have not been specific with respect to AC. The aim of this study was to verify the prevalence of ocular allergy symptoms in adolescents.
Methods: Adolescents were selected from a sample of schools and self-completed in classrooms a previously validated questionnaire on symptoms of AC. AC was considered when more than 3 episodes of ocular itching were reported in the past 12 months. Related symptoms as tearing, photophobia, foreign body sensation, impact on daily activities, and diagnosis of allergic conjunctivitis were analyzed.
Results: Questionnaires from 3120 adolescents (mean 13.3 ± 1.1 years) were analyzed. Ocular itching in the past 12 months occurred in 1,592 (51%). The most frequent associated symptom was tearing (74%) followed by photophobia (50.1%) and foreign body sensation (37.1%). The prevalence of allergic conjunctivitis was 20.7% affecting more females (56.1% vs 45.9%; $P < 0.01$). Moderate and severe interference in daily activities were reported by 66% and 21%, respectively. Diagnosis of AC was reported by 47% of them.
Conclusions: Symptoms of ocular allergy are common and cause great impact on daily activities in adolescents. Accessing risk factors and the allergic status of these patients should be the focus of future epidemiological studies on AC.

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Effects of Omalizumab in Children with Atopic Keratocojunctivitis: A New Treatment for Severe Ocular Allergies?—Report of Two Cases

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Background: Keratoconjunctivitis is a severe form of ocular allergy, difficult to control and with poor prognosis. The purpose of this study was to verify the clinical efficacy of humanized monoclonal antibody omalizumab treatment in children with this condition.
Methods: Report of 2 cases of children with severe vernal keratoconjunctivitis poorly controlled by the conventional therapeutic scheme that were submitted to treatment with Omalizumab.The disease was scored according to the severity by ophthalmologic evaluation (amount of viscous mucus, giant papillae >1 mm, aspect of cornea/keratitis) and graduation of allergic symptons (itching, tearing, photophobia), before and after the last subcutaneous administration of Omalizumab.Evaluation by Parents/ guardians using the same score, regarding to itchy eyes, runny eyes and photophobia, after Omalizumab application, was also requested.
Results: Case 1: MPOS (7 years) with vernal keratoconjunctivitis and atopic dermatitis since childhood, both with progressive severity. Recalcitrant ocular itching and photophobia, in addition had other atopic conditions such as mild asthma, rhinitis and egg allergy. Total IgE = 1323 IU/mL. Ocular manifestations poorly controlled with topical use of antihistamines, cromolyn, tacrolimus and cyclosporine. The use of topical corticosteroids was frequent, but resulted in brief improvement.Case 2: HCS (6 years) with vernal keratoconjunctivitis since 3 years age, and mild asthma and moderate persistent rhinitis. Continued use of topical tacrolimus 0.03% showed an initial improvement, but subsequent relapses resulted in frequent use of systemic prednisolone and eye drops antibiotics to control symptoms. Total IgE = 1530 IU/mL.After the second Omalizumab application, good or excellent improvement in ocular symptoms of both children was observed by allergists and parents. Ophthalmologic evaluation showed moderate improvement in the amount of slime and little or no improvement in the structural changes of the eye (cornea and appearance of giant papillae).
Conclusions: There are few reports about the use of Omalizumab in allergic keratoconjunctivitis. Our work points to the need for further research in this area as the Anti-IgE may become a promising therapy for this difficult to control condition.

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Giant Papillary Conjuntivitis without Associated Triggers. Report of Two Cases

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Background: Giant papillary conjunctivitis is associated with soft and rigid contact lens wearing, ocular prostheses, exposed sutures, extruded scleral buckle, filtering blebs, band keratopathy, corneal foreign bodies, limbal dermoids, and cyanoacrylate tissue adhesives. Patients present decreased lens tolerance, increased lens movement and awareness, mucus, irritation, redness, burning, and itching. Is bilateral and 10% unilateral. The upper tarsal conjunctiva shows inflammation, papules >0.3 mm, bulbar conjunctival injection, superior corneal pannus or opacities. Fluorescein noted papillary reaction. Histopathology: Mast cells, basophils and eosinophils were found in the epithelium and substantia propia. Histamine, Ig, IgG, IgM, C3, Factor B, C3 anaphylatoxin, Eotaxin, Neutrophilic chemotactic factor elevated in tears. Lactoferrin is decreased. Pathophysiology: The cause is unknown, factors as immunologic disease, mechanical trauma or irritation influence. Contact lenses become coated that serves as an antigen so the increased proteins in the tear film result in further coating. Treatment: Nonsteroidal anti-inflammatory agents, topical mast cell stabilizers or mast cell stabilizer-antihistamines. Replacement lenses at 2 weeks to 3 months. Daily lens disinfection with hydrogen peroxide and unpreserved saline solution. Severe should stop wearing their contact lenses for >4 weeks or refit with rigid gas-permeable lenses.
Methods: A 7 year-old female presents 6 months ago redness, pruritus, forgein body sensation, eyelid inflammation without improvement with treatments. On examination with conjunctival hyperemia, hypertrophy of papillae and epiphora.A 22 year-old male presents at 7 years old conjunctival burning, foreign body sensation, conjunctival hyperemia, hyaline secretion treated with topical antibiotics and steroids with minimal and temporal improvement. On examination, conjunctival hyperemia, giant papillae on superior tarsal bilateral predominantly left. Stool negative.
Results: We found 2 patients affected without common triggers and early onset of severe clinical manifestations and refractory to usual treatment.
Conclusions: We present 2 clinical cases of unusual presentation since both of them were pediatric presentation and Giant papillary conjunctivitis has its peak of incidence in the adult population. Besides, both patients lacked an initial trigger such as contact lens wearing or ophthalmologic surgery. Both of them had a poor response to treatment. This disease should be considered in pediatric population and start treatment inmediately to avoid complications such as loss of vision.

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Contact Allergy Due to Ophthalmic Drugs in Uruguay

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Background: The external eye is exposed to a large number of environmental, cosmetic and pharmacological allergens and the frequency of external eye diseases related to the prolonged use of ophthalmic medications and contact lens wear is increasing. Predisposing factors for contact allergy are: high exposure to topical drugs (eyelids & eye), high percutaneous absorption in eyelids, high potential for concomitant irritation and hand transfer of allergens due to frequent rubbing.
Methods: Ninety three patients 56 women and 37 men, age range 10 to 81 years old, mean age 43 years old with a clinical picture compatible with ocular allergy were referred to our Allergy Unit by the Department of Ophthalmology at the University Hospital for allergological evaluation, including a thorough history, complete clinical examination as well as laboratory techniques and skin testing. Patch-testing was performed with the standard series, an ophthalmic series of allergens developed at our unit, as well as additional allergens according to the clinical situation.
Results: Contact allergy was more frequently caused by topical antibiotics and preservatives and occasionally by mydriatic agents and topical drugs for glaucoma. The allergens more frequently implicated were Neomycin (10.7%), Bacitracin (9.6%) Thimerosal 8 (8.5%) Benzalconium chloride 5 (5.3%) Phenylephrine hydrochloride 3 (3.2%), local anesthetics 3 (3.2%), Chloramphenicol (3.1%), Polymyxin (2.1%), Kanamycin (2.1%), Gentamicin (2.1%), Tobramycin (2.1%), Beta-blockers 1 (1.7%), and others (6.1%).
Conclusions: Patients with a clinical picture compatible with ocular allergy should be referred for allergologic evaluation. A comprehensive approach will often provide clues for a presumptive diagnosis and appropriate management. When a contact allergy is found it is mandatory to avoid contact with the precipitating substance. This may simply be a case of stopping or altering an ophthalmic medication. The proper use of ophthalmic preparations should decrease the incidence of allergic contact reactions.

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Increased Frequency of γδ T Cells in Patients with Allergic Conjunctivitis

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Background: It is well known involvement of CD4+ T cells in the maintenance of allergic immune response at conjunctiva; recently, it was suggested in the mouse model that γδ T cells are needed for the ocular allergic response maintenance; however contribution of γδ T cells in human allergic conjunctivitis is still unknown. The aim of this study was to evaluate the frequency of γδ T cells in AC patients.
Methods: Patients with AC diagnosis were included. All participants gave their informed consent for blood sampling after written information was provided. Peripheral blood mononuclear cells (PBMC) were separated on a Ficoll density gradient, after that PBMC were stained with mAb against human CD3-PeCy5 and γδ-PE. The cells were analysed for marker expression by collecting 10,000 events using a FACScan flow cytometer (Becton Dickinson, CA, USA) and CellQuest Pro software. To analyse cell surface marker staining, a gate was drawn around the lymphocyte population based on their physical properties (forward and side scatter). Data were analyzed with *t* test and differences were considered statistically significant with $P < 0.05$.
Results: We observed a higher frequency of gd T cells in patients with AC, gd T cells were increased 11.9 times in AC-patients (22.63 ± 2.9%) than healthy donors (1.9 ± 1.9%) ($P = 0.002$).
Conclusions: γδ T cells are increased in allergic conjunctivitis patients. These data suggest that lipids antigens could be involved in pathogenesis of allergic conjunctivitis in humans and possibly implicated in chronic responses at ocular level, as has been suggested in the mouse model of allergic conjunctivitis.

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Zero Itch in Eyes Treated With Olopatadine Hydrochloride Ophthalmic Solution, 0.2% in Bilateral Conjunctival Allergen Challenge Studies

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Purpose: To further assess the prevention of ocular itching with olopatadine hydrochloride ophthalmic solution, 0.2% (OLO) in patients with allergic conjunctivitis.
Methods: This was a post-hoc analysis of 85 patients participating in 2 prospective, randomized, double-masked bilateral conjunctival allergen challenge (CAC) studies. Patients received OLO in one eye and placebo (vehicle) in the contralateral eye. Ocular itching was self-assessed by patients and rated on a scale of 0 (none) to 4 (severe). To assess onset of action,

eligible patients were challenged with antigen 27 minutes after dosing. To assess duration of action, patients were challenged with allergen 16 hours after dosing. The percentage of eyes with zero itching in both studies was assessed at 3 minutes post allergen challenge.
Results: The percentage of eyes with zero itch at the 3 minutes timepoint after the onset of action allergen challenge was 60.0% for OLO-treated eyes compared with 5.9% for vehicle-treated eyes ($P < .0001$, OLO vs vehicle). The percentage of eyes with zero itch at 3 minutes post allergen challenge following the 16-hour dosing was 59.8% for OLO-treated eyes compared with 22.0% for vehicle-treated eyes ($P < .0001$, OLO vs vehicle).
Conclusions: In bilateral CAC studies, ocular itching was prevented in a higher percentage ($P < .0001$) of eyes treated with 0.2% olopatadine hydrochloride ophthalmic solution when compared with vehicle as early as 30 minutes and for at least 16 hours post dosing.

CONTACT DERMATITIS

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Patch Testing Results in Contact Dermatitis from the Allergist's Perspective

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Background: Contact Dermatitis (CD) is a frequently encountered skin disease by allergists and dermatologists that results from contact with external allergens. Patch Testing (PT) remains the gold standard in the diagnosis of allergic CD. Studies evaluating PT from allergy practices are lacking.
Methods: A multi-center, retrospective chart review of PT within the last 5 years at allergy practices in 3 institutions. We report PT results using allergens in the Thin-Layer Rapid-Use Epicutaneous Test (TT) and additional supplemental allergens [North American Contact Dermatitis (NACD) Panel, Dormer Cosmetic Panel, hairdresser's panel, corticosteroid panel and personal products]. Additionally, patient characteristics including age, gender, occupation, dermatitis site, history of atopic disease and final diagnosis were also obtained.
Results: A total of 427 patients (mean age = 49.8 years) were patch tested, 82% were female, 54% reported an atopic history (history of asthma, atopic dermatitis, allergic rhinitis or food allergy), 30% were tested with TT, 60% with NACD panel, 30% with cosmetic series, 15% with corticosteroid series and 35% with personal products. The 5 most common positive PT allergens were nickel sulfate, fragrance mix I, P-phenylenediamine, thimerosal and cobalt chloride. The most common dermatitis sites were eyelid/periorbital (31%), facial (25%) and trunk (21%). 56.9% of patients were positive to at least one TT allergen. 25.6% of patients were positive to both a TT and a supplemental allergen (these patients would have been "partially evaluated" with TT allergens alone as they are positive to at least 1 TT allergen and 1 supplemental allergen). 12.5% of patients were negative to a TT allergen and positive to at least 1 supplemental allergen only (these patients would have been "missed" as they are negative to all TT allergens, but positive to at least 1 supplemental allergen).
Conclusions: Nickel remains the most common allergen. When evaluating patients with CD, testing with TT allergens alone would miss 12.5% of patients while 25.6% of patients would be only partially evaluated. As half of our patients were positive to at least 1 TT allergen, the TT remains an adequate screening tool but a more comprehensive panel may be needed to fully evaluate contact dermatitis.

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Contact Allergy to Medicaments in Consecutively Patch-tested Patients in Uruguay

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Background: Allergic contact dermatitis (ACD) to topical medicaments is common. Medicaments are responsible for approximately 30% of all cases of ACD. The most common drugs associated with ACD include topically applied antibiotics, antiseptics, antihistamines, anesthetics, nonsteroidal antiinflammatory drugs, and corticosteroids.Certain body areas are particularly susceptible (ie, genital and perianal areas, ears, eyes, face and lower legs)Predisposing factors are: occlusion (skin folds, use of bandages), application in damaged skin (stasis dermatitis & leg ulcers, and other chronic dermatitis) and long-lasting use of multiple medicamentsThe aim of our study was to study the prevalence of ACD to topical medicaments in patients with suspected ACD attending the Unit of Allergy at the University Hospital in Montevideo.
Methods: 1175 consecutive patients; 781 F (63%) 394 M (37%) with suspected ACD were patch tested with the standard series and the topical medicament series, as well as other allergens according to the clinical situation.
Results: The most frequent allergens were: Neomycin (7.1%), Thiomersal (3.8%), Benzocaine (1.9%), Bacitracin (1.9%), Propolis (1.5%), Gentamycin (1.2%), Tixocortol (1.1%) and Budesonide 24 (0.8%).
Conclusions: Contact allergy to topical medicaments is common in patients studied by a suspected ACD in Uruguay. In these cases the topical medicaments that the patient is using should be included when patch testing.

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Evaluation of Allergen Sensitivity in Patients with Contact Dermatitis in Antalya

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Background: Allergic contact dermatitis (ACD) is a delayed type of induced sensitivity (allergy) resulting from cutaneous contact with a specific allergen to which the patient has developed a specific sensitivity. This allergic reaction causes inflammation of the skin manifested by varying degrees of erythema, edema, and vesiculation. In this study, the socio-demographic characteristics, patch test were evaluated in treated patients diagnosed with Allergic contact dermatitis
Methods: The study was conducted in Antalya between 10th of November 2010 and 20th of July 2011. A questionnaire made by the investigators taking the latest literature data into consideration were used during the study. The total IgE levels were made by fluoroenzyme immunoassay method via use of ImmunoCAP kit for patch test was used. The statistical data derived were evaluated by using 14.00 SPSS software. Ki-Square test and percent ratios were used for data analysis. A P value less than 0.05 was assumed for statistical significance.
Results: During the study 457 patients (211 male, 246 female) were included. Among patients 52% belonged to 40 to 49 years age group, and 29% had University degree graduate. The total duration of the ACD was 10.11 ± 3.45 years. The total Ig E level was 112.6 ± 10.2 Ku/L. The most common

allergen was nickel, and fragrances. In this study, Allergic contact dermatitis is more common in women than in men.

Conclusions: Approximately 25 chemicals appear to be responsible for as many as one half of all cases of allergic contact dermatitis. These include nickel, preservatives, dyes, and fragrances. in this study Allergic contact dermatitis is more common in women than in men. This predominantly is a result of allergy to nickel, which is much more common in women than in men in most countries. In elderly individuals, the development of allergic contact dermatitis may be delayed somewhat, but the dermatitis may be more persistent once developed. Individuals may develop new allergies.

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Better Protection from Eczema Among Turkish Migrants' Children Carries Over from Preschool Age to Adolescence

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Background: In a cross-sectional study of preschool children born in Germany we found significantly reduced rates of atopy, eczema and asthma among Turkish migrants' children than among their domestic peers (*Clin Exp Allergy*. 2002;32:526–531). About 10 years later we re-examined children from this study population in order to investigate whether better protection from atopy among Turkish migrants' children persists into adolescence.

Methods: The setting of the original survey was screening for school eligibility in an inner-city district of Berlin/Germany. The participants were preschool children with double German or double Turkish citizenship. The main outcome measures were IgE to common aeroallergens (CAP system Phadia, Phadiatop ^{3} 0.35 kU/L) and 1-year prevalence of allergic disease symptoms (ISAAC questionnaire in German and Turkish language). All available adolescents from the first survey were included in the follow-up survey.

Results: 147 German and 154 Turkish adolescents were included. Rates of allergic sensitization tended to be lower among Turkish migrants' children than among domestic children at preschool age (7.0% vs 13.8%) and in adolescence (33.1% vs 41.7%). Likewise, lower rates of eczema among Turkish migrants' children at preschool age (7.8% vs 18.4%; $P = 0.010$) carry over to adolescence (8.7% vs 22.4%, $P = 0.008$). Rates of asthma also tended to be lower at preschool age (2.6% vs 6.1%) and in adolescence (14.0% vs 16.3%). By contrast, hay fever at any time point was not lower among the Turkish migrants' children (preschool age, 3.9% vs 3.4%; adolescent, 19.1% vs 16.1%).

Conclusions: This prospective study demonstrates that rates of allergic sensitization and of allergic diseases emerging earlier in life (eczema, asthma) tend to be persistently lower among Turkish migrants' children than among their German peers growing up in a very similar inner-city macro-environment. Further study is under way to examine potential allergy-protective factors in this cohort.

DIAGNOSTIC TEST FOR ALLERGIC RHINITIS

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Comparison of Skin and Conjunctival Reactivity to Aeroallergens

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Background: Diagnosis of allergic conjunctivitis (AC) is based on symptoms and positive skin prick test (SPT) to common aeroallergens. Allergens identified by SPT may not be clinically relevant to the eye. This study aims to compare the skin and conjunctival allergic responses to dust mites and grass pollen.

Methods: 56 subjects (29 ± 11.4 years) with ocular allergy and sensitized to dust mites and/or grass pollens were recruited for the study. Standardized extracts of *Dermatophagoides pteronyssinus* (*Der p 1* 83.8 mcg/mL), *Blomia tropicalis* (*Blo t 5* 462.5 ng/mL) and *Lolium perenne* (*Phl p 5* 399.2 mcg /mL) were used for skin test end point titration. Increasing 2-fold allergen dilutions were tested in forearms until no skin reaction was elicited. The end point was considered the dilution immediately above that one. Conjunctival provocation test (CPT) was performed with progressive doses of allergen (1:32, 1:16, 1:8, 1:4, 1:2) to the involved allergen. All tests were performed after obtaining written informed consent and out of grass pollen season. Subjects should be assymptomatic and off antiallergic medication.

Results: Of 82 conjunctival tests (30 Lp; 26 Bt; 26 Dp), 76% (62/82) occurred with 1:8 to 1:2 dilutions, 18% (15/82) with 1:32 to 1:16 dilutions and 6% (5/82) were negative. CPT were positive in 76% of subjects with *Der p 1* (10.5–41.9 mcg/mL), *Blo t 5* (57.8–231.3 ng/mL) and *Phl p 5* (49.9–199.6 mcg/mL). SPT were positive for allergens with 1:1024 to 1:128 dilutions in 22% (18/82), with 1:64 to 1:16 dilutions in 63% (52/82) and with 1:8 to 1:2 dilutions in 11% (9/82). Three subjects had negative SPT. Allergen threshold dose to trigger a response in the skin was lower than in the eye for all 3 allergens tested ($P < 0.0001$).

Conclusions: Reactivity to aeroallergens in provocation tests requires higher allergen dose for CPT than SPT. Positive SPT with standardized allergenic extracts is predictive of clinical relevance in the diagnosis of allergic conjunctivitis.

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Correlation Between Skin Prick Test and Mast Results in Patients with Chronic Rhinitis

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Background: Among methods to confirm the allergic causes of chronic rhinitis, the most common and the most reliable method is skin prick test, followed by MAST, which is reported to be compatible to skin prick test, with acceptable sensitivity and specificity. This study was designed to confirm whether MAST is reliable test in diagnosing allergic rhinitis.

Methods: Retrospective chart review was conducted with chronic rhinitis patients who visited Yeouido St. Mary's Hospital between January 2010 and June 2011. Subjects were selected with whom the results of skin prick test and MAST were found.

Results: One hundred and ninety three subjects, 111 male and 82 females, were included and the mean age was 30.08 (range 6∼77). MAST was performed for 42 inhalant allergens and skin prick test was performed for 56 allergens including histamine and control.Subjects who have one or more positive allergen in skin prick test were 132, and positive in MAST were 104. Sensitivity was 63.16%, specificity was 65.57% and efficiency was 63.92%.Number of positive allergen in skin prick test was 2.42 in average and among positive subjects, 3.53. In MAST, positive allergen count was 2.1 in average and among positive subjects, 4.0. Positive rates per common allergens in skin prick test were as follow; Dermatophagoides farinae 79.69% (106 subjects), Dermatophagoides pteronyssinus 68.42% (91 subjects), oak pollen 12.78% (17 subjects). Positive rates per common allergens in MAST were as follow; Dermatophagoides farinae 69.52% (73 subjects), Dermatophagoides pteronyssinus 59.05% (62 subjects), house-dust 50.48% (53 subjects).Skin prick test result was analyzed as from negative to 6+, according to relative size of the allergen wheal compared with histamine wheal and MAST result was analyzed as from negative to class 6, according to the concentration of the solution. When we defined correlation as difference between positive count in skin prick test and class in MAST were less than 2, the correlation rate in Df was 65.80%, 59.07% in Dp.

Conclusions: The correlation between MAST and skin prick test is not high enough to use MAST as a diagnostic test for allergic rhinitis. The more study to confirm the reliability of MAST should be conducted.

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Cutaneous Response to Patch Tests with Dermatophagoides Farinae and Dermatophagoides Pteronyssinus in Patients with Chronic Rhinitis

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Background: Rhinitis is characterized clinical by chronic runny nose, sneezing, nasal itching, congestion and postnasal discharge, among other symptoms. Itś classified as allergic and non allergic. Skin prick testing is the principal diagnosis method for allergic rhinits. However, there is a group of patients with chronic rhinopathy that have negative skin tests, the objective of this study was to determine the cutaneous response to patch tests with *Dermatophagoides farinae and Dermatophagoides* pteronyssinus in patients with chronic rhinitis.

Methods: It was a cross-sectional, observational and descriptive study. We included patients over 18 years old. They were divided into 3 groups; Group A patients who came for the first time with a history of chronic rhinopathy over 18 months of evolution and positive skin tests for aeroallergens; group B patients with chronic rhinitis with at least one year of evolution and negative skin tests; group C healthy volunteers. Patch test with *farinae* and *pteronisyinnus* were done in the subjects of all 3 groups, with readings at 48 and 72 hours.

Results: A total of 37 patients were studied, mean age 26.1 years. Twenty two were male subjects (60%). The mean lenghtof chronic rhinophaty was 10.8 years. Six patients had positive patch test to any of the mites tested; 2 (33%) in group A, 2 (33%) in group B and 2 (33%) of the control group, but it was not statistically significant ($P > 0.05$).

Conclusions: Although the results were not statistically significant, there were patients with chronic rhinitis wich had positive patch test for mites. This sensitization could be clinically significant for those patients.

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Skin Prick Test Reactivity Compared to Serum Specific IGE by ISAC in Patients With Rhinitis

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Background: Microarray technique is promising in allergy diagnosis. The aim of this study was to compare SPT with specific-IgE by microarray in a group of patients with rhinitis.

Methods: Cross-sectional study, 101 participants with rhinitis diagnosed according to ARIA (89.1% with asthma); age range 6 to 15 years. SPT was done with *Dermatophagoides pteronyssinus* (Dp), *Blattella germanica* (Bg), cat and dog allergenic extracts (IPI ASAC Brasil); a mean wheal diameter of ≥2 mm greater than the negative control was considered positive. Sera were analysed for allergen specific IgE antibodies to Dp (Der p 1, Der p 2), Bg (Bla g 1, Bla g 2, Bla g 4, Bla g 5), cat (Fel d 1, Fel d 2) and dog (Can f 1, Can f 2) allergens using a microarray system (ImmunoCAP ISAC, PMD, Austria), considered positive ≥0.3 ISU (ISAC standardized units). Categorical variables were shown as percentage and differences between the 2 methods verified by chi-square test; $P < 0.05$ was considered significant.

Results: SPT was positive to Dp in 88.1% whereas ISAC was positive to Der p 1 in 74.2% ($P < 0.001$) and Der p 2 in 73.3% ($P < 0.01$) respectively. Sensitivity of SPT was 97% and specificity was 38%. The remaining allergens caused less SPT reactions (cockroach 25.7%, cat 22.8%, dog 27.7%) and these were associated with lower detection of specific-IgE by ISAC respectively Bla g 1 (0.9%, $P = 0.09$), Bla g 2 (0%), Bla g 4 (0%), Bla g 5 (0.9%, $P = 0.55$); Fel d 1 (16.8%, $P < 0.01$), Fel d 2 (0.9%, $P = 0.06$); Can f 1 (4.9%, $P = 0.53$), Can f 2 (2.9%, $P < 0.001$).

Conclusions: SPT remains the favored method to detect IgE-mediated sensitivity to aeroallergens. SPT was highly sensitive for Dp though less specific in comparison with the IgE microarray to Der p 1 and Der p 2 allergens.

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Alteration of Smell in Patients with Persistent Allergic Rhinitis

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Background: A high percentage of patients with moderate-severe persistent allergic rhinitis (PAR) also show symptoms related to impaired smell (21–23%).Olfactory dysfunction can have a significant impact on quality of life (QoL) in these patients. The high frequency of this subjective condition not always reflect the magnitude of the problem experienced by PAR-patients in real life and usually goes unnoticed. The aim of this study was to assess the olfactory dysfunction in patients with PAR and seek the association with the PAR-severity, sleep disturbance and QoL.

Methods: We studied 50 patients with physician-diagnosed PAR consulting a tertiary medical centre, 33 (66%) were female and 17 (34%) male. Mean age 43 years old, compared with 20 healthy volunteers. Clinical history and assessment of severity based on ARIA criteria, skin prick tests with mite mix, mould and pollens, QoL questionnaire for allergic rhino-conjuntivitis (Juniper RQLQ) were done. In addition the Epworth Sleepiness Scale (ESS) and the Connecticut smell test (CST) were performed in every patient.

Results: In patients with PAR, 30% had mild PAR and 70% the moderate/severe form.48% of the patients studied had abnormalities of smell. We found an alteration of smell in 18% of mild-PAR and 60% in the severe/moderate patients ($P < .006$).There was no statistically significant relationship between olfactory impairment and sleep disturbance with the ESS ($P < .85$), nor in the alteration of smell in patients with polyps detected at physical examination ($P < .57$) or the relationship between impaired smell and smoking ($P < .36$).Patients with moderate/severe PAR also had alterations in QoL. Nasal obstruction was the most important parameter (70%) associated with the QoL worsening.

Conclusions: This study shows the impact of PAR on the olfactory dysfunction. An association between smell impairment and the severity of nasal symptoms was found. Smell impairment plays an important role in worsening QoL. CST is a tool that could be used in patients with PAR.

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Effectiveness of an Educational Intensive Course on A/I Clinical and Diagnostic Procedures

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Background: The U.S.A. Accreditation Council for Graduate Medical Education (ACGME) requires that graduate medical education programs in A/I prepare specialists to provide expert medical care for patients with A/I disorders. The A/I intensive education course (boot camp) program was implemented at the University of South Florida (USF) to facilitate fellows' education of common clinical and diagnostic procedures conducted in the specialty. Educational methods included PowerPoint presentations and demonstration of clinical and diagnostic procedures by faculty and senior fellows and hands-on participation by the fellows-in-training. The topics covered included: anaphylaxis, spirometry, exhaled nitric oxide determination, routine and special skin testing, prescribing and administering immunotherapy, asthma education and inhaler technique, management of atopic dermatitis, food challenge, patch testing, antibiotic desensitization and challenge, principles of treatment with intravenous and subcutaneous gammaglobulin, and special immunology testing.

Methods: Six A/I fellows (four 1st and two 2nd year) participated in the boot camp on July 22, 2011. All completed a 49-item multiple-choice pre-test followed by the boot camp, after which same questions were administered as post-test. Scores were compared by paired *t* test.

Results: Six participants completed the study. The average number of correct answers increased from 26.3/49 to 39.0/49 with pre- and post-test mean scores of 53.8% and 79.6%, respectively ($P = 0.009$). There was a significant difference between 1st and 2nd year fellows in test results when comparing pre- and post-test scores ($P \leq 0.05$).

Conclusions: An educational boot camp approach integrating theory and practice about A/I clinical and diagnostic procedures significantly increased the competency of A/I fellows at the beginning of their first and second year of training.

DRUG ALLERGY 1

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Non-steroidal Anti-inflammatory Drugs Hypersensitivity: Patterns of Reaction

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Background: Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most frequently groups of medications involved in hypersensitivity drug reactions. The aim of this study is to describe a group of patients with suspected hypersensitivity reactions to non-steroidal anti-inflammatory drugs.

Methods: A retrospective study of patients with a suspected history of hypersensitivity to NSAIDs, between years 2005 to 2010, was done. The drugs involved, the clinical features and interval between drug intake and clinical manifestation were studied. Drug provocation tests were carried out in some cases to confirm the diagnosis and in others to provide a safe therapeutic alternative drug.

Results: A total of 310 patients considered to have had hypersensitivity reactions to NSAIDs were analyzed (mean age = 39 years old; females = 247). Immediate reactions were reported in 209 subjects. Non-selective responders were 214. The most important suspected drugs were pyrazolones (228), paracetamol (144), acetic acid derivatives (122) and acetyl salycilic acid (120). Pyrazolones were the most important suspected drugs for the selective responders. The most frequent clinical manifestations were angioedema (162), airway involvement (96) and urticaria (66). Isolated angioedema was seen in 79 patients. Atopy was reported in 138 (44.5%) patients and chronic urticaria in 26 (8.3%). Family history of drug hypersentivity was reported by 37 patients. Drug provocation tests (DPT) for diagnosis were performed with paracetamol in 37 subjects (2 positive), and pyrazolone in one subject (negative). DPT were also performed with selective COX-2 inhibitors (31 tests) and benzydamine (45 tests) to assess their safety as therapeutic alternative drugs for those non-selective responders and for those who had a suspected history of reactions to paracetamol, respectively. Positive results were observed in 3 patients tested with COX-2 inhibitors and in one patient tested with benzydamine.

Conclusions: NSAIDs hypersensitivity was more prevalent in females and immediate reactions were more common than non-immediate ones. A great number of subjects were non-selective responders. Pyrazolones were the most commonly suspected culprit drugs. DPT is important not just for diagnosis but also to provide safe therapeutic options.

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Epidemiology of Immediate Type Adverse Drug Reactions and Rashes Elicited by Nsaid

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Background: NSAID are frequently used and can often cause adverse drug reactions (ADR) ranging from generally mild to sometimes severe and life-threatening reactions. ADRs are in most cases interpreted as pseudo-allergic, presumably non immunologic, but their dynamics and appearance in a subgroup of patients is suggestive for an IgE-mediated mechanism.

Methods: In this study, we retrospectively analysed data of 501 patients from our outpatient clinic population of the past 7 years with ADR to NSAID. Data was evaluated regarding the culprit drug or drugs, type and severity of reactions, age, gender, atopy, number of co-medication, co-morbidity and infections etc. as risk factors. Further, skin test and provocation test results were reviewed for their clinical relevance and reliability.

Results: Acetylsalicylic acid (ASA), paracetamol, diclofenac, mefenamic acid and propyphenazone were found as top five of causative drugs for ADR. The most common symptoms were angioedema, urticaria, pruritus, exanthema and dyspnea. ASA caused dyspnea, angioedema and urticaria in the majority of the cases. Diclofenac was found to be the most common culprit for severe anaphylactic reactions, followed by paracetamol and propyphenazone. Sixty percent of the NSAID reactors suffered from an atopic disease or had an atopic predisposition. There was a significant association between proven hypersensitivity reactions and reaction initiation after drug intake regarding the time interval.

Conclusions: Our data suggest that -atopic predisposition is a risk factor for intolerance reaction to NSAID, -ASS accounts for non-immunologic, intolerance reactions, whereas severe anaphylactic reactions to diclofenac and/or propyphenazone seem to be IgE-mediated, -a shorter time interval between drug intake and appearance of symptoms is supportive for clinical relevance and could be an indicator for IgE-mediated ADR. Acknowledgements: FWF project L467-B05.

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Test in Vitro to Investigate the Cytotoxicity and Cellular Nonspecific Stimulation of Basophils with Indomethacin

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Background: The prevalence of hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) is high and its in vitro diagnostic is a challenge. The basophil activation test with determination by flow cytometry (FC), of the expression rate of CD63 molecules has been much studied today. NSAIDs several have been evaluated by this technique, which still didn't happen with indomethacin; however, that we may study it is necessary to assess their effects, concentration dependants, on cell viability. We studied the viability of indomethacin dissolved in propylene glycol, analyzing the nonspecific stimulation and cytotoxicity, using in this case the basophil activation test with the use of FC.

Methods: First it was studied the safe concentration of propylene glycol for dilution of indomethacin, incubating basophils from atopic donor with this diluent. In the second phase, the indomethacin was diluted in the following concentrations: 10 mcg/mL, 1 mcg/mL, 0.1 mcg/mL and the CD63 intensity molecules expression was analysed by FC.

Results: Regarding the toxicity of propylene glycol, concentrations less than or equal to 0.5% are safe. For indomethacin, the used concentrations (10 mcg/mL, 1 mcg/mL e 0.1 mcg/mL) were viable showing absence of cytotoxicity or nonspecific stimulation.

Conclusions: Propylene glycol as a diluent of indomethacin is necessary to make at concentrations less than or equal to 0.5%. The indomethacin at concentrations of 10 mcg/mL, 1 mcg/mL and 0.1 mcg/mL proved to be not cytotoxic and without nonspecific stimulant action to basophils.

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Aspirin Desensitization Treatment: A Case Report

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Background: Aspirin (ASA) is one of the best known and most widely used drugs in the world. Patients with coronary artery disease require prolonged treatments with this drug, which is denied to those patients with histories of adverse reactions to it.

Methods: In a rapid desensitization protocol a patient with a history of ASA-induced urticaria-angioedema was treated with escalating doses of aspirin administered orally every 25 minutes.

Results: The patient completed the desensitization protocol in few hours without complications, and currently is able to take 125 mg of ASA per day without adverse reactions.

Conclusions: This report describes the first desensitization treatment with aspirin carried out in our hospital. No other case was found in the national bibliography.

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Adverse Drug Reactions to Anti-asthmatics in Patients with Bronchial Asthma

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Background: The number of self-reported adverse drug reactions (ADRs) has been rapidly increased with the active pharmacovigilance activities in Korea. However, there has been few data on ADRs to anti-asthmatics in Korea. This study was conducted to investigate the clinical characteristics of ADRs to anti-asthmatics in adult patients with bronchial asthma.

Methods: ADRs to anti-asthmatics reported to Regional Pharmacovigilance Center of Inha University Hospital by 2 physicians were collected from January 2011 to April 2011. Causality assessment of adverse events was performed by using WHO-UMC criteria and Naranjo's probability scale. Clinical information was additionally collected from electronic medical records.

Results: Twenty five ADRs to anti-asthmatics were reported in 19 (male 5, female 14) out of 228 patients with asthma. The most common offending anti-asthmatics were inhaled glucocorticoids combined with inhaled long-acting beta agonist (LABA) (12 of 19 subjects, 63.2%), theobromine (10.5%), oral LABA (10.5%), doxofylline (5.3%), acetylcysteine (5.3%), and montelukast (5.3%). Severity of ADRs was mild in most patients (13 of 19, 68.5%), and no severe ADR was detected. By frequency, oral LABA was the commonest drug associated with ADRs (2 in 17 prescription, 11.8%). ADR frequency was not different according to asthma control status. But ADRs to simultaneously prescribed drugs were more frequently detected in patients with combined upper airway diseases (ADRs to antihistamines) or patients with combined infection (ADRs to anti-infective drugs, mucolytics, oral LABA, or to SABA), or older patients with asthma.

Conclusions: Although the severity is usually mild, ADRs are relatively common in patients with bronchial asthma. Physician should monitor ADRs to anti-asthmatics or related drugs in patients with asthma, especially in older patients or in patients with multiple drug treatment for combined conditions.

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Presentation of Three Cases of Allergic Reactions to Triptorelin

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Background: Triptorelin is a drug that is frequently used in pediatrics to treat precocious puberty -an often condition in childhood endocrinology services. Despite its widespread use, there is not much research on hypersensitivity reactions to this drug. We found 3 patients that have suffered allergic reaction during the treatment with Triptorelin.

Methods: We treated three 8 year old girls diagnosed with precocious puberty that have suffered allergic reaction during the treatment with Triptorelin.Patient 1: An hour after the first dose the patient broke out in a rash over her face, trunk and upper limbs. She also showed general paleness, conjunctival erythema, arthralgia and joint swelling in both knees with functional impotence of the lower limbs.Patient 2: Five minutes after the second dose the patient showed anaphylactic reaction.Patient 3: Two hours after the second dose the patient showed generalized urticaria and tachycardia.

Results: Once overcome those events. We started to provoke the reaction by doing the progressive-controlled triptorelin test. Finally we could confirm the hypersensitivity reaction to this drug

Conclusions: The triptorelin is a drug that may cause hypersensitivity reaction. So, after the first application, we recommend to monitor the patient and also plan some actions to avoid a possible anaphylactic shock event.

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Adverse Drug Reactions in Hospitalized Patients

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Background: To describe adverse drug reactions (ADRs) in hospitalized patients.
Methods: A cross-sectional study with a questionnaire for adverse drug reactions based on European Network for Drug Allergy (ENDA) was performed. Hospitalized patients older than 12 years of age were included.
Results: A total of 150 patients were studied, 84 being female. Their ages ranged from 14 to 94 years, with an average of 55 years. The average number of medications per patient was 7.5. Fifteen ADRs were reported during hospitalization (10%). Five ADRs were classified as hypersensitivity, including 2 IgE-mediated reactions that were observed in 2 patients hospitalized for desensitization (anti-rabies vaccine and insulin). The procedure had to be suspended in these patients. Three non-IgE-mediated hypersensitivity reactions occurred: rash after non-steroidal anti-inflammatory drug (NSAID) intake, coughing and itching with angiotensin converter enzyme inhibitor (ACEI) and rash with iodinated contrast. The remaining patients (10) had common side effect reactions to several drugs. Twenty-eight patients have had prior hypersensitivity reaction, being five IgE-mediated (two with beta-lactam antibiotics, one with non beta-lactam antibiotic, one with insulin and the last one with rabies vaccine) and 23 non-IgE-mediated (8 with NSAIDs, 5 with ACEI, 3 with beta-lactam antibiotics, 3 with non beta-lactam antibiotics, 2 with iodinated contrast and 2 with other drugs). Most hypersensitivity reactions were cutaneous. In 3 patients, previous hypersensitivity reactions were not mentioned at the time of hospitalization.
Conclusions: The average number of medications administered per patient during hospitalization is high. Adverse drug reactions are very common and have great clinical relevance. Ten percent of patients presented ADRs during hospitalization and one third of them had hypersensitivity reactions, what is in accordance with literature.

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An Unusual Reaction to Intravenous Iron Sucrose

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Background: Intravenous (IV) iron dextran, the original parenteral iron formulation, is associated with a high incidence of non-IgE mediated hypersensitivity. Newer formulations of IV iron therapies include low molecular weight iron sucrose (IS) and sodium ferric gluconate complex (SFGC) without dextran, reducing severe adverse reactions by 93%. A case of a rare reaction to IV IS associated with generalized skin pruritus and difficulty in breathing is reported.
Methods: A 62-year-old Caucasian male with multiple gastric surgeries, secondary to recurrent gastric ulcers and gastric outlet obstruction, presented with severe iron deficiency anemia (IDA) requiring IV iron therapy.
Results: Chronic malnutrition and malabsorption, associated with difficulty in tolerating oral and jejunostomy tube (J-tube) feedings, resulted in a two month 30 pound weight loss. Oral iron supplementation via a J-tube did not improve the IDA. Prior administrations of IV iron dextran resulted in flushing, generalized urticaria and angioedema associated with pruritus of the face and extremities within ten minutes of infusion.The allergy/immunology service was consulted. Premedication with IV diphenhydramine, 50 mg, prednisone via J-tube, 32 mg, and IV ranitidine, 50 mg, was followed with slow administration of a test dose of IS, 25 mg, at 1.6 mg/min. Within 30 minutes of the IV IS infusion, symptoms of nausea, flushing, and generalized pruritus, and difficulty in breathing were noted. The infusion was stopped and treatment with IV methyprednisolone, 125 mg, resulted in resolution of the reaction over several hours. No eosinophilia or elevated liver transaminases occurred. Subsequently, the infusion was reattempted: pre-medications consisted of IV methylprednisolone, 60 mg, IV diphenhydramine, 50 mg, and IV ranitidine, 50 mg, 75 minutes prior to the infusion of IS, 275 mg, 1.5 mg/min. Treatment was tolerated without adverse effects.
Conclusions: A rare systemic reaction to IV IS is reported. Pretreatment with methylprednisolone, diphenhydramine and ranitidine 75 minutes before IS infusion was successful.

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Urticaria and Arthralgias in a Nine-Year-Old with Recurrent Urinary Tract Infections

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Background: Serum sickness is a type III immune complex hypersensitivity reaction occurring after exposure to foreign antigens, most commonly medications. Symptoms typically begin 1 to 3 weeks after initial exposure to the offending agent and include fever, malaise, urticarial or morbilliform rashes and arthralgias which may progress to arthritis, nephritis, neuropathy or vasculitis. We report a case of drug-induced serum sickness in a patient who had previously tolerated trimethoprim/sulfamethoxasole (TMP/SMX) for treatment of recurrent urinary tract infections.
Methods: A 9 year-old female presented with a pruritic, erythematous rash that began 2 days after completing a 10 day course of TMP/SMX for a urinary tract infection. TMP/SMX had previously been prescribed to treat recurrent urinary tract infections without adverse side effects.
Results: Initially she developed a fever and a blotchy rash with patches of erythema which started on the torso and progressed to generalized urticaria over a 24 hour period. Associated symptoms included fatigue, lethargy, generalized myalgias and arthralgias with swelling limited to the left knee, ankles and fingers. No mucosal lesions, nausea, vomiting or diarrhea were present. Pertinent findings on physical examination included mild edema of the left knee without associated erythema or warmth and proximal and distal interphalangeal joints of the hands, wrists, knees and ankles absent of an effusion, but tender to palpation with full range-of-motion. Urticarial lesions with serpiginious borders and central clearing were noted on the trunk and extremities including the palms but not soles. Hyperpigmented areas at sites of previous urticarial lesions were present. Prednisone, 10 mg 3 times daily, and cetirizine, 10 mg daily, was prescribed and within 24 to 48 hours, all symptoms improved. No further laboratory studies were obtained. Prednisone was tapered over a 2 week period and cetirizine was discontinued simultaneously without recurrence of symptoms. The patient was advised to avoid TMP/SMX indefinitely.
Conclusions: Medications are the most common cause of serum sickness with TMP/SMX being frequently implicated. Immune complex reactions generally occur a few weeks after initial exposure to a medication; however, drug -induced serum sickness should still be considered in cases to which an agent may have been previously tolerated.

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Jessner-kanoff Lymphocytic Infiltrate as a Side Effect of Immunotherapy

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Background: Allergen immunotherapy has been used in the management of allergic diseases for nearly 100 years. It is the only specific treatment for hymenoptera venom anaphylaxis. Various venom immunotherapy schedules have been designed to treat anaphylaxis. Although the effect of venom

immunotherapy is well documented, there is also an increased risk of side-effects in bee-venom-treated patients and in those with rapid dose increase.
Methods: This report describes the first case of a patient in the literature with Jessner's Lymphocytic infiltration as a side effect of venom immunotherapy. This is a chronic, benign, T cell pseudolymphoma characterized by the occurrence of recurrent, asymptomatic, smooth, erythematous, non-scaling papules or plaques. However, the exact cause of Jessner's Lymphocytic Infiltration is unknown.
Results: The case here reported was a 61 year-old male pediatrician, who has been followed by at our Immunology Service because of an immediate allergy to a bee sting managed with venom immunotherapy. His chief complaint was an anaphylactic reaction after 5 minutes of a bee sting. The onset of his symptoms was gradual and began just 25 minutes after the sting. The venom immunotherapy regimen was planned and the protocol immediately began without premedication. But during the initial phases of treatment, on the third dose of immunotherapy, he reported severe itching. After complaining of itching, many erythematous papules and plaques on his chest were developed. The lesions flared up for 3 days period just after injection and decreased afterwards. The type of lesions and their location supported the diagnosis of Jessner disease, which had also a histopathological confirmation.
Conclusions: We herein report this case to call attention to this side effect of VIT that there may be more similar cases never reported.

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Improvement of Oral Lichenoid Reaction Symptoms after Removal of Amalgam Restorations: An Anusual Case of Type IV Hypersensitivity

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Background: Chemical and mechanic iritations may play causative role in development of lichenoid reactions in oral mucosa, similar to skin, in predisposed patients. It has recently been reported that lichenoid reactions and Wickham striae with papular/reticular characteristics are observed in mucosal regions which are in direct contact with amalgam restorations (1). A 38-year-old male patient admitted initially to the Department of Oral Diagnosis and Radiology, chiefly complaining of bilateral buccal pain and itching. In his intraoral inspection, hyperkeratotic white lesions at his molar teeth level at both right and left buccal mucosa were observed. The purpose of this study is to find out the nature and decide on the management of these buccal lesions.
Methods: In dental inspection of the patient, large amalgam restorations and white lesions in buccal surface in direct contact with amalgam were observed in left first and second, and right second molar teeth region. A 4-mm punch biopsy from buccal mucosa was performed. In addition, a skin patch test with amalgam was done in back region of the patient.
Results: In punch biopsy, histopathological features were compatible with lichenoid mucositis. In addition, skin patch test results indicated a very strong positive reaction to amalgam. The lesion healed up after replacement of restorations with composite filling material. The patient, his family and his dental practitioner were strictly advised to use alternative restorative materials in case of a need for restoration.
Conclusions: Amalgam and its components may cause type IV hypersensitivity reactions (1) and, very unusually, immediate hypersensitivity (2). The clinician should be aware of all possible pathological etiologies of white lesions. If there is any doubt about the diagnosis and management of an anusual oral lesion, referral to appropriate specialists is mandatory.

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Hypersensitivity Reactions to Interferon Based Treatment for Hepatitis C: A Single Center 20-Year Experience

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Background: BA Interferon (IFN)-based therapy for chronic hepatitis C (CHC) is associated with adverse hypersensitivity reactions (HRs). However, data on HRs to IFN in every-day clinical practice are lacking. We conducted a retrospective study to identify the incidence, management and outcome of such reactions.
Methods: A review of the electronic files of all CHC patients followed in our tertiary referral center from January 1990 to November 2010 was conducted to identify patients submitted to IFN-based treatment and HRs to such treatment.
Results: During the study period, 832 CHC patients were identified, 545 (65.5%) of whom received IFN-based treatment. Overall, 221 (40.5%) patients received at least one treatment cycle with IFN-a ± ribavirin (RBV), 170 (31.2%) patients received at least one treatment cycle with pegylated (PEG)-IFN a2a + RBV and 189 (34.7%) patients received at least one treatment cycle with PEG-IFN a2b + RBV. Fifty-five treatment cycles were complicated by HRs in 54 patients (female 20, median age 39 years, range 22–65 years). Presenting symptoms of HRs were: skin rash in 46 patients (pruritic in 20), generalized pruritus in 7 patients and aphthous mucosal ulcers in 2 patients. HRs occurred in 9 patients treated with IFN-a (4.1%), 23 patients treated with PEG-IFN a2a (13.5%) and 23 patients treated with PEG-IFN a2b (12.1%) ($P = 0.002$). Management of HRs included no intervention in 18 (32.7%) cases, topical treatment in 10 (18.2%) cases, antihistamine administration in 15 (27.3%) cases, temporary cessation of treatment or dose reduction in 3 (5.5%) cases, switch from PEG-IFN to IFN-a in 4 (7.3%) cases and immediate termination of treatment in 5 (9.1%) cases. The outcome was complete remission of the HR in 33 (60%) cases, remission sufficient to allow continuation of treatment in 13 (23.6%) cases and treatment termination in 8 (14.5%) cases, while one (1.8%) patient was lost to follow-up after the HR. Overall, 2 (0.9%) patients discontinued IFN-a, 3 (1.8%) PEG-IFN a2a and 3 (1.6%) PEG-IFN a2b due to HRs ($P = 0.737$).
Conclusions: Hypersensitivity reactions to IFN-based and especially to PEG-IFN based treatment regimens are occasionally encountered in CHC patients and may rarely lead to treatment termination.

DRUG ALLERGY 2

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Hypersensitivity Syndrome Associated with Phenytoin Sodium

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Background: The drug-induced hypersensitivity syndrome (DIHS) is a systemic reaction for drug-induced idiosyncratic. We report 1 in 1000 to 1 in 10,000 exposures to aromatic anticonvulsant. In the case of phenytoin is estimated at 2.3 to 4.5 per 10,000 exposures. There is a deficit of microsomal epoxide hydroxylase causing accumulation of toxic metabolites. Occurs between 2 weeks to 3 months after drug exposure; it is characterized by maculopapular rash, erythema midface, fever, lymphadenopathy, with alteration of the hematologic system with eosinophilia, peripheral or atypical lymphocytosis. Described reactivation of herpes virus (HHV-6 and 7).

Comorbidities during the syndrome such as type 1 diabetes, encephalitis, and long-term sequelae such as thyroid dysfunction, systemic lupus erythematosus, etc.[1]

Methods: We report a 39 year old female with history of traumatic brain injury (TBI) received proflaxis with phenytoin sodium 100 mg 1vo c/8 hours, 4 weeks after starting with fever, malaise, sore throat, cervical lymphadenopathy, appeared itchy rash in face, neck. Admitted with malaise, generalized rash, edema midface, cheilitis, jaundice, cervical lymphadenopathy, axillary and inguinal and hepatomegaly.We continued to study probable hypersensitivity syndrome asking paraclinical studies including blood count, liver function tests.We initiated 1 mg/kg/d prednisone for 6 weeks and subsequent dose reduction. Exit after 5 days of hospitalization for clinical improvement.Continuous current monitoring by the outpatient department of our hospital and late complications that can occur in this syndrome.

Results: Liver function tests as well as the count of the white series was abnormal, with the following report: AST (177 U/L), ALT (154 U/L), WBC (12.430 mm^3), eosinophil (1.310 mm^3). Biopsy report unavailable.

Conclusions: Aromatic anticonvulsants (phenytoin, carbamazepine and phenobarbital) are frequent causes of DIHS. Treatment involves discontinuation of the drug involved, admission to intensive care and systemic steroids at doses of 0.5 to 1 mg/kg/d and intravenous immunoglobulin 2 g/kg.

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Drug Hypersensitivity Reactions in Hospitalized Patients: What is the Role of the Allergist?

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Background: Ten-to-twenty percent of hospitalized patients experience drug adverse reactions. There are few epidemiological data of drug hypersensitivity in inpatients in brazilian population. Our aim was to analyze the main clinical and epidemiological data of drug hypersensitivity reactions in hospitalized patients and to assess the importance of the allergist's evaluation.

Methods: A prospective study was developed in an Allergy Clinic of a Service in São Paulo, Brazil, from January 2010 to January 2011. We evaluated the cases in which the allergist was assessed. The patients were studied based on history of hypersensitivity reactions to drugs (HRD) using an adapted ENDA (*European Network of Drug Allergy*) questionnaire. We analyzed clinical and epidemiological data of drug hypersensitivity reactions and assessed differences of the allergist evaluation.

Results: Of all 80 cases in which the allergist was assessed, 65 (81%) were for HRD. The mean age was 57 years, 49 (75%) were women. Fifty (89%) experienced non-immediate reactions, 8 of them were severe adverse cutaneous reactions. Eight (12%) had just positive history of HRD, without reaction at the time of the evaluation. Neurosurgery (15), Infectious Diseases (11), Vascular surgery (8) were the main Clinics who assessed our specialty. Non-steroidal anti-inflammatory drugs (21), antiepileptics (16) and non-β-lactams antibiotics (15) were the most important pharmacological groups. Thirty (46%) patients were in use of more than 5 drugs at the time of the reaction, but in 46 (70%) evaluations there was 01 culprit drug suspected by the allergist. There was discordance between the allergist and the non-allergist opinion about the suspected drug in 13 (20%) cases. In 50% of cases other Clinics were assessed for the same reason. Eleven (17%) patients had history of HRD with the same pharmacological group before.

Conclusions: HRD is the main cause why the allergist is assessed. The pharmacological groups related to these HRD were different from the previously described. The history of HRD is still not appropriate asked from the non-allergists. The evaluation of the allergist can help to manage HRD properly.

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Allergic Reactions to Local Anesthetics: Detection by Skin Tests and Subcutaneous Provocation. Analysis of 160 Cases

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Background: Adverse reactions to local anesthetics (LA) are frequent and often referred to as allergic. Although immune-mediated reactions are rare, it should be investigated for suspected cases. The objective of this study was to determine the frequency of positive skin test to these drugs in patients with a suspected history of allergic reactions and describe the main sociodemographic characteristics of these individuals.

Methods: Retrospective study of medical records of patients attended at Policlínica Geral do Rio de Janeiro Allergic Clinic, between 2008 and 2011. The parameters evaluated were the test indication and the patient ages and gender. The drug tested was that the patient had a history of suspicion. Patients underwent skin prick and intradermal tests and subcutaneous provocation. Descriptive statistical analysis of the data was performed.

Results: It was performed 160 tests (125 female). Three of this total was excluded due to inconclusive results. In women, the highest proportion of tests was in the age group from 41 to 60 years (43%), while in males the higher concentration was at a youngest age group: 21 to 40 years (41%).The most common indication (103 cases, 65%) for the tests was a previous suspected anaphylactic reaction by LA. Seven of 157 tests had a positive result (4.4%), 6 of them occurred in women (4.8%). Only one test resulted in a type of anaphylactic reaction response (0.67%).All patients who presented positive response to the test had a history of per-anesthetic reaction that suggested an immune-mediated mechanism.

Conclusions: In patients with a history of previous reaction to local anesthetics, the skin tests with these drugs have a key role in the prevention of anaphylaxis, and on guidance for adequate anesthetic procedures.

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Protamine Allergy

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Background: An anaphylactic reaction to protamine sulfate during cardiac surgery is a rare but known entity. Preoperative prediction and outcome of such a reaction is still unclear. A 68-year-old man presented for elective coronary artery bypass grafts. His medical history included hypertension and he was non-diabetic. Review of his angiogram indicated 2-vessel coronary artery disease. According to the patient's notes, he had a known allergy to shellfish and avoids fish due to personal discomfort, although the exact nature of his reaction to fish was not well described. The information prompted the thoracic surgery team to alert the allergologist to perform an allergological checkup before thoracic surgery.

Methods: Skin prick tests were performed with standard solutions for shrimp, fish-mix, mackerel and salmon (Bencard, Munich, Germany). Protamine sulfate (CP Pharmaceuticals Ltd, Wrexham, UK) was pricked undiluted and was tested intradermally diluted 1:10. Physiological saline and 0.01%

histamine solution served as controls. A wheal with a diameter >3 mm in comparison with the negative control was scored as positive. Furthermore, in vitro allergy testing using the Phadia CAP system for specific IgE against shrimp, fish-mix, rainbow trout, rCyp p 1 and protamine sulfate was performed.

Results: Skin prick tests were positive to shrimp, fish-mix, mackerel, salmon and protamine sulfate. Intradermal testing with protamine showed a wheal diameter of 7 mm. Analysis of a blood sample showed elevated total IgE (2600 kU/L) and specific IgE to shrimp (2.94 kU/L), fish-mix (0.53 kU/L), rainbow trout (0.39 kU/L), rCyp p1 (0.53 kU/L) and protamine sulfate (0.77 kU/L).

Conclusions: Protamine sulfate is a polycationic peptide used to reverse the anticoagulant effects of heparin during cardiac surgery. It is commercially produced from the sperm of salmon and it is considered that persons who have an allergy to fish could be at risk of protamine reactions. The exact mechanisms by which it causes anaphylaxis are not fully understood. Due to a clear sensitization to fish proteins and protamine sulfate and a known allergy to shellfish we disapproved the standard anticoagulation protocol with heparin/protamine. Bivalirudin was used as an anticoagulant and the surgery proceeded without any untoward events.

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Description of Drug Allergy Study Conducted in a Teaching Hospital between October 2007 and March 2011

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Background: The World Allergy Organization (WAO) in 2003 defined 'drug allergy' as an immunologically mediated drug hypersensitivity reaction. The mechanism of drug allergy may be either IgE or non-IgE mediated. The true incidence of drug allergy is not known. There are only few studies/datasets using standardized clinical questionnaires and validated in vivo or in vitro tests to confirm the diagnosis of drug allergy. Here we have analyzed the obtained results of in vivo test in suspected drug allergy patients.

Methods: Data from the Centre of Allergies of the Clinical Hospital of the Universidad de Chile between the months of October 2007 and March 2011 was obtained. The information of the protocols of drug executed, by defining as Protocol the study of a probable allergy by 2 or more procedures, which can be: Prick Test, intradermal reaction, specific IgE and/or Test Patch.

Results: For a total of 126 drug protocols, 25% of them were trivírica vaccine, 24% β-lactams, 21% local anaesthetics and 10% to general anesthesia (inductors, muscle relaxants and Latex). Of the total of patients undergoing protocols the most of them were women, there is no clear difference between the number of children and adults. The temporal distribution of protocols was stable between the months of October 2007 and March 2009 (15 protocols/semester), to then become variable, reaching values between 10 and 29 every 6 months. Of total protocols, 30.1% were positive; only one patient presented a mild adverse reaction (local welt). The β-lactams being most often the positive drugs. Protocols involving pethidine 100% was positive, diclofenac 33%, dipyrone, ketoprofen and hydrocortisone each one 25%. The most accomplished protocol was trivírica vaccine, resulting in 100% negative. Of all negative protocols 58% went to provocation, resulting in a 8% positive, including one provocation to the trívirica vaccine.

Conclusions: Methodologicall study is very important for a possible drug allergy, because history is not enough to certify the diagnosis. To do a provocation test to a negative protocol is crucial.

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Lung Toxicity Induced by Novel Antineoplastic Therapies in Cancer Patients

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Background: Pulmonary toxicity and respiratory failure are major adverse events complicating the use of novel antineoplastic agents in the treatment of lung cancer. We aim to investigate the risk and characteristics of cytostatic-induced pulmonary toxicity caused by agents currently used to treat lung cancer.

Methods: A literature search was performed in PubMed to identify relative studies published until June 2011.

Results: Almost all categories of antineoplastic agents have been associated with some kind of pulmonary complications. Taxanes have been linked to acute pneumonitis, pleural effusion and reactions during infusion. Nucleoside analogs can cause diffuse alveolar damage, bronchospasm and acute respiratory distress syndrome (ARDS). Monoclonal antibodies are associated with pulmonary hemorrhage and hemoptysis. Acute pneumonitis and hypersensitivity reactions have been reported with podophyllotoxins, while diffuse interstitial pneumonia has been attributed to pemetrexed. Tyrosine kinase inhibitors of the epidermal growth factor receptor have been associated with acute pneumonitis, diffuse alveolar damage and pulmonary fibrosis. The exact incidence of lung toxicity caused by these agents remains unclear, although it seems relatively low. Clinical manifestation includes cough, fever, dyspnea and hypoxemia. Chest imaging reveals diffuse or patchy, unilateral or bilateral, ground-glass opacities or consolidations. It is important that other possible causes of respiratory failure be excluded when treating a lung cancer patient receiving chemotherapy.

Conclusions: Physicians should be aware of the potential of lung toxicities from antineoplastic agents, especially when they are combined with other cytotoxic drugs or radiation.

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Redness of Skin: SSSS in a 10 Month Old Healthy Baby

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Background: Infections are caused by staphylococcus bacteria commonly found on the skin or mucosal membranes of healthy patients. These bacterias can turn into blood stream and cause severe life-threatining conditions: severe erythema multiforme-like eruption of skin and lesions of the oral, genital and anal mucosa associated with fever, arthralgia and neurological symptoms. To find the correct diagnosis among mucocutaneous diseases sometimes difficult but is important for choosing the proper medication.

Methods: A 10 month old boy with symptoms starting 2 days before with upper airway tract infection, external otitis and some urticarial eruption on his body without fever. He was put on oral antihistamin and antibiotic treatment. He was reffered to our Department because of high fever, conjunctivitis, stomatitis and redness of his skin all over his body with some blister formation. He was unable to eat, he was in pain, but sleepy. After a few hours of his admission his fever became 39°C, severe exfoliation occured, and some large flaccid bullaes appeared and erupted, drained an amber-colored liquid and spreaded to cover extensive areas of his body revealing denuded skin. His history and symptoms suggested allergic reaction for his medication or autoimmun/ mucocutaneous disorder, but interestingly his laboratory tests were in the normal range. In spite of these to prevent a bacterial superinfection after bacterial culturing of throat, nose, skin, and blood, we introduced iv amoxicillin/clavulanic-acid therapy, cyclesonide eye drops, antiseptic local treatment of mouth (chlorhexidine digluconate) and skin (unguentum antisepticum). After 2 days his fever stopped and the top layer of his skin started to come off, partly powdery scales formed.

Results: The symptoms started to resolve slowly and the child became symptome free after 10 days. Bacterial culturing results confirmed the

diagnosis of SSSS. The antibiotic treatment was completed on the tenth day.

Conclusions: Symptomes and appearence of the disease suggested several diseases but the laboratory tests were normal, making the diagnosis more difficult, the supposed diagnosis did not fit properly for the patient age. Careful observation of patients and the disease, exfoliative cytology and a biopsy, microbiological investigations allow the diagnosis, ruling out erythema multiforme and drug-induced toxic epidermal necrolysis, both which are similar to SSS Syndrome.

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Desensitization Protocol to Methotrexate

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Background: A 17 year old patient was referred to Allergy outpatient clinic with history of recent anaphylaxis (wheezing, breathlessness, nausea, vomit and hypotension) to methotrexate (MTX) during the induction treatment of ALL L2. The diagnostic confirmation consisted in a skin test, with a positive response at 1:100 dilution. The case was discussed together with Pediatric Oncology service, and was agreed that MTX was necessary for the patient survival, because of that we performed the following desensitization protocol.

Objective: Evaluate the effect and safety of a desensitization protocol to methotrexate in an adolescent with acute lymphoblastic leukemia L2 (ALL L2) and allergy to methotrexate.

Methods: Desensitization protocol consisted in 2 phases. First phase consisted in premedication with hydrocortisone (IV) 1 mgkgdo, cetirizine (PO) 0.2 mgkgdo, chlorpheniramine (IV) 0.35 mgkgdo and montelukast (PO) 10 mgdo at 13, 7 and 1 hour prior to desensitization phase which consisted in an 8 hour scheme of IV infusion of 12 dilutions with increasing concentrations starting at 1:1,000,000 at 30 minutes intervals up to the full dose was completed.

Results: Patient was admitted to pediatric intensive care unit and was successfully desensitized, the full protocol was completed as expected, including pre-medication, the desensitization phase lasted 8 hours; at the second dilution (1:100,000) the patient presented nausea, requiring one extra dose of chlorpheniramine, no other adverse reactions were presented in the next 48 hours observation period. He was maintained with 50 mg/m^2 IV MTX weekly for the full anti-leukemia treatment duration (1–2 years) using the same protocol and stayed out of MTX-related adverse reactions. Today he is followed as an outpatient by our service.

Conclusions: This 12 steps MTX-desensitization protocol was effective and safe. In selected cases of severe allergic reactions to chemotherapeutic agents there where no other equally effective treatment option available, desensitization is effective and safe.

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Clinical Features of Dress Syndrome in 42 Patients

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Background: The clinical features of DRESS syndrome are complicated, and the incidence this condition is very low.

Methods: This study was a retrospective analysis of prospectively collected data in 42 consecutive patients with DRESS syndrome diagnosed between September 2009 and April 2011. We investigated the clinical features, response to treatment, and outcome of 42 patients.

Results: Study patients consisted of 18 men (42.9%) and 24 women (57.1%). The most common causative drugs were antibiotics (33.3%) and anticonvulsants (26.2%), followed by antituberculosis drugs (11.9%), allopurinol (7.1%), nonsteroidal anti-inflammatory drugs (NSAIDs) (7.1%), undetermined agents (7.1%), others (7.1%). The latency period ranged from 2 to 60 days, with a mean of 16.6 days. The longest latency period was noted in the antituberculosis drug group, 35.8 $\pm$ 16.2 days. Atypical lymphocytosis was noted in 16 patients (38.1%), and thrombocytopenia in 7 patients (16.7%). Hepatic involvement was noted in all study patients. Additionally, lung involvement was noted in 2 patients (5.8%), CNS involvement was in 1 patient (2.4%). Systemic corticosteroids were administered to 8 patients (19.0%). Complete recovery was noted in 40 patients (95.2%). Two patients had poor outcomes; one died due to opportunistic infection secondary to long-term systemic corticosteroids treatment and the other showed prorgressive deterioration of liver damage, although the final outcome is not known.

Conclusions: Drugs associated with DRESS syndrome were variable and most frequently included antibiotics and anticonvulsants. DRESS syndrome was more common than generally recognized, and most of patients with this disease showed better clinical out outcome than that has been generally expected.

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Risk Factors Associated to Mortality in Mmexican Children with Stevens-Johnson Sndrome/Toxic Epidermal Necrolysis

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Background and Objective: Identify risk factors associated to mortality in Mexican children with Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis.

Methods: Cross-sectional analytical study. We reviewed the medical records of patients with hospitalization and primary diagnosis of Stevens-Johnson syndrome (SJS) or Toxic Epidermal Necrolysis (TEN) from January 1995 to May 2011. Our study variables have been previously described. We describe median (interquartilar range: IR) and percentage. Exact Fisher test, Mann Withney U and binary logistic regression were used.

Results: We obtained 51 medical records: 24 male (47.1%), 27 female (53%). Median age was 5 years (IR 2–8). Thirty eight (76%) corresponded to SJS, four (7.8%) to SJS-TEN overposition and nine (15.7%) to TEN. Mortality was seen in 9 patients (17.6%, 6 male [66.8%] and 3 female [33.3%], $P > 0.05$). Twenty two cases (43%) were attributed to anticonvulsive drugs, twenty (39%) to antibiotics, two (4%) to non-steroid anti-inflammatory drugs, two (4%) to infection, one (2%) to chemotherapeutic drugs, and in two (4%) no trigger factor was identified. Risk factors associated to mortality were: denudation of >30% Body Surface Area (BSA) (7.1% vs 55.6% $P < 0.001$), concomitant malignancy (0% vs 22.2% $P < 0.028$), moderate leucopenia (<1,000 cells/mL) (0% vs 33.3%, $P < 0.001$), leucocytosis (>20,000 cells/mL) (7.3% vs 22.2%, $P < 0.001$), hypokalemia (<3.5 mEq/L) (5.6% vs 33.3%, $P < 0.011$), hyperkalemia (>5.0 mEq/L) (5.6% vs 22.2%, $P < 0.011$). Total bilirrubin concentration >3.6 mg/dL has tendency to associate with mortality, $P = 0.08$. Six patients (11.7%) were treated with steroids, fifteen (29.4%) with IV human immunoglobulin and one (1.9%) with both drugs, no statistical difference was observed, though the steroid-treated group showed a tendency towards mortality increase. Some variables were not able to analyze due incomplete medical records.

Conclusions: Risk factors associated to mortality in patients with SSJ/TEN identified in this study are: skin denudation >30% BSA, concomitant malignancy, leucopenia, leukocytosis, hypokalemia and hyperkalemia. Total

bilirrubin concentration >3.6 mg/dL has tendency to associate with mortality, although not statistically significant.

DUST MITE ALLERGY

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Standardization and Characterization of Dust Mite Extracts Manufactured in the USA

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Background: Standardized *Dermatophagoides* dust mite extracts are produced in the US from purified whole bodies. Growth media and the processes for separating mites from media vary among manufacturers. The FDA requires that mite extracts are standardized and labeled in AU/mL. Potency is determined using a laboratory ELISA competition method to compare the product with an FDA reference. The method measures binding of IgE from an FDA supplied sera pool to antigens bound to an ELISA plate and AU is calculated from the ability of the test extract to inhibit the binding relative to the 10,000 AU/mL FDA reference. Since this is the only FDA requirement for potency, the purpose of this study was to compare mite extracts from different US manufacturers for protein complexity, major allergen, and potency using various biochemical characterization techniques.

Methods: Der group 1 and 2 allergens were measured in mite extracts from several manufacturers produced over the last 8 years using validated ALK immunoassays. Competition IgE binding was performed using FDA references and sera pools. The effect of the immobilized extract on the relative potency compared to the FDA reference was determined. Protein profiles were determined using SDS-PAGE.

Results: The average Der 1 and Der 2 levels and ratio in 10,000 AU/mL products varied considerably (Der 1: 25–140 μg/mL, Der 2: 2–140 μg/mL). The ratio of Der 1/Der 2 was manufacturer related and ranged from 1:1 to more than 10:1. The extract used to coat the ELISA plates had a marked impact on Relative Potency (RP) with up to a 3-fold difference. RP determined by competition IgE binding was correlated with major allergen content but the difference in potency was obtained by coating with different batches of 10,000 AU/mL mites.

Conclusions: Often called a "total" IgE test, the competition IgE ELISA is highly dependent on the allergen used to coat the plastic microplate. US mite extracts with the same AU/mL can have very different Der 1 and 2 content.

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Detection of DER P 2 in the House Dust and Correlation with Mite Number in an Environmental Survey

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Background: Aeroallergen avoidance has been promoted in order to prevent sensitization and the correlation between the level of allergen exposure and sensitization has been reported. The aims of this study were to monitor the environmental mite infestation and design a Der p 2 detection kit to estimate the number of mites in house dust samples.

Methods: House dust samples were collected from 6 carpets and 2 mattresses monthly from April 2010 to March 2011. The total number of mites was counted under microscopes and Der p 2 concentrations were measured using Der p 2 ELISA kit. The detection kit was constituted using Der p 2 specific mouse monoclonal antibody as capture antibody, and rabbit polyclonal antibody as detection antibody. Both Der p crude extract and rDer p 2 were used as internal standard.

Results: The number of mites in the dust samples was significantly higher in the mattresses in comparison with that in the carpets and the total number of dust mites was higher in the summer than any other seasons. The concentration of Der p 2 component in Der p crude extract was analyzed and the result showed that each gram of Der p crude extract contained 25.53 mg of Der p 2. When the number of mites and Der p 2 concentration were measured for the correlation analysis the results showed that there was a good correlation between Der p 2 and number of mites with $R^2 = 0.9652$.

Conclusions: Dust mites were significantly increased in the dust samples collected from mattresses especially in the summer. The good correlation between Der p 2 concentration and mite numbers indicated that the measurement of Der p 2 can be used to replace direct mite count. Using the Der p 2 detection to monitor environmental mite infestation may be beneficial for allergic subjects to prevent disease activation.

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Daily Vacuum Cleaning Significantly Reduces House Dust Mite Allergen, Endotoxin and β-glucan Content of Mattresses

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Background: House dust mite allergic patients are advised to cover their mattresses with occlusive coverings; however, these are not cheap. We investigated whether daily vacuum cleaning of mattresses reduces house dust mite allergens, bacterial endotoxin and fungal β-glucan content.

Methods: Twenty volunteers vacuumed their mattress daily for 8 weeks. Dust samples, collected at two weekly intervals were analysed for house dust mite allergens (Der p 1 and Der f 1) by double monoclonal antibody ELISA and for endotoxin and β-glucan by the *Limulus* amoebocyte lysate kinetic assay. Data are presented as geometric means with 95% CI.

Results: Total house dust mite allergens (Der p 1 + Der f 1) significantly reduced from a geometric mean (95% CI) of 4.07 μg (2.44-6.79) at the start to 0.42 μg (0.21-0.81) at week 8. Total endotoxin and β-glucan were also significantly reduced from 13.6 EU (8.6-21.4) to 3.4 EU (2.3-5.0) and from 94.4 μg (57.1-156.2) to 19.7 μg (10.2-37.9) respectively (*P* for trend >0.0001). Percentage reductions in total house dust mite allergens, endotoxin and β-glucan after 8 weeks of daily vacuum cleaning were 85.1% (80.1-90.1), 71.0% (70.4-81.0) and 75.7% (70.4-81.0) respectively. This was mainly due to a 77.7% (70.8-84.7) reduction in total dust.

Conclusions: Daily vacuum cleaning of mattresses over time significantly reduces house dust mite allergens, endotoxin and β-glucan. This gives house dust mite allergic patients a practical and cheap alternative to reduce their exposure to indoor bio-contaminants.

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Differences in Indoor Allergen Quantification in Hispanic/Latino Children Living in Miami to Those Living in Latin America

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Background: Higher levels of indoor allergens can induce in children more susceptiblity to atopy and possibly asthma.

Methods: Indoor allergen sampling was collected by families of allergic children referred to our Allergy clinic. Two groupings were based on location of residence, either locally, Miami Florida (MF), or from Latin America (LA). LA children were from Dominican Republic, Ecuador, Venezuela, or Central America. All MF children were of Hispanic/Latino descent, first or second generation, from similar countries. A dust collection device, (Duststream, Indoor Biotechnologies, Charlottesville) was used to vacuum the bedroom samples. These samples came from the mattress, pillows, floors, rugs, and A/C vents. After collecting, samples were weighed, extracted, vortexed, and incubated. For allergen detection, MARIA (Indoor Biotechnologies) was used

to quantify levels of dust mite (DM) allergens, (*Dermatophagoides pteronyssinus*, Der p 1; *Dermatophagoides farinae*, Der f 1), and *Felis domesticus* (Fel d 1), *Canis familiaris* (Can f 1), *Blattella germanica* (Bla g 2). Quantification of these allergens was performed on a multiplexing instrument, Luminex 200, (Luminex Corporation, Austin, TX).

Results: Samples from 63 MF and 69 LA were returned. There was a statistical significance in total DM levels between both locations. The mean DM level was 118.7 ng/mL from MF and 241.0 ng/mL from LA ($*P > 0.05$). Both were in the moderate range for clinical exposure, 2.37 mcg/mL and 4.82 mcg/mL. Contribution of the total DM significance was from the DP species. The mean DP level was 34.1 ng/mL from MF compared to 188.6 ng/mL from LA ($**P > 0.001$). The clinical exposure of DP was moderate at 3.77 mcg/mL from LA, but in the low range at 0.68 mcg/mL from MF. No significant difference was found in DF between locations, but a minor trend towards more DF exposures in MF rather than LA exists. There was no difference found between locations with the other allergens tested. High cat allergen exposure was found in MF, but with variability and miniscule levels found in LA. Moderate dog and very low cockroach clinical exposures were found in both locations.

Conclusions: Our study reveals intriguing indoor allergen levels based on different environments that may contribute to the epidemiology of allergy/asthma in Hispanic/Latino children.

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House Dust Mite Fauna and Its Relationship to Allergen Skin Tests in Six Mexican States

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Background: House Dust Mites (HDM) are important respiratory allergens all over the world. In Mexico, there have been only few studies describing the HDM fauna, and mostly limited only to Mexico City. This study aimed to asses the HDM fauna and its relationship to allergen sensitization in different cities with climatic variations in Mexico.

Methods: A total of 60 dust samples were collected from mattresses in 6 Mexican states: Oaxaca, Tamaulipas, Veracruz, Puebla, Chiapas and Campeche; during a period from February to August 2010 and in May 2011. Mites were isolated under a stereomicroscope using lactic acid - 0.9% NaCl solution (1:1). Identification was performed on fixed slides prepared with Hoyer solution. Skin Tests were performed with allergen extracts of different HDM species in the 60 mattress' owners, which had previously been diagnosed with respiratory allergy.

Results: The *Pyroglyphidae* family was predominant, being found in 100% of dust samples. *Dermatophagoides pteronyssinus* (Dp) and *Dermatophagoides farinae* (Df) were the species most frequently found (in over 90% of samples). These findings were in agreement with the Skin Tests results, where 100% of patients were positive to Dp whereas 70% was positive to Df. It was evidenced for the first time the presence of *Blomia tropicalis* (in Tamaulipas, Veracruz and Campeche) and *Dermatophagoides siboney* (in Campeche). Both species are important allergenic sources in tropical/subtropical climates, and the last one had been previously reported only in Cuba. Other species found were *Acarus siro*, *Cheyletus sp*., *Suidasia pontificia*, and *Gamasidae* and *Oribatidae* families.

Conclusions: These results confirm the importance of pyroglyphid HDM, as indoor sensitizers in different climatic and geographical regions in Mexico, as well as, the relevance of tropical species, particularly *Blomia tropicalis*, in certain areas. They support the need of using allergen extracts of these mite species for improving allergen-specific diagnosis and immunotherapy.

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Oral Mite Anaphylaxis is Caused by Mite-contaminated Okonomiyaki Mix in Japan

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Background: Anaphylaxis after the ingestion of foods contaminated with mites has recently been reported. It is an immediate and potentially life-threatening reaction in patients with previous allergic rhinitis and/or asthma following the ingestion of mite-contaminated foods. Case series and case reports thus far have shown that mite-contaminated wheat flour is the major cause of oral mite anaphylaxis. However, we have encountered 8 cases of oral mite anaphylaxis in our hospital not caused by mite-contaminated wheat flour but by mite-contaminated okonomiyaki mix.

Methods: To review the current literature, in addition to our patients, we performed a MEDLINE search of articles on oral mite anaphylaxis in Japan up to June 2011 and collected patient characteristics, interview contents, results on specific IgE against mites, wheat, and pollen and other antigens, results of skin prick tests including those using extracts from mites and/or culprit flours, and microscopic examination results.

Results: We found thirty oral mite anaphylaxis patients in Japan twenty-eight (93.3%) of whom ingested okonomiyaki or takoyaki, prepared at home using okonomiyaki mix (24 patients) or takoyaki mix (4 patients), respectively, which was previously opened and stored for months at ambient temperature. Takoyaki mix is similar to okonomiyaki mix, which is composed of flour, dried scallop, bonito, and mackerel. The other 2 patients ingested pancake mix. Microscopic examination of thirteen patients' mixes revealed contaminating mites. *Thyreophagus putrescentiae*, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae* were found in mix samples of 4, 3, and 3 patients, respectively. The specific IgE against each mite is generally upregulated, which might be affected by cross-reactivities to other mites. Especially, the specific IgEs to *Dermatophagoides pteronyssinus* and *Dermatophagoides farina* were more than class 2 in all cases. It is suggested that mites are attracted to the flavors of okonomiyaki and takoyaki mixes and invade from a crack in a flour sack, and proliferate under favorable conditions.

Conclusions: Mite-contaminated flavored mix is a major cause of oral mite anaphylaxis in Japan.

EOSINOPHILIC DISEASES

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International Survey on Evaluation and Management of Eosinophilic Esophagitis

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Background: The criteria for diagnosis of Eosinophilic Esophagitis (EoE) have been established; however the recommendations regarding evaluation and management of patients have been debated. The purpose of this survey study is to assess how providers across the world diagnose, evaluate and treat patients with EoE and how education impacts their approach.

Methods: The link to a web-based survey was sent to the members of WAO, ACAAI and AAAAI. From October 2010 to January 2011, the participants were asked to respond to 24 questions. The qui-square test was used for comparison between groups which included: practitioners from the Unites States versus other countries, male versus female, different specialties, years in practice, academic versus private, rural versus suburban, number and frequency of patients, number of lectures and workshops the practitioners attend.

Results: Among the 200 respondents, 70% were from the United States. Majority of respondents were allergists/allergolosits. The majority responded that biopsy is required to diagnose EoE, that they do ask about personal and

family history of atopy and they do recommend allergy evaluation via testing; these were similar between all groups.When comparisons were made between the groups, these areas showed statistically significant differences:
1) Practitioners who see more patients with EoE more frequently were more likely to perform testing for immediate hypersensitivities to aeroallergens and foods.
2) Practitioners who participate more often in workshops were less likely to perfrom patch testing for foods.
Conclusions: Our survey reveals that allergy practitioners worldwide are following patients with EoE. Practitioners who see more patients with EoE more frequently are more likely to perform allergy testing in form of hypersensitivity testing to both aeroallergens and foods. This could be secondary to participation in educational sessions or more interest in searching the literature. Participation in workshops has an inverse relation to performing patch testing for foods, which may show that current education does not support this practice. In order to have a more uniform approach to patients with EoE, a consensus guideline is prudential.

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Allergen Specific Immunotherapy as a Treatment for Eosinophilic Esophagitis

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Background: Eosinophilic Esophagitis (EoE) is an inflammatory disease that reduces the ability of the esophagus to pass food, often leading to dysphagia. A relationship between EoE and food allergies has been determined. However, there have been several documented cases in which patients had negative prick skin testing (PST) results for food allergens and positive results for airborne environmental allergens, and still have a confirmed diagnosis of EoE. Recently, airborne allergens have been implicated in the onset of this condition. Studies have shown that patients sensitive to airborne allergens such as pollen have a seasonal biannual component in which the severity of EoE symptoms increase, coinciding with high pollen seasons.
Methods: We followed a 65-year-old man with a history of allergies complaining of an increase in his symptoms of allergic rhinitis and asthma. He also noted dysphagia and occasional vomiting. We noted the disease and medication course over 5 years of treatment.
Results: The patient underwent an esophagogastroduodenoscopy with biopsy, in which midesophageal rings as well as an 8 mm sessile polyp were found, suggesting EoE. Histological analysis confirmed EoE, having found >20 intraepithelial eosinophils/HPF. The patient was treated with a short term prednisone regimen, as well as maintenance medications consisting of inhaled corticosteroids and antihistamines. The patient returned 6 months after the initial consultation and still presented symptoms of EoE, at which point the patient was prescribed proton pump inhibitors. In addition, allergen specific immunotherapy was initiated for confirmed airborne allergens. The patient was examined after 5 years of immunotherapy treatment. Not only did he report that his allergic rhinitis and asthma symptoms were controlled, but his EoE symptoms had resolved.
Conclusions: Results suggest that immunotherapy for airborne allergens could be a successful treatment for EoE. A larger study is needed to determine if allergen specific immunotherapy is a viable treatment option for EoE in similar cases. Such a study could include patients with EoE and confirmed airborne allergies treated with immunotherapy while monitoring a number of eosinophilic and lymphocytic markers.

EPIDEMIOLOGY OF ALLERGIC RHINITIS

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Treatment of Nasal Allergies: Results from the Allergies Surveys in America, Asia Pacific, Latin America, and Middle East

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Background: The Allergies surveys have been conducted in several regions of the world, and provide a uniquely comprehensive insight into the prevalence and impact of nasal allergies worldwide. Here we report specifically on treatment of nasal allergies in the Allergies in America (AIA), Asia Pacific (AIAP), Latin America (AILA) and Middle East (AIME) surveys.
Methods: Patients who were previously diagnosed by a health care professional with nasal allergies (hay fever, allergic rhinitis or nasal allergies, plus sinus disease in AIAP), exhibited symptoms, and/or had received treatment, were included. Standardized questionnaires provided by Abt SRBI were used; individual questions and methodology varied slightly between regions. In total, around 90,000 households were screened, including responses from 6,081 patients.
Results: The surveys revealed that among patients receiving treatment for nasal allergies, the proportion using a prescription nasal spray varied regionally, from 21% in AIAP to 54% in AIME. Despite a high percentage of patients reporting satisfaction with their prescription nasal spray, many patients who were dissatisfied cited reasons such as lack of effectiveness and lack of 24-hour relief as primary concerns. The percentage of allergy sufferers who experienced a loss of product effectiveness over 24 hours varied regionally from 35% in AILA to 53% in AIAP. Many patients strongly agreed there were no truly effective treatments for nasal allergies, and 10% of all patients in AIA chose to change their medication several times a year. The most commonly reported side effects of prescription medications were dripping down the throat and dryness. Bad taste was also commonly reported, in all regions except North America, where drowsiness was the third most commonly reported side effect. A higher proportion of patients reported side effects with prescription sprays in the Middle East than in any other region surveyed.
Conclusions: There is still an unmet need in treatment of patients with nasal allergies worldwide. A low percentage receives treatment with prescription nasal sprays, despite this form of therapy being considered the 'gold standard' of treatments. Patients are bothered by a range of side effects generally different to those reported in drug information leaflets.

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Comorbid Allergy-related Respiratory Conditions Among Children and Adults Diagnosed with Allergic Rhinitis: Findings from Research Jointly Funded by the AAAAI AND ACAAI

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Background: We examined rates of comorbid allergy-related respiratory conditions among patients diagnosed with allergic rhinitis (AR) to characterize AR-related disease burden.
Methods: Florida Medicaid retrospective claims data (1997–2009) were analyzed to compare the likelihood of receiving targeted comorbid allergy-related respiratory conditions among AR-diagnosed (ICD-9 477.x) children (age <18 years) and adults (age ≥18 years). Targeted comorbidities included strep throat (ICD-9 034.x), conjunctivitis (372.x), otitis media (381.x-382.x), acute respiratory infections (460.x-466.x), other diseases of the upper respiratory tract (470.x-476.x and 478.x), pneumonia/influenza (480.x-488.x), chronic obstructive pulmonary disease/allied conditions (490–496), asthma (ICD-9 493.x), and atopic dermatitis (691.8).
Results: Overall rates of AR were significantly higher for children than adults (8% vs 3%, $P < 0.0001$). On average, AR-diagnosed patients had significantly more comorbid allergy-related respiratory conditions than nonAR-diagnosed patients (children, 3.7 ± 1.9 vs 1.2 ± 1.7 $P < 0.0001$; adults, 2.6 ± 1.7 vs 0.5 ± 1.0, $P < 0.0001$). Compared to nonAR-diagnosed

patients, the likelihood of receiving the following diagnoses among AR-diagnosed children and adults, respectively, were: 13 and 15 times greater for acute respiratory infection; 6 and 9 times greater for otitis media; 6 and 8 times greater for asthma; 6 and 12 times greater for upper respiratory infection; 5 and 8 times greater for conjunctivitis; 5 times greater (both children and adults) for chronic obstructive pulmonary disease/allied conditions; 5 and 8 times greater for strep throat; 4 and 3 times greater for pneumonia/influenza; and 4 and 9 times greater for atopic dermatitis. Differences between AR- versus nonAR-diagnosed groups and between children and adults were significant at the $P < 0.001$ level.

Conclusions: Compared to their counterparts who were not diagnosed with AR, children and adults with AR had a significantly greater likelihood for receiving any targeted comorbid allergy-related respiratory condition. Likelihood estimates, which were 3 to 15 times greater for AR-diagnosed patients, varied significantly for children and adults by specific comorbid condition. Given a diagnosis of AR, the likelihood for comorbid respiratory infection, asthma, otitis media, conjunctivitis, atopic dermatitis and strep throat was substantially greater for adults; the likelihood for pneumonia/influenza was greatest for children; and the likelihood for chronic obstructive pulmonary disease/allied condition was roughly equivalent for the 2 age groups.

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Survey of Rhinitis Phenotypes

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Background: Non-infectious rhinitis (NIR) is often considered a trivial disease, easily controlled by currently available drugs. Recently however, adequate attention of the scientific and regulatory environment has been called on the unmet needs of the most Severe Chronic Upper airways Diseases (SCUADs, Bousquet J et al, J Allergy Clin Immunol 2009;124:428–33). Object: An independent observational cross-sectional survey was promoted by the Italian Federation of Allergy and Clinical Immunology Societies (IFIACI) in order to identify phenotypes of NIR and the dimension, clinical features and burden of SCUADs in Italy.

Methods: All IFIACI clinical centers answering GPC standards were invited to collect data through a common questionnaire from up to 50 consecutive cases of NIR observed from January 1 to June 30, 2011 in subjects aged over 14 years. Data management, entry and analysis were performed through a validated procedure by IBIS, Milan, in respect of privacy requirements.

Results: The duration of rhinitis was 6.8 ± 6.7 years in the 2279 patients studied. Rhinitis was classified as moderate/severe in 42.9% of the 511 patients with intermittent rhinitis and in 69.5% of the 1959 patients with persistent rhinitis.81.6%of NIR had one or more positive skin tests, grass (37.2%), Dermatophagoides pteronyssinus (26.8%) and Parietaria (19.8%) being the allergens more frequently responsible for a clinically relevant sensitization. Conjunctivitis (47.3%), asthma (34.4%), sinusitis 15.5%), sleep disturbances (9.4%) and nasal polyps (6.0%) were the co-morbidities more frequently associated with rhinitis, particularly in the most severe forms. The undergoing treatment (anti-histamines in 64.4%, nasal steroids in 59.7%, anti-leukotrienes in 14.8% and oral steroids (!) in 8.1% of cases), was considered unsatisfactory in 19.1% of cases by the doctor and in 33.6% by the patients. Immunotherapy was indicated in 63.9% of subjects with a clinically relevant sensitization but it was accepted only by 51.6% of the patients, the high costs being the major cause for non- acceptance.

Conclusions: NIR is a heterogeneous entity including several different phenotypes. Allergic rhinitis patients with persisting symptoms, co-morbidities, poor response to pharmacological treatment represent a not frequent phenotype but with high social and individual costs and still unanswered health needs.

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Prevalence and Risk Factors Associated to Symptoms of Rhinoconjunctivitis in Mexican School Children. A Multicenter Study

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Background: According to ISAAC symptoms of allergic rhinoconjunctivitis (RC), have a worldwide prevalence of 8.5% in school children. Multiple risk factors had been associated with its prevalence, though little is known about the regional variations of these risk factors.

Objective: Identify the prevalence and the main risk factors associated to the presence of symptoms of rhinoconjunctivitis in the last 12 months in Mexican school children.

Methods: Cross-sectional, multicenter, prospective, based in ISAAC methodology of 9 registered sites in 8 cities (north, center and south of the Mexican Republic) with a validated and standardized survey applied to tutors of children aged 6 to 7 years old. Risk analysis was made through multivariate logistical regression, central tendency and dispersion measures were obtained with respective 95% confidence intervals.

Results: 24,902 surveys were obtained. The prevalence and 95%CI of symptoms of rhinitis was as follows: Monterrey 23%(21.4-24.5%), Mexicali 28.7% (26.9-30.5%), Ciudad Victoria 21.3%(19.7-22.8%), Villahermosa 39% (37-41%), North Federal District 45.6% (44.1-47.2%), Toluca-18.6% (17.3-20%), Tijuana 24.5% (22.9-26.1%), southeast Federal District 53% (50.7-55.4%) Veracruz 25% (23.1-26.8%) and conjunctivitis: Monterrey 8.8% (7.8-9.9%), Mexicali 13.2%(11.9-14.5%), Ciudad Victoria 7.3%(6.3-8.3%), Villahermosa 18.7% (17-20.3%), North Federal District 20.4%(19.1-21.7%), Toluca 7.3%(6.4-8.2%), Tijuana 8.7%(7.6-9.7%), southeast Federal District 25.1%(23-27.1%) Veracruz 8.7% (7.5-9.9%). The prevalence de rhinoconjunctivitis were 12.8%. Identified risk factors for the presence of rhinitis in the last 12 months were: asthma symptoms in the last 12 months OR-2.59 (95% CI, 2.25-2.98; $P \leq 0.0001$), wheezing ever OR-1.78 (95% CI, 1.61-1.96; $P \leq 0.0001$), eczema symptoms in the last 12 months OR-1.61 (95% CI, 1.35-1.93; $P \leq 0.0001$), atopic dermatitis ever OR-2.97 (95% CI, 2.52-3.51; $P \leq 0.0001$). Identified risk factors for the presence of conjunctivitis in the last 12 months were: wheezing ever OR-1.88 (95% CI, 1.64-2.16; $P \leq 0.0001$), asthma symptoms in the last 12 months OR-2.97 (95% CI, 2.52-3.51; $P \leq 0.0001$) eczema symptoms in the last 12 months OR-1.95 (95% CI, 1.58-2.41; $P \leq 0.0001$), atopic dermatitis ever OR-2.14 (95% CI, 1.81-2.54; $P \leq 0.0001$).

Conclusions: The highest prevalence of rhinoconjunctivitis in Mexican School Children is in the southeast of the Federal District.The presence of asthma symptoms in the last 12 months, wheezing ever, eczema symptoms in the last 12 months, atopic dermatitis ever, risk factors are present symptoms of rhinoconjunctivitis.

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Oral Allergy Syndrome and United Airways Disease: Is There a Functional Connection?

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Background: The airways and the upper digestive tract have a common embrional origin, and in sensitized subjects they can respond to allergens with an immediate reaction (asthma, rhinitis or oral allergy syndrome). We investigated the possible functional connection between respiratory tract and upper digestive tract by means of specific oral allergen challenges.

Methods: Patients sensitized to birch and apple were subdivided in GROUP A (N = 12; asthma and rhinitis due to birch and OAS due to apple) GROUP B (N = 10; OAS due to apple without asthma/rhinitis); GROUP C (N = 8; asthma and rhinitis due to birch without OAS). Healthy subjects represented the control group D (N = 6). Oral provocation test with apple was performed out of the pollen season. Visual analog scale for eye, nose and mouth symptoms, spirometry, nasal eosinophil count and exhaled nitric oxide were assessed before and 6 hours after challenge.

Results: There was no change in nasal and ocular symptoms before versus after challenge in all groups. On the contrary, in groups A and B the oral scores significantly increased after challenge ($P < .001$), whereas no change was seen in groups C and D. Exhaled nitric oxide and nasal eosinophils showed no change before versus after challenge in all groups. Nitric oxide was higher before and after challenge in groups A and C versus groups B and D. No change was een as well in forced vital capacity and forced expiratory volume in one second.

Conclusions: In the case of birch-apple syndrome, eating apple does not functionally or clinically affect the respiratory tract.

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Epidemiological and Clinical Characteristics of Allergic Conjunctivitis Patients in a Reference Center of Mexico City

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Background: In our country (Mexico) there are few reports about epidemiological characteristics of allergic conjunctivitis patients; despite these studies give us some information about patient profile, in most cases these studies are not always comparable due to the use of different methodologies, that is, Include only a portion of the population (elderly, infants) or there are limited to one region of the city. The purpose of this study was to know the epidemiological and clinical characteristics of allergic conjunctivitis (AC)-patients in the biggest reference center of ocular diseases in Mexico (Institute of Ophthalmology "Conde de Valenciana")

Methods: Data were obtained from clinical records. Six hundred fifteen patients with diagnosis of AC were included. Epidemiological characteristics included sex, age, residence; clinical-immunological characteristics included atopy, coexistence of other allergies, total IgE, cutaneous reactivity to skin prick test (SPT), sixty allergens were evaluated. Descriptive statistics were performed to obtain frequencies and *t* test was used to find significant differences, $P < 0.05$ was considered statistically significant.

Results: AC-Patients who received medical consultation at the Institute of Ophthalmology where predominantly from State of Mexico (47.25%), Mexico City (37.5%), and in less frequency Hidalgo, Puebla, Tlaxcala, Michoacan, Veracruz, Oaxaca, Guerrero, Chiapas and Guanajuato. 88% of AC-patients were positive to SPT (SPT+), while 12% were negative to SPT (SPT-). Age of diagnosis was significant different between SPT-AC-patients and SPT+AC-patients (14.5-years vs 17.9-years, $P = 0.02$). Male SPT-AC-patients were diagnosed younger than male SPT+AC-patients ($P = 0.001$). IgE concentration was significant increased in male SPT+AC-patients than female SPT+AC-patients ($P = 0.006$). The most common skin reactivity was against *Dermatophagoides sp* (59.1%), *Aedes sp*(54.55%) and *Blatella-Periplaneta sp*.(31.14%); we did not observe significant differences in skin reactivity between male or female SPT+AC-patient.

Conclusions: It was considered that AC-patients were negative to SPT; contrary to reported, this study showed that most of AC-patients were positive to some allergen; this result is relevant because open the possibility to offer specific desensitization as conventional treatment instead anti-histamine drugs in SPT+ population. This is the first study covering the central and southern part of our country.

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The Classification of Allergic Rhinitis and Its Cytological Correlate

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Background: The ARIA document introduced a new classification of allergic rhinitis, based on its duration and severity, which is graded on the basis of the impact of AR on daily activities and quality of life. Nasal cytology is a simple and reliable diagnostic tool to identify the presence and type of inflammation in rhinitis. Thus, we assessed severity of AR by nasal cytology on the basis of the ARIA classification.

Methods: Patients suffering from AR caused by grass pollen only, and healthy subjects were studied. The severity of rhinitis was defined according to ARIA. All subjects underwent nasal cytology, using a Rhino-probe. Scrapings were air-dryied and stained by May-Grunwald-Giemsa. Differential cell count was expressed as % of the total leukocytes. Unpaired *t* test was used for comparisons.

Results: Sixty-two grass-allergic patients (34 men, mean age 35.2 years) and 18 healthy subjects (10 men, mean age 32) were studied. 67.8% of patients had intermittent AR (33.9% mild and 33.9% moderate-severe) and 32.2% had persistent AR (14.5% mild and 17.7% moderate-severe). The patients with moderate-severe AR had significantly more mast cells and lymphocytes than those with mild AR, with a relatively smaller number of neutrophils and eosinophils. Mast cells and/or lymphocytes could be detected in only 3/30 patients with mild rhinitis, and in 19/32 patients with moderate/severe rhinitis. No difference in cell counts was found when comparing intermittent and persistent AR.

Conclusions: Moderate/severe allergic rhinitis displays a cytological inflammatory pattern different from mild rhinitis.

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Incidence of Allergic Diseases on Children under 5 Years in Juarez Hospital Mexico

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Background: Allergic diseases such as asthma, atopic dermatitis and allergic rhinitis are common disorders that have increased its prevalence over the past thirty years. Atopic diseases have a genetic basis, with expression of different phenotypes associated with chromosome 5 (5q23-25, IL-4, IL-5, IL-9, IL-13 and GM-CSF), 6 (molecules of class I and II human leukocyte antigen) 11 (11q13: β subunit of high affinity receptor for IgE) and 12 (12q: IFN-gamma,

nitric acid synthase). Asthma is defined as a chronic inflammatory disease of airway and is the most common chronic disease in children characterized by wheezing. Wheezing may occur even once it is up to 50% of all infants and children under 3 years old and topic dermatitis affecting over 10% of children.

Objective: To define incidence and prevalence of asthma and others allergic diseases in population of less than 5 years of age in Juarez Hospital Mexico.

Results: We evaluated 11,346 allergic patients on 4 years period (January 2007 to December 2010). Two thousand three hundred ninety six were ≤5 years (21.11%); 10.2% a year old or younger, 16.7% 2 years old, 18.5% had 3 years, 24.7% of 4 years and 30% 5 years old. Nine hundred ninety two patients (41.4%) were females and 1.404 (58.6%) male. One thousand two hundred thirty eight patients (51.7%) had only one diagnostic finding as most frequent cause of consultation allergic rhinitis (59.6%), followed by asthma (23%), atopic dermatitis (5.1%), prurigo by insect (4.3), immunodeficiency (1.2%) the rest had various pathologies such as contact dermatitis, gastro esophageal reflux, oral allergy syndrome, and others. The remaining patients 48.3% (1158) had more than one diagnostic. The most common associations were asthma and rhinitis 716 (30%), 72 patients (3%) with asthma and atopic dermatitis, 48 patients (2%) with some immune deficiency and asthma and/or rhinitis, 12 (0.5%) with prurigo and atopic dermatitis, 8 (0.3%) with urticaria and 11 patients (4.5%) with other diagnoses such as reflux or infections.

Conclusions: Allergic diseases are common on pediatric population and children under 5 years old asthma and rhinitis is theprincipal cause of consultation.

FOOD ALLERGY

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Effect of Hydrolysis and Polymerization on Bovine Beta-lactoglobulin Immunoreactivity

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Background: Enzymatic treatments such as hydrolysis with proteases and polymerization using transglutaminase (TG) have been studied to reduce the immunoreactivity of β-Lactoglobulin (β-Lg). Bromelain is a cisteine protease that is not usually used for production of hypoallergenic hydrolysates. TG is an enzyme that catalyses the formation of inter and intramolecular isopeptide bonds between glutamine and lysine residues. The present study is aimed at investigating the antigenic response of β-Lg polymerized by TG pre or post hydrolysis with bromelain.

Methods: β-Lg (donated by Davisco Inc), was hydrolyzed with bromelain (3% protein w/w in distilled water, 25 U enzyme g^{-1} of substrate, pH 7.5, 240 min) and then polymerized by TG (7% hydrolysate, 10 or 25 U TG g^{-1} protein, 50°C/180 min). When polymerization was carried out pre hydrolysis, β-Lg (7% w/w) was polymerized by TG (10 U TG g^{-1} protein, 50°C/180 min) in 0.1 M Cys or after heat treatment (80°C/60 min), and then hydrolyzed under the same conditions previously described. The hydrolysis reaction was monitored by pH-stat method and the samples were evaluated by SDS-PAGE/tricine. Antigenicity was evaluated by Immunoblotting and ELISA assays using sera from mice sensitized with β-Lg (IgE anti-β-Lg).

Results: The treatment with TG (10 or 25 U TG g^{-1}), post hydrolysis, lead to formation of products with a wide molecular weight (MW) distribution (3 to 26 kDa), and other products with high MW, indicating partial polymerization. The samples obtained from polymerization pre hydrolysis showed bands with low MM (<6.5 kDa) and also products >26 kDa, indicating a partial hydrolysis of the polymers. Immunoblotting analysis showed no reaction towards specific IgE with any of the samples. ELISA assay showed that the IgE-binding response to sample polymerized by TG post or pre hydrolysis with bromelain were significantly reduced (IgE ≤ 35.21 ug mL^{-1}) as compared to untreated β-Lg (IgE 216.20 ug mL^{-1} ± 27.58) ($P < 0.05$).

Conclusions: These results suggested that hydrolysis with bromelain combined with polymerization by TG was capable of reducing the antigenicity of β-Lg, being a potential method for modifying the antigenic properties of proteins.

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Immunoreactivity of Polymerized and Digested Beta-lactoglobulin to IgE from Milk Allergic Patients

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Background: Beta-lactoglubulin (β-Lg), is one of the most important allergens in bovine milk. The allergenicity is mainly associated to its stable structure, resistant to heat and digestive processes. With the purpose of decreasing its allergenicity, some processes have been studied, including enzymatic treatments using transglutaminase (TG), an enzyme that catalyses the formation of inter and intramolecular isopeptide bonds between glutamine and lysine residues which could alters both the structure and antigenic sites in the protein. The allergenicity of β-Lg hydrolysates obtained after a simulated gastrointestinal digestion (GI) and previously polymerized by TG enzyme was studied.

Methods: The β-Lg (7% w/v), donated by Davisco Inc., was modified by 2 different methods (1) heat treated (80°C/60 min) and polymerized by TG (10 U g^{-1} protein), and (2) polymerized by TG in the presence of the reducing agent Cysteine - Cys (0.1 mol L^{-1}). After modification the samples were submitted to in vitro digestion, simulating gastric and duodenal conditions (Moreno, 2005; Martos et al, 2010). The characterization of the samples was performed by electrophoresis (SDS-PAGE) and Reversed-phase high performance liquid chromatography (RP-HPLC). The allergenicity of the protein was measured by ELISA, using sera of milk allergic patients.

Results: The untreated β-Lg was resistant to pepsin while the samples polymerized by TG showed an increased in the susceptibility to pepsin, since a predominance of low molecular mass (MM) peptides, 3.0 to 6.0 kDa (by SDS-PAGE) and peptides with low hydrophilicity (by RP-HPLC) were detected. After duodenal digestion, the polymerized samples showed an increased in the intensity of the peaks with high hydrophilicity, indicating a potential susceptibility of polymerized β-Lg to GI digestion. Immunoreactivity to IgE from sera of allergic patients was retained for β-Lg polymerized after heat treatment, even after in vitro gastric digestion; while for the sample polymerized in presence of Cys it decreased considerably after pepsinolysis. After duodenal digestion, both polymerized samples showed an important decrease in the immunoreactivity response, compared to untreated β-Lg.

Conclusions: These findings showed that the polymerization alters the susceptibility of β-Lg to GI digestion and could have implications in the allergenic characteristics of this protein.

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Identification of Novel Allergens in the Fish Parasite Anisakis Simplex

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Background: The nematode *Anisakis simplex* is a marine parasite that causes allergy as well as anisakiasis in human. Here, we describe the identification of 4 novel allergens in anisakis.

Methods: Binding of human IgE to anisakis and house dust mite proteins was investigated by immunoblot with serum from individuals sensitized to anisakis or shrimp. IgE binding patterns in the immunoblots were used for the identification of major Anisakis allergens, which were analysed by mass spectrometry-based proteomics in ESI-Orbitrap, after separation on SDS-gel.
Results: Four new allergen candidates were identified. The first identified allergen was enolase, which is related to the cockroach allergen enolase. The other allergens were Heat Shock Protein-70 (HSP 70), tubulin, and glutathion-S-transferase, which are also present as allergens in house dust mite.
Conclusions: Here we describe the identification of 4 novel IgE binding allergens in anisakis. The allergens might explain IgE cross-reactivity between anisakis and house dust mite or cockroach.

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Milk Components as a Tool in Predicting Tolerance in Cow's Milk Allergy

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Background: One important point in cow's milk allergy (CMA) is to stablish predicitve factors in acquiring tolerance. The aim of this study is to evaluate if a ratio of milk components: alpha-lactalbumin (α), beta-lactoglobulin (β), casein (C) and whole milk (WM) can contribute to predict tolerance development.
Methods: It was a retrospective study that included patients with previous diagnosis of CMA evaluated at 6 years old. CMA was defined as a positive double blind placebo-controlled food challenge, open challenge or confirmed anaphylaxis plus positive specific IgE to cow's milk (higher than 3.5 kU/L or positive skin prick test), and tolerance was defined as acceptance of cow milk without previous symptoms. Specific IgE analysis to WM, α, β, and C were performed through Immunocap (Phadia AB). Ratios of milk components and whole milk (α /WM, β/WM, C/WM) were calculated and compared the results in 2 study groups: tolerant and persistent at 6 years old. Since values from both α /WM and β/WM ratios didn't follow a normal distribution, Mann-Whitney test was used to compare groups. For C/WM ratios, Student's *t* test was used as values were normally distributed.
Results: It included 49 patients (27 male/22 female), 24 tolerant and 25 persistent. Average age of Immunocap test was 2.7 years (SD = 1.4). Comparing the results from 2 groups, persistent and tolerant it was detected: no difference in α /WM ($P = 0.055$, Mann-Whitney test), higher levels of β/WM in persistent group ($P = 0.023$, Mann-Whitney test) and also higher levels of C/WM in persistent group ($P = 0.004$, Student's *t* test).
Conclusions: Higher ratios involving beta-lactoglobulin or casein components were detected in persistent patients. Thus, evaluating these markers precociously can be helpful in predicting CMA evolution.

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Uncommon Occupational Allergy to Rice: as a Food Allergen

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Background: Rice *(Oryza sativa)* belongs, with other cultivated cereals, to different tribes of the Poaceae family. It is one of the most widely produced and consumed cereals in the world but hypersensitivity reactions to this grain are uncommon Most reports describe an immunologically-mediated urticaria due to contact with raw rice or reactions after the inhalation of rice fumes, whereas reports of immediate hypersensitivity reactions after ingestion of rice are scarce.
Methods: Patient 1 (P1): A 40-year-old-man, a professional cook, presented 2 episodes of generalized urticaria minutes after rice ingestion. He tolerated the inhalation of vapours during rice-boiling, but reported icthy skin and erythema after rice handling. Patient 2 (P2): A 30-year-old-woman, pizzeria worker for the last 10 years, complaint of sneezing and rhinorrhea after handling rice for the last 2 years, and presented diarrhea and dysphagia after rice ingestion during the last year. One week before consulting she presented eyelid angioedema, chest tightness and abdominal cramping after doing exercise right after eating rice. None of the patients reported any additional atopic background. Skin prick tests with common inhalants and cereals extracts, Pru p 3 extract, prick-by-prick test with rice and rice flour and specific IgE determinations to rice were carried out in both patients.
Results: Skin prick tests to rice were positive in both patients (wheal diameter >3 mm). Skin prick-by-prick with rice and rice flour was also positive in patients 1 and 2. Serum specific IgE determinations against rice showed values of 0.8 kU/L and 1.48 kU/L for P1 and P2, respectively, out from a total IgE of 32.8 UI/mL and 23.7 UI/mL, respectively. SPT to common inhalants, to the rest of the cereals and to Pru p 3, showed a negative result.
Conclusions: We present 2 work-related cases of rice allergy with an unusual display and different clinical manifestations (urticaria, rhinitis and anaphylaxis) in 2 patients without atopic background and who worked handling rice and rice flour. No cross-reactivity with usual panallergens as LTP seemed to be involved.

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Frequency of Food Hypersensitivity Mediated by IGG in Patients Received in a Venezuelan Laboratory During 2011

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Background: Foods could cause adverse reactions, which manifested with similar symptoms that could complicate the diagnosis, that is, gastrointestinal disease, rashes, edema, eczema, asthma, anaphylaxis, others; these reactions may be mediated or not by immunological processes. In the past years there were many research studies related with different types of immunological reactions, like for example those mediated by IgG, which are characterized with delayed and insidious manifestations. These reactions could appear in hours or days after ingestion of a particular food. The intake of "toxic food" can lead to immunological reactions, which includes the formation of immune complexes, able to increase the development of gastrointestinal, dermatological, neurological, muscular and respiratory disorders. The objective of this study was to evaluate the frequency of significant specific IgG titers against some foods in patients referred to Corpodiagnostica Laboratory, (Caracas, Venezuela, an ISO 9001:2008 certified laboratory) from January to August 2011.
Methods: There were a total of 148 patients referred for serum specific IgG evaluation against foods. We measured patient's specific IgG titers against 45 foods using a commercial direct ELISA method (Dr. Fooke Labs, Germany), which is designed for the detection and quantification of specific IgG.
Results: We found detectable levels of specific IgG titers in highest frequency for: milk 69%, cheese 67%, egg 64%, gluten 54%, sugar cane 51%, followed by wheat meal, rye Meal, and other foods in smaller proportions. Moreover, in 46 patients with known clinical history, including gastrointestinal symptoms, respiratory symptoms, pervasive developmental disorder (PDD) and autism, we detected levels of specific IgG to a significant number of foods simultaneously.

Conclusions: The Specific serum IgG determination against foods could be a interesting tool to help the diagnosis of non type I Allergy reactions, and there are many published studies that have been established that the decrease or even disappearance of specific IgG titers against foods are related to the improvement of the initial clinical manifestations on some patients, but further investigations need to be performed to clearly understand the different mechanisms involved and to rule out false positive results for this test in patients without symptoms.

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IGE-mediated Responses Towards Fish Parasite Anisakis, Crab and House Dust Mite in Norwegian Shrimp Allergic Individuals

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Background: The present study investigated to what extent shrimp allergic individuals were IgE-sensitized to anisakis, crab and house dust mite and whether tropomyosin was responsible for IgE cross-reactivity.

Methods: 29 Individuals with self reported shrimp allergy were recruited by advertisements in local and national news-papers in Norway. Anamnesis was taken, skin prick tests (SPT) were performed and positive responders to shrimp were studied further with basophile activation test (BAT), ImmunoCAP analyses and western blotting.

Results: Of the 29 persons studied, 10 (34%) had positive SPT against shrimp and house dust mite, 9 (31%) against shrimp tropomyosin and 3 (10%) against anisakis. Individuals with positive SPT to shrimp all showed positive basophilic responses to house dust mite, while 43% responded to shrimp, 25% to anisakis and 36% to crab in BAT. Moreover, SPT, BAT as well as ImmunoCAP analyses showed a positive correlation of IgE-reactivity between anisakis and shrimp, house dust mite and crab. Immunoblot studies indicated that these responses are not completely explained by cross-reactivity towards tropomyosin.

Conclusions: The current study indicates a positive correlation between IgE-mediated reactions to shrimp, anisakis, house dust mite and crab, which may not be completely explained by cross-reactivity against tropomyosin.

FOOD ALLERGY CASE REPORTS

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Lentil Allergy: First Report from Venezuela

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Background: Allergy to lentils is infrequent in Latin America: this a first case report from Venezuela. A 5 year old female preschooler attended our allergology clinic with chief complaint of generalized giant urticaria inmediately after ingestion of cooked lentils; clinical history revealed frequent (>3) emergency visits, since the age of one year, with facial angioedema and generalized urticaria even from inhalation of vapors while cooking of lentils at home; moreover, also symptoms described ocurred while eating foods containing chick peas; lentils, as other beans (black, red, chick), belong to the leguminosa family along with peanuts and coconut.

Methods: Prick lancetter skin tests (H-S) to a panel of 25 inhalant and food allergens (Diater Labs, Argentina) were performed along with Prick to Prick tests to raw and cooked lentils, chickpeas, black beans, navy beans and coconut. A papule >3 mm and read at 10 minutes was considered positive.

Results: All other allergens tested were negative, that is, epithelia, molds, cockroach, grasses, mosquito, milk, egg, wheat, fishmix, shrimp and other seafood, nuts, hazelnut, almond, coconut and blackbeans.

Papules	Size (mm)	Erythema (mm)
Mite (50/50)	3 mm	10 mm
Blomia	Negative	Negative
Chickpeas	5 mm	15 mm
Navy Beans	3 mm	5 mm
Lentils (raw/cooked)	10 mm	20 mm
Peanut	3 mm	5 mm

Conclusions: 1. Prick to Prick testing confirms specific IgE presence to Lentils; our patient could tolerate peanuts and cocunut. Positive prick test to peanuts likely represent a cross reaction[1]; 2. Lupin flour (Lupinus Albus), from the Leguminosa family, is found increasingly used in industrially prepared foods and could elicit symptoms due to cross reactions, and advice to family was given accordingly[2]; 3. This is the first case report from Venezuela.

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Cow's Milk Allergy and Persistent Changes in a Multiple Food Allergy, A Case Report

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Background: Cow's milk allergy (CMA) is the most common food allergy. Clinical manifestations are mediated immediate hypersensitivity and delayed. The allergy study include: specific IgE, prick and patch test. Regarding treatment, this is based on the exclusion diet and the replacement of cow's milk hydrolysates extensive. Virtually all infants who have cow's milk allergy develop this condition in the first year of life, with clinical tolerance developing in about 80 percent by their fifth birthday.

Methods: Describe the case of a child with CMA, which moves without tolerance and also become sensitized to other foods.

Results: Female with 6 years of age. At 9 months presents watery diarrhea, weight loss and intermittent rash. Initial study (2006): Upper endoscopy: Duodenitis chronic nonspecific, total IgE: 72.60 IU/mL, IgE specific to cow's milk 10.40 IU/mL (Class III) and prick test positive. Exclusion diet starts to cow's milk, its derivatives and beef. Patient improvement. At 2 years, begins with rhinitis and diarrhea reappears with low weight. Colonoscopy (2007): Subacute nonspecific colitis histology. At 3 years old facial angioedema, throat and rash are associated with eating chicken, turkey, carrot and orange juice. New tests: specific IgE cow's milk, 24. 7 IU/mL (class IV), class II chicken. Prick test positive. At 4 years enter kindergarten, restarts with diarrhea and occasional angioedema. Cow's milk specific IgE (January 2009): 66, 6 IU/mL (class V). January 2010: 5 years post anaphylactic shock milk pudding. Besides diarrhea 10 times a day, intermittently throughout the year. Year 2011: intermittent diarrhea and specific IgE to cow's milk is kept in class V.

Conclusions: In this case the patient with CMA which evolved atypically because it has not been able to acquire tolerance. Moreover, awareness is added to other foods during their evolution. A recent study indicated a lower rate of development of clinical tolerance. As assessed by passing a milk challenge, 5 percent were tolerant at age 4 and 21 percent at age 8. Patients with persistent milk allergy have higher cow's milk sIgE levels in the first 2 years of life. Approximately 35 percent developed allergy to other foods.

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A Rare Case of Food-induced Anaphylaxis to Pink Peppercorns

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Background: The incidence and prevalence of food allergies appear to be on the rise over the past 20 years. The most common foods to produce an IgE mediated hypersensitivity reaction in adults include peanut, tree nuts, and seafood. The increased use of spices in the U.S. has resulted in a growing number of patients presenting with hypersensitivity reactions.

Methods: We report a case of a 26 year-old-female who developed anaphylaxis after ingesting pink peppercorn seasoning. The patient was diagnosed with a tree nut allergy at 18 years of age when she developed hives, vomiting and throat closure after ingesting cashews. More recently, she had 3 similar anaphylactic episodes requiring epinephrine and emergency room care when she unknowingly consumed tree nuts contained in foods while dining out (veggie burger, pesto sauce, almonds in Indian food). She again had similar symptoms while eating a home prepared meal in which tree nuts were not included. Intramuscular epinephrine was administered and she was subsequently treated with oral steroids and antihistamines. It was later determined that a new peppercorn medley with pink peppercorns was used for seasoning. The reaction did not occur when she ate the same meal without pink peppercorn seasoning. Food specific IgE testing revealed an elevated IgE for cashews (2.52 kUA/L) and pistachios (2.85 kUA/L).

Results: Pink peppercorn is not a true pepper, but dried roasted berries derived from *Schinus terebinthifolius*, a flowering plant in the family Anacardiaceae, native to South America. Common names include Brazilian Pepper, Rose Pepper and Christmasberry. Pink peppercorns are used as a spice to add a mild pepper-like taste to foods. It may potentially cause an irritating skin effect and has been associated with atopic dermatitis in canines. Interestingly, *S. terebinthifolius* is a member of the family Anacardiaceae, which include plants in the genus Anacardium (cashew nut) and Pistacia (pistachio). No allergens from this plant have been characterized but there is potential for cross-reactivity among different members of the Anacardiaceae family.

Conclusions: This is the first reported case of a patient developing anaphylaxis after pink peppercorn ingestion. Patients with tree nut allergies may need to be educated regarding this potential allergen.

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Multiple Manifestations of Food Allergy in a Patient with a Change of Eating Habits

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Background: Food-induced allergic reactions are responsible for a variety of symptoms and disorders involving the skin, gastrointestinal and respiratory tracts and can be attributed to IgE-mediated and non–IgE-mediated (cellular) mechanisms. Food allergy frequency varies according to age, local diet, and many other factors. The diagnosis of food allergy is based on clinical history, skin prick test (SPT), food specific IgE and more recently atopy patch tests (APT). If needed the use of an oral food challenge to confirm allergy or tolerance.

Methods: Describes the case of a patient with multiple manifestations of food allergy after eating habit change.

Results: Man 20 years with a history of food allergy to egg in childhood (at date in remission) asthma and rhinitis and urticaria in contact to cats. He presents an atopic dermatitis, recurrent abdominal pain and diarrhea 18 months after change in eating habits (he became vegetarian). He also presents oral syndrome with cow's milk. The patient had 4 episodes of anaphylaxis post prandial grade 3. In 3 of them the patient ate goat cheese and the other cow cheese. Also 2 of the episodes were associated with exercise. Skin prick tests with goat`s cheese: 13 mm, coẃs milk: 8 mm wheat: 3 mm, corn 3 mm, chicken 3.5 mm, egg yolk: 3.5 mm, avocado and rice 3 mm. Atopy patch test: (+ +) goat`s milk (+) peanuts and coffee. Total IgE 686 IU/mL. Foods with positive results were excluded from the diet and a complete remission of atopic dermatitis, abdominal pain, diarrhea and anaphylaxis was observed. All foods were reintroduced successfully except milk of goats and cows milk. The patient is currently asymptomatic.

Conclusions: The literature describes different kinds of manifestations of food allergy: immediate hypersensitivity (IgE mediated), delayed hypersensitivity (T lymphocytes mediated) and mixed. Highlights in this case an adult patient with a history of atopy who makes changes in eating habits, developping a food allergy to goat́s and cow s milk, with immediate (anaphylaxis, oral syndrome) and delayed manifestations (atopic dermatitis and chronic diarrhea).

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Wheat-dependent Exercise-induced Anaphylaxis Occurred in OAS Patient after Using Soap Containing Hydrolyzed Wheat Proteins: Effect of Soap on Keratinocyte Inflammasome

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Background: We present a case of Wheat-dependent Exercise-induced anaphylaxis (WDEIA) occurred in a patient previously suffering from atopic dermatitis (AD), pollen allergy and Oral allergy syndrome (OAS) after using face soap containing hydrolyzed wheat proteins (HWP) .

Methods: A 16-year old woman had contact urticaria after using face soap containing HWP and developed urticaria and dyspnea after ingestion of wheat products. We performed skin prick test, provocation test and serum IgE analysis by Western blotting.

Results: Provovation test, skin prick test for soap solution and HWP were positive and serum IgE molecules reacting to HWP were detected in the patient's sera.

Conclusions: WDEIA in this patient was considered to be induced after percutaneous sensitization with HWP in the soap. OAS is a Class 2 food allergy which is often shown in AD patients, and it is suggested that these patients have possibility to develop food allergy by percutaneous sensitization with various hydrolyzed food protein in cosmetics. We also examine the direct effects of the soap solution on keratinocytes inflammasome *in vitro* to explain the formation of percutaneous sensitization in this case.

FOOD ALLERGY DIAGNOSIS AND TREATMENT

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Possible Prenatal Sensitization: "The Case of the Hidden Cake"

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Background: To discuss the clinical case of an infant with food allergy and probably sensitization during pregnancy and/or breast-feeding.

Methods: Case report with clinical description of signs and symptoms, pictures from his skin prick tests and correlation with in vitro studies (Total IgE and specific IgE to casein, soy and egg).

Results: 7 month old boy with history of gastroesophageal reflux since 2 months old; product of the first pregnancy of a young mother with history of asthma during childhood, obtained by cesarean section. He received maternal human milk combined with normal infant formulae since birth to 5 months of age when he started other foods. He presented skin perioral rash with the ingestion of apple and sometimes with infant formulae and gastroenterologist changed to extense hydrolized formulae but the parents decided to give partial hydrolized formulae because of cost and taste. In his white blood cell count marked eosinophilia was noted (700/mL), elevation of total IgE (170 UI/mL; normal ≤ 15 UI/mL) and specific IgE (chemiluminiscence by immunoCap system) positive to Egg white (>300) (Class IV), Egg yolk (110) (Class III), Soy (260) (Class III) and Casein (21) (Class II). Skin prick tests reported (papules): negative saline control = 0 mm, positive histamine control = 5 mm, Soy = 4 mm, Cow's Milk = 12 mm, Egg = 34 mm. The boy had received cow's milk in infant formulae, soy in cookies given since 5 months of age and egg in cakes eaten by the mother in great amounts during pregnancy and breast-feeding.
Conclusions: Recomendations to avoid soy, egg and cows milk products were given to the parents, changing to an extense hydrolized formulae with good clinical results. The present case suggests that sensitization during pregnancy and breast-feeding to several foods can be present in high risk infants.

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The Evaluation of Allergen Sensitivity in Food Allergy Patients in Antalya, Turkey

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Background: In this study, the socio-demographic characteristics, skin prick test were evaluated in treated patients diagnosed with Food allergies.
Methods: The study was conducted in Antalya between 10 November 2009 and 20 September 2010. A questionnaire made by the investigators taking the latest literature data into consideration were used during the study. The total and specific IgE levels were made by fluoroenzyme immunoassay method via use of ImmunoCAP kit. For dermal prick tests Alyostal ST-IR standard allergen extracts were used. The statistical data derived were evaluated by using 14.00 SPSS software. Ki-Square test and percent ratios were used for data analysis. A P value less than 0.05 was assumed for statistical significance.
Results: During the study 173 patients: 116 female (67%), 57 male (32.9%) were included. Among patients 42% belonged to the 20 to 29 years of age group and 39% were University degree graduates. The total duration of the food allergy was 3.12 ± 0.39 years. The total Ig E level was 103.6 ± 11.5 Ku/L. The most common allergen was orange and kakao.
Conclusions: Food allergies are the most common cause of anaphylaxis and no pharmacologic treatments are available to prevent a reaction. The emergency use of epinephrine, antihistamines, and steroids are usually successful in treating a systemic reaction that is already underway. That's why; the allergen profiles of the regions must be determined and the dermal Prick tests must be prepared accordingly.

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Clinical Correlation of Prick and Prick-to-Prick Skin Tests to Food in a Group of Children with Allergy Symptoms

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Background: The food hypersensitivity IgE-mediated in children is of 1.6% to 6%. It can be manifested clinically as allergy in different devices and systems. Skin prick tests have a positive predictive value of less than 50% and 95% of negative predictive value. Prick-to-Prick tests have not been studied extensively.
Objective: To clinically correlate food hypersensitivity to Prick and Prick-to-Prick tests in a group of children with allergy symptoms in the skin, the gastrointestinal tract and the respiratory system.
Methods: A retrospective study done in the department of Pediatric Allergy of a Children's Hospital from June 2008 to May 2011. Data was taken from the records of 100 patients who gave positive to Prick and Prick-to-Prick food tests. We also looked for the clinical setting referred to by the patient. The frequency and CI 95% were analyzed by Chi^2. Out of the 100 patients, 48 were female and 52 male. These patients were grouped by age range. Fifteen patients fall within 1 to 2 years range, 15 patients fall within the 3 to 5 year range and 26 patients within the over-6-years range. Twenty patients presented asthma, 16 allergic rhinitis, 24 atopic dermatitis, 33 food allergy, 5 gastrointestinal eosinophilia, and 2 children presented other reactions. The tests were done with extracts of IPI ASAC Laboratories and fresh food. We considered that the tests that were positive were those with a wheal diameter greater than 3 mm over the negative control.
Results: 10%(95% CI, 4.12-15.88) of the patients had a reaction after the Prick test and presented clinical symptoms of which 30% were cutaneous and 70% gastrointestinal. Thirty six percent of the patients had a reaction after the Prick-to-Prick test (95% CI, 26.59-45.40)[$P = 0.005$] of which 17% developed respiratory symptoms, 22% skin, and 61% gastrointestinal. The main fresh foods with which the patients gave positive were: milk 16% (95% CI, 8.81-23.18), egg 10% (95% CI, 4.12-15.88), and wheat 7% (95% CI, 1.99-12.00). Prick tests like milk, eggs and corn could not be assessed properly by the sample size.
Conclusions: Prick-to-Prick tests are more effective than Prick to detect patients with food clinical reactions.

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Comparison Skin Prick Test Using Commercial and Native Extracts of Allergens in Diagnosis of Food Allergy

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Background: Patients with the birch pollen allergy frequently develop hypersensitive reactions to certain plant food. These reactions result from the similarity of allergen proteins structure, which are sometimes unbound phylogenetically. The aim of this study was to investigate the diagnostic value of immunoblotting method for patients with pollinosis.
Methods: Fifty eight patients were included in the study. The clinical history: the positive result of the skin prick test with the birch extract and symptoms after consumption plant food were the condition for qualifications. The immunoblotting was performed for the patients with the positive value of birch, apple, celery and/or carrot specific IgE to confirm the cross-reactivity.
Results: Sera of 13 patients (18 patients were analyzed) revealed positive results in the immunoblotting method. Sera of only 12 patients revealed the reaction against the birch pollen protein with a molecular weight 17 to 18 kDa corresponding to the main birch allergen Bet v 1. Sera of only 2 of these patients revealed the presence of antibodies cross-reacting with the apple protein with the same molecular weight, which may indicate the main allergens of these foods – Mal d 1. Serum of 6 patients revealed the presence of antibodies cross-reacting with apple and celery protein with the same

molecular weight, which may indicate the main allergens of these foods – Mal d 1 and Api g 1. Serum of only one patient revealed the presence of antibodies cross-reacting with the apple, celery and carrot protein with the same molecular weight, which may correspond the main allergens of these foods – Mal d 1, Api g 1 Dau c 1. Additionally sera of 6 persons demonstrated the presence of antibodies reacting with apple protein with the molecular weight 10 kDa which may correspond to the lipid transfer protein (LTP). Among some of the patients, antibodies which have not been identified so far reacted with birch, apple and celery proteins.

Conclusions: Although the immunoblotting is an effective method confirming the existences of the cross-reactivity, it still remains the method of verifying and supplementing other diagnostic tests, and a negative result doesn't exclude the existence of this kind of allergy.

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Natural History of Food Allergy in Childhood -3 Years' Follow up of Pediatric Food Allergy Patients

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Background: Food allergy (FA) is prevalent among children however natural history of FA is not fully clarified.

Methods: We sought to investigate the natural course of childhood FA. To follow up the transition of same patients, we collected clinical records of patients with 3 years' interval from 2008 to 2010. Four hundred ninety-one patients (male 321 and female 170) were recruited to this study.

Results: The onset of FA was at the age of 5 months ± 1 year 3 month (mean ± SD). The clinical type at the onset was with infantile atopic eczema (84.1%), and followed by immediate reactions without eczema (14.9%). The initial diagnosis age was 10 months ± 1 year 4 months, and the first visit to our department was 1 year 11 month ± 2 years 5 months. Current age of the patients was 7 years 5 months ± 2 years 11 months, and 444 patients (90.4%) had experienced immediate reactions. The number of eliminated foods decreased from 2.4 ± 1.5 items/patient (n = 1191) to 1.9 ± 1.6 items/patient (n = 926) in 3 years. The ratio of stopping elimination of major allergens was 35.9% (121/337 patients) for hen's egg, 25.6% (52/203 patients) for cow's milk and 47.8% (44/92 patients) for wheat. Fourteen patients (2.9%) had developed new food allergies, and 2 of them had experienced anaphylaxis by tree nuts. Newly diagnosed allergens were only 0.1 ± 0.3 items/patient (n = 32), and nuts (n = 6) and peanut (n = 5) were the most frequent. Seventy-nine patients (16.1%) had developed complete remission of FA in 3 years, and 21.5% of them (17 patients) had never developed immediate reactions.

Conclusions: Most of pediatric FA started during infancy with atopic eczema, and developing tolerance is expected with aging. In some patients, persistent FA is troublesome for school age children.

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Comparative Analysis of Patients with Birch Pollinosis and Patients with Associated Plant Food Allergy

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Background: Even 70% patients allergic to pollens of plants are developing undesirable symptoms after eating foods of the plant origin. It is most often a result of the cross-allergy between these allergens. The aim of the study was to compare the group of patients with pollinosis with patients with pollinosis and food allergy.

Methods: Fifty eight patients at the age above 16 were included in the study. Patients were divided into 2 groups. Patients included in the first group were birch allergic without any symptoms after eating food (23 persons). Patients in the other group had birch pollen allergy and they had reported clinical symptoms after eating foods such as: apple, celery, carrot, tomato, banana, peach, peanut and hazelnut (35 persons). The skin prick tests with pollen and food allergens (commercial and native) and serum IgE concentration (total and specific) were determined for all individuals. The immunoblotting was performed for the patients with the positive value of birch, apple, celery and/or carrot specific IgE to confirm the cross-reactivity.

Results: Patients with pollinosis and symptoms after eating plant foods were characterized by a significantly larger percentage of positive skin tests with the hazel allergen. In the first group patients revealed positive results of skin tests with food allergens, although they didn't reported the problem after consumption of them. No difference in total IgE levels was found between the 2 groups (271.5 ± 403.8 IU/mL vs 242.5 ± 340.9 IU/mL). Patients with birch allergy and hypersensitivity to food allergens showed significantly higher birch pollen specific IgE levels (11.8 ± 14.1 IU/mL vs 4.1 ± 6.6 IU/mL).

Conclusions: Sixty percent of all the patients with birch pollinosis reported manifestations symptoms after eating certain kind of food. These patients had most often clinical symptoms after eating apples, hazelnuts and of peaches, and less frequently symptoms after eating carrots, celery, peanuts, tomatoes and bananas. Although it seems that false positive results of skin tests with food allergens in the control group and the high level of the birch specific IgE might be the predictive factor of the allergy which may develop later; they require further studies.

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Frequency and Characterization of Oral Allergy Syndrome in Mexican Adults with Nasal Pollinosis

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Background: Oral allergy syndrome (OAS) is a common cause of food allergy in adults. Our objectives were to determine the frequency and to describe its clnical features in Mexican people with nasal pollinosis.

Methods: Diagnosis of OAS was made through the clinical history and a fresh-food-prick-by-prick test. The sample to estimate the frequency consisted in 100 consecutive subjects with a diagnosis of nasal pollinosis, whereas to describe its clinical featuring, we look for the findings in 30 patients with OAS from a Second Level Hospital. Statistical analysis included descriptive measures and Spearman's Rho Test for a correlation between clinical variables.

Results: The frequency for OAS was 13%. Mean age 29.9 years. By gender 26 women. Median for serum IgE was 160 UI/mL, while the average for total eosinophils was 278.2. The most common symptoms were oropharyngeal pruritus, followed by lip edema; the symptoms started in most of the cases within the first minute after eating the food. Predominant sensitizing aeroallergens corresponded to trees, among them, oaks. Twenty three different foods related to OAS were detected in total, mainly, peach (23 cases), apple (18 cases), pear (8 cases) and almond (7 cases). By anamnesis, 2 patients identified up to 8 foods. Evolution time of OAS correlated significantly to the evolution time of allergic rhinitis (Rho = 0.49; P = 0.006) and duration of OAS symptoms (Rho = 0.37; P = 0.05). Evolution time of allergic rhinitis and duration of OAS symptoms also correlated between them (Rho = 0.52; P = 0.003).

Conclusions: In a birch-free zone and sensitization to oaks and alders, as Guadalajara, in Mexico, OAS should be suspected as related to foods from Rosaceae family. The longer the evolution time of nasal pollinosis and OAS, the longer the duration of OAS symptoms.

FOOD ALLERGY EPIDEMIOLOGY

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Patterns of Sensitization to Common Food and inhalant Allergens and Allergic Symptoms in Preschool Children

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Background: The prevalence of sensitization to allergens and symptoms of allergic disease differ with regard to age, but the relationship is poorly understood. This study aimed to investigate the patterns of allergen sensitization and allergic symptoms with regard to age in early childhood.

Methods: A cross-sectional study was conducted on 629 children. Current allergic symptoms were assessed using the Korean-language ISAAC questionnaires adapted for preschool-aged children. The sensitization to five aero- and 3 food- allergens was evaluated by skin prick test.

Results: The prevalence of current asthma decreased (20.5%/8.2%), current rhinitis increased (36.1%/56.1%) with increasing age from 3 to 6 years, while no change in the prevalence of current eczema (16.9%/15.3%). Similarly, as age increased, sensitization rates to inhalant allergens increased (21%/33%), those to food allergens decreased (10%/2%). The prevalence of polysensitized children increased (8%/22%), monosensitized children decreased (18%/11%) with age, but atopic state did not change with age (27%/33%). The agreement rate between sensitization to dust mite and atopic state increased with age, showing a rate of 93% at 6 years ($P = 0.05$). The presence of atopic dermatitis in the first 2 years of life (aOR = 4.1, 2.2–7.6, $P < 0.001$) and polysensitization (aOR = 3.0, 1.4–5.0, $P < 0.005$) were significant risk factors for current rhinoconjunctivitis. In contrast, monosensitization was a risk factor for current asthma (aOR = 2.1, 1.1–4.1, $P < 0.024$) and current eczema (aOR = 2.1, 1.0–4.3, $P < 0.042$).

Conclusions: These data showed that the type and numbers of sensitization and allergic symptoms changed with age in early childhood. Polysensitization may play an important role in allergic march.

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Sensitization to Food Allergens in Patients of the Allergy Service of the University Hospital of Monterrey, Mexico

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Background: Food allergy occurs between 2 and 8% of the population and sensitization to food allergens be detected by skin prick test (SPT). To assess the frequency of sensitization to food allergens in patients attended in an allergy service of Northeast of Mexico.

Methods: We reviewed the records of patients in whom SPT were performed with food allergens extracts, from January 2008 to December 2010. The extracts were applied on the back surface with multitest in patients under 8 years old and with duotip in those over 8 years. According to age, patients were divided into 4 groups: I ≤ 2 years, II 3 to 5 years, III 6 to 18 years, IV > 18.

Results: 565 records were reviewed 56.8% of patients were female. 73.3% had at least one positive SPT. The most common diagnoses were allergic rhinitis (74.4%) and urticaria (10.4%). The most common positive SPTs in total group were: shrimp 61 (10.8%), cheese 58 (10.2%), beans 58 (10.3%), almond 57 (10.1%), Chile 53 (9.2%). According to the age groups, the most common positive SPTs were: I egg yolk in 12 patients (12.1%) and tuna 11 patients (11.1%), II peach 9 patients (11.4%) and tomatoes 8 patients (10.1%), III cheese 16 patients (13.4%), shrimp 15 patients (12.6%), almond 15 patients (12.6%), and IV shrimp 40 patients (14.9%), almond 34 patients (12.7%), beans 33 patients (12.3%).

Conclusions: Sensitization to food allergens were very common in our allergic patients. The most common sensitizing foods were shrimp, cheese, beans, and oats, although food sensitization varies among the different age groups.

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Frequency of Food-sensitization by Prick-to-Prick Test and Atopy Patch Test in Allergic Children

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Background: Food-allergy is a substantial and evolving health issue. We evaluate the frequency of food sensitization by prick-to-prick and atopy patch test (APT) in allergic children in a tertiary pediatric care center.

Methods: Cross-sectional retrospective study of prick-to-prick and APT tests made in atopic children attending to the Pediatric Allergy and Clinical Immunology outpatient clinic aged 6 months to 19 years. Patients were stratified in 4 groups according to age (<1, 1–5, 6–10 and >11 years), and by atopy-related diagnosis (asthma, rhinitis, food allergy, atopic dermatitis and eosinophilic gastroenteropathy).

Results: Total of 170 prick-to-prick with fresh foods were made, 135 were positive with the next distribution: milk 28.8%, (95% CI, 21.3-36.3%), egg white 20.1% (95% CI, 13.5-26.8%), banana 19.4% (95% CI, 12.8-26%). Sensitization to milk was most common in children aged 1 to 5 years old with 26.9% (95% CI, 17.1-36.8%) compared with corn, nuts and peanuts $P < 0.05$. Sensitization to milk was the most frequent in the food allergy diagnosis group with 27.1% (95% CI,15.8-38.5%) compared with wheat, corn and peanuts $P < 0.05$. A total of 140 APT tests were made, 105 were positive with the next distribution: soybeans 53.3% (95% CI,43.8-62.8%), peanut and chocolate both with 50.5% (95% CI,40.9-60,.0). This finding was sustained in patients with atopic dermatitis with soybean 55.6% (95% CI,36.8-74.3) compared to egg yolk. Sensitization to soybeans was most common in children aged 1 to 5 years old with 52.1% (95% CI,40.6-63.6) compared to rice and egg yolk $P < 0.05$. A different distribution was found for the 6 to 10 years old aged group: peanut 41.9% (95% CI,27.1-56.6) compared with egg yolk $P < 0.05$.

Conclusions: Milk is the most common food-allergen found by prick-to-prick in children independent of age or allergic diagnosis, with statistical significant difference, when compared to other food-allergens, in the group of food-allergy diagnosis and in the 1 to 5 years old age-group. Soybean is the most common food-allergen found in atopy patch test in the groups <1, 1 to 5 and >11 years old, independent of atopy related diagnosis, with statistical significant difference, when compared to other food-allergens in the group of atopic dermatitis and in the 1 to 5 years old age-group. For the 6 to 10 years old group peanut was the most common food-allergen found by APT, independent of atopy related diagnosis

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Increasing Incidence of Food Allergy in Zimbabwe

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Background: Data relating to allergic diseases in general and food allergies in particular in the Central African region is scant. Despite observations by

the ISAAC studies that airborne allergen sources were common, little has been reported about food allergens. We reviewed data from our laboratory and outpatient records of patients consulted to estimate the magnitude of the disease in our population.

Methods: Patients attending the only specialist allergy diagnostic facility in the country (Asthma, Allergy and Immune Dysfunction Clinic) were offered semi-quantitative allergen specific IgE antibody determination as part of their diagnostic work-up. Alongside skin-prick testing, the Euroimmun immunoblots were used to establish IgE reactivity to a variety of allergen sources.

Results: Six hundred thirty five patients were enrolled between January 2009 and April 2011. These were born between 1931 and 2010. IgE reactivity to egg, codfish, cows milk, wheat flour, rice, soya bean, peanut, hazelnut, carrot, potato and apple was investigated using the immunoblot technique. Results were scored negative or positive. The grades of positive were weak (±), low (+), moderate (++) and high (+++). Overall, 47% of the patients reacted to one or multiple allergen sources. Across the age spectrum, allergen specific IgE reactivity was most frequent against potato (16%) and peanut (15%) and lowest against milk (2.7%) and codfish (2.7%), others were intermediate. Egg white reactivity was highest in those below the age of 5 years (7%). IgE reactivity in patients born before 1959 was less than 1%. This increased to 3.4%, 4.8% and 64% respectively in those born before 1969, 1979 and 1989. Nineteen (19%) of patients born in 1990 to 1999 were reactive to a variety of food allergen sources. Likewise, 12% of those born between 2000 and 2011 were reactive. Food allergen reactivity paralleled inhalant allergen source sensitisation in all age groups.

Conclusions: In this sample of symptomatic patients we have shown that allergen specific IgE reactivity to dietary sources was high. An exponential increase in IgE reactivity in patients born between 1990 and 2011 was a surprising observation. Possible explanations include urbanisation, life-style and dietary changes in this predominantly urban population. The results call for a systematic investigation of the predisposing factors.

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Ten Years Follow up of Japanese Survey on Immediate Type Food Allergy

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Background: The food labeling system for food allergens was introduced from April 2002 in Japan. To confirm the effectiveness of the system, we regularly conduct a nationwide food allergy survey every 3 years.

Methods: The survey was conducted in cooperation with over 1000 volunteer doctors in Japan at 2001+2002, 2005 and 2008. We have sent questionnaires to contributing doctors every 3 months based on the previous survey system, and contributing doctors were asked to report immediate type food allergy cases seen by those doctors. In this survey, immediate type food allergy was defined as the patients who had developed symptoms due to food allergic reaction within 60 minutes after intake of causative foods. The details of questionnaire consisted of age, sex, cause of food allergy, symptoms, antigen-specific IgE, and type of onset.

Results: A total of 8581 immediate type food allergy cases were reported by the doctors in these surveys. The most common causative foods were hen's egg (39.0%), milk products (18.0%), wheat products (9.4%), fruits (5.3%), crustacean (4.6%), peanuts (3.7%), fish egg, buckwheat and fish (3.6%). The most common clinical symptom was observed on skin (89.7%) followed by respiratory system (29.6%). Interestingly, the causes of food allergy were completely different from infancy (egg, milk, and wheat) to adulthood (wheat, crustacean and fruits). Anaphylactic shock was observed in 10.9% of the total reported cases. The cases of anaphylactic shock were due to hen's egg (27.1%), milk products (21.4%) and wheat (18.1%). Eleven percentages of patients had been hospitalized.

Conclusions: We could clarify the detail of the immediate type food allergy cases seen in Japan for a recent decade. Based on these data, countermeasures against food allergy have been conducted in collaboration with the Ministry of Health, Labour, and Welfare in Japan in order to improve quality of life of patients with food allergy.

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Association between Cows Milk Allergy and Gastroesophageal Reflux Disease on Mexican People

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Background: The World Allergy Organization estimates 520 million people with food allergy on the world. The data that support the prevalence fluctuate in relation of the method employed to obtain these, for example, questionnaires, measurements of IgE-specific, oral challenges; the last one is considerate the gold standard. Similar situation occur to allergy to cow's milk (CMA), the prevalence reported is 1 to 17.5% in preschoolers, 1 to 13.5% in 5 to 16-year-olds, and 1 to 4% in adults. About 40% of infants referred for specialist management of Gastroesophageal Reflux Disease (GERD) have CMA. This situation increases to 56% in severe cases. These allergic reactions are typically not IgE-mediated. The gold standard for GERD is the pH measurement in 24 hours (specificity 100%), exist other test more accessible, with considerable sensivity (80%) like scintigraphy.

Methods: The objective was determinate the frequency of GERD in patients with IgE-mediated CMA. We evaluated retrospectively 20 patients with IgE-mediated CMA of a group of 47 patients with food allergy between 6 months to 39 years aged. They had one or more IgE-specific to proteins that are considered major allergens: casein, beta-lactoglobulin (BLG) or alpha-lactalbumin (A-LA). All the patients had study to discard GERD, through by scintigraphy (study with more access in our Institute). Patients with CMA and negative scintigraphy, had pH measurement. We made 3 groups each one to represent the positivity of IgE-specific to major allergens and these were associated with the presence or absence of GERD.

Results: GERD was found in 80% of patient with CMA. 77.8% of patients with IgE to casein had GERD diagnosed by scintigraphy ($P < 0.008$) Likelihood ratio obtained for this relationship was 7; 70% of patients with IgE to A-LA have GERD ($P < 0.03$), the likelihood ratio was 4. No significant difference was found between the presence of IgE to BLG and GERD. Additionally, we found that 40% of patients with food allergy without CMA presented GERD.

Conclusions: We found high association between IgE-mediated CMA and evidence of GERD on Mexican people opposed to previous literature.

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An Investigation of Food Choice Behaviour of Food Allergic and Non-food Allergic Children

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Background: Childrens food choice behaviour is influenced by a number of family and social factors. About 20% to 30% of the population modifies their diet for a suspected adverse reaction to food. Since avoidance is the mainstay of managing food allergy, it can be assumed to significantly affect food choices. It is therefore important to understand if and to what extent food allergy influences the way parents and children make their food choice decisions.

Methods: The research project has utilised an innovative observational approach in the form of a board game to investigate parental-child

communication and food choice behaviour. Parents/guardians and children were given a problem-solving task related to food choice behaviour. Each session lasted up to 15 minutes and was conducted with 5 food allergic and 7 non-allergic children (aged 4–8 years) and their parents/guardians. The sessions were videotaped and analysed by constructing a 4-category scheme, which classifies parental utterances along 2 dimensions, food choice behavioural control and food choice recognition. Observational categories were compared between the 2 groups.

Results: Preliminary findings indicate considerable variability in how parents/guardians and children with and without food allergy communicate when making food choice decisions. In general, children with food allergies seem to be more cautious and appear to have less responsibility when choosing their foods than healthy children of the same age.

Conclusions: Given the preliminary findings, this study will illuminate how food allergy affects the way parents/guardians and children make their food choice decisions.

FOOD ALLERGY GASTROINTESTINAL MANIFESTATIONS

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Probiotic Effect of the Regulation of Innate Immune Response, dc and Adaptive Cellular Immune Response and the Balance TH1, TH2, TREG Through Sensors TLR-2 AND TLR-4, on the Intestinal Mucosa in BALB/C Health Status and Balb/C Status of Exposure to LPS

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Background: The concept of improving host defense as a preventive effort in the face of exposure to pathogens through the gut mucosal immune system must be developed where the normal intestinal flora plays an important role. Probiotics through various research can improve intestinal mucosal immune system, but so far the effect of probiotics on the regulation of innate immune responses of dendritic cells and adaptive cellular immune response as well as the balance of TH1, TH2, TREG through TLR-2 sensors and TLR-4 on intestinal mucosa Balb/c healthy status and Balb/c LPS exposure status is unclear. The purpose is to examine the effect of probiotics against dendritic cells regulation of innate immune responses and adaptive cellular immune response as well as the balance TH1, TH2, TREG through TLR-2 sensors and TLR-4, on the intestinal mucosa in Balb/c health status and Balb/c status of exposure to LPS.

Methods: Male Balb/c divided into 4 treatment groups. Two groups given probiotics for 21 days, one group will be given exposure to LPS on day 15. One group will exposure by LPS alone and one group as control group without treatment. All groups terminated after a day-to-21. Immunohistochemical examination of ileal mucosa using monoclonal antibodies specific for dendritic cells, TLR-2, TLR-4, IL-1, IL-2, IL-4, IL-6, IL-10, IL-2, TNFα and TGFß.

Results: In LPS group there were downregulation both innate and cellular immune system indicates the occurrence of adaptive homeostasis disorders. In the group receiving probiotics there were upregulation both innate and cellular immune system is adaptive to indicate an alert. When the probiotic group exposured by LPS, it was still maintained by the improvement of the balance indicate TREG immune system remains in a state of homeostasis.

Conclusions: Probiotics can improve alertness status innate and cellular adaptive immune mucosa in healthy mice and can maintain the balance of TH1, TH2 and TREG so that homeostasis is maintained.

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Gluten Induced Systemic Disease (GISD) with Distinct Clinical Phenotype Different from Celiac Disease

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Background: Patients who have complex presentation involving multiple organs are difficult to diagnose. Non-infectious diseases that present with similar clinical patterns yet test negative to the known markers often arise due to certain change in environment or exposure. Such syndromes and diseases require careful study and call for new diagnostic modalities.

Methods: Patients who have complex presentation involving multiple organs are difficult to diagnose. Non-infectious diseases that present with similar clinical patterns yet test negative to the known markers often arise due to certain change in environment or exposure. Such syndromes and diseases require careful study and call for new diagnostic modalities.

Results: Average length of symptoms prior to diagnosis was 5 years. Of 42 patients 34 were previously treated for 3 or more health issues. None of the patients were previously diagnosed with celiac disease, 7 patients underwent diagnostic endoscopy with biopsies. Most prevalent symptom (94%) was severe fatigue. Following symptoms were reported on questionnaire: sleep problems requiring medications, concentration/memory problem, constipation, depression, headaches/migraine, gastroesophageal reflux, nocturnal muscle spasms, abdominal distension, joint pain, rashes, and gum recession. Most common laboratory abnormality was positive ANA with homogenous pattern. All but 2 patients tested negative to tTG, gliadin and endomyseal antibodies. Of 17 patients screened for food allergy 94% were positive for 10+4 foods by skin test. Hundred percent of patients reported significant improvement at 1 month interval with complete resolution of above listed clinical symptoms at 6 months. Best recovery was achieved in patients when treatment regimen included supplemental therapy with CoQ10, fish oil and digestive enzymes based on papain. Of 25 patients attempted gluten introduction after complete clinical recovery 100% reported relapse of symptoms within 48 hours following gluten challenge.

Conclusions: We report the emergence of new clinical phenotype of non-celiac gluten induced systemic disease (GISD). Although recent publications specifying existence and possible explanation of this condition arise, mechanism is not understood. Thus further studies are needed to facilitate recognition, testing and understanding of GISD.

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Patterns of Food Allergens in Kenyan Children

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Background: To determine the patterns of food allergens in children presenting to pediatric gastroenterology clinic at the Aga Khan University Hospital, Nairobi.

Methods: This data includes children evaluated from March to November, 2010. All the children presenting for evaluation of various gastrointestinal symptoms and who had positive history of atopy in at least one first degree relative were included. History of reccurent cough was sought and the skin was examined for eczema. Skin Prick Test was perfomed by an expert in allergy and immunology. Prick to Prick Test was done for local foods where commercial antigens were not available. Positive tests were followed by an exclusion and rechallenge progamme but this was excluded from analysis due to poor compliance. Analysis was performed to determine frequencies and associations of the different gastrointestinal symptoms and food allergens. Both skin Prick and Prick to Prick results were analysed together.

Results: The commonest food allergens in order of frequency were cow milk (65%), egg (35%), beef (26%), beans (14%), chicken, corn, wheat, soya and rice (9%), fish (8%) and peanut (5%). Common local infant complementary

foods including potatoes, bananas and vegetables all tested positive in 4% of the children. Pumpkin tested positive in one infant who had presented with rectal bleeding. Majority of the children had positive tests to multiple foods. Only 14% of the children had negative tests. The commonest gastrointestinal (GI) symptoms were abdominal pain (38%), constipation (36%), vomiting (14%), diarrhoea (11%), failure to thrive (9%) and colics (3%). Majority of the children had multiple GI symptoms. Eczema and cough were associated symptoms in 9% and 3% of the children respectively.

Conclusions: The prevalence of food allergy as suggested by this study is high in Kenyan children and contributes signficantly towards gastrointestinal morbidity. While cow milk, egg and beef are the commonest allergens, the emerging allergy to local infant complementary foods is also significant. The high frequency of multiple allergens partly contributed to poor compliance in the exclusion rechallenge programme due to lack of options on alternative foods.

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Coincidence of Celiac Disease and Gluten Allergy

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Background: The type I or IV of hypersensitivity reactions according to Gell and Coombs classification may be responsible for clinical symptoms observed after ingestion of gluten - containing products. The mechanisms of these reactions are either IgE-dependent or IgE-independent. Celiac disease based on IgE-independent mechanism is classified as gluten hypersensitivity. Clinical manifestation of celiac disease and gluten allergy is often similar. Correct diagnosis of this disease is particularly important due to the different long-term therapeutic procedures. We would like to asses of the incidence of celiac disease in children with gluten allergy.

Methods: The study involved 50 children with abdominal pain, chronic diarrhea, recurrent respiratory and ears inflammation and skin lesions - patients of the Immunological and Gastroenterology Outpatient Clinic of Institute of Mother and Child. The allergy to gluten was confirmed on the basis of positive peripheral blood lymphocytes blast transformation test and detection of allergen-specific IgE antibodies to gluten (f79). In all children plasma concentration of immunoglobulin classes A, G M and IgA or IgG antibodies against tissue transglutaminase (tTGA) were measured.

Results: In children on the study group the type IV of hypersensitivity reaction to gluten was diagnosed. In 3 children specific IgE antibodies to gluten was also confirmed (f79 - I type hypersensitivity). Anti-tissue transglutaminase antibodies both IgA and IgG were detected in 2 children in whom the concentration of IgA and IgG in serum remained within normal range for age. In these children celiac disease was confirmed by jejunal biopsy.

Conclusions:

1. The predominant frequency of type IV of hypersensitivity reactions in children in response to the gluten antigen should be taken into account in diagnosis of food allergy.
2. In children diagnosed with gluten allergy the test for celiac disease should be performed.

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Immunoreactivity of ß-Lactoglobulin and Identification of the Peptides Generated after Simulated Orogastrointestinal Digestion

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Background: The aim of the study was to evaluate the allergenicity of one of the main allergens from cow milk, β-lactoglobulin (β-Lg) after being digested through a simulated orogastrointestinal digestion and to identify those peptides generated during the digestion process.

Methods: The digestion was performed in 3 steps by using simulated oral, gastric and duodenal fluids. Digestibility of β-Lg was assessed by SDS-PAGE and RP-HPLC. IgE binding of native β-Lg and hydrolysates was evaluated by indirect ELISA, using the sera from 6 milk-allergic patients. The peptides produced during the orogastointestinal digestion, were identified by liquid chromatography tandem mass spectrometry analysis.

Results: Results showed that β-Lg was progressively degraded during the digestion. Intact β-Lg was observed after the gastric phase and in the first stages of the duodenal digestion. However, no residual β-Lg was observed at the end of the duodenal phase. Immunoassays showed that during the in vitro gastric and duodenal digestion immunoreactivity decreased progressively with an EC50 value increased 150 times at the end of the digestion. Among the products of digestion, 146 peptides were identified. No peptides were found in the oral phase. Forty five peptides were detected in the gastric phase, 71 in the duodenal, and 30 were common in both phases. Between those identified peptides, 4 of them with the sequences LIVTQTMK, GLDIQK, IDALNENK, and VLVLDTDYK had been previously described as epitopes of β-Lg.

Conclusions: β-Lg is progressively degraded during the digestion process. Similarly, β-Lg allergenicity is reduced through the simulated digestion with a severe reduction at the end of the duodenal stage. From the digestion products, 147 peptides have been identified. Studies are underway to evaluate the ability to cross the intestinal barrier and to bind to human-IgE of the most relevant identified peptides.

HEALTH OUTCOMES FOR ASTHMA

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Associations between Self-reported Adherence to Asthma Anti-inflammatory Therapy and Risk Factors for Non-adherence (NA) in Pediatric Patients

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Background: Identifying patient adherence status and reasons for non-adherence are important components of asthma management. GINA 2008 Guidelines have identified risk-factors associated with poor adherence

Methods: Three hundred sixty one parents of children with intermittent and persistent asthma (59.6% male; 64.1% Caucasian; mean age 8.07 years) completed the AsthmaPACT, a 96-item asthma survey hosted by the Asthma and Allergy Foundation of America website. The AsthmaPACT identifies risk-factors for not following treatment recommendations as well as medication use. Asthma surveys were completed from August 2009 thru June 2011.

Results: Descriptive statistics indicated that 259 of the sample reported giving their child one or more of the anti-inflammatory medication prescribed. Of these, 69 (27%) were diagnosed as NA, operationalized as whether a parent reported giving the child anti-inflammatory medication "less than prescribed by their physician." During the 4 weeks prior to completing the survey, 43.0% were having symptoms daily and 39.4% were using albuterol MDI daily. In this cross-sectional data set, items intended to relate risk factors to NA were examined using chi square (χ^2). Parents who claimed that their child receive less anti-inflammatory medication than prescribed, were more likely to report: 1) symptoms from emotional states: crying $\chi^2(df = 2) = 8.643$ $P = 0.013$; frustration $\chi^2(df = 2)$ 6.202 $P = 0.045$; anger $\chi^2(df = 2) = 11.029$ $P = 0.0042$); Parent more likely to see child as anxious or a worrier $\chi^2(df = 2) = 6.527$ $P = 0.038$; 2) Child's Quality of Life (QoL): is more likely to be effected at school $\chi^2(df = 2) = 12.963$ $P = 0.002$; and interfere with family activities χ^2

(df = 2) = 8.856 $P = 0.012$; 3) Parent's QoL is more likely to interfere with work χ^2 (df = 2) = 16.517 $P < 0.001$; recreational activities χ^2 (df = 2) 17.759 $P < 0.001$ and family activities χ^2 (df = 2) = 16.517 $P < 0.001$; 4) Parents are more likely not to agree regarding asthma management χ^2 (df = 2) = 7.677 $P = 0.022$; not to agree with relatives/caregivers on how to manage asthma χ^2 (df = 2) = 9.853 $P = 0.007$; lack confidence in teachers/school personnel to manage asthma at school χ^2(df = 2) = 20.216 $P < 0.001$.

Conclusions: The AsthmaPACT provides an assessment of 1) risk-factors for non-adherence and 2) patient self-report of adherence, and is readily available as a tool to individuals with asthma who have access to the Internet. Findings in this study are consistent with GINA 2008 Guidelines regarding common risk-factors for non-adherence and specifically to the child's emotional state and QoL for both the child and parent. The AsthmaPACT might be considered for symptomatic patients to identify barriers to treatment and diagnose adherence status.

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Inability of Medical Students to Use of Three Types of Inhaler

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Background: Several studies have demonstrated that a significant percentage of health care professionals are deficient in both knowledge and skill regarding the inhalers. But no data is available about the assessment of inhaler technique and knowledge among medical students in Korea. The aim of this study was to evaluate the proficiency and knowledge of medical students in proper use of 3 kinds of inhalers (metered dose inhaler, turbuhaler, and diskus).

Methods: We enrolled 40 third-year medical students who are on hospital training course. The participants received 25 to 35 minutes of instruction from a trained nurse educator for asthma. Three month later, we assessed their knowledge and skill regarding inhaler use. They were asked to discriminate each type of 3 devices and to demonstrate the use of each device using placebo inhalers. Also, they were asked about the prevention and management for local adverse reaction induced by inhaled corticosteroids (ICS). Participants's inhaler skill was assessed into 3 levels as good, inadequate, and poor for each device type.

Results: Only 12.5% (5/40) of medical students could explain the merits of inhalation therapy compared to oral route. 67.5% (27/40) of participants could not discriminate all types of inhaler devices. With regards to prevention and treatment option for ICS-related local side effects, only 22.5% (9/40) answered correctly. Subjects with good performance grade were found in 12.5% for metered dose inhaler, 40.0% for turbuhaler, and 57.5% for diskus.

Conclusions: We conclude that large percent of medical students were deficient in knowledge and proficiency regarding the inhalers. A brief educational session with demonstration by trained asthma nurse was not effective in enhancing inhaler technique or increasing knowledge on inhaler treatment.

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Impact of Providing Physical Education Teachers with Information about Asthma When Training Children and Adolescents with This Disorder

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Background: To assess the impact of providing physical education teachers with information about asthma and the progression of this disorder when training children and adolescents with this disorder.

Methods: A descriptive, applied, prospective, longitudinal and evaluation study was conducted with the participation of 160 children, with ages ranging from 9 to 12 years and 320 children aged 13 to 14 years from 4 different schools. Two subgroups for each age were established with a similar number of members. A subgroup with 80 students and another with 160 students were headed by 2 teachers instructed in handling students with asthma while the 2 remaining subgroups were headed by 2 teachers who did not have any knowledge about asthma. The following aspects were assessed: prevalence and severity of asthma, exercise-induced asthma, physical fitness and maximum expiratory flow at the beginning of the study and 6 months later.

Results: An 18.5% prevalence of asthma was observed among the 480 students; 28.1% in children from 9 to 12 years and 13.7% from 13 to 14 years. In the group of asthmatic children from 9 to 12 years, significant differences were observed in favor of asthmatic students whose teacher had received instruction with regards to: decreasing the severity of asthma ($P = 0.000$), lower incidence of exercise-induced asthma ($P = 0.0001$), increase in the results of physical fitness tests ($P = 0.009$). In the group of asthmatic children from 13 to 14 years old, statistically significant differences were also reported in favor of students whose teachers had received training with the following results: drop in exercise-induced asthma ($P = 0.000116$), higher values in the physical fitness tests of all students ($P = 0.00000$) and also in students with asthma ($P = 0.009436$). At the end of the study, both groups exhibited a significant increase in the maximum expiratory flow measurements of students in the group aged 9 to 12 years ($P = 0.000$) and in the group aged 13 to 14 years old ($P = 0.001$).

Conclusions: Teachers with knowledge about asthma had a positive impact on physical fitness and lowed exercise-induced asthma in students.

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Asthma Knowledge among Parents and/or Caregivers of Asthmatic Children Attending a Practical Allergy Course

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Background: Asthma is one of the most frequent chronic diseases, with worldwide prevalence of 1 to 18%. Patient and the patient's family education is considered by all International Guides fundamental to achieve this disease control. The aim of this study is to asses the asthma knowledge among parents and/or caregivers of pediatric asthmatic patients before and after attending to a Practical Allergy Course given at Hospital Infantil de Mexico Federico Gomez by the Pediatric Allergy Department.

Methods: Transversal Study that included 115 persons attending to a Practical Allergy Course that answered the previously validated instrument to asses the asthma knowledge among parents or caregivers NAKQ (*Newcastle Asthma Knowledge Questionnaire*); its Spanish version consisting in 31 questions; before and after the practical course. A descriptive annalysis was made; usefullness of the course was determinated by x^2. Stadistical packagge used was SPSS 17.

Results: A total of 115 questionnaires were applied, only 99 were properly answered and were included in the analysis; from these 35 were male and 64 female; 80% with high-school and middle school schooling; 92% were small families with 1 to 3 children; 90% of the families had only one child with asthma; 63% was receiving the practical course for the first time. Before attending the practical course the mean answered questions was 30 and after attending the mean answered questions was 31 (LR = 57.465; $P < 0.000$); for the first evaluation the mean correct answers was 19 and the latter 22 correct answers, finding statistical significant differences (LR = 30.253; $P < 0.000$).

Conclusions: We found improved asthma knowledge among parents and caregivers of asthmatic children after attending to a Practical Allergy Course.

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Ezhengtricity 2010: a Free Novel Way to Confidentially Administer, Track, Receive and Score Medical Questionnaires Instantly

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Background: Medical questionnaires are important for assessing allergy patients. However, current methods of administering questionnaires are cumbersome, expensive, and laborious to accurately administer, track and score. eZhengtricity is a simple Google Documents based workflow, coupled with customized Excel formulas, that allow researchers to create, collect and score confidential health questionnaires that are globally accessible, with minimal setup time and maintenance.

Methods: eZhengtricity utilizes a Google Documents account as a platform to create online questionnaires. Google automatically hosts the online questionnaire with a unique URL that can be provided to patients. The researcher provides patients with a unique study ID that is used to submit questionnaire responses. By using a unique study ID, researchers ensure confidentially of questionnaire data. Patient questionnaire responses are instantly submitted online to a secured "Cloud" database. In the Cloud database, the data is automatically sorted, scaled and scored by custom Excel formulas. Researchers can instantly access the database and download results in a variety of formats including PDF and XLS for further analysis using the researcher's statistical software of choice.

Results: eZhengtricity provided questionnaire scores from submitted questionnaires instantly, while paper versions required manual double entry and manual sorting of patient data for analysis. Better overall quality of patient responses was obtained with eZhengtricity compared to paper questionnaires. Submitted responses to eZhengtricity had 100 percent completion while submitted paper responses had incomplete responses. Patient compliance for eZhengtricity was comparable to paper questionnaires. eZhengtricity also allowed monitoring of patient's progress on completing questionnaires.

Conclusions: The flexibility and robustness of eZhengtricity complement longitudinal and cross-sectional studies. Compared to paper questionnaires, eZhengtricity is a cost effective, logistically easy, and superior way to administer confidential questionnaires.

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Usefulness of Asthma Control Test Questionnaire, FEV1 and Exhaled Nitric Oxide Level (FENO) for the Clinical Assessment of Elderly Asthma

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Background: Asthma remains a prevalent disease with significant morbidity and mortality, therefore numerous markers or measurements for the evaluation of its severity are available. Functional parameters, clinical assessment and biomarkers of inflammation are the most used. Also the diagnosis and treatment of asthma are often focused on young patients. This study was intended to determine the usefulness of patient-based questionnaire, Asthma Control Test score (ACT), forced expiratory volume in 1 second (FEV1) and exhaled nitric oxide (FeNO) for clinical assessment of elderly asthma patients.

Patients and Methods: Sixty seven (67) patients with a diagnosis of asthma more than 65 of age were enrolled. They performed spirometry, FeNO measurement and answered the ACT questionnaire. ACT is scored on a scale from 5 to 25 with higher values reflecting better control. Spirometry measures that met the American Thoracic Society criteria were included. FeNO was measured with values ≥35 ppb indicating probability of airway inflammation. Qui-square test was used for statistical analysis.

Results: 67 patients (15% female), mean age of 72.3 (65–89) were included. 25 patients (37.3%) were very poorly controlled, ACT ≤ 15 and mean values of FEV1 81.5+21.5 (% predicted) and mean FeNO of 41 ± 35 ppb. Thirty patients (44.8%) were not-well-controlled, ACT 16 to 19, FEV1 89% ± 16.8, FeNO of 40 ± 36 and 12 patients (17.9%) were well-controlled, ACT ≥ 20, FEV1 93.3 ± 16.8 and FeNO of 44 ± 35. FEV1 as >80% of predicted in 62.4% of patients (ACT 7–25) and 75% of patients with ACT ≥ 20 had FEV1 > 80%. The relation between ACT and FEV1 in this study was statistically significant ($P = 0.014$). There was no correlation when we evaluated ACT/FeNO and FEV1/FeNo variables ($P = 0.45$, 0.41 respectively).

Conclusions: A good correlation was found between ACT and FEV1, with higher ACT scores reflecting less bronchial obstruction. FeNO values had no correlation with ACT or FEV1, indicating that this marker of inflammation had less interest for assessment of asthma control in these elderly patients. In spite of these data, we still advise that the clinical assessment of asthma should be based on a combined approach that involves clinical aspects, functional parameters and biomarkers of inflammation, because elderly patients may have reduced symptom perception and have multiple co-morbidity.

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Systematic Review of the Recommendations on the Prevention of Allergic Manifestations in Children

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Background: A systematic review of the literature was performed to gather all official recommendations on the prevention in infants of allergic manifestations (AM), and, more specifically, atopic dermatitis (AD), by using hydrolyzed infant formulas (HF) whether partially or extensively hydrolyzed (PHF; EHF).

Methods: OVID MEDLINE and the grey literature were searched by 2 reviewers using the keywords AM, AD, prevention and guidelines. A third person acted as adjudicator in case of disagreement. Of interest were recommendations pertaining to the prevention of AM issued by national or regional associations of medical professionals.

Results: This review yielded 11 sets of guidelines published for Australia, France, Germany, Spain, Switzerland (all n = 1), Europe and the US (both n = 3), 1999 to 2010. Most guidelines included AD either specifically (n = 3) or within AMs. Most guidelines recommended a period of exclusive breastfeeding ranging from 4 to 6 months, and mentioned it as a major component of the primary prevention of allergic manifestations. Six guidelines (of which 2 recommended PHF over EHF) endorsed the use of HFs for the prevention of AM in "at risk" infants when exclusive breastfeeding was not or no longer possible. Two other publications did not recommend specific HFs, but formulas with documented reduced allergenicity. The need for an appropriate level of nutritional support was stressed in one publication. Five guidelines acknowledged that not all HFs have the same clinical protective benefit. Four publications underlined the importance of sound clinical evidence when determining the preventive efficacy of HFs and questioned the process leading to the development of national recommendations. None of the guidelines based their recommendations on recent evidence from meta-analyses of a specific brand of PHF.

Conclusions: HFs, specifically PHFs, is endorsed for the prevention of AMs, but not consistently. The need for a strong validity of the clinical evidence is

acknowledged by national or regional medical associations without however specific steps for relying on all the published evidence. Hence, recent evidence regarding the preventive efficacy of a specific brand of PHF, based rigorous clinical research, should provide the basis for new evidence-based recommendations.

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The Relationship Between Emotional Cognition and the Symptom Gap in Patients with Bronchial Asthma: the Effects of Alexithymia and Empathy

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Background: When symptoms are poorly controlled, patients with bronchial asthma may show a symptom gap: a cognitive divergence between the true severity of symptoms and the severity evaluated by the patients themselves. The aim of this study was to determine which factors (emotional cognition of the self and others) are associated with this symptom gap.

Methods: Forty-two patients with bronchial asthma, who were found with the Comprehensive Asthma Inventory (a bronchial asthma symptom questionnaire) to have psychosocial factors associated with a deep concern about the onset of asthma attacks, were studied by means of validated scales for alexithymia (the Toronto Alexithymia Scale-20) and for empathy (the Interpersonal Reactivity Index: IRI) and questions about how patients evaluate the severity of asthma.

Results: Of the patients, 42.5% showed a cognitive divergence regarding asthma symptoms. The scores for "perspective taking" on the IRI were significantly higher in patients who felt symptoms were less severe than they actually than in patients who felt symptoms were more severe than they actually were. No association was found between alexithymia and the symptom gap.

Conclusions: The results show that empathy, the ability to understand the emotions of others, is associated with a symptom gap in patients with bronchial asthma and that high scores for "perspective taking" on the IRI may indicate problems of treatment and symptom control in asthma.

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Asthma Control and Quality of Care of Adult Asthma Patients in Primary Health Care Facilities in Saint-Petersburg, Russia

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Background: This study was performed to assess the control asthma and quality of care of asthmatic patient in primary health care facilities in Saint-Petersburg, the second largest city in Russia.

Methods: We conducted telephone interviews with 205 asthma outpatients (aged 24 to 90 years). Asthma control was assessed by using the Asthma Control Test (ACT).

Results: During the past 12 month spirometry were performed in 26.8%. Only 2% of outpatients were consulted by allergist and 26.8% - by respiratory physicians. Inhaled corticosteroids were prescribed to persistent asthma patients in 79.1%, oral steroids for maintenance therapy were used in 7.3% of outpatients. Fixed combination of budesonide/formoterol and fluticasone/salmeterol were used in 45.4%. Asthma was uncontrolled for 72.2% of patients.

Conclusions: Quality of diagnostics and treatment of asthma in primary health care is not sufficient and should be improved.

HEREDITARY ANGIOEDEMA

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A 26-Year Review of Long-term Safety of a Human Pasteurized C1 Inhibitor Concentrate

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Background: Hereditary angioedema (HAE) is a rare disorder characterized by C1 inhibitor (C1-INH) deficiency, resulting in periodic attacks of acute edema. C1-INH replacement therapy is recommended as first-line therapy for treatment of acute HAE attacks, demonstrating rapid onset of symptom relief within 30 minutes or less. CSL Behring's human pasteurized C1-INH concentrate has been marketed since 1985 for the treatment of acute HAE attacks in Germany and numerous other countries.

Methods: We reviewed spontaneous reports of adverse drug reactions (ADRs) received by CSL Behring for its human pasteurized C1-INH concentrate, covering the 26-year period from 1985 until 31 December 2010.

Results: During the reporting period, human pasteurized C1-INH concentrate representing more than 550,000 treatments was distributed. A total of 101 cases of suspected ADRs were reported worldwide, with 62 cases covered by the product's known safety profile: allergic- or anaphylactic-type reactions (11; in very rare cases involving shock), chills and fever (4), lack of effect (26), suspected virus transmission (6; not attributed to the product), and thrombosis (16). Only 2 cases of thrombosis occurred when the product was used in the labelled indication; causality was assessed as unlikely in both cases (pre-existing cerebromalacia in 1 patient, and unspecified underlying pro-thrombotic condition in a second patient with morbid obesity). The other 14 cases of thrombosis occurred during off-label use of the product (substantially higher doses than indicated). Three reports were no ADRs (product exposure during pregnancy, administration failure). Of 36 cases involving isolated reports of varying symptoms not covered by the known product safety profile, causality to the product was established for only 1 case (lightheadedness and dizziness). According to the Council for International Organizations of Medical Sciences criteria, the overall ADR reporting rate for human pasteurized C1-INH concentrate is "rare".

Conclusions: Human pasteurized C1-INH concentrate has a well-established safety profile based on 26 years of post-marketing experience with more than 550,000 treatments. The product is safe and well tolerated when used at the recommended dosage in the treatment of acute HAE attacks.

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Efficacy of Icatibant Versus Fresh Frozen Plasma for Attacks of Hereditary Angioedema: Analysis of Indivudual Symptoms by Attack Site

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Background: Hereditary angioedema (HAE) is a rare disorder characterized by funcional deficiency of C1 inhibitor (C1-INH) resulting in unpredictable, acute swelling attacks at varied locations. Icatibant, a selective bradikinin B2 receptor antagonist, is a novel treatment for acute attacks of HAE. The aim of the present study was to compare the efficacy beteween icatibant and fresh frozen plasma (FFP) in the acute attacks of HAE.

Methods: We performed a retrospective analysis of acute attacks of HAE in a tertiary hospital. We compared the efficacy of icatibant with fresh frozen plasma as control group. Efficacy was measured as the median time to onset

of symptoms relief and the improvement of HAE and the median time to end of the attacks. Safety was assessed in terms of adverse events. All participants gave written informed consent.

Results: There were 21 acute attacks, 14 for icatibant and 7 for FFP. The median time to onset of symptoms relief was 27 and 45 minutes for icatibant and FFP respectively ($P = 0.106$). The median time to complete resolution of all simptoms was 240 and 2880 minutes respectively for icatibant and FFP ($P = 0.002$). All patients with Icatibant experienced generally mild transient injection-site reactions (erythema and swelling, and pain) wich resolved spontaneously without intervention. No drug-related serious adverse events were observed with icatibant and administration of FFP was not associated with infections of human inmunodeficiency virus, or hepatitis virus.

Conclusions: Icatibant was effective and generally well tolerated, providing rapid regression of symptoms associated with acute HAE attacks at all anatomic sites.

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Characterization of the Factors Triggering an Edematous Attack in Hereditary Angioedema

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Background: Hereditary angioedema due to C1-inhibitor deficiency (HAE-C1-INH) is characterized by recurrent attacks of subcutaneous and/or submucosal edema. The mechanisms involved in the development of edematous attacks are being researched extensively and thus, abundant information is available. By contrast, only a few surveys have been conducted on the triggering factors of attacks.

Methods: Data recorded between 2004 and 2010 by 97 HAE patients in their diaries have been analyzed.

Results: Eighty-nine of these 97 patients could identify possible factors, potentially related to the onset of attacks. Events associated with an increased propensity for having an attack were physical exertion in 64, mental stress in 53, and mechanical trauma in 53 of these patients. The average number of triggering factors recognized by patients was 2.7 in males and 4 in females. Based on the records of patient diaries, 3176 attacks were diagnosed and patients could identify the triggering factor in 30 per cent of these. The leading provoking factor was mental stress (21%). Analyzing interim distribution during a year showed a higher-than-average number of attacks in March, May, October, and December in almost all the 7 years studied. Clustering of the attacks in March was particularly typical of males and of attacks with an unknown provoking factor. Attacks triggered by stress clustered in the spring and in the autumn. Examining the trigger factors based on the location revealed different patterns among the trigger factors.

Conclusions: According to our results, 92% of patients can identify a factor that triggers an attack – this proportion is higher than that published in the literature. It is important to explore triggering factors, because avoiding these may reduce the number of apparent attacks. Physical exertion was the most common provoking factor. A possible triggering factor could be identified in almost one-third of the attacks. The seasonal clustering of stress-induced attacks shows similarity with the acute exacerbations of psychosomatic disorders. This suggests that psychological support may positively influence the course of the disease.

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Hereditary Angioedema: Report of Ten Mexican Patients at West National Medical Center in Guadalajara City

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Background: Hereditary angioedema (HAE) is an autosomal dominant inherited condition characterized by swelling of the skin, subcutaneous tissue, and the walls of almost all organs, including upper respiratory and gastrointestinal systems. The aim of this paper is to show the medical community clinical characteristics of 10 Mexican patients with HAE.

Methods: We reviewed medical records of 10 patients with hereditary angioedema.

Results: All are women, mean age 36 years; 4 of them with C4 0 mg/dL and the rest with serum levels less than 7 mg/dL. In all patients, C1 INH was determined quantitatively with low serum levels. It was also carried out qualitative determination of C1 INH with negative results in all patients. In 1 patient it was diagnosed also systemic lupus erythematosus.

Conclusions: All patients presented here have HAE type I and the diagnosis was made according to the criteria defined by Cicardi Zingale. They have been long-term treated with danazol with different response, dose range of 100 to 400 mg daily, depending of clinical response in each patient. In only 2 of them was used a selective bradykinin B2 receptor antagonist icatibant with good response.

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Clinical Features and Outcome of 82 Patients with Hereditary Angioedema

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Background: Hereditary angioedema due to C1 inhibitor deficiency is clinically characterized by relapsing skin and mucosal swelling, abdominal pain and life threatening upper airway obstruction. It still is a disease poor known by physicians and underdiagnosed.

Methods: We analyzed the clinical features and outcome of patients with Hereditary Angioedema from the Clinical Immunology and Allergy Division of University of São Paulo and compared them with literature.

Results: A total of 82 Hereditary Angioedema patients have been studied, 59 female and 23 male, with ages between 9 and 67 years. They belonged to 33 families and usually had begun to present clinical symptoms within the second decade of life. Diagnosis had been made from 06 months to 59 years after first symptoms. Spontaneous swelling was frequent, but attacks were also precipitated by trauma, pressure and emotional stress. Skin swellings were presented in 77 patients and abdominal pain attacks were related by 56 patients. Respiratory symptoms were experienced by 45 patients, 31 of them presented laringeal edema. Low levels of C4 had been noticed in all patients. Ninety percent of the patients presented quantitative deficiency. Prophylactic treatment with attenuated androgens was administered in low doses to 50 patients and was totally effective in 45, without significant side effects. Sixteen patients presented few or none manifestations without prophylactic medications.

Conclusions: The described patients are similar to those reported in literature and the prophylactic treatment with attenuated androgens has been effective in controlling manifestations. The diagnosis is still late for some patients.

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Differences of Complement Activation Profile between Type I and Type II of Hereditary Angioedema Due to C1-inhibitor Deficiency

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Background: In hereditary angioedema (HAE), diverse mutations in the C1-inhibitor gene may produce either normal C1-inhibitor protein in insufficient

quantities (HAE type I), or a dysfunctional protein in normal or even excessive amounts (HAE type II). Previously, we have found strong association between baseline level of functional C1-inhibitor and severity of HAE. Our aim was to investigate complement activation products in HAE, during a follow-up period, and to analyze the relationship between these products and severity of disease.

Methods: 107 HAE patients (96 HAE type I, 11 type II) and 113 healthy control subjects were included. C1rC1sC1-INH, C3bBbP, and SC5b-9 levels were determined using ELISA methods in single EDTA-plasma samples of controls and in 4 samples from patients taken in 4 subsequent years. Between-group differences were evaluated with the Mann-Whitney test, and correlations were calculated using non-parametric Spearman's correlation coefficients.

Results: Median levels of C1rC1sC1-INH (60 U/mL [40–113] vs 8 U/mL [4–10]; $P < 0.0001$) and SC5b-9 (0.6 U/mL [0.4–1.2] vs 1.8[0.9–2.8]; $P < 0.0001$) differed between patients and controls. Significant differences were found between HAE type I and type II as regards median C1rC1sC1-INH level (54 U/mL [33–97] vs 31 U/mL [21–49], $P < 0.0001$), and in an opposite manner with C3bBbP median levels (6 U/mL [4–12] vs 10 U/mL [8–17], $P = 0.0002$). Level of C1rC1sC1-INH correlated with the number of attacks ($r = 0.3546$, $P = 0.0004$) in HAE type I, but not in HAE type II. Dividing the patients into 2 subgroups based on danazol therapy, significant association ($r = 0.3705$, $P = 0.0026$) was found between level of C1rC1sC1-INH and annual attack number only in patients not treated with danazol. Similar results were found as regards the number of C1-inhibitor vials administered, which correlated with the level of C1rC1sC1-INH only in HAE type I ($r = 0.4288$, $P < 0.0001$) and in patients not treated with danazol ($r = 0.4783$, $P < 0.0001$).

Conclusions: Monitoring the level of C1rC1sC1-INH is mostly informative in HAE type I patients, who are not treated with danazol. No correlation was found in HAE type II patients between level of C1rC1sC1-INH and disease severity markers. As this observation may be explained by the small number of HAE type II patients, multicenter studies are needed, including more HAE type II patients.

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Peculiarities of HIV-specific Immune Response in Discordant Couples

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Background: In HIV discordant couples (one parther is HIV-infected, another is HIV-uninfected) HIV-negative partners often remain uninfected for a long time despite long, stable, often unprotected sexual contacts with HIV-infected partner. The increase of time of living together accompanying the decrease of the incidence of HIV infection in HIV-negative partner. The features of HIV-specific immune response in HIV discorgant couples was investigated.

Methods: Thirty-three HIV discordant couples from Moscow region living together <1 year (2 couples), 1 to 3 years (18 couples), 4 to 5 years (9 couples), 6 to 10 years (4 couples) were included in the investigation. Sera of 33 HIV-uninfected partners from HIV discordant couples (17 men and 16 women) were tested for HIV-specific antibodies by enzyme immunoassay and immunoblot. Viral load was estimated by polymerase chain reaction (PCR).

Results: Antibodies against HIV gp160 were detected in 3 persons (9,1%), against p68/66—in 3 persons (9,1%), against p52/51—in 3 persons (9,1%), against g34/31—in 3 persons (9,1%); total—in 6 persons (18,2%). All of them were defined as HIV-uninfected by PCR. In 4 of 6 persons HIV-specific antibodies were not detected after finishing of risk behavior.

Conclusions: It is possible to suggest that detected antibodies against HIV gp160, p68/66, p52/51, p34/31 in HIV-uninfected people are caused by contact with HIV (according to literature data, non-specific stimulation may cause the appearance of antibodies binding the other HIV antigens: p55, p24/25 and g18) and may contribute to maintainance of HIV-negative status of uninfected partners in HIV-discordant couples. The cohort of high exposed but HIV-uninfected people was formed during immunological monitoring of HIV discordant couples in Moscow region. This cohort is available for systematic observation and is perspective for further investigation of mechanisms of resistance to HIV infection and correlates of immune protection. Now the cohort is expanded.

HIV-RELATED PROBLEMS

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Detection of Dengue Virus in HIV-1-infected Patients during the Epidemic in 2009 in Colima, Mexico

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Background: This study reports a case series of HIV-1-infected patients that had dengue infection during the outbreak in 2009 in Colima, Mexico and it analyzes the effect of the interaction in relation to the progression of HIV disease.

Methods: Whole blood samples from 22 HIV-1-infected patients who were suspected to have dengue infection were analyzed. The diagnosis of dengue infection was confirmed through the detection of NS1 antigen using SD Bioline Dengue Duo Rapid Test. Dengue virus serotype was determined by RT-PCR technique. Amplicons were cloned and submitted for automated sequencing for both strands. Comparison of the sequences with all of those published in GenBank (NCBI) was done using Blast Software. Written informed consent was obtained under the protocol approved by the Ethical Review Committee of the Center for Biomedical Research, University of Colima.

Results: We tested 22 whole blood samples from HIV-1-infected patients in our laboratory, and 7 were positive for Dengue virus type 1. Two strains of DEN1 were identified in these infections. The strains were DENV-1/MX/BID-V3664/2006 (GenBank: GQ868499) and DENV-1/MX/BID-V3744/2008 (GenBank: GQ868529) with a similarity of 99% each. CD4+ cells remained at normal levels and it was not observed an accelerated progression of HIV disease.

Conclusions: This is the fifth and largest report dealing with a coinfection among HIV and Dengue virus in the world, and the first report documented in Mexico. The lack of complications associated with this interaction suggests that this combination is relatively benign. Little has been documented about the interaction among these pathogens and further research is needed to understand the biology of HIV reproduction in the context of coinfection with Dengue virus. Furthermore, this report supports the circulation of multiple genetic variations of DEN1 in hyperendemic areas which may complicate the epidemiological panorama of the disease in those areas.

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HPV, HSV2, HIV AND Chlamydia Trachomatis Infections as a Potential Accompanying Factor for Immunodeficiency and Development of Allergic Processes. Final Results

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Background: Infections caused by various microbes may induce immunodeficiency and allergies.
Methods: Clinical and laboratory tests were conducted on 579 potentially healthy people (172 women and 407 men, between 25 and 30 years), performed twice: in a diagnosis and after 6 to 12 months. Lymphocytes and NK cells from peripheral blood were assessed using cytometry. G, A, M immunoglobulin concentrations were determined by the turbidimetry. IgE concentration was measured by ELFA. HSV2, HIV and *Chlamydia trachomatis* infections were detected on the basis of presence of IgM and IgG antibodies tested by ELISA. For the assessment of HPV infections, DNA from the urinary-tract, squamous, and epithelial cells was tested through PCR. The statistical analysis was undertaken using regression analyses.
Results: In 579 people in the case of 65 people HPV infections were confirmed 10% men, 14.8% women. In 65 patients, in 1 case concentration of IgA was decreased, in 7 cases IgM. In 21 cases, there were higher concentrations of IgE. During the cytometric analyses a decreased number of T CD3+ was found in 3 cases, BCD19+ in 5, TCD4+ in 5, T CD8+ in 4, and NK cells in 8 cases. The check for HSV2 was positive for 17 people: 1.5% men, 6.4% women. In this group in 3 cases the concentration of IgA was decreased; in 2 cases IgM was lowered, in 4 cases there were higher concentrations of IgE. Decreased number of lymphocytes CD19+ was observed for 1 person and for 1 person NK cells. *Chlamydia trachomatis* infections were positive in 10 cases: 1.5% men, 2.3% women; in this group 1 person had lower IgA and 2 persons had increased concentrations of IgE. HIV infection was negative for all the groups. The examination was repeated for 171 out of 579 people after 6 months. HPV infections were positive in 12.9% cases: 14.9% men, 10.8% women; HSV2 in 11 persons: 2.3% men, 10.7% women; *Chlamydia trachomatis* in 4 cases: 2.3% men 2.4% women.
Conclusions: No significant correlation was observed between HPV, HSV2, HIV and *Chlamydia trachomatis* infections and a relevant deviation from the norm of the investigated immunological parameters.

HYMENOPTERA ALLERGY

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When Honeybees Attack: Adrenal Insufficiency as a Late Consequence of Massive Exposure

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Background: Evaluations of massive envenomation events have not commonly shown an increased risk for adrenal insufficiency.
Methods: A 77 year old woman and her 80 year old husband live part of the year in Bolovia where they have kept hives of Africanized honey bees for many years. Neither of them had shown evidence of bee sting hypersensitivity in the past. While tending their hives in a remote area, both were exposed to a massive number of stings (he $>$ 600, she $>$ 200) and barely survived. They are both wondering if they have become sensitized as a result of this event. After discharge from the hospital in Bolivia, she began to experience lethargy and was hospitalized again in Seattle with nausea, vomitting and eosinophilia. Abdominal CT scans showed bilateral adrenal enlargement/masses. Medline, PubMed and Google Scholar searches were performed looking for reports of adrenal insufficiency and bee sting anaphylaxis/exposure.
Results: Evaluation showed evidence of adrenal insufficiency and she has responded to replacement therapy. Subsequent abdominal CT scans have shown shrinkage and involution of both adrenal glands. Both husband and wife were evaluated for stinging insect hypersensitivity and found to be allergic only to honey bee venom and have begun desensitization. They intend to continue to keep honey bees in Seattle but not in Bolivia.
Conclusions: A single publication of 3 autopsy studies (Huang, I et al, JACI 1971) looking at venom-specific IgE in tissues showed intense localization in the serum and myocardium in 3 of 3 subjects and adrenal glands in 2 of 3 subjects all of whom died following a single honey bee sting. This would suggest that adrenal insufficiency may be a delayed complication of near-fatal massive envenomation and may play a role in immediate fatal events.

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Efficacy of Immunotherapy With Allergenic Extract of Aedes Aegypti in the Treatment of Large Local Reaction to Mosquito Bites in Children

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Background: Allergic reactions to insects are a global problem. The objective of this study was to assess the efficacy of immunotherapy with allergenic extract of *Aedes aegypti* for the treatment of large local reactions (LLR) to mosquito bites in children.
Methods: Experimental, comparative, prospective, longitudinal and randomized none blinded study was conducted. We included 2 to 15 year old children with a history of large local reactions to mosquito bites. Sensitization was confirmed by a positive prick test. One group was treated with subcutaneous immunotherapy with extract of *Aedes aegypti* during 5 months and a second group received only antihistamine as needed. Diary symptoms and medication use were recorded in each case. The presence of adverse reactions to immunotherapy was also documented.
Results: A total of 35 patients from August 2009 to September 2010. Twenty-eight patients completed the study (16 male were included, with mean 7 $\pm$ 2.5 years) 15 in the immunotherapy group and 13 in the control group. The immunotherapy group showed a decrease in the diameter of the wheal and flare as well as the duration of the reaction and the use of drugs, from the third month of treatment, compared with the control group ($P < 0.001$).
Conclusions: Our results suggest that immunotherapy with extract of *Aedes aegypti*, could modify the natural history of LLR to mosquito bites in children. Additional studies are needed to determine the optimal length treatment of the scheme and its long-term effects.

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Specific Venom Ige Decrease during 5 Years of Venom Immunotherapy (VIT): Clinical Relevance in Stung and Not Stung Patients

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Background: As the question of how long VIT should last in order to provide long-term protection is a long-standing issue, we evaluated the specific venom IgE decrease throughout 5-years-long VIT in 3 groups of yellow jacket (YJ) venom-allergic patients: stung during the first 3 years of VIT (SP3), during the last 2 years (SP5) and patients not stung (NS).
Methods: We retrospectively evaluated 232 patients submitted to 5-year-long VIT. Specific venom IgE levels were determined at the baseline, after 3 and 5 years of VIT (CAP method, Phadia, Italy). All stung patients were clinically

protected. ANOVA analysis evaluated differences among CAPs and in each CAP value among the 3 groups. MANOVA multivariate analysis evaluated differences in overall CAPs and the effects of age, gender, Mueller grade and stings number. A $P < 0.05$ was considered statistically significant. Data were analysed by 'SPSS' 13.0 (SPSS Inc., Chicago, IL). We called NS patients to check if they were stung after VIT discontinuation.

Results: We selected 84 NS, 72 SP3 and 76 SP5 patients. Specific YJ-IgE levels decreased during VIT, as CAPs are statistically different at time 0, 3 and 5 ($P < 0.001$). Considering CAP levels at the first control (CAP3), NS patients presented lower values than SP3 patients ($P = 0.002$); no significant difference was found between NS and SP5 patients. At the last control (CAP5), CAP values of NS and SP5 patients were different ($P = 0.002$) as well as between SP3 and SP5 patients ($P = 0.014$). No significant difference was found between NS and SP3 patients. By MANOVA, IgE decrease was inversely correlated with Mueller grade ($P = 0.012$) and age ($P = 0.002$). We recalled all NS patients by phone, 7/84 (8.3%) patients related one well tolerated sting, as they did not develop any allergic reaction.

Conclusions: In everyday practice if a patient never stung during VIT fulfils the temporal criterion, but specific IgE are not negative, a decrease of IgE levels ranging from 57 to 70% in respect to baseline might be a satisfactory parameter for stopping VIT. As a further confirmation of our conclusions, even if not statistically significant, all not stung patients were clinically protected after VIT discontinuation.

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Skeeter Syndrome, a Case Report and Literature Review

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Background: The worldwide prevalence of allergic reaction to mosquito bites is unknown. Some patients who suffer from local reactions have also systemic symptoms.

Methods: A 3 year old female who suffered from mosquitoes bites in her left lower extremity, had a large local reaction with erythema, edema, itching, pain and blisters of 5 × 6 cm. It was accompanied by fever of 38.5°C and emesis. She had a positive skin prick test for *Aedes aegypti w*ith diagnosis of Skeeter Syndrome. The patient was treated with antihistamine during 10 days and analgesics for 3 days. She was given antihistamine treatment for 10 days and analgesics for 3 days.

Results: Skeeter syndrome is defined as a large local reaction induced by mosquito bites associated with systemic symptoms (fever and vomiting) with specific IgE for mosquito identified by skin testing. The primary management of Skeeter syndrome is prevention of mosquito bites, the use of repellents and protective clothing. It is also important the symptomatic management control of pruritus with the use of antihistamines or if necessary topical steroids. Overall children with Skeeter syndrome remain healthy, except for the recurrence of large local reactions to mosquito Stings.

Conclusions: The early recognition of Skeeter syndrome is important to give the right management and to prevent unnecessary diagnostic tests and treatments that can increase the risk of adverse reactions and costs.

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Bee venom Immunotherapy with Standardized Extract, Two Case Comunication and Clinical Progress

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Background: Bee venom immunotherapy is a safe and effective treatment, indicated in patients with previous history of severe systemic reactions to bee venom, demonstrating succesful desensitization in more than 90% of cases with standardized extract. Currently in Mexico there is no standardized extract commercially available for treatment, despite of having high activity of beekeeping and occupational exposure with at least 17,478 registered stings per year and an annually honey production of nearly 70 tons.

Methods: We present the clinical progress of 2 patients with history of severe systemic reactions to bee venom and occupational exposure, both with demonstrated sensitization by specific IgE and who underwent specific immunotherapy with standardized extract (Alk-US) reaching a maintenance weekly dose of 100 mcg (PLA_2) for the last 4 years.

Results: Both patients sufered of accidental stings after reached the maintenance dose presenting mild local reactions to stings. Both patients had very different clinical course presenting a wide variety of adverse reactions during desensitization protocol; from mild local to generalized reactions all generally well tolerated allowed to reach the maintenance dose with succesful desensitization proved by accidental exposure without severe systemic reactions.

Conclusions: Bee venom specific immunotherapy with standardized extract is a well tolerated and efective treatment preventing the development of life threathening reactions in sensitized patients. It is important to promote the use and availability of standardized extract in developing countries with poor safety measures and high occupational exposure.

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Clinical Case. Bee Venom Anaphylaxis

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Background: Skin testing remains the principal confirmatory test for sensitization to hymenopteravenoms. Mechanisms on how venom induces vascular permeability in the skinfollowing intradermal testing are elucidated and how tolerance is induced followinghigh-dose venom exposure. For management, venom immunotherapy remains the mosteffective treatment. Use of immunotherapy in large local reactors to reduce morbidity is discussed. Baseline serum tryptase levels have been identified as one potential markerfor severe systemic reactions to a subsequent sting. Bee venom immunotherapy is effective in most patients immediately after the conventionalmaintenance dose has been reached. In the minority of patients who are not protected withthis dose, an increased maintenance dose will provide appropriate protection immediately after itis achieved usually by 3 to 6 months withstanding protocols. Thus, the dosage of the maintenance dose seems to be the major factor affectingprotection from re-stings rather than the accumulated venom dose or the durationon the Maintenance Dose. A rush protocol would be recommendedif the patient's risk of being stung againbefore standard immunotherapy could work wereconsidered high. Although immunotherapy is oftenadministered by allergists, it may be deliveredby any practitioner who is willing to observe the patientand to treat anaphylaxis if it should occur.

Methods: A 17-year-old man reported being stung by a bee in his workplace. He had been stung several times before, with no clinical manifestations. This last time, he developed face edema, respiratory distress, dyspnea, vomiting recieveing treatment with hydrocortisone. Some time later, he was stung another time, presenting more severe symptoms including dyspnea, stridor, altered mental status, hives, so he was taken to a local clinic where he received epinephrine, dextrose, was hospitalized 4 hours until clinical remission. How should his case be managed subsequently?

Results: Intradermal test was positive with a dilution 1:200000.

Conclusions: For patients with a clear history of anaphylaxis such as the one described in the vignette, information should be provided on avoidance and on the use of emergency treatment with epinephrine auto-injectors. Patients should be advised to carry an auto-injector and to wear a medical alert bracelet.

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Urticarial Vasculitis After Bee-sting Therapy

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Background: Bee-sting therapy is one of the oriental traditional medical therapies. Some chemical components of bee venom have been known to have anti-inflammatory effects. Recently, traditional therapists use one chemical component (e.g. Apitoxin) for injection therapy using a syringe, instead of sting method with bee itself as to be known traditional method. 31-year-old woman had a lower back pain because of mild HIVD in lumbar spine for 5 months. She had bee-sting therapies for several times for 4 months. During this period, she didn't have any side effects and pain was improved. Her back pain recurred 4 weeks ago and had bee-sting therapy again. The traditional doctor performed intramuscular injections of 1 mL of Apitoxin on her lower back muscle. After 4 days, reddish skin lesions and swelling developed on her legs and spread to trunk. She was transferred and treated with systemic corticosteroid and antihistamine.
Methods: Serum speicific IgE and IgG were measured by immunoCAP for and skin biopsy performed accompanied with managements.
Results: High levels of specific IgG but negative of IgE to honey bee venom were observed by immunoCAP. Skin biopsy was revealed as an urticarial vasculitis.
Conclusions: We report the case that suspicous to be serum sickness developed after bee-sting therapy.

IGE

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Levels of IL-4, INF-&GAMMA; Total IGE and IGG4 in Serum of Allergic Children within Areas of Risk of Lead Exposure in Torreon Coahuila, Mexico

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Background: There are precedents to suggest that lead exposure may increase the severity of allergic disease in children. In Torreon Coahuila is known the problem of lead contamination and its association with the body burden in children. The aim of this study was to evaluate clinical and biochemical characteristics of allergic disease in children living in areas at risk of lead exposure.
Methods: We included children between 6 and 11 years old with clinical diagnosis of allergy, who were attending by allergic consultation in the Center of attention Heavy Metals in Torreon, Coahuila, Mexico. Medical evaluation was performed following the diagnostic criteria described by ARIA, Global Initiative for Asthma and the Hanifin and Rajka criteria for atopic dermatitis. Skin tests were applied to 47 common allergens in the region. Were quantified in serum, the levels of IL-4, IFN-γ and IgG4 by ELISA, total IgE levels by chemiluminescence and lead in blood by spectrophotometry AA.
Results: We present the results of 33 patients (16 girls/17 boys) aged 8 ± 1.38. The main risk factors for allergy were current animal contact (66.7%), past animal exposure (60.6%) and passive smoking (51.5%). The predominant allergy diseases: rhinitis (97%), conjunctivitis (43.8%) and atopic dermatitis (33.3%). The allergens with the higher prevalence of responses were: thickets (91.2%) and grass (88.2%). The average blood lead level was 4.36 μg/dL ± 2.13 and median total IgE 660 IU/mL. We present the analysis of the levels of cytokines, total IgE and IgG4 according to the types of allergy, severity and frequency of the disease.
Conclusions: IgE levels according to the type of allergic disease, severity and frequency seem to be related to the balance IL-4/INF g. The IgG4 seems to be positively related to total IgE levels in rhinitis, conjunctivitis and dermatitis and negatively with Asthma and other allergies. No association was found between blood lead levels and total IgE.

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Relationship of Blood Lead Levels with Total Ige in Teenagers with Environmental Exposure in Torreon Coahuila, Mexico

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Background: There are precedents that suggest gender differences in the relationship of lead in blood with serum total IgE. The aim of this study was to evaluate in a population of teenagers attending 9 schools in Torreon, Coahuila, the relationship of lead in blood with total IgE and their dependence on gender.
Methods: We included 230 teenagers (105 females, 125 males) between 11 and 14 years of age, from a cohort of children evaluated for its history of lead exposure since 2000. Clinical diagnosis was performed to detect allergies; skin tests were applied for 47 common allergens in the region. IgE levels were quantified in serum by chemiluminescence and the blood lead levels by spectrophotometry AAS.
Results: The average blood lead levels in allergic group were of 4.86 ± 2.9 μg/dL and in the non-allergic group 5.1 ± 2.7 μg/dL. There were not gender differences between allergic group versus non allergic group, however, among the types of allergic diseases, a higher percentage of males had rhinitis, conjunctivitis and asthma, compared with the females. The blood lead level in males was significantly higher (5.61 ± 3.3 mg/dL) compared with females (4.22 ± 2.1 mg/dL) and the regression analysis between blood lead levels with total IgE was significant in males and not in females.
Conclusions: Gender differences observed appear to be explained by blood lead levels, however, we should consider the contribution of other variables in the model.

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IgE from Birch Pollen Allergic Patients Cross-reacts with Two Distinct Bet V 1 Related Proteins in Mung Beans: VIG R 1 and Cytokinin-specific Binding Protein

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Background: Mung beans (*Vigna radiata*) contain 2 Bet v 1 related proteins: Vig r 1, a member of the PR-10 subfamily, and cytokinin-specific binding protein (CSBP), a protein with low sequence identity (31%) to Bet v 1. We aimed to compare Vig r 1 and CSBP to Bet v 1 regarding biochemical and immunological properties.

Methods: Percent surface identity between Bet v 1, CSBP and Vig r 1 was calculated based on structural alignments using an algorithm considering backbone conformations and identities of aligned residues. The allergens were expressed in *Escherichia coli* and purified by metal chelate affinity and ion exchange chromatography. Secondary structures were compared using circular dichroism (CD) spectroscopy. Binding and cross-reactivity of IgE from Bet v 1-sensitized patients' sera to rCSBP, rVig r 1.0101 and rBet v 1.0101 were examined by ELISA and ELISA inhibition.

Results: Structural comparison of the 3 proteins revealed that 29% of the solvent-accessible surface area of CSBP was identical to Bet v 1, while Vig r 1 and Bet v 1 shared 50% surface area. In addition, 2 surface patches, conserved between Bet v 1 and CSBP, were identified as potential cross-reactive epitopes. 30% and 79% of Bet v 1-sensitized birch pollen allergic patients' sera ($n = 33$) showed IgE binding to CSBP and Vig r 1, respectively. Of 12 Bet v 1-sensitized patients, who reported reactions or had positive prick-to-prick tests to mung bean sprouts, 10 showed IgE binding to Vig r 1 and 7 to CSBP. Bet v 1 completely inhibited IgE binding to CSBP and Vig r 1. Furthermore, CSBP showed inhibitory activity on IgE binding to Vig r 1 and vice versa.

Conclusions: This study demonstrates IgE cross-reactivity between Bet v 1 and CSBP, despite their low sequence identity. In addition to Vig r 1, a PR-10 subfamily member, IgE binding to CSBP might contribute to allergic reactions in mung bean sprouts.

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Heterogeneity of the Ige Response to Allergenic Determinants of Cefotiam in Serum Samples From Patients with Cefotiam-induced Occupational Allergy

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Background: Exposure to cefotiam could cause IgE-mediated occupational allergies in hospital personnel. However, the clinically available serologic test has not been widely accepted, and the antigenic determinant of this drug is unclear. We investigated patterns of the IgE response to cefotiam in patients with occupational allergies to cefotiam.

Methods: A total of 161 health care workers and 86 nonatopic healthy controls, never exposed to antibiotics, were recruited from a single tertiary hospital and the general population. A questionnaire regarding work-related symptoms associated with cefotiam was administered. Serum specific IgE antibodies to cefotiam-human serum albumin (HSA) conjugate was measured by enzyme-linked immunosorbent assay (ELISA). Patients with work-related symptoms to cefotiam and positive specific IgE antibody to cefotiam were selected and ELISA inhibition studies were performed using sera of these patients. The inhibitors included various concentrations of free and conjugated cefotiam, ceftriaxone, ceftizoxime, and HSA alone.

Results: Four patients showed work-related upper respiratory symptoms and high levels of serum specific IgE to cefotiam-HSA conjugate compared to controls. Significant inhibition patterns to free cefotiam and cefotiam-HSA conjugate were noted in patient 1 on ELISA inhibition testing, while minimal inhibitions to the other cephalosporins, both free and conjugated, were noted. In the other 3 patients, significant dose-dependent inhibitions were noted with additions of cefotiam-HSA conjugate, while minimal inhibitions were noted with free cefotiam. Among the patients, patient 2 showed minimal inhibitions with the other cephalosporins, both free and conjugated, while patient 3 and 4 showed marked dose-dependent inhibition with ceftriaxone-HSA and ceftizoxime-HSA respectively.

Conclusions: The specific IgE response to cefotiam-HSA conjugate in patients with occupational allergies occurs against the hapten or new allergenic determinant in which heterogeneity of the antigenic determinant were noted depending on the individual.

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Evaluating Total Serum IgE Levels in Patients with Chronic Hepatitis B and C

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Background: Liver disease has been considered a prominent cause of IgE elevation. Significant differences may be observed depending on the cause of liver damage. For viral hepatitis, increased IgE concentrations have been observed during acute hepatitis A and B. Chronic hepatitis B carriers may also have high IgE levels. But no data on serum IgE levels in chronic hepatitis C and hepatitis B patients have been reported. The aim of the study was to evaluate serum IgE levels in patients with chronic hepatitis C and hepatitis B and to corelate with atopic patients.

Methods: Serum IgE levels were determined in 568 adult patients with chronic hepatitis B, in 47 patients with chronic hepatitis C, and 311 patients with atopic diseases.

Results: The averages of serum IgE levels were 103,9 IU/mL in chronic hepatitis C, 95,1 IU/mL in hepatits B patients, and 126,6 IU/mL in atopic patients. There was no statistically significant difference between hepatits B and hepatits C patients. Total serum IgE levels were lower in patients with either chronic hepatitis C or hepatitis B than the atopic group.

Conclusions: According to the results presented, chronic hepatitis C and hepatitis B are not prominent causes of increased serum IgE values. Further studies are needed to clarify the differences and significance of IgE levels between hepatitis and atopic patients.

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Relationship Between Total Serum IgE, Atopy, and Obesity in Children With or Without Family History of Atopic Disease

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Background: Prevalence of obesity and atopy had been increased simultaneuosly. The relationship between obesity, atopy, and total serum IgE had been estimated. The aim of this study is to find out the relationship between total serum Ig E, atopy, and obese children with or without family history of atopic disease.

Methods: This was a cross sectional study. There were 160 children aged 6 to 11 years which were divided into 4 groups: obese children with and without family history of atopic disease and normal weight children with and without family history of atopic disease. Atopic was defined by positive result of one of allergens skin prick test and ECLIA method were done for total serum IgE. Significancy for categorical data used Chi-Square test. Logistic regression

model were used to examine the relationship between obesity, total serum IgE, and atopy.
Results: We measured the total serum IgE of 155 children. The number of obese and normal weight children with family history of atopic disease who had high level of total serum IgE were 30 and 25 respectively, whereas these children who had normal level of total serum IgE were 6 and 15 respectively [OR = 1.9 (95% CI 0.9-3.9)]. On the other hand, obese and normal weight children without family history of atopic disease who had high level of total serum IgE were 21 and 11 respectively, whereas these children who had normal level of total serum IgE were 18 and 29 respectively [OR = 1.7 (95% CI 1.1-2.7)]. The number of obese and normal weight children without family history of atopic disease who had atopy were 38 and 9 respectively, whereas these children who had non-atopy were 2 and 31 respectively [OR = 13.3 (95% CI 3.5-52)], but there was no relationship between atopy and obesity in group with family history of atopic disease ($P = 0.314$).
Conclusions: There were relationship between high level of total serum IgE and obesity in group with and without family history of atopic disease and also relationship between atopy and obesity in group without family history of atopic disease.

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The Candidate Peptides in IgE for Allergy Vaccine Design

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Background: The World Allergy Organization in 2011 estimated that 30 to 40% of the world population is now affected by one or more allergic conditions. Since the IgE plays a central role in the expansion and regulation of allergic response that seems the IgE elimination is the best approach in the control of asthma and allergic diseases. Now, an anti-IgE antibody as a drug (Xolair) is available and efficient but is expensive with short half-life. As good and more efficient substitution IgE peptide-based vaccines has been proposed.
Methods: In this study, we analyzed all potential antigenic peptides on the constant region of the Ig epsilon chain (Fcε). For determination of B cell immunodominant epitope, we used the antibody epitope prediction tools. In continuing candidate peptides were done BlastP to avoid nonspecific antibody reactions with other human proteins in the NCBI database. And then, to preparation of vaccines, peptides were synthesized and conjugated by Tetanus toxoid (TT). To immunogenicity analysis of vaccines, the rats are being immunized with vaccines or TT as control.
Results: By Kolaskar and Tongaonkar antigenicity algorithms 20 peptides with putative epitopes were selected. Homologous sequences and also previous studies peptides were excluded, 13 peptides remained that used for vaccine preparation. The produced vaccines are being analyzed for their effect on induction of anti-IgE antibody production. Peptides based on antibody production or not, were divided in 2 groups.
Conclusions: Active immunization by IgE peptide based vaccines can be triggering production antibodies against self-IgE that are effective in preventing and control of IgE levels as an important factor in asthma and allergic diseases.

IMMUNODEFICIENCY

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Severe Autoimmunity with Polyarticular Joint Disease Requiring Anti-TNF Therapy and T+B-NK+ Immunodeficiency in a Family with Small Stature and Intermediate Radiation Sensitivity

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Background: We have identified a family in which 3 of 4 children are affected with significant autoimmunity and immunodeficiency that does not fit any of the known disorders. We have embarked to characterize their defect and describe a completely new disorder.
Methods: Whole Exome Sequencing, T and B Cell Immunophenotyping, Radiation Sensitivity, Bacteriophage.
Results: The oldest affected child is female with severe polyarticular arthritis (treated with etanercept), eczema, diarrhea, short stature and numerous infections including pneumonia. She is s/p bone marrow transplant using a matched sibling donor, is fully engrafted and doing well. The second affected child was also female and had numerous episodes of pneumonia, bronchiolitis, otitis media and conjunctivitis. She died at 11 months from presumed fulminant CMV hepatitis. The third affected child is male with hypothyroidism, chronic diarrhea, alopecia totalis, eczema, multiple food allergies, reactive airway disease and short stature. All had normal CD4+ and CD8+ T cell and NK cell numbers but marked B cell lymphopenia. T cell immunophenotyping demonstrated a modest decrease in effector memory T cells. Mitogens were normal. B cell immunophenotyping demonstrated a dramatic block in B cell development at the transition from immature to mature B cells suggesting a defect in immunoglobulin gene rearrangement. All affected patients were hypogammaglobulinemic. Immunization with bacteriophage ΦX174 to more thoroughly evaluate humoral immune responses demonstrated a poor immunoglobulin response with only modest amplification and markedly decreased immunoglobulin class switching. Radiation sensitivity testing using skin fibroblasts was performed and demonstrated an intermediate radiation sensitivity. Sequencing of the *RAG1*, *RAG2*, and *Artemis* genes was normal. Evaluation via western blotting of other components of the DNA repair machinery that lead to defective immunoglobulin gene rearrangement and radiation sensitivity was normal.
Conclusions: The overall clinical and laboratory picture of severe autoimmunity with a T+B-NK+ phenotype is unusual and does not fit any known immune defect. The CMV susceptibility suggests that even though T cell numbers and proliferation are normal, there may be a subtle defect in T cell function. We are currently in the process of whole exome sequencing and optimistic we will find a novel defect in DNA repair.

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Autoimmunity in Patients with Allergy and Immunodeficiency: as Result of the Immune Chronic Inflammation

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Background: Autoimmunity is present in several patients that have allergy and immunodeficiency; however there are few reports that correlate these 3 immunological problems. Our objective was to study the association of these 3 problems where the deregulation of the T reg cells has a roll in triggering a chronic inflammation and the clinical expression.
Methods: We included 8 patients with symptoms of autoimmune disease, such as autoimmune hypothyroidism, dermatomiositis, systemic vasculitis, autoimmune uveitis, Wegener's granulomatosis, antiphospholipid syndrome, Kawasaki's disease and SLE with allergic disease and T and B lymphocytes immunodeficiency. We did the clinical history, skin test and also immunological evaluation with immunoglobulins, IgG subclasses, T lymphocytes absolute numbers and specific antibodies, all of them had diagnosis of allergy, with immunodeficiency and autoimmune disease.
Results: There were included 8 patients, with moderate to severe allergy and recurrent infections, from 3 to 66 years of age, 1 child (12.5%) and 7 adults (87.5%), 7 women (93.3%), 1 men (12.5%) with allergic rhinitis 8 (100%), combination of allergic rhinitis and other allergic disease 2 (25%), asthma 1 (12.5%), atopic dermatitis 1 (12.5%). Also all the 8 patients had humoral, cellular immunodeficiency and autoimmune problems, 7 of them received

IVIG therapy on the basis of the immunodeficiency, with evident improvement, 1 did not received and had some improvement of their symptoms.
Conclusions: We found out that the 8 patients with autoimmunity had allergy and also mixed T and B immunodeficiency. We conclude that the physicians should be aware of the correlation in chronic inflammation and the presence of the 3 immunological clinical problems to give appropriate treatment and improve the prognosis of these patients.

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HPV, HSV2, HIV AND Chlamydia Trachomatis Infections as a Potential Accompanying Factor for Immunodeficiency and Development of Allergic Processes. Final Results

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Background: Infections caused by various microbes may induce immunodeficiency and allergies.
Methods: Tests were conducted on 579 potentially healthy people (172 women and 407 men, between 25 and 30 years), performed twice: in a diagnosis and after 6 to 12 months. Lymphocytes and NK cells from peripheral blood were assessed using cytometry. G, A, M immunoglobulin concentrations were determined by the turbidimetry. IgE concentration was measured by ELFA. HSV2, HIV and *Chlamydia trachomatis* infections were detected on the basis of presence of IgM and IgG antibodies tested by ELISA. For the assessment of HPV infections, DNA from the urinary-tract, squamous, epithelial cells were tested through PCR. The statistical analysis was undertaken using regression analyses.
Results: In 579 people in the case of 65 people HPV infections were confirmed 10% men, 14.8% women. In 65 patients, in 1 case concentration of IgA was decreased, in 7 cases IgM. In 21 cases, there was higher concentration of IgE. During the cytometric analyses a decreased number of T CD3+ was found in 3 cases, BCD19+ in 5, TCD4+ in 5, T CD8+ in 4, and NK cells in 8 cases. The check for HSV2 was positive for 17 people: 1.5% men, 6.4% women. In this group, in 3 cases the concentration of IgA was decreased, in 2 cases IgM was lowered, in 4 cases there were higher concentrations of IgE. Decreased number of lymphocytes CD19+ was observed for 1 person and for 1 person NK cells. *Chlamydia trachomatis* infections were positive in 10 cases: 1.5% men, 2.3% women, in this group 1 person had lower IgA and 2 persons had increased concentrations of IgE. HIV infection was negative for all the groups. The examination was repeated for 171 out of 579 people after 6 months. HPV infections were positive in 12.9% cases: 14.9% men, 10.8% women; HSV2 in 11 persons: 2.3% men, 10.7% women; *Chlamydia trachomatis* in 4 cases: 2.3% men 2.4% women.
Conclusions: No significant correlation was observed between HPV, HSV2, HIV and *Chlamydia trachomatis* infections and a relevant deviation from the norm of the investigated immunological parameters.

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A 3 Year-old Child with Specific Antibody Deficiency and Allergic Rhinitis. A Case Report

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Background: Specific antibody deficiency (SAD) is a humoral immunodeficiency characterized by normal levels of IgG, IgA, IgM and IgG subclasses but a failure to polysaccharide antigens, manifested with recurrent bacterial respiratory infections. To establish the SAD diagnosis an inadequate IgG antibody response to more than 50% of pneumococcal serotypes after unconjugated pneumococcal immunization are needed. An adequate response is defined as a post-immunization titre of ≥1.3 μg/mL or ≥4 times the preimmunization value.[1,2]
Methods: The record of 1 patient was review and relevant clinical data was collected. A review of the literature about SAD was made.
Results: A 4-year old male with family history of atopic disease, esophageal reflux at 3-months, he began with recurrent upper respiratory tract infections at 1-year old, 1 to 2 events per month, fever (39–40° C), persistent cough and hyaline rhinorrhea, nasal itching and sneezing he was treated with multiple antibiotics, inhaled and oral corticosteroids with mild clinical recovery between episodes. A normal blood cell count and normal levels of IgG 1219 mg/dL, IgA 146 mg/dL, IgM 98 mg/dL and IgG subclasses were determined. Allergic rhinitis and asthma were diagnosed at 3-years old, percutaneous prick skin test was positive to *Dermatophagoides farinae, Salsola pestifer, Phleum pratense, Heliantus sp.* and specific immunotherapy was started. Despite of treatment he continued with recurrent infections so specific antibody response to polysaccharide pneumococcal antigens was evaluated, he responded less than 50% to 14 pneumococcal serotypes after 23-valent unconjugated pneumococcal vaccine, so SAD was diagnosed and treated with prophylactic antibiotic, pneumococcal polysaccharide conjugated vaccine (10-valent) and specific immunotherapy. He showed clinical improvement, with few mild infections, and controlled rhinitis and asthma.
Conclusions: There are several Primary Immunodeficiency Diseases related to allergic diseases as IgA deficiency and SAD. In the atopic patient that does not improve in spite of specific immunotherapy further investigations are needed to exclude them.

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Silvery-gray Hair Patient with neurologic deterioration

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Background: Griscelli syndrome is a rare autosomal recessive condition characterized by pigmentary abnormalities, particularly greying of the hair. Type 1 is associated with severe neurological impairment and type 2 with immunological problems, whereas type 3 is limited to the pigmentary phenotype.
Methods: We describe the presentation of a 3 year old female silvery-gray hair patient with neurological deterioration.
Results: A 3 year-old Mexican female was refered to our hospital. Relevant history: Consanguinity parents, 2 males from father side died in infancy, both presented grayish hair. Normal development milestones until 2 and a half years of age. (Including bladder and bowel control). Immunizations up to date. No prior history of infections. At 11 months of age cutaneous lesions leaving atrophic scars, with a chronic evolution. At 2 years 6 months old she started presenting demential picture, with impaired language, abnormal gait, with a significant decline of previous level of functioning. Hospitalized in another state hospital with diagnosis of Infection of central nervous system. Due to worsening evolution despite treatment she was refered to our institution. She was admitted to Intensive Care Unit, requiring mechanical support due to a pneumonia. On physical examination the most striking

feature was an unusual silvery-gray pigmentation of her hair, eyebrows and eyelashes, crackles in both lungs, no adenomegalies, no hepatosplenomegaly. Analysis of hair shafts was carried out at the time of hospital admittance and showed abnormal clumping of the pigment granules, as seen in Griscelli syndrome. During her clinic evolution the neurological deterioration was progressive. Serial exams for haemophagocytic syndrome (accelerated phase) were negative (ferritin, transaminases, CBC, triglycerides etc). Her condition deteriorated during the following days. Treated at the Intensive Care Unit with multiple broad spectrum antibiotics, she developed respiratory insufficiency, refractory shock, multiorgan dysfunction, and died on her 23rd hospital day. A cerebral biopsy reported necrosis and chronic inflammatory infiltrate.

Conclusions: The results of molecular analysis is in process: griscelli type 2 (rab27a mutation) or elejalde syndrome (myo5a mutations) are the 2 considerations.

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Differences in Humoral and Cellular Immunity in Young and Old Individuals

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Background: The immune system changes with the age. In this study we characterized immune changes by performing immunologic screening profiles on aging individuals (graduation thesis).

Methods: This study was performed at Akdeniz University, in the Faculty of Medicine, Dept. of Immunology. Healthy volunteers consisted of a young group (22 donors) and an older group (45 individuals). Using flow cytometry analysis, CD3, CD4, CD8, CD16, CD19, CD28, CD40, CD45, CD56, CD80, CD86, CTLA-4 and with ELISA IL-1 β, IL-2, IL-6, IL-10, IFN-γ, TNF-α expression were evaluated, along with and NK activity and induced cytokine expression (by bioassay/ELISA respectively).

Results: No statistical differences were observed between the 2 groups in expression of CD3, CD8, CD19, CD80, CD86, CD16, CD 56 or CD28. A higher frequency of expression of CD4, CTLA-4, CD40 and CD45 was seen in older subjects by comparison with young subjects. Cytokine profiles expressed by stimulated monocytes from the 2 groups showed no difference in IL-1 β, IL-2, IL-6, IL-10, TNF-α and IFN-γ production levels. Cytokine profiles expressed by stimulated lymphocytes from the 2 groups showed no difference in IL-1 β, IL-2, IL-6, IL-10, TNF-α and IFN-γ production levels.

Conclusions: We found increased expression levels of CD40 and CD45 levels in healthy older (>55 years old) versus young individuals (media age 28 years). CTLA-4 expression levels were also higher in elderly subjects, with no difference in CD28 expression levels between young/elderly individuals.

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Analysis of the Immune Status in the Acute Phase of Viral Respiratory Infections in Children

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Background: Viral infections can cause severe symptoms in the upper and lower respiratory tract. These are very common in childhood and occasionally seem to be an intractable problem. The aim of our study was to investigate the serum cytokine levels and other inflammatory parameters in the acute phase of viral respiratory infections and after 1 month.

Methods: We investigated the peripheral blood cell, leukocyte counts, C-reactive protein (CRP) levels, serology of respiratory viruses and serum IL-1, IL-2, IL-4, IL-6, IL-10, IL-13, IFN-gamma and TNF-α levels in children suffered from acute viral infection (group 1, N = 40) and in healthy controls (group 2, N = 20).

Results: Based on serology and direct identification of viruses from nasopharyngeal secretion RSV was detected in 40%, adenovirus in 20%, parainfluenza in 33% and EBV in 7%. In acute phase of infection the patients had moderately elevated leukocyte (9729 ± 658 vs 7405 ± 416, $P < 0.05$), monocyte count (8.48 ± 0.58% vs 5.84 ± 0.34%, $P < 0.001$), CRP levels (9.62 ± 3.14 mg/L vs 1.66 ± 0.58 mg/l, $P < 0.05$) and decreased eosinophil count (2,15 ± 0,34% vs 5,25 ± 0,81%, $P < 0,05$) and elevated IL-6 (4.28 ± 0.77 pg/mL vs 1.50 ± 0.25 pg/mL, $P < 0.01$), IL-10 (9.17 ± 2.86 pg/mL vs 1.47 ± 0.28 pg/mL $P < 0.05$), IL-13 (9.56 ± 2.15 pg/mL vs 1.38 ± 0.24 pg/mL, $P < 0.01$), IFN-γ (25.36 ± 9.73 pg/mL vs 1.11 ± 0.08 pg/mL, $P < 0.05$) and IFN-γ /IL-4 ratio (22.13 ± 9.56 vs 1.03 ± 0.08, $P < 0.05$) compared with controls. One month after the acute phase most inflammatory parameters normalized, monocyte count (8.48 ± 0.58% vs 5.05 ± 0.52%, $P < 0.05$), IL-6 (4.28 ± 0.77 pg/mL vs 0.80 pg/mL, $P < 0.001$) and IFN-γ (25.36 ± 9.73 pg/mL vs 5.14 ± 1.8 pg/mL, $P < 0.05$) levels decreased and eosinophil counts (2.15 ± 0.34% vs 3.62 ± 0.48%, $P < 0.05$) increased.

Conclusions: Our results show that the protective proinflammatory cytokines, such as IFN-gamma (induced by TNF-α from monocytes) and IL-13, in association with an anti-inflammatory cytokine, IL-10, and mildly elevated other inflammatory parameters are increased in children with acute viral infection. A single parameter, elevated monocyte count, can indicate the viral origin of the infections.

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Immunomodulatory Effects of Human Bone Marrow-derived Mesenchymal Stem Cells

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Introduction: Human mesenchymal stem cells (MSCs) have great plasticity and the potential for therapeutic applications[1] Due to the fact that MSCs could reduce the incidence severity of graft versus host disease[2] We have investigated the immunologic properties of human marrow-derived MSCs.

Material & Methods: Bone marrow was obtained from healthy human donors of bone marrow to a related patient at Bone Marrow Transplantation Center, Nemazi Hospital, after obtaining approval of the Ethics Committee and Written informed consent. The Mononuclear cells derived over the Ficoll-Paque density-gradient, and plated in tissue cultures dish. The adherent cells expanded rapidly and maintained with periodic passages until a relatively homogeneous population was established. The MSCs were characterized by immunophenotyping and differentiation into osteoblast and adipocytes. Alloreactivity was studied after adding the MSCs to allogeneic lymphocytes in mixed lymphocyte reaction cultures.

Results: Flow cytometric analysis, and the differentiation potential into osteoblast and adipocytes showed that more than 90% of human MSCs were positive by specific markers and functional tests. Indeed, The MSCs expressed CD90, and CD73. But not CD80, CD40, and HLA class II. They also were negative for the hematopoietic markers CD34, and CD45. The MSCs do not induced proliferation of allogenic lymphocytes and suppressed them.

Conclusion: The human marrow-derived MSCs do not elicit alloreactive lymphocyte proliferation. The results suggest that these cells have potentials for allogenic transplantation.

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IMMUNOTHERAPY

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Allergen Standardisation in Allergens and Allergoids—Challenges and Considerations

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Background: The range of therapeutics and dosing schedules for allergen preparations and allergoids produced and used clinically are considerable. Standardisation of allergy immunotherapies is considered a positive step; however there are difficulties in identifying universal metrics for standardisation. Many advocate the use of major allergen content whilst others advocate total allergenicity. Additionally as a compounding argument, where major allergen is used, many disagree on what the major allergen is for certain species.

Methods: Major allergen content measurement allows a consistent recognised measure, and IgE responses of a serum pool are often dominated by IgE against major allergens. However issues such as specificity of different assays toward isoforms and other variants of single allergens often results in diverging allergen contents that can cause unexpected and misleading disparity. Other aspects that increase complication are the relevance to modified allergens, use of adjuvants and differing dosing regimes.

Results: The major allergen content of key products in different therapeutic formats has been measured.

Conclusions: This has been performed in conjunction with techniques such as total allergenicity, as allergy treatments and therapeutics require careful characterisation to allow supply of consistent, safe and efficacious products.

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Therapeutic Effect and Safety of Tropical Mite Allergen Vaccines by Subcutaneous Route in Allergic Asthmatics Patients

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Background: Allergen-specific subcutaneous immunotherapy (SCIT) is presently recognized as a biological response modifier, as it is the only available treatment able to influence the natural course of allergic disease. Extensive clinical evidence supports its efficacy. Safety concerns are related to the risks of anaphylactic reactions during treatment. Standardization of allergen vaccines in terms of allergenic activity allows a more precise control over the administered doses and can be, therefore, very relevant for both efficacy and safety of SCIT. House Dust Mites (HDM), particularly *Dermatophagoides pteronyssinus (Dp), Dermatophagoides siboney (Ds)* and *Blomia tropicalis (Bt)* have been described as very relevant allergen sources in Cuba, with a strong association to respiratory allergy symptoms.

Objective: To asses the efficacy and safety of standardized allergen vaccines of these 3 mite species (Valergen, Biocen, Cuba) in Cuban asthmatic patients.

Methods: Three Double-Blind Placebo-Controlled clinical trials were performed in 40 patients each, showing asthmatic symptoms and positive predominant Skin Prick Test (SPT) to each mite, respectively. Half of patients received the active treatment consisting of subcutaneous injections with increasing doses, up to 6000 BU.

Results: The total 1 year cumulative dose was 63035 BU, in an average of 20.5 injections. The treatment was effective in the reduction of clinical symptoms (up to 32%, 95%CI: 28-36%; $P = 0.0006$) and medication intake (23%, 95%CI:18-28%), as compared to control treatment. The skin sensitivity to the allergens decreased significantly ($P = 0.0001$), with regard to the beginning of the treatment. The allergen amount needed to induce a positive SPT increased 297-fold. An improvement of the lung function was observed, expressed in a modest Peak-Expiratory-Flow increase ($P < 0.05$) and reduction of PEF daily variability. SIT was considered effective in 71% of patients. The frequency of local adverse reactions was 2.4 % of injections.

Conclusions: The results indicates that immunotherapy, using standardized House Dust Mite vaccines, including tropical species, is effective and safe for the control and amelioration of the asthma in our population.

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Therapeutic Effect and Security in Asthmatics Adult Patients Treated with Dermatophagoides Pteronyssinus Allergen Sublingual Immunotherapy

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Background: The specific active immunotherapy, employing vaccine of allergen of mite is a treatment considered as effective for the respiratory allergy and asthma. The sublingual route has minor risk of systematises reactions. The objective of this study was to determine the therapeutic effect and security of sublingual immunotherapy (ITSL) employing the standard vaccine VALERGEN-DP (BIOCEN, CUBA) in a population of asthmatic Cuban patients.

Methods: A phase II Clinical Trials double blind, placebo controlled in a total of 40 adult patients with mild or moderate asthma and specific sensibility preponderant to this mite. Half of patients received drops by sublingual route with growing doses up to 2000 UB.

Results: The treatment was effective in the reduction of clinical symptoms and medication intake as compared to conventional treatment in control group. The cutaneous sensibility to this mite was significant reduced, increasing in 1.9 log; the amount of necessary allergen to provoke a positive Prick Test. An improvement of the lung function was observed with a significant reduction ($P < 0.05$) of expiratory pick flow variability. The frequency of local reactions were only 0.58% of administration.

Conclusions: The VALERGEN-DP vaccine is an effective treatment and profitable against asthma in our population and guarantee its generalization in the Allergy Services of our health system.

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Safety of Sublingual Immunotherapy with Standardized Vaccines of Domestic Mites

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Background: Allergen-specific immunotherapy consists of administering gradually increasing doses of the allergen, to which the patient is sensitized, aiming at achieving tolerance to it and decreasing clinical symptoms. The sublingual immunotherapy (SLIT) was introduced as an alternative to subcutaneous route. Its use is being increased in the world and in Cuba, using standardized vaccines owing to greater safety. The objective of this study was to determine the safety of sublingual standardized vaccines of 3 domestic mite species (Valergen, Cuba) and its adverse events in allergic patients from the Calixto García University Hospital in Havana, as well as the frequency of its prescription.

Methods: Descriptive and cross sectional study design, which included 130 patients with treatment of SLIT with VALERGEN-DP (Dermatophagoides pteronyssinus), VALERGEN-DS (D. siboney) and VALERGEN-BT (Blomia tropicalis) (BIOCEN, Cuba), who attended the Allergy Service in the period January-September 2010. Age distribution: mean 19.6 years (range 1–75), 40.7 % was younger than 18 years.

Results: The multiallergen vaccine was the type of vaccine most used (63.8%). The most common allergen was D. pteronyssinus followed by B. tropicalis. 71.55% of administered allergens vaccines were in maintenance phase. We found 4 adverse events (3.1% of patients), all local, mild, and not requiring treatment or change of vaccination dosing schedule.

Conclusions: The Valergen vaccines by sublingual route are safe and well tolerated in Cuban allergic patients.

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The Effect of Specific Immunotherapy on the Clinical Response in Patients with Grass-pollen Induced Rhinoconjunctivitis

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Background: Specific immunotherapy (SIT) has a significant potential in the treatment of allergic rhinitis and allergic conjunctivitis. The aim of the study was to evaluate the effect of specific immunotherapy (SIT) in patients with grass-pollen induced allergic rhinitis and allergic conjunctivitis.

Methods: Twenty-six patients with pollen induced rhinoconjunctivitis and positive history for more than 2 years were included in our study. They had skin prick test of $\geq$ 5 mm, age range from 18 to 44 years and all underwent conjunctiva provocation tests before and after 1 year of SIT. Clinical severity score of nasal and conjunctiva symptoms during the season was assessed by 4-point arbitrary rating scale from 0 to 3. Conjunctiva provocations were performed out of the season until allergic symptoms occurred, achieving the allergen threshold dose (ATD).

Results: After 1 year of SIT, we have noticed reduction of clinical symptoms present in allergic conjunctivitis: burning, itching, lacrimation and hyperemia ($P < 0,05$). We have found also reduction in clinical symptoms of allergic rhinitis: secretion, irritation, itching and nasal blockade ($P < 0,01$). The patients tolerated significantly higher allergen doses in provocation tests after 1 year of SIT, reaching new ATD.

Conclusions: SIT reduces the clinical symptoms of allergic rhinoconjunctivitis and modifies the inflammatory response after specific allergen challenge.

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Does Sublingual Immunotherapy Work with an Immune Deviation Mechanism?

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Background: We aimed at finding out the immunological mechanisms of SLIT by studying the activity of IgE specific for the epitopes of Phleum in patients treated with SLIT for grass allergen and in a control group.

Methods: 30 patients allergic to grass were included in the study:

- 15 patients carried out a pre-seasonal SLIT for 2 years with the 5 grass mix extract from Stallergenes.
- 15 patients were not treated with SLIT.

Eligible patients: Clear symptoms of seasonal rhinoconjunctivitis during the past year, positivity to Phleum skin prick tests (+++-) and specific IgE (3.5 kU/L). Prick tests were performed with extracts from Stallergenes; serum specific IgE for Phleum and rPhlp1, rPhlp2, rPhlp5, rPhlp6, rPhlp7, and rPhlp12 were determined through the Unicap system 100 IgE FEIA (Phadia Usala, Sweden). Wilkoxon and Fischer method were performed. Rast Inibition rpPhlp1/rpPhlp1, rpPhlp1/rpPhlp2 and rpPhlp1/rpPhlp4 were evaluated.

Results: IgE for rPhlp7 and rPhlp12 present only in some patients did not show significant modifications. Most patients treated with SLIT for 2 years, and all those showing improvement in symptoms, showed a less evident increase of specific IgE for rPhlp1 and rPhlp5 if compared with that of minor allergens, ie, rPhlp2, rPhlp4, rPhlp6. This difference was absent in control patients and in patients not showing clinical improvement. In patients showing clinical improvement the IgE ratio rPhlp5/rPhlp2 was significantly decreased ($P = 0.02$). A RAST inhibition study showed no cross-reactivity between rPhlp1/rPhlp2 and rPhlp1/rPhlp4.

Conclusions: After 1 and 2 years of SLIT, the data show the following results:

- a significant increase of specific IgE for minor allergens and a less evident increase of specific IgE for major allergens in patients showing a clinical response to SLIT
- a drastic decrease in IgE ratio for rPhlp5/rPhlp2. These results suggest that SLIT not only induces a TH2-TH1 isotypic switch, but also can act with a mechanism of immunological replacement. In fact, the production of specific IgE for minor allergens (rPhlp2, rPhlp4, rPhlp6) tends to replace the production of specific IgE for major allergens (rPhlp1, rPhlp5).

IMMUNOTHERAPY TRAINING

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Immunotherapy (IT) Training in Canada: Perspectives of Fellows-in-training on the First Immunotherapy Training Manual

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Background: Allergen immunotherapy (IT) is a key component of allergy practice, however fellows state that there is inadequate IT exposure during their training. In response, the Canadian Society of Allergy and Clinical Immunology (CSACI) unveiled the first ever IT Training Manual for fellows-in-training at the annual 2010 CSACI meeting. The manual was distributed during a faculty-led teaching session. This was a pilot investigation to determine the perspectives of fellows in training about the IT training manual.

Methods: Canadian fellows-in-training in Allergy and Clinical Immunology (list derived from CSACI) were contacted via email to complete a survey (using survey monkey), both quantitative (Likert scales) and qualitative, to assess their opinion on the faculty-led session on IT and the IT Training Manual.

Results: Sixty-nine Canadian fellows-in-training were invited to complete the survey and 16 (23%). Fifty-four percent of 13 respondents were in their first year of fellowship. Seven respondents (58% of 12 respondents) attended the 2010 CSACI fellow-in-training session and received the IT Training Manual. One respondent commented that it was "more information than we've had in all of our fellowship!" The same 7 respondents "somewhat liked" or "liked" the large group format, but felt that the experience could be improved in the future with the addition of cased-based learning in smaller groups. One respondent commented that "as in intro, it was good in a larger setting." All 7 respondents felt that their understanding of IT was positively impacted by the faculty-led session. Eighty-six percent of 7 respondents indicated that the Training Manual "somewhat impacted" to "very much impacted" their understanding of IT. One commenter stated that "it is the basis of my knowledge thus far." Most respondents (86%) preferred the current paper booklet format of the IT Training Manual.

Conclusions: The results of this pilot survey demonstrate that some fellows-in-training found the faculty-led session on IT and the IT Training Manual useful. Future studies will help to further elucidate the utility of these 2 educational interventions.

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Immunotherapy (IT) Training in Canada: Current Experience of Fellows-in-training

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Background: Allergen immunotherapy (IT) is a key component of allergy practice of allergy. Canadian fellows-in-training have expressed concern that they receive inadequate exposure to IT in their training programs.

Methods: Canadian fellows-in-training in Allergy and Clinical Immunology, identified through the Canadian Society of Allergy and Clinical Immunology (CSACI), were contacted via email to complete a pilot survey (using survey monkey) to assess their exposure to, experience with, and comfort level in using IT.

Results: Sixty-nine Canadian fellows-in-training were invited to complete the survey and 16 (23%) completed at least part of the survey. Fifty-four percent of 13 respondents were in their first year of fellowship. Fifty percent of 12 respondents were internal medicine trained. Eighty-three percent of 12 respondents acknowledged exposure to IT during their training. Eighty percent of 10 respondents had previously written a prescription for IT; 71% and 43% of 7 respondents had written 1 to 5 prescriptions for aeroallergen and stinging venom IT, respectively. Only 50% of 12 respondents felt comfortable prescribing IT. The most common reason cited was lack of experience; however, one respondent wrote that he/she would feel uncomfortable prescribing IT without using the standardized hospital IT form. Sixty-seven percent of 12 respondents had previously administered IT to a patient. Sixteen percent of 12 respondents felt uncomfortable administering IT due to lack of experience. Fifty percent of 12 respondents had treated a patient having an allergic reaction to IT and 100% of these same respondents felt "somewhat comfortable" to "very comfortable" in responding to an allergic reaction to IT. Seventy-five percent of 12 respondents agreed that a formal clinical rotation in IT would be helpful.

Conclusions: The results of this pilot survey demonstrate that Canadian fellows-in-training in Allergy and Clinical Immunology are not receiving adequate exposure and training in IT. Future studies will help to explore this subject in more detail.

INCIDENCE AND PREVALENCE OF FOOD ALLERGY

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Nationwide Survey of Immediate Type Food Allergy in Japan

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Background: The food labeling system for food allergens was introduced from April 2002 in Japan. To confirm the effectiveness of the system, we regularly conduct a nationwide food allergy survey every 3 years.

Methods: The survey was conducted in cooperation with over 1000 volunteer allergists in Japan at 2001, 2002, 2005 and 2008. We sent questionnaire to contributing doctors every 3 months based on the past survey system, and contributing doctors were asked to report immediate type food allergy cases seen by those doctors. In this survey, immediate type food allergy was defined as the patients who had developed symptoms due to food allergic reaction within 60 minutes after intake of offending food. The details of questionnaire consisted of age, sex, cause of food allergy, symptoms, CAP system, and type of onset.

Results: A total of 8581 immediate type food allergy cases were reported by the doctors. The most common offending foods were hen's egg (39.0%), milk products (18.0%), wheat (9.4%), fruit (5.3%), crustacean (4.6%), peanuts (3.7%), fish egg, buckwheat and fish (3.6%). The most common clinical symptom was observed on skin (89.7%) followed by respiratory system (29.6%). Interestingly, the causes of food allergy were completely different from infancy (egg, milk, and wheat) to adulthood (wheat, crustacean and fruits). Anaphylactic shock was observed in 10.9% of the total reported cases. The cases of anaphylactic shock were due to hen's egg (27.1%), milk products (21.4%) and wheat (18.1%). Eleven percentages of patients had been hospitalized.

Conclusions: We revealed the current condition of the immediate type food allergy cases seen in Japan recent decade. Based on these data, countermeasures against food allergy are ongoing in collaboration with the Ministry of Health, Labour, and Welfare in Japan in order to improve quality of life of patients.

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The Prevalence of Food Allergy in Children under 2 Years in Three Cities in China

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Background: To estimate the prevalence and clinical features of food allergy in children aged 0 to 2 years.

Methods: From January to February, 2009 and January to May, 2010, all well-infants and young children between the age of 0-2 years attending routine health visits at the Department of Primary Child Care, in Chongqing, Zhuhai and Hangzhou were invited to participate the study. Parents completed questionnaires and all children were skin prick tested to a panel of 10 foods (egg white, egg yolk, cow milk, soybean, peanut, wheat, fish, shrimp, orange and carrot). Based on the results of SPT and medical history, the subjects should undergo the suspected food elimination and oral food challenge under medical supervision. Food allergy was confirmed by the food challenge test.

Results: There were 1,687 children recruited by the consent of their parents. Of 1,687 children approached, 1,604 (550 for Chongqing, 573 for Zhuhai and 481 for Hangzhou) fulfilled the study criteria for diagnosing food allergy. 100 children were confirmed to have challenge-proven food allergy in 3 cities (40 for Chongqing, 33 for Zhuhai and 27 for Hangzhou). The prevalence of food allergy in 0 to 2 years old children in Chongqing was 7.3%, in Zhuhai was 5.8% and in Hangzhou was 5.5%. There was no significant difference in the prevalence of food allergy in children under 2 years among the 3 cities, and the average prevalence for food allergy in children under 2 years was 6.2%. Egg was the most common allergen, followed by cow milk.

Conclusions: The prevalence of food allergy in 0 to 2 years old children in China was 5.5% to 7.3%. There was no significant difference in the prevalence of food allergy in children under 2 years among the 3 cities. Egg was the most common allergen, followed by cow milk.

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Skin Sensitization to Carmine Before Onset of Systemic Allergy to Ingested Carmine

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Background: Allergic sensitization to food can occur through skin exposure. We investigated anaphylactic cases due to carmine, a food additive extracted from Dactylopius coccus.

Methods: Screening all patients, who visited our department from January 2000 to December 2009, we identified 2 new such cases. Both had history of rash induced by certain cosmetics containig carmine. We further investigated previous case reports of carmine allergy, whether skin sensitization antedated food allergy or not.

Results: Case 1: A 26-year-old woman visited our hospital because of anaphylaxis occurred within 5 minutes after ingesting a Japanese YOKAN (sweetened and jellied bean paste). IgE antibodies against common food allergens including beans and wheat were all negative. As the paste contains carmine, we tested specific IgE antibody, which was positive. She had been avoiding using certain cheeks and lips for 2 years, since they cause erythema. These cosmetics emerged as containing carmine. Abstaining from the food additive made her free from anaphylaxis. Case 2: A 30-year-old woman came to our hospital for dyspnea, uriticaria, and bilateral blepharedema, immediately after drinking Campari soda. Her past history was prominent, as she had 4 episodes of anaphylaxis in 4 years, requiring emergency transport twice. All anaphylactic episodes occurred in Italian restaurants when she drank cocktails, which might contain carmine in Campari soda. She had been also sensitive to certain rouges since several years before the first onset of anaphylaxis. It became clear that the rouges contained carmine. In literatures, we found 22 cases with allergy to ingested carmine. It is surprising that all cases were women (aged 25 to 52), while occupationally sensitized patients are predominantly men. As far as we could know, 85.7 % of (6/7) mentioned cases had previous history of sensitization to cosmetics containing carmine.

Conclusions: In many cases with allergy against ingested carmine, the route of first sensitization was not via intestine but skin. This is similar to suspected peanut sensitization mechanism and might be a paradigm of food allergy. As allergic reaction to carmine mainly directed to impurities, using highly purified carmine is desired not only for foods but also for cosmetics.

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Milk, the Most Commonly Undeclared Food Allergen Causing Unexpected Allergic Reactions in Sweden between 2004 and 2011

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Background: Allergy to milk proteins is a common allergic manifestation, especially among children. Different types of food products could be a risk factor for milk allergic individuals. According to the European Community Directive 2000/13/EC the list of ingredients shall include all the ingredients of the foodstuff, however with some exceptions. In 2003 Directive 2003/89/EC entered into force stating that milk and other ingredients, which are common elicitors of food allergic reactions, shall always be declared in the labeling.

Objective: To investigate which undeclared food allergen that most commonly has caused unexpected allergic reactions in Sweden between 2004 and 2011, ie, since 2003/89/EC entered into force, and to compile data regarding the reactions to this food allergen.

Methods: The medical care, school personnel and control authorities have since 1990 been encouraged to report allergic reactions to foods, which do not declare the ingredient causing the allergic reaction, to the Swedish National Food Administration. Also, the suspected foods have been provided for analyses. Food allergens, e.g. caseins (a group of milk proteins), were analyzed with Enzyme Linked Immunosorbent Assay and/or Rocket Immunoelectrophoresis.

Results: Forty-eight cases of unexpected allergic reactions to foods, in which the causing food allergen was detected, were reported between 2004 and 2011. The most commonly detected food allergen was milk (21) followed by peanut (9), egg (6) and wheat (5). The persons who suffered from unexpected allergic reactions to milk were all children or teenagers. Mild symptoms were reported as well as anaphylactic reactions. One death was most likely caused by an allergic reaction to bread contaminated with milk. The lowest doses eliciting allergic reactions were calculated to be 2 to 6 mg casein. The types of foods causing the reactions were chocolate, ready-made meals, meat products, sauces, bread and a vegetarian milk substitute. The unexpected allergic reactions to milk were caused by mislabeling in 7 cases and to contamination in 14 cases.

Conclusions: Although rare, allergic reactions to undeclared food allergens may occur. Milk was the most commonly undeclared food allergen causing allergic reactions in Sweden between 2004 and 2011.

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Cross Sectional Study of 1,822 Pediatric Food Allergy Patients

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Background: The aim of this study is to clarify the cross section of pediatric food allergy patients. We investigated the profiles of food allergy (FA) patients seen in our department.

Methods: The number of food allergy patients seen in our department from January to December in 2010 was a total of 1,822 (male: 1207, female: 615, mean age: 5.8 ± 3.8 year). We collected and analyzed the clinical information of these patients from our medical record. We obtained information on the age of FA onset & FA diagnosis, clinical types of FA at the onset, causative food allergens, other allergic complications, and application of oral immunotherapy (OIT).

Results: The average age of FA onset was 8 months, and that of diagnosis was 1 year old, respectively. The most common clinical types of FA at the time of onset were infantile atopic dermatitis (AD) type with food allergy (66.4%) followed by immediate type (30.8%). Food allergens avoided by the patients were the total number of 4,203 items (2.1 items as average). The most common eliminated food was hen's egg (1,245 cases; 29.6%), followed by cow's milk (786 cases; 18.7%), peanut (449 cases; 10.7%), and wheat (407 cases; 9.7%). Food-dependent exercise-induced anaphylaxis (FDEIA) was the total of 18 cases, and the most common causative food for FDEIA was wheat (10 cases) followed by peach (4 cases). One hundred and seventy five cases (9.6%) were currently receiving OIT. Main causative foods under OIT were hen's egg (63 cases), cow's milk (80 cases), and wheat (30 cases). The average starting age of OIT was 7.1 years old. Regarding complications of allergic diseases other than FA, 1119 (61.4%) had atopic dermatitis, and 541 (29.7%) bronchial asthma.

Conclusions: We were able to clarify the cross section of food allergy patients in our department and to obtain the basic data to follow continuous transition of these patients.

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Surface Plasmon Resonance Imaging: New Tool for Immunodiagnostics of Food Allergy

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Background: Food allergy affects as many as 5 to 8% of children and 2 to 3% of adults. The milk is an important source of food allergens. The Surface Plasmon Resonance imaging (SPRi) is an optical technique used for measuring simultaneously several hundreds of biomolecular interactions (about 400 interactions) in real-time and in a label free environment. The aim of our study was to measure avidity of milk allergens with their antibodies by the SPRi.

Methods: The biochip gold surface was functionalized by mixed layers of acid and alcohol. Milk allergens (β-lactoglobulin and α-lactalbumin) and ovalbumin (used as negative control) were then immobilized by covalent bonds on the biochip surface. After saturation step, some solutions with different concentrations of polyclonal antibodies - whole serum and purified antibodies - were injected in the SPRi-plex™ system (Horiba Scientific, Genoptics). The surface coverage and the detection limits of the target antibody were measured. The avidity of the couple antigen/antibody was then calculated.

Results: For the couple β-lactoglobulin and whole serum from rabbit sensitized with this allergen, the surface coverage of antibody increased from 0.7 to 1160 pg/mm^2, when we injected 4 and 340 nM of antibody, respectively. The avidity of this couple is 0.7 nM. The detection limits are 2 and 0.8 nM by SPRi and ELISA, respectively. For the couple α-lactalbumin/purified anti-α-lactalbumin antibody, the surface coverage of antibody increased from 20 to 1000 pg/mm2, when we injected 10 nM and 100 μM of antibody, respectively. The avidity of this couple is about 5.2 nM and 60 nM by SPRi and capilary electrophoresis, respectively. The rate of antibody detection limit obtained by SPRi compared to what is obtained by ELISA is 35%.

Conclusions: A Good proportionality of SPRi and ELISA signals was observed according to antibody concentrations. A high specificity binding and an excellent avidity between allergens and their antibodies was also shown. Limits of detection obtained with SPRi were comparable to those obtained with ELISA.

MASTOCYTOSIS

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Mastocytosis and IgE-dependent Sensitization: Report of 2 Cases

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Background: Mastocytosis is a heterogeneous disease, with abnormal accumulation of mast cells in one or more organs. Hyperplasia is often found in the bone marrow and peripheral sites such as skin, gastrointestinal mucosa, liver and spleen. The clinical manifestations are due to release of mast cell mediators and tissue infiltration; however, there is no direct relationship between total mast cell mass and symptoms of liberation.

Methods: Describe 2 cases of mastocytosis that manifest with anaphylactic shock and also have IgE-dependent allergy.

Results: Case1: Man of 62 years consulting for intraoperative anaphylaxis with an expected elevated serum tryptase (54 mg/L) during episode. The skin test were positive to vecuronium, rocuronium and Izofran and the other drugs and latex were negative. Specific IgE to quaternary ammonium latex and beta-lactams were negative. The tryptase remains elevated (23 mg/L) 6 weeks after surgery. Bone marrow biopsy showed mast cell infiltration of 10% CD 34 staining less than 1% and 10% CD117. Co-CD25 and CD117 were 25% compatible with mastocytosis. CT neck, thorax, abdomen and pelvis were normal. The upper and lower endoscopy revealed polyps in gastric antrum, the histology was nodular foveolar hyperplasia. Case 2: Female, 38 years consulted for 3 episodes of anaphylaxis following the ingestion of fish, shellfish and quinoa. The skin prick test was positive to white fish and shrimp, specific IgE were positive to white and blue fish and shrimp. The initial serum tryptase was 11 mg/L, 3 months was 14 mg/L. Later, patient had a new anaphylaxis episode, after unnoticed consumption of fish. Bone marrow biopsy compatible with mastocytosis. The study with lower and upper endoscopy with chest and abdominal CT scan ruled out visceral involvement.

Conclusions: Both cases of systemic mastocytosis show an IgE sensitization to drugs and to food whose main manifestation was anaphylactic shock. In the literature, anaphylaxis was reported in up to 22% of mastocytosis, mostly men, associated with different triggering stimuli such as muscle relaxants, but not food. Therefore it is essential to rule out the presence of mastocytosis in patients complaining of anaphylaxis even in those with allergy study showing IgE-dependent sensitization.

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Mastocytosis: Importance as Differential Diagnosis in Skin Diseases. Report of Two Cases

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Background: Is a heterogeneous disorder characterized by clonal proliferation of mast cells (MCs) leading accumulation in different organs. Pathologic activation of KIT due to a mutation in codon 816 replacing

aspartic acid for valine: KIT-D816V (>93%) has been identified. *Cutaneous Mastocytosis (CM),* Classified in Urticaria Pigmentosa (UP), solitary mastocytoma, diffuse, and telangiectasia macularis eruptiva perstans (TMEP). The most common is the Urticaria Pigmentosa as fixed, reddish brown macular or papular, urticate in physical irritation (Darier's sign). WHO Diagnostic Criteria for cutaneous Mastocytosis: Presence of at least 1 of skin lesions with Focal dense MC infiltrates (>15 MCs per cluster) or diffuse (>20 cells per high-power field).

Methods: We report 2 cases of patients with this disease who were not diagnosed at first. A 51 years old female, who noticed 20 years ago, the appareance of itchy "spots" in thorax, abdomen and extremities, progressively increasing in number and size, receiving unspecified treatments without improvement. On examination, we found brown macules with sharp borders, 0.3 to 0.5 cm erythema and Darieŕs sign, disseminated lesions on thorax, shoulders and extremities. A 45 year old female, who noticed 2 years ago, the appareance of freckles in neck, arms, thorax and legs progressively increasing in number, who in stress are itchy. Receiving multiple treatments without improvement. On examination disseminated brown macules with sharp borders <0.5 cm with Darieŕs sign.

Results: In both patients, the biopsies taken had findings compatible with mastocytosis (inflammatory infiltrate with perivascular lymphocytes, histiocytes and mast cells). Mast cells were not quantified. We realized a genetic study in search of c-kit mutation. Once the diagnosis was considered and treated accordingly, they had a good control of symptoms.

Conclusions: Mastocytosis is diagnosed by clinical features and histological infiltrate of mast cells. The skin is the organ most frequently affected. These patients previously received multiple treatments with no clinical improvement suggest inadecuate diagnosis. Histologically, compatible although no quantificate mast cells, but a mutation of c-kit was found. It is important to consider this disease in the differential diagnosis of pruritic skin disorders since an appropriate treatment with an improvement in quality of life also must be aware of the risk of anafylaxis and its potential triggers.

MECHANISMS OF ASTHMA AND ALLERGIC INFLAMMATION

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Human Mononuclear Phagocytes Are Regulated by a Cross-talk with Epithelial Cells

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Background: Cell-cell interactions are particularly important for modulating the monocyte to macrophage transition in tissue compartments. Both cell membrane contacts and soluble signals from the environment might be involved in these interactions. The aim of our study was to characterize gene expression profiles of human mononuclear phagocytes induced by a co-culture with epithelial cells.

Methods: Human THP-1 macrophages were co-cultured with A549 epithelial cells either directly or separated by a filter insert. At different time points, THP-1 cells were aspirated and the mRNA expression was evaluated by multiplex Real-time RT-PCR, the release of selected cytokines was evaluated by Luminex technology or ELISA. The phenotype of both cultured cells was evaluated by flow cytometry.

Results: Co-culture with epithelial cells induced a number of cytokine genes (IL-1 beta, IL-6, IL-10, TNF alpha, IL-19, GM-CSF, …etc) together with upregulation of genes associated with NFkappaB activation including REL, RELB, transcription co-activator BCL3, MALT gene, and NFKB1 subunit. Our recent study has confirmed the role of NFkB signalling by inhibition of IL-6 release from co-cultured cells by p65 siRNA transfection[1]. Phenotypic pattern of THP-1 cells co-cultured with epithelial monolayers showed maturation and activation associated changes such as CD14 upregulation associated with higher release of the soluble form (sCD14) from macrophage membrane.

Conclusions: Our data suggest that properties of human mononuclear phagocytes in tissues are highly influenced by their immediate interactions with other, e.g. epithelial cells. These factors might be of particular importance in final steps of differenciation of monocytes/macrophages into fully competent effector cells.

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Activation of PAR-2 Induces Myofibroblast Transformation via a TGF-β and GSK-3β/β-catenin Dependent Pathway in Tissue Remodeling in the Asthmatic Lung

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Background: Asthma is a chronic inflammatory lung disease, and airway remodeling denotes the pathophysiologic modifications of normal airway wall structure, including changes in the composition and organization of the airway wall's cellular and molecular constituents. These structural alterations are largely irreversible in chronic severe asthma and lead to symptoms associated with chronic airflow limitation. However, the pathogenetic mechanisms leading to these responses remain unclear. According to recent reports, lung-resident fibroblasts and smooth muscle cells have been implicated in the pathogenesis of airway remodeling. Myofibroblasts are proposed to be the primary effector cells of lung fibrotic responses and are characterized by expression of α-smooth muscle actin (α-SMA) stress fibers. Transforming growth factor (TGF)-β is known to induce the transformation of fibroblasts to myofibroblasts. Protease activated receptor (PAR)-2, a G-protein-coupled receptor activated by serine proteases such as trypsin and mast cell tryptase has been recognized as a key molecule in inflammation and fibrotic changes. We hypothesized that activation of PAR-2 induces TGF-β and α-SMA expression and hence may be one of the potential mechanisms of airway remodeling in asthma.

Methods: Cultured human lung fibroblasts (MRC5) were exposed to trypsin (5 nM) or a specific activating peptide, PAR-2AP. Secreted TGF-β was measured using ELISA. Cell associated α-SMA was assessed by Western blot analysis and immunostaining and activation of downstream signaling pathways was assessed by Western analysis.

Results: Activation of PAR-2 by trypsin or PAR-2AP induced TGF-β secretion that peaked between 4 and 8 hours. These were correlated with activations of c-fos and c-jun. Induction of α-SMA expression peaked between 4 and 24 hours. Treatment with trypsin or PAR-2AP also induced phosphorylation of GSK-3β on serine 9 and nuclear translocation of β-catenin.

Conclusions: Activation of PAR-2 induces TGF-β secretion through the AP-1 transcription factor complex leading to myofibroblast transformation via the GSK-3β/β-Catenin Pathway.

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Plasminogen Activator Inhibitor-1, Fibrinogen and Lung Function in Adolescents with Asthma and Obesity

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Background: Obesity promotes a low-grade systemic inflammatory state that may act on the lung to exacerbate asthma. There is little information on the relationship between systemic inflammation and lung function in children and adolescents.
Methods: One hundred and seventy eight adolescents (boys and girls) were involved, 4 groups were divided according to their diagnosis: non-obese and non-asthmatic controls (n = 38), non-obese asthmatics (n = 31), obese non-asthmatics (n = 62), obese asthmatics (n = 47). The levels of PAI-1 and fibrinogen were determined in blood samples. The lung function was evaluated by measuring forced expiratory flow in 1-second (FEV1) and forced vital capacity (FVC1).
Results: Compared to healthy controls, obese adolescents with or without asthma showed higher levels of fibrinogen (328.4 ± 54.9, 324.9 ± 68.9 and 289.2 ± 61.5 mg/dL, respectively) and PAI-1 (36.0 ± 17.3, 53.2 ± 22.3 and 52.6 ± 24.7 ng/mL, respectively) and reduced FEV1/FVC ratio (87.7 ± 7.7, 81.6 ± 8.6 and 81.7 ± 6.9, respectively). In the whole studied subjects, FEV1/FVC ratio showed significant inverse correlation with PAI-1 (r = -0.185), fibrinogen (r = -0.157), BMI (r = -0.303), insulin(r = -0.198) and HOMA (r = -0.173). In the 78 asthmatic subjects, FVC correlated positively with BMI, no significant correlation was observed between FEV1/FVC ratio and BMI, HOMA, PAI-1 or fibrinogen.
Conclusions: Our data demonstrated that the degree of systemic inflammation and the degree of obesity in the whole studied groups correlated to the reduced lung function. Further studies are needed to identify the pathophysiologic mechanism for such association.

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Peculiarities of Immune Response in Young Children with Recurrent Wheezing

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Background: Wheezing is a very common symptom in young children. However some questions of immune response are unclear for subsequent prediction in recurrently wheezy children. We studied immunological status of kids with recurrent wheezing.
Methods: 31 children with acute episode of wheezing were included in this study (24 male, 7 female) aged from 1 to 5 years, admitted in Vladimir Children Clinical Hospital. These children were the main group. Control group included 6 children with no signs of chronic and acute inflammatory diseases. Examination included studying clinical data, detecting in blood serum subpopulations of lymphocytes, expression of Toll-like receptors (TLR-2, TLR-4) on surface of monocytes (rMFI) and number of pro-inflammatory monocytes (CD14+CD16+).
Results: We revealed high frequency of bronchial obstruction (more than 5 episodes) at 30% of children in main group. 30% of children had allergic diseases (atopic dermatitis, allergic rhinitis) in history. In group of children with recurrent wheezing revealed increased levels of pro-inflammatory monocytes (9,44 ± 1,55% vs 5,39 ± 0,79%) and expression of receptors TLR-2 (8,28 ± 0,44 conventional units vs 6,59 ± 0,98). In children with recurrent wheezing an inverse correlation was found between frequency of respiratory infections and level of expression of TLR-2. For frequency of acute respiratory infection up to 6 times in year the level of expression of TLR-2 was 9,11 ± 0,31 and for children with monthly episodes of acute respiratory infections level was 7,6 ± 0,25 (r = -0,380, $P < 0,05$). Expression of TLR-4 was also tended to lower level in sickly children (2,2 ± 0,16 and 2.7 ± 0,14), however, no significant differences weren't revealed (r = -0,370, $P > 0.05$). At the same time in patients with allergic diseases showed significant reduction in expression levels of TLR-4 compared with patients without atopy ($P < 0,05$).
Conclusions: Increased levels of pro-inflammatory monocytes and expression of TLR-2 correspond to local inflammatory reaction and adequate immune response against background of acute respiratory illness in children with relapsing course of bronchial obstruction. Changes of TLR-2 and TLR-4 in group of children with recurrent wheezing confirm, on the one hand, risk of bronchial asthma in children with predisposition to atopy. On the other hand these changes can be the result of oppression of innate immunity in children with persistent character of bronchitis.

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Participation of Invariant NKT Cells (Vα24Jα18) during Asthma Exacerbation in Children

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Background: Invariant NKT cells (or type 1 NKT cells) co-express CD3 marker and NK receptors (CD56, CD161) and use a single type of TCRα chain (Vα24Jα18 for humans), comprising CD4-CD8-, CD4+ and CD8+ subsets. Participation of these cells and their cytokines in asthmatic children, in stable conditions and under exacerbation, was studied.
Methods: Three groups on children (6–12 years old) were selected: 1) asthmatics under exacerbation attack (AE) within the first 24 hours after the attack and before starting any treatment; 2) asthmatics with stable asthma (SA), without symptoms for at least a month before bleeding; and 3) healthy controls (HC) without history of asthma, atopy and with normal lung function were selected in the Allergy and Clinical Immunology Service, Hospital Infantil de Mexico. Invariant NKT cells and subset levels as well as intracellular cytokines were evaluated in whole blood by 4-color flow cytometry (antibodies against CD3, CD4, CD8, CD161, Va24, IL-4 and IFN-g).
Results: Proportion of iNKT cells among total CD3+ cells in HC group was 0.9%, while in SA patients they were increased up to 2.6%; interestingly, during exacerbation such cells were dimished (1.8%). Concerning iNKT CD4+ cells were 0.6% in HC, 1.8% in SA, and 0.7% in AE, while iNKT CD8+ cells were 0.1% in HC, 0.7% in SA, and 0.4% in AE. Both iNKT cell subsets expressed intracellular IFN-g and IL-4 cytokines in AE, SA and HC but predominantly IFN-g in iNKT CD8+ cells from AE patients.
Conclusions: iNKT cells participation in asthma pathogenesis was confirmed. Increase of IFN-g production in patients with exacerbations, may provide a regulatory environment to stabilize the condition.

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Cytokine Profile Characterization in Patients Infected with AH1N1 Influenza Virus

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Background: In 2009, an outbreak of severe respiratory infection caused by influenza AH1N1 virus affected Mexican people, previously in 1996 in Guangdong province (China) an outbreak of H5N1 influenza started spreading throughout Asia and the western Palearctic in 2004 to 2006. Chinese patients were studied and it was observed a deleterious immune

response related to cytokine storm, mainly characterized by higher levels of IFN and other proinflammatory cytokines causing fatal infections or severe clinical outcome. Until now, is unknown the cytokine profile involved during AH1N1 infection, thus it was the aim of this study.

Methods: Serum samples were obtained from 39 infected patients and their close contacts from the first wave outbreak of influenza AH1N1 and were storage at –80°C until cytokine determination, Human Inflammatory and Th1/Th2/Th17 Cytometric Bead Array Kit was used to determine cytokine concentration in serum samples. *Cytokine protein arrays* were performed to know relative expression of 36 cytokines with the Profiler Array Membrane from R&D Systems. The results are reported on relative units (RU). It was performed with ANOVA test, considering $P < 0.05$ as statistically significant.

Results: We did not find significative statistical differences between patients and their close contacts in IFN-γ, IL-1ß, IL-2, IL-4, IL-6, IL-8, IL-10, 12p70, IL-17A, and TNF evaluated with cytometry. However, the proteomic analysis showed a significant increased ($P < 0.05$) in G-CSF, I-309, sICAM-1, IL-1Ra. IL-16, IL-23, IL-27, I-TAC, MIP-1α, and E1-Serpin compared with the closed contacts.

Conclusions: AH1N1 patients showed higher levels of IL-27. We observed more RU of sICAM expression in patients and closed contacts, possibly due to the IL-27 signaling. IL-23 were increased in AH1N1 patients, this cytokine is involved in the IFN-γ secretion and in the generation of memory CD4 T cells. These results suggest that AH1N1-patients developed an immune response characterized by IL-27 and IL-23. We need more studies to determine if this cytokines are related with the memory response induction.

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Basal T Cell Subpopulations of Normal Humans Vary by Stress Hormone Receptor Polymorphisms

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Background: Psychological stress has been correlated with allergy and asthma activity although there are clearly individual differences in the responses to the same stressor. These individual differences could be influenced by stress hormone receptor binding affinity, which could be altered by single nucleotide polymorphisms (SNPs).

Methods: We categorized differences in immunoregulatory profiles from peripheral blood mononuclear cells (PBMC) of 207 normal volunteers according to various glucocorticoid (GCR) and beta-2 adrenergic receptor (B2AR) polymorphisms. Subjects were genotyped for SNPs by real time RT-PCR, and Th1, Th2, Th1/Th2 ratio, and CD3+CD4+CD25hiFoxp3+ cell numbers were measured using flow cytometry. Each immune parameter in the SNP groups was compared to the wild-type (WT) gene.

Results: Significant differences were observed in B2AR SNPs Gly16Arg for Th2 (means: WT gly/gly, 1.89; arg/arg, 2.58; $P = 0.003$) and Th1/Th2 ratio (medians: WT gly/gly, 10.18; arg/arg, 6.89; $P = 0.004$) and Gln27Glu for Th1 (means: WT gln/gln, 17.21; gln/glu, 19.4 $P = 0.031$; glu/glu, 19.82 $P = 0.049$). No differences were observed based upon GCR SNPs tested (BCL1; NC363S; TTh1111; A3669G).

Conclusions: These data suggest that SNPs from various components of the stress-immune network (such as hormone and cytokine promoters and receptors) may be useful for subgrouping of immune responses to more accurately evaluate psychoneuroimmunological components of stress risk in individual subjects. This approach has significant clinical potentials in identifying those patients who may be most susceptible to stress effects on their immune balance.

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The Protective Effects of Exogenous IGFBP-3 on Allergic Airway Inflammation through Blockade of vegf Production

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Background: Bronchial asthma is a chronic airway inflammatory disease that is usually accompanied by increased vascular leakage, resulting in plasma exudation. Vascular endothelial growth factor (VEGF) plays as a pro-inflammatory mediator as well as a vascular permeability factor in bronchial asthma. Insulin-like growth factor (IGF)-I is also involved in the inflammatory process associated with bronchial asthma and it has been demonstrated to stimulate VEGF expression. The IGF binding proteins (IGFBPs) are a complex family of proteins which bind IGFs with high affinity. IGFBPs, especially IGFBP-3, display distinctive properties and can interfere with various biological processes. However, there are little data on the effect and the molecular basis of IGFBP-3 on allergen-induced bronchial inflammation and airway hyper-responsiveness.

Methods: This study was aimed to investigate the related signaling regarding the action of IGFBP-3 on bronchial inflammation and airway hyper-responsiveness in allergic airway disease of mice.

Results: In this study with an ovalbumin (OVA)-induced murine model of allergic airway disease, the increases of HIF-1a/HIF-2a activity and VEGF protein levels in lungs after OVA inhalation were blocked substantially by the administration of IGFBP-3. We also showed that the increased numbers of inflammatory cells of the airways, airway hyper-responsiveness, and increased levels of IL-4, IL-5, IL-13, and vascular permeability in lungs after OVA inhalation were significantly reduced by the administration of IGFBP-3.

Conclusions: These results indicate that IGFBP-3 may attenuate antigen-induced airway inflammation and hyper-responsiveness through the modulation of vascular leakage and VEGF expression mediated by HIF-1a/HIF-2a in allergic airway disease of mice.

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Antioxidants Attenuate Airway Remodeling by Regulating NF-ÊB, NRF2, and HIF in a Murine Model of Chronic Asthma

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Background: Reactive oxygen species (ROS) play a crucial role in the pathogenesis of acute and chronic respiratory diseases. Antioxidants have been found to ameliorate airway inflammation and hyperresponsiveness in animal models employing short-term exposure to allergen. However, little data are available on the effect of antioxidants on airway remodeling and signaling pathways in chronic asthma.

Methods: In the present study, we used a long-term exposure murine model of allergic airway disease to evaluate the influence of an antioxidant, L-2-oxothiazolidine-4-carboxylic acid (OTC) or α-lipoic acid (LA) on airway remodeling and to explore possible transcription factors and kinases involved in this effect.

Results: Long-term challenge of ovalbumin (OVA) increased ROS production, airway inflammation, and airway hyperresponsiveness, and developed features of airway remodeling such as excessive mucus secretion, subepithelial fibrosis, and thickening of the peribronchial smooth muscle layer. Administration of OTC or LA reduced these features of asthma including airway remodeling, which was accompanied by suppression of transforming growth factor-β1, vascular endothelial growth factor, and T-helper 2 cytokines. In addition, OVA-induced activation of nuclear factor-κB (NF-κB), nuclear factor erythroid 2p45-related factor-2 (Nrf2), hypoxia-inducible factor (HIF)-1α, and HIF-2α was reduced by OTC or LA. Our results also showed that OTC or LA down-regulated phosphoinositide 3-kinase activity and decreased phosphorylation of p38 mitogen-activated protein kinase but not extracellular signal-regulated kinase 1/2 or c-Jun N-terminal kinase.

Conclusions: These findings demonstrate that OTC and LA can inhibit activation of NF-κB, Nrf2, and HIF and thus attenuate allergen-induced airway remodeling, suggesting that antioxidants may provide therapeutic benefit in chronic asthma and other airway disorders.

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CCL3L1 Protein Did Not Affect IL-6 Expression, but Significantly Up-regulated IL-10 Expression in the Allergic Response

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Background: Previously, we found that the mean copy number of CCL3L1 in patients with asthma was significantly lower than that of control subjects (3.13 vs 3.75, $P = 0.001$). We investigated its possible molecular mechanism using a human monocytic cell line stimulated with house dust mite extract.

Method: The THP-1 human monocytic cells were stimulated with various concentrations of HDM extract. After stimulation, assay-on-demand gene expression products (Applied Biosystems) were used to evaluate mRNA expression of CCL3L1 (Hs 00609691_ml), IlL-6 (Hs00174131_ml), and IL-10 (Hs00961622_ml) levels as measurement of mRNA levels by real time PCR.

Results: Treatment of THP-1 cells with various concentration of HDM extract induced marked up- regulation of the expression of cytokines IL-10 and IL-6, which indicated that allergic responses were efficiently induced. Recombinant CCL3L1 protein had no effect on cytokine expression of THP-1 Cells in absence of HDM extract stimulation. In the presence of HDM extract (10 ug/mL) stimulation, CCL3L1 protein significantly up-regulated IL-10 expression (Ratio to ng/mL CCL3L1) dose-dependantly (0 ug/mL CCL3L1 + 0.3;12.4, 10 ug/mL CCL3L1; 15.8+ 1.1, 50 ug/mL CCL3L1; 16.8+ 0.3, 100 ug/mL CCL3L1; 18.0+ 0.8, ($P > 0.05$), but did not affect IL-6 expression ($P > 0.05$).

Conclusion: The significantly elevated asthma risk in subjects with a low copy number of the CCL3L1 gene which may be down-regulating IL-10 expression, not IL-6 expression.

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Caspase-9 is Involved in CD30 Activation Induced Eosinophil Apoptosis

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Background: We evaluated whether ligation of CD30 incite the apoptosis, and investigated the mechanisms of CD30 induced eosinophil apoptosis is dependent on caspase activation.

Methods: We purified eosinophils using MACS system. Expression of CD30 on eosinophils were measured and eosinophils were cultured in the wells pretreated with anti-CD30 mAb and isotype control IgG1, IL-5 and dexamethasone in RPMI 1640 media supplemented with 10% FBS, and the apoptotic rate were measured using flow cytometry. To evaluate whether caspase-9 is involved in CD30- induced eosinophil apoptosis, the apoptotic rate was evaluated with addition of caspase-9 inhibitor and the expression of procaspase-9 was also measured using Western blot.

Results: The apoptotic rates of eosinophils cultured in the presence of anti-CD30 mAb were significantly increased to 29.1 ± 6.1% and 47.3% ± 4.7% compared with 17.1 ± 6.7% and 29.4 ± 9.2% of the control at 4 and 24 hours, respectively (both $P < 0.05$). Caspase-9 inhibitor suppressed the mAb induced eosinophil apoptosis from 54.8 ± 6.9% and 71.5 ± 11.6% to 24.5 ± 6.0% and 47.8 ± 11.4% at 18 and 36 hours, respectively (both $P < 0.001$). We also showed the expression of procaspase-9 with the mAb was diminished compared with that of the control and of IL-5.

Conclusions: This study showed CD30 activation enhances the eosinophil apoptosis and the effect is mediated by Caspase-9 activation.

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Role of NLR (Nucleotide Oligomerization Domain (NOD)—like Receptor) on Allergic Inflammation in a Mouse Model of Allergic Rhinitis

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Background: Recently, a new set of pattern-recognition receptors, the nucleotidebinding oligomerization domain (Nod)-like receptors (NLRs), have emerged. Their activation, either by allergens or microbes, triggers an inflammatory response. Objective: To investigate whether recognition of bacterial microbial-associated molecular patterns in the nose may result in susceptibility to developing allergic reactions, and to understand the molecular mechanisms by which such triggers block natural tolerance.

Methods: Ligands of intracellular microbial-associated molecular pattern recognition receptors—the nucleotidebinding oligomerization domain (Nod)-like receptors, Nod1 and Nod2—were given intranasally with antigen, and their ability to modulate airway tolerance was analyzed. Seventy 2 mice were randomized to one of 6 groups: control ($n = 12$), AR (n = 12), pre NOD1 group (n = 12), pre NOD2 group (n = 12), post NOD1 group (n = 12), and post NOD2 group (n = 12). All mice except for the control group were sensitized by an intraperitoneal injection of ovalbumine (OVA) and aluminum hydroxide. Two weeks after sensitization, all sensitized mice were challenged intranasally with OVA. The control group was received phosphate buffered saline intranasally. The allergic symptom after the final challenge was recorded. Interleukin (IL)-5, interferon-γ (IFN- γ), and IL-10 levels in nasal lavage fluid (NALF), as well as serum OVA-specific IgE levels were measured. The number of eosinophils in lamina propria was evaluated. The levels of T-bet, GATA-3, and Foxp3 mRNA expression in splenic mononuclear cells were determined by real-time polymerase chain reaction.

Results & Conclusion: We show that a Nod-like receptor is a novel, previously unrecognized, pathway that adversely links innate and adaptive immunity and leads to allergic rhinitis.

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MUTANT IL-3: A Common Down Regulator for Components of IGE Mediated Signal Transduction Pathway

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Background: FcepsilonRI mediated signal pathway in basophils and mast cells leads to release of histamine and other mediators. Interestingly, basophils from 10% to 20% of the population do not release histamine and other mediators on activation of the IgE signal transduction pathway and this has been attributed to the absence of tyrosine kinases Lyn and Syk.

Objective: To investigate the association between histamine releasibility, total serum IgE, expression of IgE receptor and role of IL-3 with reference to non-releaser phenotypes in Indian population.

Methods: Basophils from peripheral blood of healthy adults were purified by density gradient centrifugation and negative immuno-selection. Histamine release assay was performed flourometrically. Total serum IgE was estimated by ELISA and assessment of IgE receptor expression was carried out by flow cytometry. Assessment of Lyn and Syk expression were carried out by flow-cytometry.

Results: Histamine release after ConA challenge varied from 0% to 100% in Indian subjects. Eighteen percent subjects showed less than 5% histamine release (non-releasers). Flow-cytometric analysis revealed a significantly reduced expression of FcepsilonRI in non-releaser basophils ($P < 0.05$). Total serum IgE levels were also significantly low ($P < 0.05$) in non-releasers. Flow-cytometric analysis revealed a significantly reduced expression of Lyn and Syk kinases in basophils ($P < 0.05$). Histamine release also significantly correlated with expression of Lyn and Syk kinase ($P < 0.05$). Non-releasers showed the presence of SNP at +79 (T-C), which leads to the one amino acid change at 8th position in the mature IL-3 from serine to proline.
Conclusions: About 18% of the Indian subjects studied showed non-releaser phenotype and also had reduced serum IgE levels and FcepsilonRI expression reduced Lyn and Syk kinase expression. Non-releasers have shown the presence of less potent isoform of IL-3/P8, which is suspected to be common factor responsible for the non-releaser phenotype. This needs to be extended to a larger sample size and could be a potential target for the development of therapeutics for allergic patients.

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IL-17 Role in the Regulatory Function of B Cells

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Background: B lymphocytes are known to be important cytokine sources in inflammation and play a pathogenic role by producing autoantibodies in a number of chronic immunological diseases. However, B cell depletion therapy induced an exacerbation of symptoms in some patients with autoimmune disorders, revealing that B cells play a critical anti-inflammatory role mediated by IL-10 release. We therefore investigated the human B cell regulatory subset producing IL-10 in response to stimulation.
Methods: Highly purified B cells were obtained from tonsils by using a multiple-step separation procedure which included rosette depletion, adherence depletion, CD3+ cell magnetic-activated depletion and CD19+ magnetic-activated positive cell selection. CD20+ purity was verified by flow cytometry. The CD19+CD20+ B cells were stimulated with CpG oligonucleotide, IL-4, IFN-gamma, anti-CD40, IL-17A and IL-17F, either alone or in combination. The expression of both IL-6 and IL-10 mRNA was analyzed by quantitative RT-PCR and by ELISA. B regulatory cell subsets expressing IL-10 and the markers CD5 and CD1d were quantified by FACS analysis. B cell proliferation was determined by 3H thymidine incorporation or CFSE labeling.
Results: Expression of IL-10 mRNA and protein in purified B cells from tonsils was weakly stimulated by anti-CD40 antibody, CpG oligonucleotide or with IL-17. When B cells were simultaneously stimulated with IL-17, anti-CD40 antibody and CpG oligonucleotide, the mRNA and protein expression of IL-10 was strongly increased ($n = 3$; $P \leq 0.001$). B cells proliferation was also significantly increased. In contrast, stimulation with IL-4 alone or in combination with anti-CD40 antibody, decreased the expression of IL-10 ($n = 3$; $P \leq 0.001$).
Conclusions: TLR9 receptor stimulation synergizes with CD40 and IL-17 receptors stimulation in the induced proliferation and potent release of IL-10 cytokine while decreasing IL-6 production in B cells. These novel findings provide evidence that B lymphocytes might be an important source of the anti-inflammatory IL-10 cytokine, and provide novel evidence that stimulation of B lymphocytes with IL-17 cytokine could be an important regulatory mechanism in immune responses.

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Role of TH-17 Cytokines in Steroid Insensitivity in Peripheral Blood Mononuclear Cells. Relationship to GR-alpha and GR-beta Expression

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Background: Inhaled corticosteroids represent the most common treatment for asthma. Although most asthmatic patients respond well, a significant proportion of severe asthmatics require higher doses or even fail to respond to oral or inhaled corticosteroids. We previously reported that glucocorticoid receptor-beta is associated with corticosteroid resistance in airway epithelial cells from asthmatic patients and that Th-17 cytokines increase steroid insensitivity via a mechanism involving GR-beta upregulation. We aim to investigate whether IL-17A and F cytokines enhance steroid unresponsiveness in PBMCs from normal subjects and severe asthmatics via the upregulation of GR-beta isoform.
Methods: PBMCs were cultured for 48 hours in the presence or absence of IL-2, IL-4, IL-17A, IL-17F or IL-23 cytokines. Expression of GR-alpha, GR-beta, GILZ and IL-6 was determined using Q-RT-PCR and/or Western blotting. Response to Dexamethasone was determined on the inhibition of PHA-induced proliferation by Dexamethasone (IC50) using either ^{3}H-thymidine or CFSE-labelled cells. Response of the cells to Dexamethasone-induced apoptosis was determined by Annexin-V staining.
Results: Treatment of PBMCs with IL-17A+IL-17F combined significantly decreased the mRNA expression of GR-alpha while that of GR-beta was significantly upregulated. IL-2+IL-4 in combination significantly decreased GR-alpha expression but had no effect on GR-beta receptor expression. IL17A+IL17F+IL23 combined induced the highest ratio of GR-beta/GR-alpha in PBMC from normal subjects. Either IL-17A+F or IL-2+IL-4 combinations significantly decreased the inhibitory effect of Dexamethasone on PBMC proliferation (IL-17A+F IC50 = 190 nM Dex; IL-2+4 IC50 = 1060 nM Dex), when compared to the control without cytokine stimulation. In the presence of Dexamethasone, IL-2+IL-4 but not IL-17A+IL-17F, inhibited the expression of the glucocorticoid-inducible leucine zipper gene (GILZ) in PBMCs from both normal (60%) and asthmatics (45–50%), which was correlated with significantly higher apoptosis in cells stimulated with IL-2+IL-4.
Conclusions: IL-17A, IL-17F, IL-2, and IL-4, which are known to be upregulated in the blood and lung tissue of asthmatics, contribute to steroid insensitivity of severe asthmatic patients by modulating the expression of GR-alpha and GR-beta receptors on peripheral blood PBMCs. GR-beta could protect PBMCs from Dex-induced apoptosis. Furthermore, the increased GR-beta/GR-alpha ratios by both IL-17A+F and IL-2+4 cytokines correlates with the decreased inhibitory effect of Dexamethasone on PHA-induced PBMC proliferation.

OCCUPATIONAL ALLERGIES

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Prevalence of Latex Sensitization Between Medicine and Dentistry Students from Nuevo Leon University

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Background: Latex allergy has become an important health problem in the last 2 decades. Sensitization in general population is about 1%.[1] Healthcare workers have a frequency of 2% to 25%.[2] There is not information about this issue in Mexico. Our objective was to know and compare prevalence of latex sensitization in last grade medicine and dentistry students of the Nuevo Leon University.
Methods: This was an observational, prospective and comparative study. Last grade medicine and dentistry students were invited to participate. Spanish version of the Latex Allergy Questionnaire (ACAAI recommended) and skin tests for latex: prick test (SPT) (latex extract Allerstand 1:20 w/v), prick by prick (PBPT) (latex gloves) were performed in every patient. Positive control was histamine 10 mg/mL and glycerinated solution for negative control (allerstand) using duotip test disponsable. SPT and PBPT were read 15 min after application and positive result were interpreted as a wheal diameter of 3 mm more than negative control. Data were analyzed for demographics with Statistical Package for Social Sciences (SPSS v16.0), for comparison between groups of sensitized patients fisher exact test was performed.
Results: Study included 378 patients, 213 (56.3%) dentistry students and 165 (43.7%) medicine students. Male/female ratio was 1.2/1 for medicine and 0.36/1 for dentistry. Average age was 23 years in both groups. General sensitization to latex was 7.1% (27), per group medicine was 6% (10) and dentistry 7.9% (17). Almost to all commercial extract, only one patient in each group was positive to gloves PBPT. By questionnaire 10.9% medicine group and 17.3% of dentistry group report symptoms with latex, but only 14.8% of dentistry group was Skin test positive, no one in medicine group. Rhinitis or conjunctivitis symptoms were found in 48.1% of sensitized patients. Most frequent foods associated with symptoms were pineapple (2.6%), fig (2.1%), avocado (1.9%) and kiwifruit (1.6%). There was no statistical difference between both groups sensitization ($P = 0.549$).
Conclusions: Latex sensitization was more common in healthcare students than references in general population but symptoms referred to latex no always are demonstrated by IgE sensitization, so delayed mechanism must be take in to account to get a better diagnosis and treatment approach.

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Profile of Latex Sensitization in Children with Myelomeningocele of São Paulo, Brazil

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Background: Latex allergy is an important cause of occupational allergy and is responsible for numerous allergic reactions in sensitized individuals.
Methods: The study included 55 children with myelomeningocele followed at a specialized center. In addition to a standard questionnaire and skin tests for immediate cutaneous hypersensitivity to aeroallergens and total latex, the patients underwent determination of serum total and specific IgE to latex and its fraction recombinants.
Results: The rates observed were 45% for sensitivity and 20% for latex allergy (sensitization with clinical symptoms). Twenty-four (43.6%) patients were atopic and the average age at the first episode of reaction to latex was 44.5 months, with cutaneous reactions being the most frequently reported (72.7%). Specific IgE to fractions rHev b1, 3, 5, 6.1 and 6.2 were detected in more than 50% of patients allergic to latex. The group comprising sensitive and allergic patients was different from non-sensitized subjects regarding the following variables: atopy, rhinitis, angioedema, average number of surgeries, patients with 4 or more surgeries, use of ventricular peritoneal shunt, the presence of at least one skin tests for immediate cutaneous hypersensitivity positive for aeroallergen and serum total IgE greater than 200 KU / l. Multivariate analysis showed as significant: current asthma, atopy and the number of surgeries undergone.
Conclusions: Our study documented the raised prevalence of awareness and latex allergy in patients with myelomeningocele. Specific IgE to fractions rHev b1, 3, 5, 6.1 and 6.2 were detected in more than 50% of children with myelomeningocele who are allergic to latex. The number of surgeries that the patients were submitted to determined higher levels of specific IgE, especially rHev b5 and 6.01. History of current asthma, atopy, and having undergone 4 or more surgeries were independent risk factors identified for latex allergy.

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Specific IgE to Recombinant Allergens of Latex and Foods in Patients With Spina Bifida

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Background: To identify the profile of specific IgE to recombinant allergens of *Hevea brasiliensis* and fruits in patients with spina bifida and latex allergy.
Methods: Cross-sectional study with 210 pacients aged 0 to 18 who have spina bifida and who have been followed in a Reference Hospital in Sao Paulo, Brazil. Patients were submitted to a questionnaire about immediate latex allergy symptoms.Their blood were collected for the detection of serum specific IgE to latex, specific IgE to rHev b1, 3, 5, 6.01, 6.02, 8, 9, 11, and specific IgE to avocado, banana, chestnut, potato and papaya, through ImmunoCAP technique.
Results: Patients' mean age was 7.9 years, and 108 (51%) were female. The mean time to the first surgery was 40 days, and patients presented an average of 4 or more surgeries during their lives. Forty-seven (22%) patients reported symptoms related to latex, predominantly cutaneous symptoms (85%). The latex recombinant allergens most related with symptoms were rHev b1 (19 patients, 68%) and rHev b3 (11 patients, 39%). On the other hand, tests were also positive to rHev b5 (9 patients, 32%), rHev b6.01 (12 patients, 43%), rHev b6.02 (12 patients, 43%), rHev b9 (patients 1, 4 %), and rHev b11 (9 patients, 32%). All tests were negative to rHev b8. Although, 36 (17%) patients tested positive to at least one of the food allergens, they did not present symptoms related to them. Balloons and latex gloves were the main objects associated with the onset of symptoms.
Conclusions: In this study, the prevalence of latex allergy was 22%. We observed a different profile of latex sensitization in relation to the literature. Patients do not present latex-fruit syndrome, in spite of cross-sensitization.

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Association between Clinical History and Specific IgE Recombinants Latex Allergens

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Background: To identify the profile of sensitization to latex allergens in patients with spina bifida, with and without symptoms of latex allergy.
Methods: Cross-sectional study with 210 pacients aged 0 to 18 who have spina bifida and who have been followed in a Reference Hospital, in São Paulo, Brazil. Patients were submitted to a questionnaire for immediate symptoms related to latex allergy and they were classified as symptomatic (S) or asymptomatic (A), depending the presence of immediate symptoms on exposure to latex. Their blood were collected for the detection of serum total IgE, specific IgE to latex, and specific IgE to rHev b1, 3, 5, 6.01, 6.02, 8, 9, 11, through ImmunoCAP technique.
Results: Patients' mean age were 7.9 years and 108 (51%) were female. S patients were 47 (22%). For these patients, 28 (60%) had at least one specific IgE positive test and 19 (40%) presented all tests negative. The A cases accounted for 163 (78%) patients. For these patients, 57 (35%) had at least one specific IgE test positive and 106 (65%) presented all tests negative. The

prevalence of sensitization to recombinant latex allergens is not the same among patients S and A: rHev b 1 (S = 68%, A = 49%), rHev b3 (S = 39%, A = 28%), rHev b5 (S = 32%, A = 21%), rHev b6.01 (S = 43%, A = 23%), rHev b6.02 (S = 43%, A = 19%), rHev b8 (S = 0, A = 2%), rHev b9 (S = 4%, A = 5%), rHev b11 (S = 32%, A = 23%).

Conclusions: In this study, the prevalence of latex allergy in spina bifida patients is 22%. In symptomatic patients, the sensitivity of specific IgE tests is very poor. The profile for rHev b positivity is different in symptomatic and asymptomatic patients.

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Occupational Flaxseed Allergy (Conjunctivitis): A Case Report

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Background: K.F. a19 y/o male, with history of atopy (food/drug allergy, atopic dermatitis, asthma and or rhinitis) developed conjunctivitis (without cough or rhinitis) on the third month of exposure to an enviroment of dust from sieving of grounded flaxseeds (imported brown organic Canadian Flaxseeds). Exposure to this dust caused severe itching and tearing with prominent development of "red eyes" quickly after begining of exposure with complaints abating during weekends. Due to eye scratching he also developed significant palpebral edema and purulent discharge.

Methods: Prick skin Testing (H-S Lancetter, results read at 15 minutes, with positive and negative controls) with a panel of 20 inhalant and food allergens (Diater Labs,Argentina) was performed.

Results: Commercial Allergens were found negative at 10 minutes reading (0 mm papule/0 mm erythema) for inhalants such as: mites, blomia t epithelia, grass pollen, shellfish, fish mix and coconut; only positive finding was to mold mix (5 mm papule/10 mm erythema). Prick to Prick skin (PtP) testing to a solution of flaxseed: 1 gram of flaxseed brought by patient from work place/ 1 mL of phenol saline, was positive at 20 minutes (papule 12 mm/erythema 25 mm). This same solution was applied to 5 controls (with no symtomps after ingestion of esposure to flaxseed) and found negative.

Conclusions: Patient improved with use of goggles and removal from sieving area, remaining free of symtomps, as of today. Patient refused mucosal/oral challenge with a solution of flaxseed or other allergy diagnostic procedures. Though PtP skin testing may suggest a possible IgE mediated reaction.

(1) Unable to be confirmed by other means (challenge, IgE intears for flaxseed, etc); this is-to our knowledge- the first case of isolated conjunctivitis from exposure to flaxseed sieved dust. Flaxseed Allergy, in spite of its wide spread used and human consumption (mainly as dietary fiber) has been infrequently reported, with occasional cases of anaphylaxis.
(2) We report a case of isolated conjunctivitis on exposure to dust from sievings of ground flaxseed.

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PATHOPHYSIOLOGY OF CHILDHOOD ASTHMA

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Involvement of Il-10 Gene Promoter Polymorphisms in the Susceptibility for Childhood Asthma

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Background: Asthma and atopy have a complex background which may result from the interaction of genes and environments. Interleukin (IL)-10 is known to play various roles in immune-regulating and anti-inflammatory responses. The aim of this study was to evaluate the possible effect of the IL-10 promoter polymorphisms on susceptibility to childhood asthma.

Methods: We recruited 333 patients with atopic asthma, 55 with non-atopic asthma, and 248 normal controls. We performed a genetic association study of 3 genetic polymorphisms (IL-10–1082A>G, IL-10 –819T>C, –592A>C) of the IL-10 promoter.

Results: There was no difference between atopic asthma, non-atopic asthma and normal controls in allele, genotype or haplotype frequencies of these IL-10 polymorphisms. However, the –1082A>G polymorphism and ATA haplotype in the IL-10 promoter gene were associated with airway hyperresponsiveness (AHR) and the –819T>C, –592A>C, and ATA and ACC haplotypes were also shown to be related with serum eosinophil cationic protein (ECP).

Conclusions: Our results suggest that the polymorphisms within the IL-10 promoter may have a disease-modifying effect in asthmatic airway.

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Serum NT-3 and NT-4 Levels are Associated with Clinical Severity in Asthmatic Children

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Background: Neuronal modulation of inflammation and airway hyperresponsiveness has been well described in asthma and neurotrophins provide the link between inflammation and neuronal dysfunction. In humans, elevated BDNF, NGF and NT-3 levels have been found in bronchoalveolar lavage fluid (BALF) following allergen provocation. Moreover, BDNF levels are significantly higher in untreated asthmatic patients in comparison to those treated with inhaled glucocorticoids and non asthmatic controls. It has also been shown that allergic inflammation increases local all 4 neurotrophins production that are important mediators of eosinophil survival in BALF. The aim of this study was to analyze if levels of neurotrophins in serum of asthmatic pediatric patients are altered in the course of disease (exacerbation and asymptomatic period) and therefore may serve as potential biomarkers for disease activity or symptoms severity.

Methods: In the study we included 98 children diagnosed with asthma. The blood was collected twice: during exacerbation and in the asymptomatic period. The serum levels of 4 neurotrophins (BDNF, NGF, NT-3, NT-4) were analyzed with use of DuoSet ELISA Development Kit (R&D). Statistical analysis was performed with Statistica v. 9.0.

Results: Analysis revealed no significant differences in neurotrophins levels in serum between asthmatic patients during asthma exacerbation and asymptomatic period. However, we found that serum levels of NT-3 and NT4 correlate with disease severity, being significantly lower in mild asthmatics as compared to patients with moderate and severe asthma ($P < 0.01$).

Conclusions: Our results suggest that neurotrophins levels do not seem to correlate with the clinical symptoms activity in the course of asthma, however 2 of them (NT-3 and NT-4) correlate with disease severity.

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Association between Eosinophilic Airway Inflammation and Persistent Airflow Limitation in Asthmatic Children

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Background: Eosinophilic airway inflammation contributes to persistent airflow limitation in adults with severe asthma. We aimed to evaluate the association between eosinophilic inflammation in induced sputum and pulmonary function, and persistent airflow limitation in children.

Methods: A total of 92 asthmatic children and 72 control children were enrolled in this study. Eosinophil count (%) and eosinophil cationic protein (ECP) levels were measured in induced sputum. We performed spirometry and methacholine challenge test while measuring total eosinophil count, total serum IgE, and serum ECP in all subjects. Subjects with persistent airflow limitation were defined as the patients with postBD FEV1/FVC below the lower limit of controls, which is subtraction of 2 standard deviation from the mean ratio.

Results: Asthmatic children had significantly higher levels of sputum eosinophils (18.1 ± 21.5 vs 0.5 ± 1.3%, $P < 0.001$) and sputum ECP (2.3 ± 0.7 vs 1.6 ± 0.6 log ug/L, $P < 0.001$) compared to controls. No differences in sputum eosinophils and ECP among 4 asthmatic groups divided by the degree of persistent airflow limitation. Sputum ECP level had statistically significant inverse correlation with postbronchodilator (postBD) FEV1 ($r = –0.307$, $P = 0.001$) and postBD FEV1/FVC ($r = –0.286$, $P = 0.002$), whereas sputum eosinophils didn't show any correlation with postBD FEV1 and postBD FEV1/FVC.

Conclusions: Our findings suggest that sputum eosinophilic inflammation, especially ECP, is associated with pulmonary function and persistent airflow limitation, which is manifested by low postBD FEV1 and postBD FEV1/FVC.

PEDIATRIC ASTHMA

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Not All Who Wheeze Have Asthma—Tracheal Diverticulum with Stenosis of Trachea in 9 Years Old Boy

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Background: A tracheal diverticulum (TD) is very rare congenital malformation. The prevalence is about 0.3% in children over 10 years of age according to fiberoptic bronchoscope studies and it is rarely reported in clinical practice (3). Here we describe our recent exprience in succesfully diagnosing and treating a 9-years old box suffering from membranous stenosis of trachey with trachea diverticulum.

Methods: A 9-year old boy (personal history negative as to trauma of respiratory tract and intubation and atopy) was admitted to hospital with wheezing and progressive dyspnoe during the 6 months to restrict basic locomotion and reading of text. Multislice computed tomography of the chest showed surprising incidental finding of a tracheal diverticulum (6 mm × 2 mm) and 3-dimensional reconstruction CT stenosis of trachea approximetly 1,5 cm below vocal corde and orificium of tracheal diverticulum (the 2nd cartilage of trachea). Pulmonary function tests revealed reduction of spirometric values, with no post-bronchodilator change. Subsequent flexible bronchoscopy showed circular stenosis of trachea and orificium of TD. Subsequently, the vaporization by NdYAG laser - Sharplan 3000, with energy of 30 W was performed via flexible bronchoscopy under general anesthesia with a laryngeal mask. The dilatation by balloon (Boston Scientific) was performed to widen the diameter of trachea up to 8 mm.

Results: After 1 week, pulmonary function test revealed normal parameters without pathological symptoms.

Conclusions: In conclusion, we have summarized the case of an 9-year old boy with membranous stenosis of trachey and trachea diverticulum, a very rare congenital anomaly. This abnormality can be clearly diasgnosed by multislice CT and 3-dimensional reconstruction CT stenosis of trachea. Using the interventional bronchoscopy of membranous circular stenosis of trachea is adequate solution in children too.

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Reccurent Wheezing in Childhood—Is It Always Asthma?

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Background: Clinical presentation of the bronchial obstruction in children is most often highly suggestive of bronchiolitis, recurrent wheezing or asthma.

Methods: We present the cases of 2 patients diagnosed with recurrent bronchiolitis and asthma, non-responsive to treatment.

Results: The first patient, a 9-year-old boy presented wheezing, non-productive cough, dyspnea, aquous rhinorrhea, sneezing and nasal itching interpreted as allergic asthma associated to allergic rhinitis as he was sensitized to house-dust mites and dog. A treatment with inhaled corticosteroids and antihistamine was prescribed with little improvement of asthma symptoms. Six months later the patient presented for vomiting and productive cough. Thoracic ultrasound suggested achalasia, diagnosis confirmed through esophageal manometry and barium swallow. Surgical treatment led to resolution of asthma-like symptoms with persistence of a mild intermittent rhinitis. In the second case, a female patient presented 2 episodes of uncomplicated bronchiolitis during the 6th and the 7th month of life and a 3rd episode of bronchiolitis complicated with pneumonia during the 8th month of life. When admitted for the 3rd episode, she presented an oxygen saturation of 91% in ambient air. Thoracic ultrasounds oriented the diagnosis towards a diaphragmatic hernia, confirmed through barium swallow and barium enema. The surgical treatment of the hernia determined the resolution of respiratory symptoms. Unfavourable clinical course, despite correct treatment in both cases required additional investigations which finally led to the correct diagnosis and treatment.

Conclusions: For the differential diagnosis of non-responsive bronchial obstruction in children, one must think to digestive diseases. Ultrasound was the elective non-invasive method in diagnosing our cases.

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Bronchial Hyperresponsiveness in Children with Suggestive Asthma Symptoms

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Background: To describe the accuracy of bronchial challenge tests (methacholine and manitol) to measure bronchial hyperresponsiveness in a group of pediatric patients with suggestive symptoms of asthma.

Methods: We selected 27 patients who attended consecutively to our outpatient clinic complaining of 1 or 2 symptoms of asthma. They showed a normal baseline spirometry and a negative bronchodilator test. All of them underwent unspecific bronchial provocation challenges. Methacholine was performed using the tidal volumen technique and a PC20 ≤ 8 mg/mL was considered positive. Dry-powder mannitol (Osmohale TM) was administered according to the manufacturer's recommendations and the challenge was considered positive if a PD15 ≤ 635 mg resulted. We performed both tests with an interval of at least 1 week. Asthma drugs were avoided during the 2 weeks previous to every challenge. Skin prick tests (SPT) to the most common aeroallergens were also performed.

Results: Mean age was 9 (ranged 7–15) years, 18 (66.6%) children were male. Symptoms referred were: 14 (51.8%) cough, 10 (37%) seasonal cough or shortness of breath, 5 (18.51%) cough or shortness of breath due to physical exercise and 1 (3.7%) cough or wheezing related to respiratory infections. SPT were positive in 59.2% of the children. Eighteen (66.6%) out of 27 patients had bronchial hyperresponsiveness, and 10 (37.03%) were non atopic. All patients with a positive response to manitol showed also positivity to methacholine. Mean methacoline PC20 among responders was 0.64 ± 4.08 mg/mL. Manitol was performed in 16 children, and resulted positive in 8 cases (50%) with a mean PD15 of 146.8 ± 246.49 mg. In 2 (25%) out of 8 patients with negative manitol resulted a positive methacholine.
Conclusions: Methacholine and manitol challenge tests detected bronchial hyperresponsiveness in more than a half of the studied children with suggestive asthma symptoms. Methacoline was more sensitive than manitol.

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Relationship between Fractional Exhaled Nitric Oxide (Feno) and Forced Expiratory Volume in One Second (Fev1) and Forced Vital Capacity (Fvc)i Children with Asthma

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Background: Measurement of fraction of exhaled nitric oxide (FeNO) is a relatively simple, noninvasive, and reproducible test for detection of endogenous inflammatory signals in childhood. The aim of this study was to evaluate the correlation between FeNo levels and forced vital capacity (FVC) and forced expiratory volume in the first second (FEV1) in a group of steroid-naive childhood asthma.
Methods: The study was conducted in a group of 60 steroid-naive asthmatic children (50 atopic and 20 nonatopic; mean age 7 years) who presented to Kyung Hee University Hospital and 20 healthy children. All patients underwent measurement of FeNO, skin prick tests with common inhaled allergens, and blood eosinophil, and flow-volume spirometry. FeNO levels were measured by chemiluminescence during exhalation into the NO analyzer. Measurements of FeNO in parts per billion (ppb) and spirometry, including FEV1 and FVC, were performed.
Results: Compared to the healthy volunteers, FeNO was elevated in both groups of asthmatics. The mean FeNO level in the asthmatic children was 18.6 ppb. FeNO in the atopic asthma group was higher than in the group of nonatopic asthmatics. There was statistically significant correlation between FeNO levels and FEV1 ($r = -0.36$, $P < 0.016$) and FVC ($r = -0.40$, $P < 0.01$).
Conclusions: FeNO levels were related with pulmonary functions in childhood asthma. Thus measurement of FeNO is a promising clinical tool for assessing asthma.

PEDIATRIC ASTHMA EPIDEMIOLOGY

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Evaluation of the September Epidemic of Asthma Exacerbation in Children in Our Practice

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Background: Know that the rate of asthma exacerbations are increased in September after summer vacation with the beginning of school year. Investigators have been studied this problem and it was supposed that the main cause could be the stress associated with school return what can worsen asthma symptoms. Beside this children returning to school after summer vacation are reexposed to respiratory viral infections, sensitizing allergens in the school enviroment, and can be connected with poor compliance in the medication in the summer period.
Methods: We stared to investigate that what could be the causative factors in children who suffered dyspnoe and other signs of asthmatic exacerbation from September 2008, could we present the increasing number of these patients in hospitalization rate, and could we confirm the changing compliance of the regular medication during the summer period? A short questionaire was constructed and was given the patients who were admitted to hospital (162) with asthma exacerbation symptoms. Then 45 patients were selected for a longer follow up to investigate their compliance in medication. We investigate from the database of our Hospital the asthmatic patient's admission rate from 2006.
Results: We could present from 2006 the increasing number of patients admitted because of asthma exacerbation in September in every year. We could present the increased number of schoolage patient among all of the admitted patients in the fall season. We compared the genders which were similar. We found that the symptom of asthma was worse in the fall season. We confirmed the higher number of patients suffering from viral infections. But the changing rate among patient who stopped the medication during summer was low as 13%.
Conclusions: We could confirm the September epidemic of asthma exacerbation among our patients as well. Compare the international investigations the main cause of the September epidemic of asthma connecting with the beginning of the school year and the increasing number of viral infections at this period of the year. Fortunately our patient compliance was good but we have to continue our patients' education from time to time.

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Elevated Asthma Prevalence in Mexican-American Children in El Paso, Texas

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Background: In the United States, among Hispanics, Mexican American have the lowest rate of asthma[1,2] This study was designed to determine the prevalence of asthma among 5 to 17 year-old children, in El Paso Texas, a community area with a 65.8 % of Hispanic of origin Mexican families.
Methods: Of March 2006 to May 2010, a cross-sectional screening survey was administered to 1108 children of 751 families selected at random from 50 strata of the El Paso County. We used self-reported history of physician-diagnosed asthma. Data were analyzed to determine the prevalence of lifetime and current asthma. Associations between asthma outcomes and variable trigger were evaluated. Chi-square tests were used for statistical comparison. A P value less than 0.05 was considered to be significant. Multivariate logistic regression (GENMOD) adjusting for repeated measures for the family was used to determine the risk of childhood asthma.
Results: Self-reported physician-diagnosed asthma was reported for 25.8 % of children, and current asthma identified in 20.5 % respectively. The prevalence was statistically higher in boys than tin girls ($P < 0.05$). 243 (90%) Children asthmatics are atopic and 437 (51.8%) children non-asthmatics are atopic. Smoking occurred inside 23.8% of households.26.3% of children had an indoor dog or cat and 21.2% of caregivers reported cockroaches inside the home.
Conclusions: Prevalence of physician-diagnosed asthma in Hispanic of Mexican origin, ever asthma and current asthma, were higher than those reported from the Centers for Disease Control and Prevention, the prevalence of asthma in 2007. Although most children with asthma are atopic (90%) a significant proportion (51.8 %) of atopic children do not have asthma. Children with a parent with asthma were almost twice as likely (OR = 2.40) to have asthma compared those without a parent with asthma. Children with a parent and grandparent with asthma were over 4 times likely to have asthma compared to those without a parent and grandparent with asthma

(OR = 4.97). Maternal asthma confers greater asthma risk to offspring than do paternal or parental asthma.

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Prevalence of Bronchitis and Revealing of the Risk Factors in the Children's Population

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Background: It is well known that with change oc climatic conditions cases of various diseases increase and especially, with cold climate, the frequency of acute respiratory diseases, especially, the influenza, rhinites, bronchitis, etc. grows.

Objective: To study of prevalence of bronchitis and its risk factors in children's population.

Methods: Study was conducted in the selected pediatric clinics of Tbilisi and involved 698 children from 6 months to 5 years age, based on the random and representative groups. Epidemiological study was conducted by cross-section method. Questioning was provided based on the questionnaire specially developed for this purpose. Study of the factors of the cause significance was provided on the basis of anamnesis data. Obtained results were processed by means of special software package SPSS/V11.5.

Results: According to the questioning, acute bronchitis was indicated 3 times, in 56.2% of the children's population, of which 47.4% were boys and 52.6% - girls. 43.8% of the population suffered complications in a form of pneumonia. In 21.9% of cases bronchitis was diagnosed for the first time. Wheezing was regarded as a risk factor (78.5%), serous nasal discharge (87.3%), cough, regarding its nature (68.3%) (short cough, wet cough productive cough), in part of the respondents lacrimation was indicated (35.6%), there was also indicated in children the immunodeficiency, sex, socioeconomic status, heredity factor, overcrowded homes. Prevalence of the symptoms of bronchitis was quite higher ($P < 0.05$) among girls, compared with the boys. 98.9% of the respondents with the symptoms of bronchitis stated that the disease was of seasonal nature, mostly from early October to end of March ($P < 0.01$).

Conclusions: Thus, single-stage epidemiological study showed that frequency of bronchitis in children's population is quite high, with prevalence among girls (59.9%).

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Atopic Phenotype in Children under 6 Years with Persistent Wheezing in El Salvador

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Background: Asthma is the most common chronic disease of childhood and the leading cause of childhood morbidity[1]. Even if an early intervention could improve their symptoms, the diagnosis of asthma in the first years of age is difficult. This study is the first effort to describe the atopic profile and the risk of developing asthma in a group of children from El Salvador with recurrent wheezing.

Methods: A questionnaire was designed for parents to determine the atopic background, while skin tests were performed in children. We used the modified Asthma Predictive Index (APIm)[2] to assess the risk of developing asthma.

Results: 65 children under 6 years were evaluated, with an average age of 3.5 years. The average age of onset of wheezing was at 11 months of age. Family history of asthma, chronic rhinitis and eczema were presented respectively at 25%, 19% and 8% of the population. 42% of our population presents allergic rhinitis and 37% eczema. Among the factors related to wheezing risk, we found that one third of the population was born via caesarean section with a breastfeeding average of 3.76 months; also we found the presence of pets in 26% of households, a passive smoking and exposure to wood smoke in 17% and 35% of the studied population respectively. 23 children were sensitized to respiratory allergens. Dust mites were found in 73% of children sensitized. The APIm was positive in 66% of the population.

Conclusions: This is the first cohort of children described under 6 years with recurrent wheezing in El Salvador. We found an early presentation of wheezing, caused not only by viral conditions. These children had strong personal and family atopic background with a high rate of sensitization to respiratory allergens, especially dust mites. Most of the children studied are at risk of presenting asthma in later ages.

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Comparison of Exhaled Nitric Oxide and Spirometry in Hispanic/Latino Children Living in Miami to Those Living in Latin America

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Background: Differences in atopic markers of inflammation has been shown to be due to varying environmental exposures between individuals. There is sparse information in the literature to compare the levels of atopic inflammatory markers in Hispanics/Latinos from distinctly different environments. Our aim was to study the levels of these clinical inflammatory markers in this population with similar levels of allergy/asthma control but from differing environments.

Methods: A retrospective review was limited to Hispanic/Latino children referred to our Allergy clinic over 6 months. These children were referred by their pediatrician for diagnosis of asthma and/or reactive airways disease. Respiratory tests of spirometry with Koko (nSpire Health, Colorado) and exhaled NO with MINO (Aerocrine, Sweden) was performed in all children by ATS guidelines. Collection of laboratory results of serum eosinophils and total IgE was also done. Two groupings were made based on the location of family residence, either locally in Miami, Florida (MF) or Latin America (LA). All patients in the MF group were of Hispanic/Latino ancestry, either first or second generation. The country of ancestry represented in the MF group were Colombia, Costa Rica, Cuba, Ecuador, El Salvador, Mexico, Nicaragua, Venezuela. The patients in the LA group were coming from Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, and Venezuela.

Results: Thirty-five children fromMF group and 29 children from the LA group were found. The mean age in the MF group was 8+3 years of age and in the LA group was 9+4 years of age. There was statistical significance

between eNO in both groups. The mean eNO was 23ppb in the MF group and 41ppb in the LA group. Normal eNO based on age and height for both groups is less than 15 to 20 ppb. There was no statistical significance between FEV1% in spirometry between both groups. The mean FEV1% in the MF group was 95 + 13%, and the mean FEV1% in the LA group was 92 + 9%. No differences were found between groups with either laboratory measures of serum eosinophils or total IgE.

Conclusions: Our analysis confirmed that despite similar levels of allergy/asthma control, there was a difference found in eNO in Hispanics/Latinos. This may be attributable to differences in environmental exposures between MF and LA.

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Maximum Expiratory Flow in Health Children from the Metropolitan Area of Monterrey Mexico

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Background: Studies have been conducted to obtain MEF (maximum expiratory flow) reference values in healthy children. Factors such as the regionś altitude, humidity, local temperature, and the characteristics of the study population cause changes in airway resistance that produce different MEF values. The objetive of this study is to establish normal reference values for MEF in healthy children from the metropolitan area of Monterrey, Nuevo Leon, Mexico and compare them with established reference values from other states of Mexico and the United States.

Methods: We carried out an observational, cross-sectional, descriptive, comparative study in healthy 6 to 8 year old children, both gender. A questionnaire that included information about age, weight, and height was applied. Flowmetry was performed with a Truzone portable peak flow meter and the highest of 3 values was recorded.

Results: We included 2282 children (1085 boys and 1197 girls) from 19 randomly selected elementary schools. The MEF values obtained were plotted on graphs in MEF percentiles according to gender and height. When compared with MEF reference values for authors from different locations, differences were found.

Conclusions: The variation observed in MEF values in our population compared with studies performed in other populations shows the need for clinical demographic data from each region to establish and use characteristic reference values.

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Viral Respiratory Infections and the Development of Atopy and Asthma

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Background: There is an association between severe RSV bronchiolitis in early childhood, recurrent wheezing, asthma, and allergy in later childhood. And also becomes increasingly evident that other viruses such as RV, also showed association with the development of asthma. The objective of this study is to know the relationship between viral respiratory infections in the first 5 years of age and the development of atopy and asthma.

Methods: This study is a prospective follow-up study in 2 communities, 9 years after a respiratory infection study was performed. Assessment included questionnaires, physical examination, skin prick tests (SPT), pulmonary function test (PFT), and reversibility testing.

Results: Three hundred thirty-two children, age 7 to 14 years, including 182 (54.8%) boys, were enrolled in the study. In 86 children, histories of viral respiratory infections (RSV, RV, and hMPV) were detected. The rate of positive SPT was high (81.6%), and 15 (4.5%) children showed dermatographism. The percentage of positive SPT among children with and without viral respiratory infections was almost similar (83.4% vs 85.4%). The positive SPT $>$ 1 in children with history of viral respiratory infections was 65.9%; 5.9% with 1 positive, 27.1% with 2 to 3 positive, 20% with 4 to 5 positive and 18.8% with $>$ 5 positive; while the positive SPT $>$ 1 in the non viral respiratory infections was 75,3%; 9.3%, 23.9%, 30.4%, and 21.1%, respectively. The difference between those 2 groups of children was not significant ($P = 0.076$). History of asthma in the children with history of respiratory infections was higher compared with the non infections group (19.7% vs 8.1%). However, the spirometry results show no difference ($P > 0.05$) of FEV1 $<$ 80%, FVC $<$ 80%, FEV1/FVC $<$ 80% and bronchodilator response $>$ 12%, between those 2 groups.

Conclusions: The positive rate of SPT in the children is high, but no difference is found between history of viral respiratory infections in early life in relation to the later development of atopy and asthma. The spirometry test results show no difference between the 2 groups.

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Clinical Characteristics of Eosinophilic Asthma Compared to Noneosinophilic Asthma in Children

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Background: Asthma is a heterogeneous and complex chronic inflammatory disease of the airways. Asthma can be classified as eosinophilic asthma (EA) or noneosinophilic asthma (NEA). We investigated whether children with EA and NEA manifest different clinical characteristics.

Methods: A total of 158 children with EA and 89 children with NEA were enrolled in this study. We performed pulmonary function and methacholine challenge tests, and measured blood eosinophil count, total serum immunoglobulin E (IgE), serum eosinophil cationic protein (ECP), and sputum cell counts.

Results: There were no significant differences in age, sex, and body mass index between the EA and NEA groups. The blood eosinophil count and serum ECP were higher in EA than in NEA, whereas the total serum IgE was similar in both groups. Pulmonary function, as measured by forced expiratory volume in 1 second (FEV_1), forced expiratory flow at 25 to 75% of forced vital capacity ($FEF_{25–75\%}$), and postbronchodilator (postBD) FEV_1 were significantly decreased in children with EA compared to those with NEA. In EA, FEV_1, $FEF_{25–75\%}$, and postBD FEV_1 correlated negatively with sputum eosinophils. In NEA, FEV_1/forced vital capacity (FVC) and $FEF_{25–75\%}$ correlated negatively with sputum neutrophils. Sputum eosinophils (in EA) and sputum neutrophils (in NEA) increased with increase in asthma severity.

Conclusions: The pulmonary function of children with EA is significantly lower than that of children with NEA. In addition, pulmonary function and asthma severity are associated with eosinophilic inflammation in EA and with neutrophilic inflammation in NEA.

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Correlation between Quality of Life and Treatment Adherence in Childhood Asthma

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Background: Asthma is a chronic disease that around 3 million people suffer from in the world, it is more common the most of them during childhood.

Methods: Determinate correlation between quality of life (QL) and treatment adherence (TA) on childhood asthma, in pediatric patients between 3 to 17 years old with diagnosis of bronchial asthma. Transverse, retrospective and correlational study, they were evaluated 59 young patients with confirmed diagnosis of bronchial asthma, in a period of 2 months (between May to June, 2011), they were evaluated by 2 tests, the Tucson Children's Assessment of Sleep Apnea (Tu CASA) which was modified to QL in children with asthma and the Morisky Green Levine test was modified and validated to asthma disease and TA, the variables were about LQ: snore, mouth-breathing, drowsiness, behavior and academic performance, and about treatment adherence: if the patients forgive to take their medicine , schedule for taking correctly medication, suspension because the patient feels good or bad (in this case attributed to the drugs), knowledge of effects of medication, if the pediatric patients need help, and who help them. Miscalculation of 5 percent and reliability of 95%, Pearson`s correlation coefficient to evaluate LQ and AT based on test score.

Results: It was found good LQ in 46 children (77.9%) and 13 patients with regular LQ (22%), about TA was good in 32 patients (54.3%) and regular to bad TA in 27 children (45.8%), Pearson's correlation coefficient was 0.4, and it was evaluated with Student's t, and it's statistically meaningful, $P = 0.05$.

Conclusions: LQ and TA are connected significantly, because it's a part of the complete treatment to control asthma, following closed treatment showed be an important aspect, because there are patients with good life quality and following partially treatment.

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Effect of Diet Supplementation with Epa-Dhe on Pulmonary Function Tests and Metacholine Bronchial Challenge Test in Obese Mexican Children

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Background: There is scarce and conflicting data of the effect of diet-supplementation with EPA-DHE on lung physiology in obese children and adolescents.

Objective: Evaluate the effect of diet-supplementation with EPA-DHE on pulmonary function tests and methacholine-bronchial challenge test in obese Mexican children and adolescents.

Methods: Randomized single blinded controlled clinical trial. Sample consisted in obese children and adolescents with hypertriglyceridemia attending our clinic, they were randomly assigned to either group 1 (G1), which received 3 gr/day of EPA-DHEA, or group 2 (G2), which received 3 gr/day of gelatin as placebo daily for 2 months. Spirometry and methacholine challenge tests were made to both groups at baseline, and 1 and 2 months later. We obtained central tendency and dispersion measures, and differences were analyzed by Student's *t* test for independent samples, considering $P < 0.05$ as statistical significance, also intra-group paired differences were made.

Results: The total sample consisted of 97 obese children and adolescents with mean age of 12 ± 1.3 years (range of 8–16 years), 46 females (46.9%) and 51 males (53.1%). At baseline both groups had similar spirometric and metacholine challenge-test values G1: FVC: 3.48 L/min, FEV1: 3.07 L/min, FEF25 to 75% 31.3 L/min; G2: FVC: 3.33 L/min, FEV1: 2.92 L/min, FEF25 to 75% - 3.3 L/min ($P > 0.05$). FEV1 was significantly reduced in active treatment group with baseline mean (3.07 L/min) compared to visit 1 (2.94 L/min) and to visit 2 (2.92 L/min).

Conclusions: Diet-supplementation with EPA-DHEA had no effect on bronchial hyper-responsiveness assesed by methacholine challenge test after 1 and 2 months of treatment. However diet-supplementation with EPA-DHEA showed a deleterious effect on FEV1 in the active treatment group, of notice, this was only a spirometric finding, no clinical effects were observed during treatment.

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Use of Complementary and Alternative Medicines by Children Suffering from Asthma at Mangalore, India

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Background: Patients with chronic diseases including asthma, have a greater tendency to use Complementary and alternative medicine (CAM) as they are more concerned about the adverse effects of conventional medicine, dissatisfaction with their medical care, as well as a subjective feeling of health improvement with use of CAM. The aim of this study was to determine the prevalence of the use of CAM, reasons for use of CAM, and sources of information about CAM among paediatric asthmatic patients in outpatient department and urban health centre.

Methods: Following approval from Institutional Ethics committee, the data for this cross-sectional study was collected from parents of 125 paediatric patients diagnosed with asthma for more than a year waiting to see the doctor in the outpatient clinic in teaching hospitals and urban health centre of Kasturba Medical College, Mangalore, India during the period from March 2010 to September 2010. A pre-tested self-administered questionnaire in Kannada was distributed to the parents, the purpose of the study was explained, assurance of anonymity was conveyed, and emphasized that the patient's decision to complete or decline to complete the survey would not affect his/her healthcare quality in any way. Written informed consent was obtained from the participants.

Results: Data regarding 125 children with a mean age of 9.06 years were collected, the majority were male (n = 76, 60.8%). The prevalence of ever-CAM use was 72.8% (n = 91). Sixty-three males (69.2%) used CAM compared to 28 females (30.8%) ($P < 0.001$). Fifty-six (61.5%) CAM users had not discussed use of CAM with their doctors. The main reason of non-disclosure was "the doctor never asked" (n = 59, 64.8%), and the main sources of information about CAM were family and relatives (n = 45, 49.4%). The majority of asthmatic patients used Ayurvedic medicines and mixtures (n = 35, 38.5%), foods (n = 18, 19.7%) and herbs (n = 16, 17.6%). About 76% (n = 69) of asthmatic patients perceived CAM as good for their disease management.

Conclusions: Use of CAM among asthmatic patients is relatively high, particularly among females. The majority of asthmatic patients valued the use of CAM. Health education of asthmatic patients about CAM is highly recommended.

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Long-term Follow Up Outcomes of Early Intervention with Anti-Inflammatory Therapy in Patients with Asthma Under 2 Year-old

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Background: To evaluate the 8- and 11-year follow up outcomes on the basis of various parameters including remission rate, pulmonary function, FeNO, IgE level and RAST in children with asthma who developed recurrent asthma attacks and started early intervention with anti-inflammatory treatment for active remission induction before 2 years of age.

Methods: This study investigated 63 children who presented with recurrent wheezing between October 1998 and September 2000 and were diagnosed with asthma in early childhood. After 3 to 5 episodes of recurrent asthma attacks were observed, administration of regular controller medications (ICS and LTRA) was started. Subjects were evaluated for the above parameters in 2008 and 2011.

Results: Subjects comprised 41 males and 22 females, with a mean age at symptom onset of 13.9 months, a mean age at treatment initiation of 18.2 months and a mean IgE level of 485.4 IU/mL at 2 years of age. Among the subjects, 68.3% and 85.7% were positive for specific IgE antibody against dermatophagoides pteronyssinus (Dp.) and egg white, respectively, at 2 years of age, and 87.3% were positive for specific IgE antibody against Dp. at 3 to 4 years of age. The severity of asthma at treatment initiation was intermittent in 9 children, mild persistent in 31, moderate persistent in 18 and severe persistent in 5. The prevalence of asthma symptoms among these children improved to 9.5% after 3 years and 1.6% after 6 years of treatment. The 8-year follow up outcome was evaluated in 53 children at a mean age of 10.2 years. The long-term remission (^{3}a5 years) rate was 84.9% (100% for intermittent, 88.9% for mild persistent, 71.4% for moderate persistent and 75.0% for severe persistent cases). A mild decrease in pulmonary function was observed in 27.2% of cases while a mild increase in FeNO was observed in 48.8% of the children.

Conclusions: Children who had undergone early intervention with anti-inflammatory therapy achieved higher long-term remission rates when compared with those in previous Japanese studies, although 65.1% of them had mild abnormalities in pulmonary function and/or FeNO levels. The 11-year follow up outcome of these children is also reported.

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Asthma Treatment May Be Useful to Treat Recurrent Wheezing in Infancy

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Background: There are controversies in treating recurrent wheezing (≥3 episodes) in pre-school children. The aim of this study was to verify changes in treatment of recurrent wheezing infants.

Methods: Cross-sectional study using a standardized and validated questionnaire (EISL: *Estudio Internacional sobre Sibilancias en Lactantes*) that covers physician diagnosis of asthma, and frequency, severity, and treatment of wheezing episodes. Regarding treatment specific questions are: Has your baby been treated with inhaled short-acting β_2-agonists by metered dose inhaler or nebulizer? Has your baby been treated with inhaled corticosteroids? Has your baby been treated with antileukotrienes? Has your baby been treated with oral corticosteroids? Parents of infants, ages 12 to 15 months that attended to Health Centers for routine immunization were interviewed between August/2005 to December/2006 (EISL Phase I) and September/2009 to September/2010 (EISL Phase III). Categorical variables are showed as proportion and differences verified by chi-square test.

Results: Three thousand and 3 parents of infants answered questionnaire in the EISL Phase I and 22.6% had recurrent wheezing episodes. Five years later, in the EISL Phase III, 1003 parents participated in the survey and 19.8% had recurrent wheezing ($P = 0.1$). Inhaled short-acting β_2-agonists continued to be prescribed in the same frequency (89.6% vs 86.5%, $P = 0.21$), however anti-asthmatic drugs were more used [antileukotrienes (6.9% vs 33%, $P < 0.001$), inhaled steroids (23.6% vs 37.5%, $P = 0.001$) and oral steroids (18.6% vs 26.5%, $P = 0.01$)] and doctor diagnosis of asthma has increased (16.2% vs 23%, $P = 0.03$). There were reductions on night-time symptoms (73% vs 61.5%, $P = 0.001$), severity (59.3% vs 42%, $P = 0.001$) and emergency room visits (69.3% vs 41.5%, $P < 0.001$) for recurrent wheezing infants, but no difference was seen in hospitalization (17.1% vs 12.5%, $P = 0.12$).

Conclusions: Recurrent wheezing treatment in infancy has increased in past years and may have contributed for reducing emergency room visits, night-time symptoms and severity for wheezing infants.

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Trans oro Pharyngeal Spacer for Inhalers

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Background: Many of the patients suffering from bronchial asthma (BA) and COPD do not use the inhalers properly inspite of adequate education, resulting in inadequate relief. The external spacer (es) with the inhaler needs an inspiratory rate of 25 ltsmt, not portable and costly. Also the aerosol deposition in the airways ranges from 20 to 40%only. Wheezy patients with inadequate usage of the inhalers, cleft lip and cleft palate, geriatric and odentulous category, obese asnd short neck individuals cannot take the inhalers properly. Hence an inspiratory effort independent-transoropharyngeal spacer (Tops) is developed.

Inclusion criteria:

1. Adults and children above 5 years of age of both sex.
2. Subjects of bronchospasm with or without comorbid cleft lip and cleft palate.

Exclusion criteria:

1. Patient with exaggerated gag reflux.
2. Unconscious patient.

Apparatus:

1. Mini Wright's Pefr Meter.
2. Tops: it is a patented device made up of ethylene vinyl acetate copolymer. It has a receptacle for the inhalers, body with an angulation of 110 degrees bent and a curved tail piece, 150 degrees. Length - 10 cms, internal diameter - 10 mm, snugly fitting in the oropharynx, the distal end overlying the epiglottis as seen in mri pharynx.
3. External spacer.
4. Salbutamol mdi.

Procedure: One hundred and fifty subjects (m: f 95:56), within the age range of 8 to 81 years were enrolled in the study from 1st Feb 2007 to 1 April 2007. Pefr was measured before and after the aerosol delivery using tops and external spacer as conduits at ampm respectively, coinsiding with diurnal variation of bronchomotor tone. Four children had cleft lip and palate.

Results: The pefr in lt/mt was grades as: below 200l (severe), 200 to 300 (moderate), 300 to 400 (mild), above 400 (very mild). There were 80 (53%) in the severe, 50 (33%) in moderate,15 (10%) mild, 5 (4%) very mild. With the tops + inhaler 80% had improvement by 60% increment of pefr (one puff-100 mcg). With the es (2 puffs–200 mcg) plus inhaler there was only 10% increment. Thus the improvement with the former was significant ($P = 0.9641$, $r = 0.9660$); radioactive isotope scan showed 80% deposition in the lungs with tops versus es (40%). A lateral study found advantage over rotahaler and nebulizer.

Conclusion: Inhaler with tops is a better device for delivering aerosol.

PRIMARY IMMUNODEFICIENCY

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Intravenous Immunoglobulin in Leukocyte Adhesion Deficiency

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Background: Leukocyte adhesion deficiency (LAD) is a primary immunodeficiency disease (PID) caused by a defect in neutrophil adhesion, characterized by skin ulcers, poor wound healing and recurrent bacterial infection. Intravenous immunoglobulin (IVIG) is used to treat patients with PID, but in LAD is not rutinely used. Treatment consists in prompt antibiotic, G-CSF for chronic ulcers and the only definite therapy is bone marrow transplantation (BMT). We present the case of a child with LAD, who was treated with IVIG with a good response before BMT.

Methods: We present a case report of a 2 year-old male, second child of consanguineous parents (cousins 1st grade). His sister had omphalitis and umbilical abscess and died at 6 months with candidiasis and perianal infection. There were 6 episodes of infectious diseases from birth to 6 months: At 11 days of life presented with omphalitis. At 2 months, upper respiratory tract infection with poor response to antibiotics. At 4 months he presented with suppurative otitis media, and was transferred to our hospital with suspected immunodeficiency, with neutrophilia (up to 95900). He was treated with IV antibiotics, and after resolution with prophylactic antibiotics. At 6 months had gastroenteritis and 1 week later septic shock. Treatment with intravenous immunoglobulins (IVIG) was started.

Results: After IVIG was initiated there were only 6 episodes of infectious diseases from 6 months to 2 years, including in the cord blood stem cell transplantation (CBSCT) period: at 9 months, gastroenteritis; at 15 months balanosposthitis (ecthyma gangrenosum), at 17 months had cellulitis in the hand and buttocks and oral candidiasis. CBSCT was performed on February 2011, at 1 year 11 months, but didn't engraft. He was discharged with prophylactic antibiotics and cyclosporine. At 2 years he had catheter associated sepsis. Currently the patient is receiving monthly IVIG, fluconazol, TMP SMX, Acyclovir and in protocol for BMT and has remained stable.

Conclusions: IVIG is not routinely used in LAD. In our case, monthly IVIG resulted in improvement with less infectious episodes. We suggest the use of IVIG as an adjuvant tool for the treatment of patients with LAD before BMT.

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Descriptive Analysis of the Immunological Behavior of Patients with Ataxia Telangiectasia Attended in the National Institute of Pediatrics in the Past 30 Years

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Background: Ataxia Telangiectasia is an autosomal recessive disease characterized by progressive neurological impairment, ataxia, oculo-cutaneous telangiectasia, immunodeficiency, recurrent infections sinopulmonary and cancer predisposition processes. It does not exist in clinical practice guidelines for boarding and management of these patients, neither a suggestion of monitoring.

Methods: Automated search was requested file to the department of clinical records to identify patients diagnosed with Ataxia Telangiectasia. We included all that had clear and complete information to the variables analyzed.

Results: It was a description of variables by central tendencies and dispersion for continuous and categorical variables that were analyzed for frequencies and/or proportions. Included is determination of immunoglobulins IgG and IgA in 35 patients, 34 of 35 IgM and IgE in 9 patients. We observed in 5 patients hypogammaglobulinemia and 13 patients hypergammaglobulinemia. In relation to IgA, 17 patients had a deficiency and 6 of them high levels for their age, IgM in 13 patients reported figures above the percentile for their age. Altered IgE was found in one patient. IgG subclasses were determined in 9 patients and showed alteration in 9 of them. The IgG1 was not altered in anyone of the patients, low IgG2 was found according to age in 7 patients, 2 patients with low IgG3, and low IgG4 in 8 patients. The presence of lymphopenia was observed from the first test, in 14 from 28 patients. In a second measurement was observed in 17 from 25 patients. In the third measurement was observed in 13 form 21 patients.

Conclusions: In the Ataxia Telangiectasia it has been reported that it could be affected almost all the subtypes and subclasses of immunoglobulins, as hypogammaglobulinemia that could be corrected by exogenous administration. We suggest supervise levels of IgG during follow-up of patients and establish decision-subclasses according to the possibilities of each working group, according to the context of clinical infections. Based on our result we suggested that the monitoring of this disease is through an algorithm of clinical boarding.

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Alteration of Humoral and Cellular Immunity in Patients with Ataxia-Telangiectasia at Reference Center in Sao Paulo, Brazil

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Background: To analyze the levels of immunoglobulins and the number of T and B lymphocytes in patients with ataxia-telangiectasia (AT) followed in outpatient immunology.

Methods: A descriptive and retrospective study of medical records of patients diagnosed with AT followed at Federal University of Sao Paulo, Brazil.

Results: Of 24 patients studied, 5 (21%) had levels of IgG below the age-normal percentile 3 (p3), 3 patients (14%) had values around the 10th percentile. IgA values were below the p3 in 11 (46%) subjects; draws attention to high IgM in 14 (58%) individuals. Anemia was found in only 3 patients (12.5%), in the first case the etiology was probably iron deficiency, the second had a diagnosis of Waldestrom Macroglobulinemia and the third was with sepsis. Seventeen (70.8%) had total lymphocyte count below the p10, marked leukopenia (below p3) was observed in 5 (20.8%). Neutropenia ($<$1500 cells /mm^3) was observed in only 2 (8.3%) and eosinophilia ($>$500 cells /mm^3) in 6 patients (25%). In 79% (19/24) of patients the lymphocyte subpopulation was analyzed, and 17 (89.5%) of 19 subjects showed low number of CD3+ cells compared with controls of similar age. The number of CD4+ T cells was below the p10 in 21 of 23 evaluated patients (91.3%). Interestingly, in most patients the number of CD4+ T cells was between 200 and 500/mm^3, suggesting severe depression of cellular immunity. Only one patient had a high number of CD8+ T lymphocytes, in 15 (65%) of 23 subjects the number of CD8+ T cells was below p10. Eight patients underwent a CD19+ cell count, and all of them showed low values. NK cells were quantified in 7 individuals, 3 (43%) cases showing high levels.

Conclusions: Most patients treated in our department showed dysgammaglobulinemia, and low number of lymphocytes T and B.

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Clinical Features of Patients with Ataxia-Telangiectasia at Reference Center in Sao Paulo, Brazil

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Background: Clinical symptoms of patients with ataxia-telangiestasia (AT) followed in outpatient immunology.

Methods: A descriptive study using chart review of patients diagnosed with AT

Results: Retrospective data were analyzed in the medical records of 24 patients, 19 males and 5 females. Three of these patients were not included in the sample, for presenting insufficient data for analysis. Of the 21 patients, there were 5 families with 5 pairs of siblings. Three families had a positive family history. Consanguinity was observed in 5 (26%) of 19 couples in the sample. Seventeen (81%) patients had ataxia as the first symptom, beginning between 6 months and 7 years of age (median 18 months). Three patients with symptoms started with a telangiectasia and recurrent infections. The onset of symptoms ranged from 15 days old to 7 years of age (median 17 months). Age at diagnosis ranged from 1.5 year to 17 years old (median 5 years). Intravenous immunoglobulin was given for 16 of 23 patients (69.5%), prophylactic antibiotics were given for 15 (65.2%) and vitamin supplement for 12 patients (52.2%). Comorbidities: asthma was present in 6 patients (26%), allergic rhinitis in 3, and bronchiectasis in 3. Other less frequent comorbidities were diabetes (1), atopic dermatitis (1), sarcoidosis (1) and idiopathic thrombocytopenia (1). In evolution, 11 patients (52%) had dysphagia started between 3 and 18 years (median: 12.5 years). The most common infections were upper respiratory tract (83%), pneumonia (79%), sinusitis (66%), diarrhea (54%), tonsillitis (45%) and otitis (25%). Four patients lost follow-up, of the 20 remaining cases there were 8 deaths occurring between 13 and 18 years old. Causes of death were respiratory failure (3 cases), pneumonia (3), leukemia (1) and lymphoma (1).
Conclusions: Recurrent infections, dysphagia, and ataxia were the most frequent symptoms in our sample, and respiratory problems were the main cause of death among these series.

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Global Prevalence and Types of Autoimmune Diseases Found in Children with Primary Immunodeficiencies; A Single-Center Experience

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Background: Autoimmune manifestations in primary immunodeficiencies (PIDs) are not uncommon, and they are more frequently observed in defects affecting lymphocytes and their regulatory mechanisms. There is a wide variability in prevalence, ranging from immune defects in which autoimmunity defines the syndrome, others with a very high prevalence of autoimmune manifestations, defects with a moderate prevalence, and those in which autoimmunity is rather an exception than the rule.
Objective: We aimed to determine the prevalence of autoimmunity in children with PIDs from our hospital, to delineate their clinical features.
Methods: An internal register was consulted to identify autoimmune diseases in our patients with PIDs. Their clinical files were then reviewed for diagnostic workup, age of presentation and outcome.
Results: We identified a prevalence of 18.8% (47 out of 250 patients, 68.1% male patient), within a period of 40 years (1970–2010), with autoimmune manifestations in the context of PID. Of which most are still alive: 35 (74.5%); lost to follow-up: 3 (6.4%), Dead: 9. Known or probable consanguinity was reported in 25.4%, 36.2% had a positive family history. 12.8% also had an allergic disease; none had cancer. The most frequent AI type was Systemic Autoimmune disease (11 case, 23%), followed by Organ-specific autoimmunity (15 cases, 32%), cytopenias (8 cases, 17%), and just antibodies (6 cases, 13%). Other than Autoimmune lymphoproliferative syndrome (ALPS), in which autoimmunity is a case-defining feature, the group of well defined (Hyper-IgE Syndrome (HIES), and Wiskott-Aldrich Syndrome (WAS)) were the PIDs with more cases of autoimmune disease, followed by phagocytosis deficiencies and antibody deficiency.
Discussion: The overall prevalence of autoimmune disease is relatively high PID syndromes such as ALPS, moderate levels in HIES, WAS and defects of phagocytosis and antibody interestingly. Interestingly, most of our patients with HIES have an autosomal-recessive pattern of inheritance and no identified mutational diagnosis; nearly all of our patients with CGD are receiving chronic subcutaneous therapy with human recombinant interferon gamma. Regular follow-up visits are justified for surveillance for complications and frequent treatment adjustments, given the delicate balance between immunosuppression and infection prophylaxis that is required in the care of these patients.

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Malignancies Associated to Primary Immunodeficiencies. A 40 Year Review

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Background: Cancer has been cited as the second leading cause of death after infection in children and adults with primary immunodeficiencies (PIDs). There seems to be a complex relationship between PIDs, viral infections to which are susceptible, and the development of cancer. Defective immunosurveillance most markedly in cells with strong antigenic potential that have undergone viral induction is a major factor, as support for this the most common cancer subtype is lymphoma. Some estimates suggest that more than 20% of carcinomas in patients with PID are infection induced, Epstein Barr virus being particularly well established cofactor. The risk of cancer in patients with PID is estimated between 4 to 25%, although could be higher in some subtypes of PID. The PIDs most commonly associated to cancer are Ataxia Telangiectasia, common variable immunodeficiency, Wiscott-Aldrich syndrome, severe combined immunodeficiency, and selective Iga deficiency.
Objective: We aimed to determine the prevalence of cancer in children with PIDs, in our hospital, and to determine clinical features and risk factors.
Methods: An internal register was consulted to identify cancer associated in patients with PIDs. The clinical files were reviewed for diagnostic workup, age of presentation, risk factors and outcome.
Results: We identified a prevalence of 1.2% (3 out of 250 patients) within a period of 40 years (1970–2010), with cancer diagnosis in the context of PID. PIDs subtype included, 2 patients with ataxia telangiectasia, both dead, one developed lynfoblastic leukemia and the other patient developed diffuse B cell lymphoma. Third patient with X linked lynphoproliferative syndrome (SAP mutation), with positive family history, developed burkitt lymphoma, still alive.
Discussion: The overall prevalence of cancer is relatively low to moderate in PID syndromes. Ataxia Telangiectasia continues to be the most highly associated cancer PID. Regular follow-up visits are justified for surveillance for complications. The prognosis in patients with cancer and immunodeficiency is worse than immunocompetent individuals.

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An Earlier, More Severe Presentation of G6pc3 Deficiency in a Male Infant From Mexico

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Background: Severe congenital neutropenia is a bone marrow failure syndrome characterized by severe neutropenia present from birth. We present

a case of G6PC3 deficiency presenting at an earlier age, with a more severe clinical picture than previously reported.

Case report: A 3-month-old boy, born to nonconsanguineous parents was delivered by C-section at 35 weeks gestation. He was admitted to neonatal intensive care unit for prematurity and poor respiratory effort requiring mechanical ventilation. Aggressive antimicrobial therapy was started for nosocomial pneumonia and severe persistent neutropenia. Physical examination: Poor weight, chest accessory venous vasculature, parasternal systolic murmur grade I left, testicles not palpable in scrotal sac. Laboratory workup> Total leukocyte blood count with 2400 mm^3, total neutrophils 200 mm^3. Echocardiogram revealed pulmonary hypertension: 58 mm Hg, foramen ovale with bidirectional shunt. Abdominal ultrasound: kidneys with hydronephrosis grade I in the right kidney and grade III left, confirmed by Excretory urography. Esophago-gastroduodenal Series: velopalatal incompetence, pyloric hypertrophy, spontaneous gastroesophageal reflux and upper third of the esophagus. Hearing screening reported bilateral hearing loss. Nissen fundoplication, Stamm gastrostomy and pyloromyotomy were performed. Treatment with Recombinant human G-CSF was started (3–5 mg Kd) with good response. Mutational analysis revealed a single-nucleotide deletion in exon 2, which results in a frameshift and premature stop codon, predicting a nonfunctional trunk protein.

Conclusion: Severe congenital neutropenia type 4 is an autosomal recessive condition, which was defined recently with identification of the causative mutations in G6PC3 and is characterized by congenital neutropenia and variable developmental disorders: cardiovascular (atrial septal defects, pulmonary hypertension) and/or urogenital system (urachal fistulations and cryptorchidism). Some patients show a peculiar visibility of subcutaneous veins. Patients with G6PC3 deficiency lack mature neutrophils in the bone marrow and have increased susceptibility to apoptosis in peripheral neutrophils. Recombinant human G-CSF is the first-line therapy. This is only the second case identified in Latin America, and the first one in Mexico. Compared to what has been previously reported, however, our patient presented earlier and with a more severe clinical picture, including bilateral hydronephrosis. Stem-cell transplantation has never been performed in G6PC3 deficiency, but it's being considered in this case given the patient young age and severity.

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Immunoglobulin a Deficiency, HPV and Oral Cancer

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Background: Selective IgA deficiency is the most common primary immunodeficiency. Serum IgA level lower than 7 mg/dL is considered selective IgA deficiency. Most people with selective IgA deficiency are asymptomatic, with incidental findings. Others may present recurrent respiratory infections, allergic symptoms, other infections and autoimmune diseases. It represents a genetically heterogeneous group of abnormalities. We report 2 cases of IgA-deficiency, HPV, and cancer, which required oral mucosa and tongue surgery.

Methods: Case I: Female patient, 30 years old. Medical history: vaginal HPV and Herpes. No promiscuous conduct. Complaint: recurrent infections. Physical exam: oral white lesions are observed. Laboratory findings: serum immunoglobulin A: lower than 7 mg%, secretory immunoglobulin A: lower than 1 mg%. Both exams were repeated and determinations showed low values. Cytology - Glucose - serum protein electrophoresis - Ig G - Ig M - CD3 - CD4 - CD8 - CD19 - CD56 all determinations showed normal values. HIV I /II: negative. Biopsy of oral mucosa with the following report: severe dysplasia and intraepithelial carcinoma. Signs of HPV. Surgery was performed on oral mucosa with the following pathology report: moderately differentiated squamous cell carcinoma. Microscopic, morphological changes related to cytopathogenic viral effects. The patient presented good evolution. Case II: Female patient 40 years of age. Medical history: HPV and genital herpes. No promiscuous conduct. Complaint: leukoplakia in tongue edges. Physical examination: oral white lesions. Laboratory serum immunoglobulin A: value obtained: lower than 7 mg%. Cytology - Glucose - serum protein electrophoresis - Ig G - Ig M - CD3 - CD4 - CD8 - CD19 - CD56 with normal values. HIV I/II: negative. Surgery was performed in tongue and regional lymph node. Tongue Pathology: moderately differentiated squamous cell carcinoma with negative edges. HPV (+) PCR.

Conclusion: We report on the possible association between selective IgA deficiency - HPV - Cancer which has not been previously reported in time. We suggest further screening of these possible associations and detailed monitoring of these patients.

QUALITY OF LIFE MEASURES IN ASTHMA AND ALLERGIC DISEASES

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Management of Twenty-Five Pediatric Patients with Hereditary Angioedema (Hae) Undergoing Home Treatment—A Clinical Surveillance Program

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Background: Hereditary angioedema (HAE) is a rare disorder characterized by C1 esterase inhibitor (C1-INH) deficiency. Clinically, HAE is characterized by relapsing episodes of edema at various body sites followed by disease-free intervals of variable duration. Episodes of upper airway obstruction (usually laryngeal edema) are potentially life-threatening and many patients died by asphyxiation in the families. In literature Longhurst et al, Buygun et al and Levi et al showed improvement of quality of life in patients with hereditary angioedema due to home treatment with C1-inhibitor-concentrate.

Methods: We investigated in a cohort study the integration of a clinical surveillance program into home treatment of pediatric patients suffering from hereditary angioedema. Parameters investigated were overall coping of the pediatric patient with home treatment, documentation of efficacy/safety of C1-INH concentrate (Berinert$^{\hat{a}}$ P, CSL Behring, Marburg), regular control of laboratory parameters (C1-inhibitor (INH) activity, C1-INH antigen, C4, hepatitis A, -B, -C-, HIV-1/2-, and parvovirus B19 serology) and quality of life parameters (hospitalization, absence from school).

Results: Twenty-five pediatric HAE patients (6 male, 19 female) have so far been investigated. Twenty-one patients suffer from HAE type I, 4 patients from HAE type II. Median age is 13.7 years (range: 2.8–17.4 years), first diagnosis of HAE took place at the median age of 5 years (range: 0.1–15.9 years) and first manifestation of HAE at the median age of 3.9 years (range: 0.3–11.7 years). Plasma C4 complement was reduced in nearly all patients (median: 2.4 mg/dL; range: <1.4–10 mg/dL) except one patient. All patients coped well with home treatment, compliance was excellent, clinical findings during regular medical control remained in the normal range and all parameters confirmed an improved quality of life, e. g., patients had not been hospitalized nor had they been absent from school. There were no adverse drug reactions due to administration of C1-INH concentrate.

Conclusions: Home treatment might be also a valuable option for pediatric HAE patients not affecting compliance negatively and providing a significant positive impact on health-related quality of life.

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The Impact of Nasal Allergies: Results from the Allergies Surveys in America, Asia Pacific, Latin America, and Middle East

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Background: The Allergies surveys have been conducted in several regions of the world, and provide the first worldwide comparative data on the prevalence and impact of nasal allergies. Here we report specifically on the impact of nasal allergies on daily life and work productivity in America (AIA), Asia Pacific (AIAP), Latin America (AILA) and Middle East (AIME) surveys.

Methods: Patients who were previously diagnosed by a health care professional with nasal allergies (hay fever, allergic rhinitis or nasal allergies, plus sinus disease in AIAP), exhibited symptoms, and/or had received treatment, were included. Standardized questionnaires provided by Abt SRBI were used; individual questions and methodology varied slightly between regions. In total, around 90,000 households were screened, including responses from 6,081 patients.

Results: Patients reported that allergies have a big impact on their daily lives, including limiting indoor and outdoor activities, work and having pets. A high percentage of those surveyed missed work or had their work performance affected by allergies in the past year, with work productivity decreasing by 23% in AIA, 24% in AIAP, 33% in AILA and 30% in AIME when allergy symptoms were at their worst. Nasal allergies also interfered with many patients' sleep, and were associated with feelings of depression, anxiety, irritability and tiredness. In terms of the impact of symptoms, 38% of those surveyed in AIA, 53% in AIAP and 46% in AILA reported that they could not tolerate the discomfort of an allergy attack without relief.

Conclusions: Nasal allergies have a big impact on patients' lives all around the world, and there is still an unmet need for effective treatments that reduce symptoms. As a result, work productivity levels and daily activities are hugely affected in a large proportion of individuals with nasal allergies, throughout the world.

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The Impact of Nasal Polyposis on Quality of Life Using the Eq-5d Health Profile

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Background: Even though nasal polyposis (NP) is not a severe life-threatening disease, it has a considerable negative impact on health-related quality of life (HRQL). The goal of this study was to analyze HRQL in a large sample of patients with NP compared to the general population in Spain.

Methods: The EQ-5D survey, which includes a descriptive system and is composed of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), and the EQ visual analog scale (EQ VAS) were applied to patients with NP.

Results: NP patients (N = 1,170; mean age 49 ± 15 yr, 35.5% female) completed the questionnaire. NP patients had a lower EQ VAS score (63.8 ± 21.5; $P < 0.05$) than the general population (71.3). NP patients having some or extreme problems reported higher overall percentages for all EQ-5D domains: mobility (13.3, $P < 0.05$), self-care (8.2, $P < 0.05$), usual activities (26.6, $P < 0.05$), pain/discomfort (55.6, $P < 0.05$), and anxiety/depression (32.6, $P < 0.05$, compared with the general population (10.9, 2.0, 6.4, 25.8, and 13.7, respectively). Mean EQ-5D index values (0.78 ± 0.24) were also lower than the general population (0.89; $P < 0.05$). There were no differences between mean EQ-5D index values when gender, age group, or tobacco consumption was compared.

Conclusions: These results confirm, by using EQ-5D questionnaire, that nasal polyposis has a negative impact on HRQL compared to the general population.

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Predictors Affecting the Quality of Life of Patients with Bronchial Asthma

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Background: The purpose of this study was to assess the influence of socio-demographic factors, gender and level of anxiety on quality of life in patients with asthma.

Methods: Asthma control test (ACT), Quality of Life Questionnaire Short Form-36 (QoL-SF-36) and *State-Trait Anxiety Inventory* (STAI) were used as research tools. Disease severity was assessed according to GINA guidelines. Sixty five patients with asthma hospitalized at the Department of Allergology, Wroclaw Medical University, Poland between November 2010 and January 2011 entered the study, 39 women aged (mean ± SD) 58.2 ± 15.2 and 26 men - 54.8 ± 15.4.

Results: Results observed in analyzing the STAI-measured trait anxiety we found that anxiety as a trait was less severe in men versus women (47.4 v 40.6; $P = 0.01$) also the state anxiety tended to be less severe in men; however we didn't find statistical significance. QoL-SF-36 results revealed lower quality of life of female when compared to male patients. Both the summed quality physical (PCS) and mental functioning (MCS), women scored lower than men: PCS: 32 versus 37 and MCS: 41 versus 48 points. Education increases the QoL measured by SF-36 questionnaire in PCS domain (Ht = 9.74; $P = 0.020$). Also, professional activity of patients and the duration of the disease influence both domains: MCS (Ht = 17.84; $P = 0.001$); PCS (Ht = 9.98; $P = 0.040$) and PCS ($r_s = -0.450$; $P = 0.0001$) and MCS ($r_s = -0.251$; $P = 0.046$), respectively. Also disease severity correlated inversely with QoL in both sub-domains PCS (Ht = 12.21; $P = 0.006$), MCS (Ht = 8.88; $P = 0.030$). As it could have been anticipated, the level of asthma control (measured with ACT) correlates with QoL: PSC ($r_s = 0.571$; $P < 0.0001$); MCS ($r_s = 0.373$; $P = 0.003$). According to our data from QoL-SF-36 questionnaire age, type of work, marital status and smoking did not affect significantly patients' quality of life.

Conclusions: Better education, professional activity and good disease control have positive impact on QoL of asthmatic patients, while disease severity and duration deteriorate it. Since women show much higher anxiety medical personnel attitude to female patients should consider it.

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Correlation between Severity of Allergic Rhinitis and Impairment of Quality of Life in Allergic Adolescents

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Background: Determine severity of the disease and its correlation with the degree of impairment in quality of life in adolescent patients with allergic rhinitis.

Methods: Were captured 124 adolescents aged 10 to 17 years, attending the outpatient Allergy Service at Social Security Hospital in Mexico, diagnosed with Allergic Rhinitis (AR). Before the clinical evaluation to confirm the diagnosis, severity of Allergic Rhinitis were classified according to criteria of Allergic Rhinitis and its Impact on Asthma (ARIA), and were administered the Adolescents Quality of Life Rhinoconjunctivitis Questionnaire (AdolRQLQ).

Results: In determining the frequency and intensity of symptoms of allergic rhinitis according to the ARIA classification of the degree of severity was

more frequent, in 48%, moderate Persistent AR; followed by mild persistent AR in a 30%, moderate intermittent AR 14%, mild intermittent AR 5% and severe AR only 3%. By applying the questionnaire AdolRQLQ we found moderate affectation of the quality of life in 73% of patients, a severe affectation in only 14% and slight in 13%. However, when performing the correlation between the severity of the disease and the degree of impairment of quality of life, we don't find a proportional relationship as there are patients who see the quality of life decreased significantly, even though the disease is classified as mild and vice versa. For example: 79% mild persistent AR patients scored for moderate affectation of the quality of life, only 13% for slight and 8% severe; while none of the adolescents scored for AR severe deterioration of the quality of life, all of them were classified with mild impairment.

Conclusions: Adolescent patients with allergic rhinitis are affected quality of life this involvement is not directly proportional to the severity of the disease. Treatment, in addition to seeking control of symptoms, should provide the support needed to improve their quality of life.

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Chronic Urticaria Quality of Life Questionnaire (Cu-Q2 Ol) and Urticaria Activity Score (Uas)

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Background: Chronic urticaria (CU) is a disease defined by the presence of wheals and itching for more than 6 weeks. Depending on its severity, it may impair the patients' quality of life (QOL). The questionnaire Cu-Q2oL designed by Dr. Walter Canonica's group, specifically evaluates quality of life in patients with chronic urticaria (CU-Q2oL); in Spanish it has been validated by Dr. Valero, et al.

Objective: We aimed to investigate if there is an association between severity of chronic urticaria and quality of life of patients in our service, using the questionnaires: CU-Q2oL and urticaria activity score (UAS).

Methods: Universe: Consecutive patients with chronic urticaria who answered the questionnaires CUQ2OL and UAS. Diagnosis of CU was based on a detailed history, physical examination, laboratory studies and autologous serum skin test (ASST) for Autoimmune Urticaria (UCAI). Spearman's Rho correlation coefficient was calculated between Severity (UAS) and Quality of Life (CUQ2OL). Comparisons between groups were performed using chi square and One-way ANOVA.

Results: 50 patients, (82% women, mean age 41 years) were included. The largest etiology group was Autoimmune: 60% of cases; A direct linear relationship between the severity of and quality of life was found to be statistically significant (r^2 0.511, $P < 0.0001$). A greater severity was generally reported in the autoimmune group.

Conclusions: Patients with more severe urticaria, particularly with major complaints of itching and sleep loss, have a lower quality of life, especially those patients with autoimmune urticaria. We found a good correlation between both questionnaires, so in the future clinicians may anticipate that patients diagnosed with moderate or severe chronic urticaria might have a considerable drop in their quality of life, and therefore their management and follow-up should be viewed holistically.

RADIOCONTRAST MEDIA ALLERGY

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Frequency, Characteristics and Outcome of Immediate Hypersensitivity Reactions Due to Iodinated Contrast Media

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Background: To determine the frequency, characteristics and outcome of immediate hypersensitivity reactions to iodinated contrast media (ICM).

Methods: A retrospective review of immediate hypersensitivity reactions to ICM that occurred between 2006 and 2008 in King Chulalongkorn Memorial Hospital was performed. Severity of the reactions was graded by Ring and Messmer's classification.

Results: A total of 34,365 ICM were administered for radiologic procedures during the study period. There were 193 immediate hypersensitivity reactions, representing the frequency of 0.56%. Mild (grade I and II) and severe (grade III and IV) reactions developed in 181 (0.53%) and 12 (0.03%) patients, respectively. The most common reactions were skin manifestations (rash, urticaria and angioedema) which occurred in 179 patients (92.7%). Respiratory, gastrointestinal and cardiovascular symptoms developed in 12 (6.2%), 2 (1%) and 10 (5.2%) patients, respectively. The patients who have allergic diseases more frequently developed grade III reactions (particularly asthmatic attack) than other reactions. Anaphylaxis, defined as multi-organ involvement, occurred in 8 patients (4.1%). Two patients (1%) had cardiopulmonary arrest. No fatality was reported. Seventy-nine patients (40.9%) had previous exposure to ICM, while 23 patients (11.9%) experienced previous reactions to ICM and of that 14 patients (60.9%) developed the reactions despite premedications. A history of previous reactions to ICM and pre-medications use were not found to be associated with severity of the reactions. Mean time to onset of reactions was 13 minutes after ICM administration and almost all patients (188, 97.4%) developed the reactions within 30 minutes. One hundred seventy-five patients (90.7%) received active treatments. Antihistamines, corticosteroids and epinephrine were administered in 172 (89.1%), 33 (17.1%) and 9 (4.7%) patients, respectively. Five patients (6.2%) required cardiopulmonary resuscitation. Median time of symptoms resolution was 30 minutes after receiving treatments and almost all patients (187, 96.9%) recovered within 60 minutes.

Conclusions: Immediate hypersensitivity reactions to ICM are uncommon. Most patients develop mild reactions and respond well to treatments. The patients with allergic diseases may have a greater risk of asthmatic attack after receiving ICM. Although severe reactions are rare, all patients should be observed under medical supervision for at least 30 minutes after ICM administration.

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Frequency of Positive Skin Test for Iodinated Contrast in Outpatient Clinic of Allergy in Rio De Janeiro, Brazil

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Background: Adverse reactions to iodinated contrast agents (IC) can be related from a mild to life-threatening event. This frequency varies from 0.2 to 12.7% depending on the type of IC used. Some studies suggest that these reactions may be related to an IgE-mediated mechanism.

Methods: Retrospective study of medical records from patients attended from January 2008 to June 2011 with suspected history of, or risk factors for, reactions to IC. Patients underwent SPT with undiluted IC iopromide used histamine and saline as controls. In those with negative tests were performed intradermal tests with 0.02 mL of IC diluted with saline 1:10. The sample was also evaluated in relation to age, sex, comorbidities, presence of atopy and previous reactions to IC (PRIO). Descriptive statistical analysis of data was performed.

Results: We analyzed 27 patients (22 F, mean age: 55.2 years ± 17.4 SD; 59% were atopics). Only one patient (F, 37 years with allergic rhinitis) without PRIO showed positive reaction to intradermal test (3.7%). Five patients (18.51%) with PRIO had negative SPT.

Conclusions: IgE-mediated immune reactions are not common for IC. However, when present contraindicates the use of the compound used in skin testing or other composed of the same pharmacological class. Although the skin tests for IC are not yet fully standardized, its performance can be useful to guide both the patient and the radiologist.

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Test and Manage Protocol for 841 Patients Requiring Iodinated Contrast Media (Icm) in Pediatrics

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Background: ICM's adverse effects are quite frequent and potentially serious. The use of protocols to test and manage patients receiving ICM could help to decrease the adverse effects because they advise against the studies or prescribe the administration of premedication; however, its use in pediatrics is still limited. We describe the results of the use of a test and management protocol for pediatric patients requiring ICM.

Methods: All the patients of a pediatric hospital prescribed with ICM between 31st January 2008 and 5th March 2011 were included. The following variables have been analyzed: age, sex, type of study to be performed, diagnoses and hospitalized or outpatient, risk (regular, increased or non-advised) and the presence of adverse reactions. We also analyzed the relation between risk and age, sex and condition (chi cuadrado o t test). Significance level $P < 0.05$.

Results: We included 841 patients (56.9% male, age = 92.7 ± 24.5 months, 60% hospitalized). The most frequent test was chest Tc (36%) and the most frequent diagnosis was solid tumors (25%). Patients with increased risk were significantly lower than those with regular risk (75.7 ± 69.7 months vs 109.7 ± 61.6, $P < 0.001$). During the research period there were no adverse effects.

Conclusions: The classification of risk groups by this Goverment Buenos Aires City protocols allows a rational management of the patients requiring ICM and minimize the adverse effects.

SEVERE AND FATAL ASTHMA

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Severe Asthma: Report of Five Clinical Cases at West National Medical Center, Imss in Guadalajara City, Mexico

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Background: Severe asthma can be defined as that which is inadequately or poorly controlled despite an appropriate therapeutic strategy that is adjusted to clinical severity. The aim of this work is to present clinical evidence of 5 patients with high suspect to bear severe asthma.

Methods: We review medical records of 5 patients with high suspect to bear a diagnosis of severe asthma.

Results: We present 5 patients, 4 of them were women and just one man. Mean age 49 years old. Two of the patients were detected with nasosinusal polyposis and sensitivity to the aspirin. One of them was diagnosed to bear allergic bronchopulmonary aspergillosis (ABPA). Laboratory blood results reporting: In 4 of the subjects, eosinophils more than 500 cells/mL. IgE with high serum levels in and in the patient with ABPA even with serum levels of 1890 UI/mL. Spirometry values with severe obstructive pattern with FEV1 less than 60% in 3 patients and in 2 of them with obstructive/restrictive severe pattern. In all patients, continuous use of inhaled corticosteroids at high doses alongside another antiasthmatic drug. Usually a long-acting β2-adrenergic, antileukotrien agents, methylxantins and in most of them with daily requirement for short-acting β2-adrenergic rescue medication and with more than 3 or more courses of oral corticosteroids in the last year.

Conclusions: Because of the clinical findings of our patients, respiratory function test and characteristics of the treatment which they have had during the last 5 years we consider that our patients bear severe asthma according with American Thoracic Society and is our purpouse to share with other immunoallergist our clinical experience in this field.

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Risk Factors for Bronchial Asthma in Central Havana in the Period 1995–2010

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Background: Results of research conducted in Havana (Centro Habana municipality's population) in the period 1995 to 2010 to evaluate possible risk factors for death from asthma are presented. The objective was to determine the correlation between the factors that influence asthma deaths in this country. Assessing risk factors for asthma death psychosocial factors, occupation, housing conditions, work and study center, smoking, comorbid illnesses by organ systems, level of care between exacerbations and in them, background risk of death from asthma, perennial or discontinuation of corticosteroids recent assistance to emergency services or hospitalization in the last year of the death, level of care between exacerbations and in them, and severity of the allergic family history and place and date of death.

Methods: We performed a retrospective study of cases with asthma that died of adult from 1995 to 2010. A total of 109, they surveyed the families of 65 for a 59.63% and an equal number of controls. Of all respondents 36 were women (55.39%) and 29 men (44.61%) and an average age of 55.8 years (53.7 for women and 58.4 for men).

Results: Univariate analysis of the level of schooling had a RD = 2.68, the per capita financial <$ 100.00 an RD = 2.32, smoking a RD = 2.76, in cardiovascular disease DR = 2.46 and no care between exacerbations had a RD = 2.43. The multivariate logistic regression analysis found significant association with a poorly ventilated RD = 7.29, relative risk (RR) of 5.93, lack of sun RD = 4.85 RR = 7.41; pets RD = 2 30, RR = 5.82; smokers RD = 2.76 RR = 14.81; the use of beta2 agonist> 3 teams/RD = 18.4 months RR = 69.93 and the severity of the disease RD = 8, 80 RR = 23.47.

Conclusions: Inadequate socioeconomic conditions (lack of ventilation, sun and presence of pets and cigarette smoke in households as poor management of the disease (use of beta 2 agonist > 3 teams / month) are risk factors for death from asthma. Deaths from asthma were more common outside the hospital in winter.

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Dolichyl Phosphate Dependent Mechanism of Exacerbations in Asthma: P-Glycoprotein Overexpression and E-Cadherin Loss

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Background: In asthma exacerbations there is a functional hyporesponsiveness of glucocorticoid (FHG) receptors (GR) on T cells, disbalance in activity of IL-2, IL-4, IL-10 and E-cadherin loss. Dolichyl phosphate (DolP) plays an essential role in cytokine synthesis, in constancy of glycoproteins of the GR and E-cadherin expression. The present study was carried out to estimate the role of DolP in mechanism of exacerbations.

Methods: The samples obtained from 82 patients with with frequent exacerbations (APFE group) (median duration > 14 day a year) and 83 patients without exacerbations over 12 months (APWE group). Dolichyl phosphate was defined in T-cells. Soluble E-cadherin was measured with ELISA in sputum and in bronchial epithelial cells (BEC). The intensity of glycoprotein synthesis in IL-2, IL-4, IL-10 and GR was estimated based on the number of starting glycosylation complexes (SGC) and radioimmunoassay.
Results: In APWE group Blood Dol concentration was 221.6 + 15.4 ng/mL and urinary Dol concentration was 16.2 + 4.5 mkg/mmol. In APFE group blood Dol was increased up to 4 times making up 455.2 + 31.7 ng/mL and urinary Dol concentration was increased up to 400%, making up to 32.2 + 4.7 mkg/mmol and 2 times in comparison with APWE group. APFE group had 3 to 4 times higher E-cadherin levels in sputum than APWE group. The synthesis of DolP was 7.5-fold decreased in T-lymphocytes in APFE group. APFE group T-cells membrans contain 5.6 to 6.4% of P-glycoprotein-170 as a marker of FHR receptors which differ from APWE ones in Pgp content by 9 to 11 times. DolP in the concentration 10 to 6 M aid 7 to 9-fold reducing P-glycoprotein-170 content in membranes of APFE T-cells to 0,4 to 0,6% and prevent loss of E-cadherin in BEC. T-cells from APFE group cultivated with corticosteroids and Polyprenol restore the possibility to induce IL-10 synthesis in vitro, enhanced the expression of alpha GP isoforms and made these cells more responsive to steroids.
Conclusions: DolP level and N-glycosylation dirorders could correlate with P-glycoprotein overexpression in FHG in T-cells and E-cadherin loss in EC in asthma exacerbations. Dol detection in blood and urine opens up possibilities for exacerbations control and management.

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Distribution of Asthma Mortality in Various Districts of Salvador, Brazil

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Background: Brazil still does not have a national program to combat asthma. Isolated initiatives have been developed in a non-standardized fashion. The Program for Control of Asthma in Bahia (ProAR) was established in Salvador, Bahia, in 2003, aiming for the control of the most severe cases.
Objective: To analyze time trends in mortality from asthma and its distribution in the districts of Salvador (2000–2009) and to correlate mortality rates with social indicators.
Methods: Observational study of deaths from asthma registered by the National Database of Mortality according to ICD-10. Mortality rates were calculated per 100,000 inhabitants and analyzed by simple linear regression. The distribution of mortality for asthma in the period was mapped into the 12 health districts of Salvador. The correlation of the number of deaths in Salvador with GDP per capita, HDI and Index Gini was evaluated.
Results: The average asthma mortality in Salvador between 2000 and 2009 was 1.542/100.000 inhabitants, with a declining trend ($R^2 = 0.539$, b = –11.1, $P = 0.016$). Deaths occurred more frequently in women than men (66% vs 34%). Asthma mortality rates were higher in subjects > 35 years. There was a reduction at ages younger than 1 year, 5 to 14 years, 25 to 34 years, and 45 to 54 years with a sharp decline between 55 and 64 (–8.14/100,000). The mortality rate (19.68/100,000 inhabitants in 2009) was higher for individuals > 75 years. The highest mortality rates were noted in more populated and poorer areas with less infrastructure and access to health services. It was observed that 78% of the deaths occurred in hospitals or health facilities. Deaths rates for asthma correlated directly with the district Gini index (rho = 0.400, $P = 0.505$) and inversely with HDI (rho = –0.300, $P = 0.624$), though not statistically significant.
Conclusions: Asthma mortality in Salvador is concentrated in the poorest areas with less infrastructure and access to health services, most commonly affecting women and the elderly. There was a reduction in mortality during the study period, possibly related to interventions for asthma control in the municipality. Mortality from asthma behaves differently in each district of the city.

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Geographical Distribution of Deaths from Asthma in Salvador, Brazil (2000–2009)

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Background: Salvador is the 3rd largest city of Brazil with 3 million inhabitants, divided into neighborhoods with remarkable social inequalities, varied infrastructure and access to health services.
Objective: To evaluate the geographic distribution and identify areas of risk for asthma deaths in the city of Salvador, Bahia, Brazil (2000–2009).
Methods: Observational descriptive study of deaths from asthma according to ICD-10 in the period between 2000 and 2009, with information obtained from the National Database of Mortality of the Ministry of Health of Brazil. The distribution of deaths was mapped with points and public primary care facilities including emergency care units were located in the geographical grid of the City by the software Arcview. The risk areas were identified by the method of Kernel. Correlation between the number of deaths and number of health care units was assessed using the Spearman test.
Results: We geocoded the location of 395 of 409 deaths from asthma (96.58%) occurred during the study period. It was observed that 78% of deaths occurred in hospitals or health facilities. The highest density in areas of risk and the highest concentrations of death from asthma occurred in more populated and underprivileged areas. There was a direct correlation between the number of public primary health facilities and the number of deaths (rho = 0.667, $P = 0.018$).
Conclusions: Asthma deaths in Salvador are concentrated in the poorest areas of the city where there are a great number of public primary health facilities. The geographic distribution of deaths indicates that current practices in primary care are insufficient to prevent deaths from asthma in Salvador, Brazil.

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Measurement of Long-acting Natriuretic Peptide (Lanp) in Exacerbation of Asthma

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Background: Evidence exists that atrial natriuretic peptide (ANP) is a regulator of smooth muscle airway tone and is a potent bronchodilator and immune modulator in animals. Objective: Long-acting natriuretic peptide (LANP), encoded by the same gene and derived from the same pro-hormone

as ANP, was measured in patients with acute asthma exacerbation pre- and post-treatment with systemic or inhaled glucocorticosteroids.
Methods: Measurement of LANP was obtained from plasma samples in 15 subjects with acute asthma exacerbation, by an enzyme immunoassay technique. A repeat measurement of LANP was obtained 5 to 7 and 10 to 14 days after initiation of treatment.
Results: No significant differences were found compared to baseline in plasma LANP level after treatment of the asthma exacerbation ($P = 0.8904$). The average LANP values were 2.12 higher in the oral glucocorticosteroid group versus the inhaled glucocorticosteroid group, ($P = 0.0608$). There was no significant difference in LANP levels between male and females ($P = 0.5743$), with antibiotic use ($P = 0.9437$), or with age ($P = 0.6384$).
Conclusions: Plasma LANP level did not differ before and after treatment for an asthma exacerbation. Measuring plasma LANP pro-hormone was not helpful in assessing treatment outcome of asthma exacerbation.

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Is It Really Difficult-to-treat Asthma? Don't Forget Other Causes of Wheeze

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Background: One in 4 asthma patients may not have their condition adequately controlled and experience persistent symptoms despite treated with high healthcare utilization. But do all of them really have asthma?
Methods: Here we present 3 cases; all were diagnosed as asthma, had been treating with multiple bronchodilators, even oral steroids and were not responding to the treatment. And so they were refered to our clinic as having difficult-to-treat asthma as candidates for omelizumab therapy.
Results: Case1: A 44-year-old female presented with 18 years history of dyspnea, wheeze and chronic cough. Her FEV1 was 37% of the predicted (0.93 lt), FVC and FEV1/FVC were subnormal and showed no reversibility. CT scan showed a deformed trachea with a diverticula in the posterior region with cystic bronchiectasis in lung parenchyma, bilaterally. Bronchial endoscopy showed dyskinesia extending almost totally throughout the tracheobronchial tree with complete expiratory collapse. Her diagnosis was changed as Mounier-Kuhn syndrome. Case 2: A 19-year-old female presented with 11 years history of persistent wheezing and dyspnea which were progressively increasing for the last 5 years. Her FEV1 was 85% and the FEV1/FVC % 77 of the predicted, showed no reversibility. Her CT scan was in normal limits. Fiberoptic bronchoscopy revealed a severe airway stenosis like a pinhole at the beginning of the right main bronchus, adjacent to the carina. Excluding her asthma diagnosis she underwent a balloon dilatation procedure, which improved her symptoms. Case 3: A 50-year-old female presented with 16 years history of dyspnea, wheeze, chronic cough. Her FEV1 was 40% of the predicted (0.91 lt), and showed reversibility of 28%. She had an elevated total IgE level of 1126 IU/mL with serum eosinophilia of 5.5%. Her HRCT scan revealed bilateral central bronchiectasis with fleeting pulmonary parenchymal opacities. Her sensitization to Aspergillus fumigatus was shown by positive skin testing. She was diagnosed as having allergic bronchopulmonary aspergillosis and oral itracanosole with steroid were added to her treatment which improved her symptoms.
Conclusions: Although all patients' symptoms looked like asthma, and all diagnosed as having asthma for many years, the diagnosis should always be confirmed before accepting them as "difficult-to-treat".

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Sensitization Profile in Severe Asthma

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Background: The role of IgE reactions to common allergens still remains unclear in severe, difficult-to-control asthma.
Objective: To analyze the IgE mediated sensitisation to common inhalant allergens in adult patients suffering from severe difficult-to-control asthma according to GINA guidelines.
Methods: One hundred and twenty three patients (57 women and 56 men, mean age 52.7 ± 10.1 years) were included into the study. The detailed personal and family history was assessed by the use of an original questionnaire. Skin prick tests (Allergopharma, Germany) and specific IgE serum level against common inhalant allergens (Poly–Check, Immunogenetics, US) and spirometry were performed.
Results: 79 (64%) patients had a positive family history of asthma. Mean time of asthma duration was in average 20.8 ± 15.1 years. Late onset of asthma (above 50 year of age) was observed in 61 (50%) subjects. 17 (14%) patients were current and 29 (24%) former smokers. Atopy estimated on the basis of the presence of at least one positive skin prick test was observed in 81 (68%) patients, mostly in men. Mean total serum IgE level was 80.2 ± 17 IU/L (range: 2.7–1205.4). House dust mites allergy was predominant and confirmed in 49 (40%) patients with mean specific IgE against D.pteronissinus 17.4 ± 10.2 IU/L and against D. farinae 18.2 ± 9.2 IU/L. Alternaria and cat allergy were diagnosed in 20 (16.4%) and 29 (23.6.3%) subjects respectively. The prevalence of inhalant sensitization was more frequently observed in those with asthma and other allergic disease than in patients with asthma alone (Table 1). It was statistically significant in chi-quarter test for $P < 0.01$
Conclusion: Positive family history of asthma, late onset of disease as well as IgE sensitivity to inhalant allergens are the common features of severe, difficult-to-control asthma. However, inhalant sensitivity occurs predominantly in cases of asthma concomitant with other allergic diseases.

TESTING FOR SENSITIZATION

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Utility of Component-Based Allergen Chip (Immunocap Isac) in Diagnosis of Allergic Rhinitis

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Background: Component-resolved diagnostics (CRD) using microarray technology has recently been introduced into clinical allergology. Component-based Allergen Chips (ImmunoCAP ISAC) provide novel assays that allow semi-quantitative measurements of IgE and IgG4 antibodies against a background of 103 allergenic components simultaneousl.
Objective: We sought to introduce component-based microarray Allergen Chips (ImmunoCAP ISAC) and evaluate the utility of microarray-based IgE detection in the diagnostic workup of allergic rhinitis. We compared this new diagnostic tool with established methods of allergen-specific IgE detection.
Methods: 86 Allergic rhinitis patients who were diagnosed with allergic rhinitis by history taking, physical examination, and skin prick test were included. The number of Males versus females was 58 versus 28. Mean age was 26.6 years old. We included data that was the result of a skin prick test, ImmunoCAP specific IgE and ImmunoCAP ISAC (D.P., D.F., tree, fungus, weed). We compared sensitivities and analyzed correlations of ImmunoCAP and ISAC.
Results: Sensitivity of ImmunoCAP and ISAC assays were 80% and 78.9% and there was a significant correlation. The more severe the symptom the stronger the positive degree. When we analyzed components of D.P. ISAC nDer p1 and nDer p2, which are specific components of D.P., they showed a high positive rate. In the case of D.F. nDer f1 and nDer f2, which are specific components of D.F., they showed a high positive rate. There was

a positive correlation between a positive numerical value for the ISAC specific component and for the ImmunoCAP D.P, D.F.
Conclusions: ISAC is a reliable method for diagnosing allergic rhinitis. Further studies of the utility of ISAC in SIT patients are needed.

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Prevalence of Skin Reactivity to Blomia Tropicalis Antigen in Patients with Respiratory Allergy at Hospital Universitario De Puebla

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Background: Published studies shows that the sensitization to Blomia tropicalis mite plays an important roll on the development of allergic diseases. The aim of our study is to determinate the prevalence to skin reactivity to Blomia tropicalis' antigen in patients with respiratory allergy.
Methods: We conducted a descriptive, observational, prospective and transversal study being the criteria for inclusion: male and female patients aged 2 to 58 who came for first time at our service with diagnosis of asthma, rhinitis or asthma more rhinitis. We evaluated the skin reactivity by skin prick test to Blomia tropicalis' antigen. Descriptive statistics was implemented by estimating summary measures and dispersion.
Results: From a total of 110 patients, their mean age was 16.25 (2–58), 50% were males, 92% were from urban areas and 7.3% from rural areas. Of the patients studied 2.7% had asthma, 73.6% had rhinitis and 23.6% both diagnoses. The prevalence of positive skin reactivity to Blomia tropicalis was 24.5%. The prevalence of positive skin reactivity for the rhinitis subgroup was 59.3% and for the asthma/rhinitis subgroup was 40.7%, while in the asthma subgroup the prevalence was 0%.
Conclusions: The high prevalence of skin reactivity to Blomia tropicalis indicated the importance of including Blomia tropicalis in routine diagnostic testing and immunotherapy treatment.

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Prevalence of Sensitization to Parietaria, Pinus, Cupressus and Morus Pollens in Patients from Craic

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Background: The pollens of *Cupressus, Parietaria, Pinus and* Morus are important causes of allergic respiratory diseases. In a study of pollen concentration in Monterrey in 2004, these pollens occupied the first places in frequency. The objective was to determine the prevalence of sensitization to *Parietaria, Pinus, Cupressus and Morus* in patients from CRAIC (Regional Center of allergy and clinical immunology, Monterrey, México)
Methods: Is an observational, cross-comparative, double-blind study in which patients were included if they underwent prick tests to aeroallergens in CRAIC between October 2009 and February 2010. All patients underwent skin testing with allergen extracts for *Parietaria, Pinus, Cupressus and Morus* pollens 2 of each, a weight-volume (dilution 1:20) and other units.
Results: We included a total of 256 patients, 140 female (53.1%), 130 (50.8%) were under 18 years. The prick test with allergenic extract of *Cupressus* was positive in 39 (15.2%) patients with W/V and 18 (7%) patients with PNU, the prick test to *Parietaria* allergenic extract was positive in 3 (1.2%) patients W/V and 4 (1.6%) patients with BAU, the prick test with *Pinus* allergenic extract was positive in 4 patients (1.6%) with W/V and 2 patients (0.8%) with PNU, and the prick test with *Morus* allergen was positive in 19 patients (7.4%) with W/V in 8 patients (3.1%) with PNU. Of the 44 aeroallergens our center applies *Cupressus* (1:20) ranked 7th place.
Conclusions: *Cupressus* sensitization was high in our study group (15.2%). Consideration should be the routine use of allergen extract of *Cupressus* for diagnosis and treatment in patients with respiratory allergy.

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Prevalence of Skin Reactivity to Antigen Mus Musculus in Patients with Respiratory Allergy

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Background: It has been reported worldwide high prevalence of sensitization to antigen *Mus musculus* (mouse) in patients with allergic respiratory diseases.[1,2]
Methods: We performed a cross-sectional, observational, prospective and descriptive study in patients of both genders, from 2 to 58 years old, attending for the first time to the service of Allergy and Clinical Immunology in the University Hospital of Puebla, with clinical symptoms suggestive of asthma, allergic rhinitis, or both, for a period of 6 months. Each patient underwent clinical history and prick skin test with epithelial antigen *Mus musculus*. Data were analyzed with the program SPSS-Statistics 18.
Results: We included 110 patients, 50% were women, mean age was 24.1 years (SD 16.2) 92.7% were from urban areas and 7.3% rural. The overall prevalence of skin reactivity to antigen epithelial *Mus musculus* was 1.8%, the corresponding to patients with allergic rhinitis were 2.4% and the remaining subgroups were nonreactive. One of these patients worked with laboratory animals including *Mus musculus*, which represented 33% of patients with positive skin reactivity.
Conclusions: The results presented here support the relevance of implementing skin testing with antigen *Mus musculus* only in those patients who suffer from respiratory allergy and who have a history of recurrent exposure to it.

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Atopy Patch Test to Aeroallergens Extracts is Useful In Allergic Diseases Diagnosis When Skin Prick Test is Negative

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Background: The atopic diseases are generally diagnosed by performing skin prick tests (SPTs) to different aeroallergens. However, when this study results negative, it is possible to perform atopy patch test (APT). This technique has been introduced to evaluate sensitization to aeroallergens in patients with atopic eczema dermatitis syndrome. Nevertheless, its role in other allergic diseases has not been proved. Objective: Evaluate aeroallergens response using skin prick test (SPT) and atopy patch test (APT) in patients with allergic diseases.
Methods: Retrospective cohort study of individuals who performed SPT and APT as part of allergic diseases study. The study subjects were patch and skin prick tested to house dust mite (*Dermatophagoides*), trees, grass and fungi

mix, cat and dog dander, among others. The tests were performed at the respiratory allergic disease center of Santa Maria Clinic in Santiago, Chile, between January 2010 and April 2011.
Results: Fifty-five patients were included, 18 (33%) males and 37 (67%) females, median age 6 years (range from 3 months to 62 years), with the following diagnosis: atopic dermatitis syndrome (60%), allergic rhinitis (58%), contact allergic dermatitis (16%), asthma (9%), recurrent bronchial obstructive syndrome (7%), allergic rhinoconjuctivitis (4%), chronic cough (4%), recurrent acute otitis media (2%) and recurrent laryngitis (2%). They underwent usual SPTs and APTs with multiple aeroallergens extracts. Of the 55 patients, 22 showed a positive SPT and 32 a positive APT; in 14 (25%) both, SPT and APT were positive. In 8 (15%) the SPT was positive and APT negative, while in 18 (33%) the SPT was negative, but the APT positive. Fifteen (27%) were negative to both tests.
Conclusions: Our results show that APT might be a useful diagnosis test in patients with allergic diseases and that its routine use can improve their diagnosis.

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Clinical and Laboratory Studies of the Fate of Intranasal Allergen

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Background: The nose is generally the first site of contact for inhaled particles including allergen, however the precise way in which allergen is handled by the nose is unknown.
Objective: This study aimed to describe the dispersal of Der p 1 allergen by measuring the recovery of allergen following nasal administration and to evaluate whether Der p 1 can be detected in nasal biopsies after natural exposure and nasal challenge.
Methods:

1) Der p 1 allergen was administered intranasal to 20 non-atopic healthy subjects and recovery of Der p 1 was measured in the nasal wash, nasal mucus and induced sputum up to 30 minutes after challenge.
2) In 8 subjects (5 atopics) Der p 1 was sprayed intranasal into one nostril and 30 minutes later a biopsy was taken, the contralateral nostril served as a negative control. Immunohistological localisation of Der p 1, IgE positive cells, macrophages was undertaken. Eosinophils were shown by H-E staining.

Results:

1) Less than 25% of total allergen inserted into the nasal cavity was retrievable after aqueous or particulate allergen challenge. Most allergen was retrieved from the nasal mucus.
2) Under baseline conditions, in atopics and non-atopics, mild Der p 1 tissue staining in nasal epithelial tissue was observed. Following challenge epithelial Der p 1 staining increased both in atopics and non-atopics, while increased staining of lamina propria was found in atopics only. Also increased eosinophils, macrophages and IgE positive cells were observed in areas of higher concentrations of Der p 1 staining in the epithelium, mucous glands and lamina propria compared to the contralateral unchallenged nasal mucosa and also compared to the nonatopics.

Conclusions: Der p 1 allergen is detected in nasal tissue after natural exposure and independent of atopic status. After challenge the nose effectively retains allergen which is mucosally located. Furthermore in atopics allergen is bound to epithelial cells and rapidly transported to the subepithelial lamina propria where it can bind to IgE-bearing mast cells and recruit eosinophils and macrophages facilitating induction and persistence of inflammation.

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Effect of Enzymatically Modified Isoquercitrin, a Flavonoid, on Symptoms of Japanese Cedar Pollinosis

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Background: The prevalence of allergic diseases has increased all over the world during the last 2 decades. Dietary change is considered to be one of environmental factors that cause this increase and worsen allergic symptoms. If it is the case, an appropriate intake of foods and beverages with antiallergic activity is anticipated to prevent the onset of allergic diseases and ameliorate allergic symptoms. Flavonoids, ubiquitously present in vegetables, fruits or tea possess antiallergic and antioxidant effects, so that we examined the efficacy of a flavonoid on clinical symptoms of Japanese cedar pollinosis.
Methods: We investigated the efficacy of enzymatically modified isoquercitrin (EMIQ), a quercetin glycoside, to relieve symptoms of Japanese Cedar pollinosis by 3 different clinical trials. In either trial patients were randomly assigned to the EMIQ group or the placebo group and took one capsule containing EMIQ plus corn starch or corn starch only twice a day. The efficacy was evaluated with the total symptom, medication or QOL score. Study 1 (reference 1) and 2 (reference 2); EMIQ (100 mg/day) versus placebo, for 8 weeks, started after (study 1) and before (study 2) the onset of pollen release, Study 3; EMIQ (200 mg/day) versus placebo, for 4 weeks, started after the onset of pollen release.
Results: In study 1 and 2, during the entire study period, ocular + medication score for the EMIQ group was significantly lower ($P < 0.05$) than that of the placebo group. When limited to the period, total symptom + medication score for the EMIQ group was significantly lower than that for the placebo group in all 3 studies.
Conclusions: These results indicate that intake of EMIQ, a quercetin glycoside proved to be effective for the relief of symptoms caused by Japanese cedar pollinosis.

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Prevalence of Allergen Sensitization in Children with Atopy Suspicion between Six Months and Five Years of Age

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Background: Classically we have been taught that the skin prick test (SPT) must be performed over 4 years of age mainly because of the lack of sensibility the test has on younger children, now a days the utility of the SPT in younger children with atopic history is controversial and it would help make an early diagnosis. The objective of this study is to describe the prevalence of allergen sensitization in children between 0 and 5 years of age that have atopic history. We also describe the sensitization percentages to the most relevant allergens according to age group.
Methods: SPT performed between January 2006 and July 2010 at the Respiratory and Allergy Department of Clínica Santa Maria to children with

atopic story were analyzed. A standard base of 21 allergens from LETI laboratory was used.
Results: Seven hundred and fifty two children with SPT were studied; they were divided into 2 groups. Group A corresponding to children between 6 and 24 months of age, group B corresponding to children between 25 months and 5 years of age. In group A 76 SPT and group B 676 SPT were performed. The total number of SPT positive to 1 or more allergens was 46.4%. (Group A: 6.4%, group B 40%). The most prevalent allergens according to age were: group A: grass 16%, egg 16%, cat dander 10% and house dust mite (Dermatophagoides pteronyssinsus and farinae) 10%. Group B: grass 15%, house dust mite 13.6%, fungal allergens (Aspergillus an Alternaria) 11.4%, trees 9% and cat dander 6.6%.
Conclusions: A high sensitization percentage to grass and egg is seen under 24 months of age. Egg sensitization diminishes significantly over 2 years of age, on the other hand house dust mite and fungal sensitization increases with age which could be explained by a longer exposure time in genetically predisposed children. Forty-six percent of the children are sensitized to 1 or more allergens which make us question the classical indication that SPT will be done over 4 years of age. When high suspicion of atopic history, a SPT should be performed independently of patient age.

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Prevalence Allergic Diseases and Allergic Sensitization among Urban Office Workers as Compared with a Forest Service Workers

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Background: Asthma, allergic rhinitis (AR), and atopic dermatitis (AD) are the most prevalent allergic diseases and number of studies has shown an increase in prevalence of both all over the world in recent years. Although little about the prevalence of asthma, AR, and AD in Korean adults. And the incident sensitization to common allergens in the setting of sensitization to an occupational allergen has not been described. Our aim was to determine the prevalence of living and working place in adults. And also, determines the sensitization to common allergens in subjects with incident sensitization to a work-related allergen.
Methods: We performed questionnaire survey and allergy skin prick test with 27 common inhalant allergens among 294 subjects (response rate, 94.9%, n = 279) age 19 to 54 years in Seoul and forest service workers. One hundred thirty four subjects were forest service workers and 145 subjects were urban office workers.
Results: The mean age was 33.7 ± 7.6 years. There were 141 man and 138 women. A history of asthma was noted in 3.8% and a history of AR was noted in 28.7%. And a history of AD was noted 21.3%. The each group of sensitization to allergen were 40.3% (urban) and 60.0% (forest), ($P = 0.002$). The most common allergen was mites. The sensitization to birch allergen were more high in urban office workers ($P = 0.01$).
Conclusions: The prevalence of allergic rhinitis in urban areas was high. And urban officer workers were also high with sensitization rate compare to forest workers. The interesting results were the pollen sensitization rate in urban areas showed higher tendencies. More research will be needed in futures.

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Photoaging Attenuates Skin Test Response to Histamine More Than Natural Aging

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Background: Clinical experience suggests that skin test reactivity is often decreased in photo-exposed skin versus sun-protected skin in older individuals. The current study was designed to address whether photoaging or natural aging of skin causes a greater diminution in skin test reponse.
Methods: Prick-puncture skin tests to histamine were performed on sun-exposed and sun-protected areas in younger (n = 61, age 20–50) and older (n = 63, age 60–87) adult volunteers who were recruited for skin prick testing because of suspect allergic rhinitis and/or allergic asthma. The skin was scored for photoaging by physical examination and coloration was measured by a colorimeter.
Results: There was no observed difference in wheal and flare response to histamine when patients were stratified by age alone. However, photoaging was significantly correlated with decreased skin reactivity to histamine on the upper back (a sun-exposed area) as compared to the lower back (a sun-protected area). In patients with the most severely sun-damaged skin, there was a trend toward decreased skin reactivity in all areas.
Conclusions: Skin test reactivity to histamine is negatively correlated to the degree of photoaging and is independent of patients' chronological age. This result has clinical implications for patients with significant photoaging, suggesting that care should be taken to perform skin testing on anatomic sites in sun-protected areas. In patients with severe photoaging, allergen-specific IgE testing should be considered to avoid possible false-negative interpretation of skin-prick testing.

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Hla and Chronic Urticaria with Positive Autologous Serum Skin Test among Brazilians

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Background: Many autoimmune diseases are associated with certain alleles of the human leukocyte antigen (HLA) system, and recent studies have shown that, in many cases, chronic urticaria has autoimmune etiology. An association between class I and II alleles of the major histocompatibility complex (MHC) and idiopathic chronic urticaria (ICU) has previously been observed in different populations, but there are still no studies on Brazilian populations in this respect. The involvement of MHC classes I and II (loci A, B and DR) in Brazilian patients with ICU and a positive autologous serum skin test (ASST) was investigated and compared with a healthy population group.
Methods: DNA was extracted from the blood of 42 patients with ICU (28 women; mean age ± SD: 44 ± 12 years; range: 19 to 88 years) and MHC classes I and II alleles were determined using the polymerase chain reaction (PCR) and a laboratory test for oligonucleotide hybridization using a single-filament probe. The frequencies of these alleles in patients with chronic urticaria were compared with the frequencies in 1000 genetically unrelated voluntary blood donors from the same region of Brazil. The diagnosis of idiopathic chronic urticaria was based on the patients' clinical histories and routine laboratory tests. Only the patients with positive ASSTs were selected. The allele distribution results from the patient and control groups were analyzed using odds ratios and 95% confidence intervals.
Results: No statistically significant differences were found between the ASST-positive patients with chronic urticaria and the control group, in relation to the MHC classes I and II alleles studied.
Conclusions: We found that in this population group, there was no specific association between the HLA alleles studied (HLA-A, HLA-B and DRB1) and ASST-positive chronic urticaria. We believe that further population

studies are needed in order to investigate the possible existence of this association.

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CD63 Expression, IL3 Receptor, IGG Autoantibody and Autologous Serum Skin Test Accuracy in Patients with Chronic Urticaria in Brazil

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Background: Recently, a laboratory technique called basophil activation test (BAT) using flow cytometry (FC) got demonstrated through the expression of CD63 molecules that basophils of atopics donors can be activated when stimulated by serum of patients with CU (supposedly autoimmune). This paper aims to analyze the autologous serum skin test (ASST) in relation to the BAT as well as evaluating the IL3 receptor (CD123) and nonspecific autoantibodies IgG bound to basophils of patients with chronic urticaria.

Methods: We studied 33 adults (24 women) with CU with a mean age of 42.5 + 14 years, of which 22 with ASST positive and 11 with ASST negative. It was done through the analysis by FC of CD63 molecules expression on basophils from an atopic donor after stimulation by serum of these patients. We used as control the serum from 4 volunteers (without urticaria). Also we researched the CD123 molecule expression and IgG nonspecific autoantibodies in basophils from patients with CU.

Results: We found 21 (63.6%) patients with positive BAT, of these 14 (66.6%) were ASST positive and 7 (33.3%) were ASST negative. Taking as parameter the BAT, we found an accuracy of 54.5% for the ASST, a sensitivity of 66%, specificity 33%, positive predictive value of 63% and negative predictive value of 36%. Comparing the expression intensity (mean with SD) of IgG autoantibodies in patients' basophils with positive and negative ASST there was not statistical difference (for a $P < 0.05$); the same was true when comparing the autoantibodies (IgG) between groups with BAT positive and with BAT negative. We also didn't find statistical difference (for a $P < 0.05$) of receptor expression of IL3 (CD123) between the groups.

Conclusions: Taking as parameter the BAT for diagnosis of autoimmune CU this study found that ASST is accurate about 55%. There was no statistical difference when comparing the expression of IgG nonspecific autoantibodies and CD123 molecule, between groups.

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Comparison of the Modified Autologous Serum Skin Test and the Cd63 Basophil Activation Test in Chronic Urticaria

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Background: The modified CD63 basophil activation test in the diagnosis of chronic autoimmun urticaria was first described in 2004 by Szegedi et al. We demonstrated that the strongly sensitized basophils of atopic donors can be successfully used without the addition of IL-3 for the in vitro evaluation of autoimmun urticaria. Positive correlation was found between the basophil CD63 expression test and the autolog serum skin test (ASST), and between the CD63 test and the gold standard histamine release assay.

Methods: We examined 50 patients with chronic ordinary urticaria and with the help of a validated questionnaire urticaria score index was calculated. ASST with the patient's own diluted (1:10, 1:100) and undiluted sera, and CD63 basophil activation test on atopic donor basophils were performed. Pearson's exact test was used to analyze the correlation between the results of the CD63 assay and the urticaria score index.

Results: Based on our results ASST performed with diluted sera of chronic urticaria patients did not show correlation with the results of the CD63 assay. A significant correlation was found between the CD63 assay and the score index representing severity of disease.

Conclusions: ASST with diluted sera of chronic urticaria patients does not have any additional information on the diagnosis of autoimmun urticaria. In the CD63 basophil activation assay the degree of the CD63 cell surface expression can give information on the severity of the clinical signs.

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The Frequency of Positivity in Autologous Serum Skin Test in Patients with Chronic Idiopatic Urticaria

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Background: Describe the frequency of positive results in autologus serum skin test among patients with cronic urticaria.

Methods: Trans-sectional study of patients with CIU refered to traitment in policlínica geral do Rio de Janeiro, brazil. Autologus serum intradermal injections were used to estabilished the sensitivity. Negative and positive controls were made with 0.9% intradermal saline solution and skin prick test with histamina 1:100 solution. Autoreactivity was considered positive when wheal reached 3 mm at least, 1.5 mm larger than saline solution at 30 minute interval. Antihistamines drugs were interrupeted 72 hours before test. Dates on race, age, sex, and informations about length and how often the symptoms persist, personal history of atopy (PHA) and angioedema (AE), autoimmune disease (AID) and physical (PF) and not physical factors (NPF) related with the worsening of urticaria were registered during appointment. K square and τ student tests were used in this work.

Results: Eighteen patients, from 2008, march to 2011, march, were investigated (15 f; 12 w; age 50,67 ± 16,93 yr). Eleven patients presented positive AAST (61.1%) with a mean wheal diameter = 9,64 ± 2,66 mm (negative control = 6,33 ± 3,63 mm; $P < 0{,}001$). All of the positive asst occurred in patients over 60 years old. The mean length of the desease was 21,78 ± 22,95 months. Continuous symptoms were saw in 83.3%, pruritus, the major one (94.4%). Angioedema and PHA were present in 61.1% and 27.8%, respectively. NPF of symptoms worsening like drugs, food, emotional stress or alcoholic beverages were complaint of 72.2% of individuals, whereas 22.2% complainted about worsening with colinergic PF or dermographism. Joint pain (33.3%) were the complain the most frequent and 7 patients, mainly whose with positive ASST, had elevated thireoid antibody levels ($n = 5$; $P > 0.05$).

Conclusions: The positive asst frequency was 61%, comparable to values found in the liretature. Association among social-demographic and clinical aspects was not observed. We emphasize the prevalence of joint pain and angioedema as associated symptoms and the more frequence of AID laborotory finds. The procedure proved safe and precise and worth value in the screening diagnosis of autoimune etiology for patients with CIU.

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Eleven Cases of Angioedema with Eosinophilia Treated in a Single Hospital in Japan

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Background: Angioedema with eosinophilia (AE) is mostly reported in Japanese patients, and only as case reports. In this study, we aimed to determine the prevalence, clinical and laboratory characteristics, and courses of AE; the therapies for AE and the outcomes; and to evaluate whether steroid therapy for AE is necessary or not.

Methods: The patients whose blood samples showed an eosinophil count of ≥2000/μL, among the samples tested for blood cell counts and differential counts between Jan. 2006 and Oct. 2010, in Japanese Red Cross Medical Center, were first included. Among these patients with AE were extracted. The AE diagnosis was based on angioedema developing concurrently with eosinophilia and improving with the recovery from eosinophilia.

Results: All of the 11 patients were Japanese young females. One patient with clear arthralgia showed radioisotope accumulation in the joints by bone scintigraphy, and was diagnosed as having arthritis. The peak peripheral blood eosinophil count was 7,839 ± 6,008 (2,130–23,170)/μL after visiting our hospital. An increase in white blood cell count was only due to an increase in eosinophil count. Serum C-reactive protein and Immunoglobulin E levels remained almost normal. Peripheral blood eosinophil count decreased steadily for 8 weeks after the first visit, regardless of steroid use. Edema in all of the patients and arthralgia in 6 patients improved within 12 weeks. None of the patients had a recurrence of AE.

Conclusions: AE developed in Japanese young females and likely showed a single course. In AE, the count of eosinophil of 10^4/μL was observed. Only eosinophil count increased without changes in changes in the counts of other leukocyte series. Serum C-reactive protein and Immunoglobulin E levels remained almost normal. The eosinophil count in AE patients will return to the normal level within 8 weeks even without steroid therapy.

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Chronic Urticaria and Infections

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Background: Chronic Urticaria (CU) is a group of diseases that share a distinct skin reaction pattern. Triggering of urticaria by infections has been discussed for many years but the exact role and pathogenesis of mast cell activation by infectious processes is unclear. The remission of annoying spontaneous chronic urticaria has been reported after successful treatment of persistent infections.

Objective: To describe the infections found in chronic urticaria patients in our service, by performing a complete medical history, physical examination, laboratory studies and cultures.

Methods: Universe: Consecutive patients with chronic urticaria, with a detailed history, physical examination, laboratory studies underwent clinical viral panel, cultures, biopsy for detection of H. Pylori.

Results: A total of 50 patients, mostly women 82% and 18% men, mean age 41 years. 42% of the total population had salmonella, proteus infection in 20% and 8% brucellosis. Crossed with urinary tract infection 6% of the population. Five patients had positive stool in 3 patients Endolimax nana was isolated and 2 patients reported Giardia lamblia, 5 patients (10%) women had undergone cervicovaginitis 2 of them infected with S. haemolyticus, the rest was cultivated E. faecalis, and T. Gardenella vaginalis, respectively. Was isolated in 2 patients and one patient H.pilory HCV infection.

Conclusions: Infections may play a causal role of UC in some cases. Were identified in 42% of cases and gastrointestinal infections by most common cause Salmonellosis. As for genitourinary tract infections, intestinal parasites, Helicobacter pylori, were treated appropriately with antibiotic therapy, found a successful resolution of urticaria mainly in patients infected with Helicobacter pylori. There is growing evidence that persistent infections in chronic urticaria are important triggers, particularly in the case of infection by Helicobacter pylori, so If an infection is identified, it should be appropriately treated and it should be checked whether eradication has been achieved.

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Chronic Urticaria Associated with Thyroid Disease

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Background: Chronic urticaria has an incidence of 15% in the general population and sometimes is associated with chronic diseases such as rheumatoid arthritis, vitiligo and thyroid disorders. Chronic urticarial is characterized by wheals lasting more than 6 weeks, with alterations of the upper layers of the skin only. On histopathology there is a perivascular infiltrate characterized by T CD4 and CD8 lymphocytes and other inflammatory cells. Cytokines produced by lymphocytes, mast cells and other cells increase the expression of vascular adhesion molecules. Other mediators such as histamine increase vascular permeability causing edema, clinically represented by wheals. Treatment of chronic urticaria includes first and second generation antihistamines as first line treatment. Sometimes there is a poor response to there drugs and second line treatments such as immunosupressors are indicated. A search for systemic disorders is helpful to identify associated pathology which makes chronic urticaria reluctant to therapy.

Methods: We performed a retrospective study considering patients with chronic urticaria attending our clinic during the last 5 years. Three hundred patients with urticaria were considered, with 16% (50 patients) with a chronic disease. Six patients with chronic urticaria were associated with thyroid disease.

Results: We considered 6 patients with chronic urticaria with altered thyroid function tests; 4 with subclinical hypothyroidism and 2 with subclinical hyperthyroidism. All of them had a poor response to antihistamines. When a thyroid disorder was identified, they received appropriate treatment achieving control of chronic urticaria. Treatment with antihistamines was continued.

Conclusions: Chronic urticaria is a disease often associated with systemic disorders including thyroid disease. We found an association with thyroid pathology in 2% of patients with chronic urticaria, with remission of cutaneous symptoms after treatment of endocrinologic disorder. No patient had clinical manifestation of thyroid disease so it is important to perform thyroid function tests to patients with chronic urticaria since identification of these disorders and appropriate treatment helps to control cutaneous symptoms.

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Epidemiology of Urticaria Cases in the Allergy Service from a Third Level Medical Center. Six Year Experience

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Background: The purpose of this study is to report the cases of Urticaria diagnosed in the Allergy service from a Third level medical centre since its creation in July 2005.

Methods: This is a descriptive, retrospective, transversal study from July 2005 to February 2011. Selected medical records of patients apply for diagnostic criteria for an allergy disease. EAACI/GA2LEN/EDF/WAO guideline 2009 was used to make diagnosis of urticaria. Patients were classified by age and sex, and how many of them had skin prick test, also how many patients began treatment with immunotherapy.

Results: Thirteen thousand seven hundred and thirty seven consultations were attended in the Allergy service between the period mentioned; 2,337 medical records of patients were selected; 1,608 patients applied for a specific diagnosis for an allergy disease; 90 completed criteria for urticaria, after allergic rhinitis, asthma an atopic conjuntivitis. 49 (54.4%) patients were found to be in the range of 30 to 40 years; 36 (73.4%) of them were female. The majority of urticaria patients were in the range of 40's with 28 (18 F/10 M) corresponding to 31.1% of total of patients. 43 patients were classified with acute urticaria, 26 as chronic urticaria. 19 patients presented angioedema at the time of diagnosis. Skin prick test were made in 27 patients only in 10 were positive and began immunotherapy. Patients with positive skin prick test results with 9 at dust mites, 4 cockroach, 3 mosquito, 3 fungus and 8 grass and tree pollen.
Conclusions: Urticaria represents the fourth cause of incidence in allergy diseases in this study. Female sex is more frequently affected in the range of 30 to 40 years of age. We found statistical data comparable with international information, that forms part of our data base en Mexican patients in our center, also we standaridzed procedures for testing physical urticaria.

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Frequency of Autoreactivity Demonstrated by Autologous Serum Skin Test in Patients with Chronic Urticaria in the Valley of Mexico During a Period of 8 Years

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Background: Urticaria is a skin disease characterized by rapid emergence of hives, accompanied or not with angioedema. Usually lasts less than 24 hours. Approximately 12 to 24 per cent of the population will have hives or angioedema at least once in their life. Some patients with chronic urticaria has been classified as autoimmune. The autologous serum skin test (ASST) has been used to show pro-inflammatory circulating endogenous factors and it is regarded as a test for autorreactividad. The autorreactividad does not define an autoimmune urticaria, but may be an indicator of the presence of autoreactive antibodies with the capacity of to activate the mast cells however functional antibodies need to be confirmed through of release of basophils histamine test from basophils (BHRA) and its specificity immunoassay (Western Blot or ELISA)-confirmed. Objective: to evaluate the auto-reactivity by autologous serum skin test in patients with chronic urticaria idiopathic in a study of 8 years. Material and methods: we made 216 ASST and autologous plasma skin test (APST) in patients with chronic urticaria without specific cause identified, of any age, during the period of 2003 to 2011.
Results: Thirty five thousand patients were evaluated only 261 patients not identified the cause (0.6%) and we realized ASST, of these 190 (88%) were negative, and 26 (12%) were positive, 20 (76.9 %) were female and 6 (23.1%) male, the median of age for women was 30 years ago with medium of 28 and men average 29 years and median 20. Of the 26 patients one was positive for anti-thyroglobulin senior titles (1: 170) .dos with positive anti unclears and one with pANCA and cANCA positive of a total of 216 patients, 156 (72.2) had APST and 60 (27.8%) were positive, 46 (76.6%) women and 14 (23.3 %) men. Mc Neman concordance between tests $P < 0.0001$ and Kappa index gives us a highly significant concordance $P < 0.0001$. The correlation between ASST and APST by Sperman was high significance value of $P < 0.001$. The correlation of both tests was moderately high (76.8%).

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Chronic Idiopathic Urticaria and Neglected Toxocara Infection

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Background: The diagnosis of chronic idiopathic urticaria is stated when all possible causes of urticaria are excluded. Toxocariasis is a parasitic infection induced by a nematode belonging to the family of Ascaridae with generally affects cats and dogs. Human infestation is caused by the accidental ingestion of embryonated eggs of Toxocara; the larvae do not develop into adult worms but may migrate to several organs, giving rise to a number of clinical expressions, including chronic urticaria.
Methods: From 2005 to 2011 in our Allergy Unit were selected 336 patients with a positive result for IgG antibodies to Toxocara canis as assessed by ELISA or Western blotting (WB). Of them, 52 patients (33 F, 19 M, age ranging from 19 to 76 years old), suffered from chronic urticaria that lasted from 3 to 10 years and was poorly responsive to antihistamines. In all these patients anthelmintic therapy was prescribed using mebendazole (one 100 mg tablet b.i.d. for 3 days), repeated after 20 days up to 3 times. In case of insufficient improvement, albendazole (one 400 mg b.i.d. for 5 days) was used, repeated after 2 months.
Results: All patients showed a complete remission of urticaria and a decrease in serum IgG levels to Toxocara canis. In 29 patients (60%) a negative result to ELISA and WB was observed.
Conclusion: These findings suggest taking into account the role of Toxocara canis in patients with apparent chronic idiopathic urticaria. In patients with positive IgG to Toxocara anthelmintic therapy achieves remission of urticaria.

URTICARIA CASE REPORTS

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Mucocutaneous Disease as a Presentation of Hereditary Angioedema. Report of 2 Cases

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Background: Hereditary angioedema is an autosomal dominant disease the affected gene encodes c1 esterase inhibitor located on chromosome 11q12-q13.1. The worldwide incidence ranges from 1 in 10,000 to 1 in 50,000. Three varieties are described. Type I is chacarterized by a lack of functional protein with complete absence of C1-INH activity. Type II has a dysfunctional protein with reduced activity of C1-INH. While Type III is due to mutations in the gene for clotting factor XII or defects not identified. Clinically is characterized by recurrent non itchy edema on skin and mucous membranes associated with pain syndromes, nausea, vomiting, diarrhea and compromise of the airway that is unresponsive to epinephrine, antihistamines and angioedema conventional therapy. Because of this, it is imperative to establish the diagnosis to initiate early treatment with recombinant C1-INH or preventive treatment if there is no replacement therapy.
Methods: We present 2 cases with atypical manifestations characterized by fixed angioedema located in labial mucosa.
Results: Case 1: 23 years old health female with labial angioedema for 2 years without improvement in spite of having multiple treatments, including immunosuppressive agents. During the evaluation were discarded infectious, autoimmune and endocrine diseases, with only positive for type II hereditary angioedema with decreased function of C1-INH antigen: 76% (78–122%). Case 2: 53 years old female with history of hypothyroidism and type 2 diabetes in control, with 2 years of labial mucosa angioedema unresponsive to treatment. During his study the only finding was decreased levels of C1 esterase inhibitor: 19% (21–39%). In both cases the evolution has been torpid to treatment with androgens, getting partial response with immunosuppression based on azathioprine.
Conclusions: The cases presented correspond to an atypical presentation of hereditary angioedema and in spite of the treatments have only been able to obtain partial response. In the setting of having the replacement therapy improvement in symptoms is expected, offering the patients a better quality of life.

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Plasmapheresis in a Patient with "Refractory" Urticarial Vasculitis

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Background: Immune complexes have been found in the circulation approximately 30 to 75% of patients with urticarial vasculitis and much evidence supports the role of these immune complexes in the pathogenesis of urticarial vasculitis. Plasmapheresis is effective in removal of these immune complexes. However, few cases have been reported regarding the use of plasmapheresis in the treatment of urticarial vasculitis.

Methods: A 35-year-old woman presented with history of recurrent episodes of generalized painful urticarial plaques often lasting 9 years associated with swelling of her parts of body. Examination revealed multiple urticarial plaques distributed all over the body (particularly in the extremities, palms and soles). The initial laboratory studies, including a complete blood count, thyroid function tests - thyroid autoantibodies, erythrocyte sedimentation rate, hepatitis markers, liver and renal function tests, urinary analysis, stool analysis for parasite ova, total IgE, C3, C4, C1q, CH50, C1 inhibitor levels and antinuclear antibodies were found to be within normal range. Skin prick tests were performed with commonly consumed foods in Turkey found to be negative. A biopsy from an affected area of skin revealed an urticarial vasculitis. Based on the biopsy results, the patient was diagnosed with UV. Treatment with H1/ H2-antihistamines and oral corticosteroids (1 mg/kg/day) had been unsuccessful; therefore hydroxychloroquine 400 mg/day was added. Unfortunately hydroxychloroquine was stopped in the second month due to the emergence of an adverse event (keratopathy). The patient underwent plasma exchange 2 times with an interval of 6 months. Five percent albumin solution as replacement fluid was used. One plasma volume was processed in each session. Apheresis procedure was performed with the "Cell Separator" device. The plasmapheresis procedures were completed without any adverse events. At 13 months after the plasmapheresis, the urticarial plaques were reappeared, but the severity and duration of symptoms were lower than before the plasmapheresis. The newly lesions were re-treated with short-term oral antihistamine regimen.

Conclusions: In conclusion, the presented report supports the usability of plasmapheresis in patients with "refractory" UV. Further clinical studies are needed to confirm our experience.

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Delayed Diagnosis of Hereditary Angioedema. A Case Report

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Background: Hereditary angioedema (HAE) was first described by Quincke in 1882 and appointed by Osler in 1888, is a rare disease caused by deficiency of gene esterase inhibitor C1 (C1 INH). Prevalence varies from 1:10,000 to 1:150,000. The attacks are usually sporadic and often associated with traumatic or stressful events. Treatment included management of acute attacks and prophylactic therapy in specific situations where attacks may occur.

Methods: A 40-year-old male with a family history of father facial angioedema. He had experienced 15 episodes of angioedema during the previous 5 years. During these events than lasted 3 to 5 days edema affected his eyelids, lips, hands, feet and testicles. And sometimes was associated to abdominal pain and shortness of breath. He went several times to medical office and emergency room, where he received treatment with antihistamines without improvement.

Results: The laboratory evaluation of complement components showed C4 2s0.8 (NV 20–50), CH50 10.1 (NV 20–50), C1 inhibitor quantitative <1.2 ng Eq/mL (NV $>$ 10.7), and C1 esterase inhibitor functional 104% (NV $>$ 67%), once the diagnosis of type I hereditary angioedema was done, we started danazol therapy that has prevented recurrence of symptoms.

Conclusions: It is important to do a detailed history for the diagnosis and treatment in cases of angioedema. Most patients improve when receiving the right treatment. Recurrent angioedema events even with treatment, the physician must search for malignity and/or autoimmunity disease.

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Urticaria Pigmentosa. Case Report

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Background: Mastocytosis is a disorder characterized by an abnormal proliferation of mast cells and release of cell mediators. The incidence is 1 per 1000 skin diseases attending in dermatology services. Mastocytosis can be divided into 3 different clinical variants: cutaneous, systemic and malign mastocytosis. Urticaria pigmentosa is the most common variety (70–90%) of mastocytosis. Of all cases 55% ocurr during the first 2 years of life. When the bone marrow, lymph nodes, liver and spleen are affected the disorder is called systemic mastocytosis.

Methods: Case 1: A 20 month old male with history of penicillin and erythromycin allergy, as well atopic family history. Began at 4 months with itchy brown-marrow papules in the back, then generalizated except palms and soles. The lesions were exacerbated by heat and rubbing. There was no fever, weight loss, or any other systemic symptoms in the history. Blood count and biochemical laboratories were normal. Skin biopsy reported the presence of mast cells, confirming urticaria pigmentosa diagnosis. The management included antihistamines, restricted diet and emollients with improved of symptoms. Case 2: A 9 month old male with no history of atopy. At the first visit he had 4 months with skin lesions characterized by hyperpigmented maculopapular eruption, scattered on head, over trunk and extremities. Darierś sign was positive. Skin biopsy is performed with confirming the diagnosis of mastocytosis.

Conclusions: The urticaria pigmentosa diagnosis is mainly clinical, with emphasis on the Darierś sign, which is pathognomonic and positive in 90% of cases. In some cases a skin biopsy is required to confirm the diagnosis.

Antihistamines are the first line of treatment. Symptoms relieve spontaneously before adolescence in 50% of pediatric patients. In some cases, a malignant transformation of mastocytosis could occur, condition that is called "mast cell leukemia".

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A Case of Chronic Urticaria Complicated by Raoultella Ornithinolytica Urinary Tract Infection, Bronchospasm and Angioedema

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Background: *Raoultella ornithinolytica* (formerly *Klebsiella ornithinolytica)* has been recovered from water, soil, plants and occasionally mammalian mucosae. It is one of the organisms that cause histamine fish poisoning by converting histidine to histamine as it possesses the enzyme histidine decarboxylase.

Methods: We report a case of a 51 year old woman with a history of rheumatic heart disease, allergy to aspirin and penicillin, reflux oesophagitis, atopic dermatitis, stress incontinence and a cystocele attributed to chronic obstructive pulmonary disease. She presented to the emergency unit with a 5 years history of urticaria of unknown cause, complicated by symptoms of a urinary tract infection and 3 episodes of angioedema in the preceding 10 days. She was not on regular medication but on intermittent prednisone, promethazine and was recently treated with omeprazole and sucralfate for reflux oesophagitis. She denied previous use of angiotensin converting enzyme inhibitors. Urine culture grew *Raoultella ornithinolitica* (>100 000 CFU/mL) after 3 days.

Results: The angioedema resolved on treatment of the UTI with oral ciprofloxacin. She was lost to follow-up and when seen 3 years later she still had intermittent flares of urticaria, but had had no episodes of angioedema.

Conclusions: *R ornithinolytica,* most commonly described as a causative agent of histamine fish poisoning in humans, possesses histidine decarboxylase, an enzyme that converts histidine into histamine. The resulting elevated levels of histamine usually do not cause severe disease but complications can arise in people with chronic histamine mediated diseases.

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A Case of Idiopathic Recurrent Isolated Orbital Angioedema with Exophthalmos

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Background: Idiopathic angioedema is a term applied to recurrent episodes of angioedema of unknown etiology. The following is a case report of idiopathic recurrent isolated orbital angioedema with exophthalmos which responds to prolonged courses of oral corticosteroids.

Methods: A 67 year old Caucasian female with aspirin exacerbated respiratory disease (AERD) sought treatment for an acute, progressive painless left eye swelling with exophthalmos without visual deficits or urticaria. High dose corticosteroids were initiated followed by a low maintenance dose. The swelling subsided after one year of corticosteroid therapy.Ten years later, orbital swelling with exophthalmos returned in the same eye. No medications, such as aspirin[1] or non steroidal anti-inflammatory drugs,[2] were associated with the swelling. A CT of the orbits revealed an isolated proptosis with swelling of the medial and inferior rectus muscles and mild hypertrophy and swelling of the left lacrimal gland. A complete history and physical examination were negative. The family history likewise was negative.

Results: High-dose systemic glucocorticoid therapy was initiated. Symptoms resolved after 1 month of tapered corticosteroid therapy, however, swelling reoccurred in the orbit within one week. Low dose maintenance corticosteroids were reinitiated with resolution of the orbital swelling. Work-up for acquired C1 esterase deficiency is negative.

Conclusions: An atypical case of recurrent idiopathic isolated orbital angioedema with exophthalmos in a patient with AERD and no triggering factor, systemic findings and a negative evaluation is presented.

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A Case of Multiple Simultaneous Urticarial Syndromes Refractory to Treatment

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Background: We report the case of a patient with 3 forms of physical urticaria and his response to treatment.

Methods: An atopic asthmatic 11 year old male was evaluated for a history of recurrent pruritus with a variable, erythematous rash unresponsive to therapy. Since the age of 5 years, he has experienced small red, raised, pinpoint, pruritic "bumps" over his entire body except the palms of his hands and soles of his feet. The duration of the lesions was generally 5 minutes to about 1 hour. They occurred with exercise, stress, cold air, and cold water. At the time of the evaluation, the patient was treated with oral levocetirizine 5 mg daily and hydroxyzine 50 mg at bedtime without resolution of symptoms.

Results: In clinic, the patient had a positive ice cube test, a positive dermatographia test and a negative warm test tube test. Methacholine and autologous sweat testing were declined. Otherwise he had a normal physical examination with a negative Darier sign. Laboratory studies did not reveal a disease process responsible for the urticaria. Based upon his historical symptoms and clinical findings, he was diagnosed with 3 distinct types of physical urticaria; cholinergic urticaria, cold urticaria and dermatographia. The dose of anti-histamine therapy was doubled and the patient returned to clinic in 4 weeks to report that his symptoms were slightly improved but had not resolved.

Conclusions: Physical urticarias are usually controlled by antihistamine therapy but refractory cases are not uncommon. This patient also has poorly controlled asthma for which he is scheduled to start omalizumab therapy upon turning 12 in 1 month. We will continue to follow this case to observe if omalizumab has an effect upon his urticarial symptoms.

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Chronic Urticaria as First Sign of Sarcoidosis

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Background: Sarcoidosis is a granulomatous multisystemic disease of unclear etiology, which can affect any organ. The cutaneous manifestations are present in 20% to 35% of patients. Cutaneous lesions have been classified as specific and nonspecific, depending on the presence of noncaseating granulomas on histologic studies. Specific lesions include maculopapules, plaques, nodules, lupus pernio, scar infiltration, alopecia, ulcerative lesions, and hypopigmentation among others. The most common nonspecific lesion is erythema nodosum. Others include calcifications, prurigo, erythema multiforme, nail clubbing, and sweet syndrome. Urticaria does not belong to nonspecific nor specific lesions of this illness. Diagnosis is based on 3 criteria: a compatible clinical and/or radiological picture, histological evidence of noncaseating granulomas, and exclusion of other diseases. There is no standarized therapy but corticosteroids are the mainstay of treatment for sarcoidosis. We report a case of undetermined chronic urticaria which after 6 months displayed compatible symptoms with respiratory disease associated with systemic involvement.

Methods: A 34-year-old man followed in our department due to a chronic urticaria, during 6 months with no good response to anti-histaminic treatment; refers non specific constitutional symptoms, including fever, weight loss, fatigue dyspnea and dry cough for 2 months. Skin prick test with standard aeroallergens and foods are done. Laboratory test (incluiding ECA levels), functional study; tuberculine test, chest x-ray, CT scan and lung biopsy were performed.

Results: Skin prick test and tuberculine test were negatives. Angiotensin-converting enzyme was high (ECA: 141). We observed a mixed process with negative bronchodilator response in pulmonary function test and a moderate disminution in diffusing capacity. Difuse and bilateral reticulo-nodular infiltration with mediastinal and hiliar lymphadenopathy was observed in X-chest. Lung biopsy: Noncaseating granulomas were observed. The diagnosis was Sarcoidosis, stage II. The patient remains asymptomatic regarding cutaneous and respiratory symptoms, after fulfilling oral corticoiteroids treatment for sarcoidosis.

Conclusions: Chronic urticaria can be the tip of an iceberg indicating more changes in other organs. The importance of considering cutaneous sarcoidosis in the clinical differential diagnosis of an urticaria relies on the association with systemic involvement, partial treatment response and the convenience of the skin as a tissue source for histologic analysis.

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Life-Threatening Angioedema without Urticaria (Ae-U)

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Background: This paper addresses diagnosis and treatment of life-threatening angioedema without urticaria (AE-U) with emphasis on newer concepts on patient safety and updated knowledge about pathophysiology. AE-U may be idiopathic, hereditary or acquired secondary to adverse "allergic" reactions to aspirin (ASA), angiotensin-converting enzyme inhibitors (ACEIs), angiotensin-receptor blockers (ARBs), non-steroidal anti-inflammatory drugs (NSAIDs), or other drugs. Serious adverse reactions to these drugs are becoming more common as they are increasingly prescribed for hypertension and other cardiac disorders.

Methods: We used electronic databases to gather information on angioedema. We also documented and analyzed a case of drug-induced acquired angioedema from ACEI resulting in repeated intubations and prolonged ICU stays.

Results: Case report—A 69 year old female presented with rapidly progressive swelling of the tongue. She was intubated and underwent cricothyrotomy. She had been admitted in 2003 and 2005 for angioedema; in 2003 she was instructed to avoid OTC cold medications, ACEIs, and NSAIDS, and in 2005 told she had an allergy to ACEI, ARBs, ASA, and NSAIDs. Although this was noted in her charts, the PMHx and allergy list were incorrect or inconsistent throughout her subsequent admissions and office visits from 2005 to 2008. This data suggests 3 serious concerns for patient safety: (1) documentation of "drug allergy," (2) ED diagnosis and treatment of angioedema, (3) follow-up from ED to outpatient care for angioedema. Once initiated, serious upper airway obstruction may take seconds to days to progress. After starting the drug, it may take days to years before a serious episode occurs, highlighting the significance of proper documentation in medical records. ED diagnosis may be difficult but should differentiate between angioedema with and without urticaria as the latter does not respond well to IV antihistamines, commonly given as first-line treatment in the ED. Newer treatment options for angioedema may include C1-INH concentrate, ecallantide, and icatibant. Outpatient follow-up should include workup for HAE, AAE, and angioedema with urticaria (AE+U) by a specialist. A proposed algorithm for AE-U is presented.

Conclusions: Severe AE-U may be difficult to diagnose and treat in the ED—patient safety may be improved with documentation, newer treatments, and outpatient follow-up.

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Urticarial Rash Associated with Chest Pain

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Background: Urticaria may be the first manifestation of an underlying systemic disease (tumors, infections, collagen vascular or thyroid disease. Differential diagnosis must be made with many entities that can be manifested with a similar skin injury.

Methods: A 49 year-old man who during 2 years has monthly multi-days episodes of generalized pruritic papular skin lesions, responding to steroids but not to antihistamines. Occasionally associated with joint pain. Two skin injuries biopsies informed of simple urticaria.One year after skin lesion onset, he began with chest pain episodes suggestive of angina pectoris with elevated necrosis enzyme markers and ischemic changes on EKG. Angina episodes were sometimes preceded by skin lesion outbreak and it responded to steroid. Coronary catheterization was negative twice, so the diagnosis was vasospastic angina. Later he presented cough, wheezing, elevation of transaminases, LDH, FA, GGT, CPR and fibrinogen, 800 eosinophils in peripheral blood. Sputum eosinophils 40 to 60%.Chest X-Ray objective a thickened left hilum and doubtful left parahilar infiltrated.

Results: Allergologic study—Skin prick test with aeroallergens and wide food battery were negative. Specific IgE against Anisakis, latex, Echinococcus and other blood parameters including serology, autologous patient serum skin test were all normal/negative. Tryptase determination at baseline and during skin lesion shoot: normal. Other explorations—ECO-cardio: inferior basal akinesia and inferoposterior hypokinesia, LVEF 60%, normal RV systolic function and valves. CT scan visualize mediastinal and abdominal adenopathy, splenomegalia and ureterolithiasis. Mediastinoscopy and biopsy of right paratracheal grainy adenopathy confirms the diagnosis of sarcoidosis. ACE: 250 U/L. Gallium67 scan suggestive mediastinal sarcoidosis. Heart RM scan: no evidence of morphological criteria for cardiac sarcoidosis diagnosis.

Conclusions: Sarcoidosis is a multisystem granulomatous disease of unknown etiology. It may affect almost any organ, predominantly lung, lymph nodes and skin. Cardiac involvement is 25% but only symptomatic in 5%. We report a patient with sarcoidosis and vasoespastic angina. Itś described cases of cardiac sarcoidosis and vasospastic angina. In this case we cannot demonstrate cardiac injury. Sarcoidosis is a great simulating of cutaneous lesions and it can imitate to urticaria.

URTICARIA TREATMENT

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Application of Intravenous Immunoglobulin for Treatment of Chronic Autoimmune Urticaria

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Background: To develop a patogenetically justified method for treatment of the autoimmune form of chronic urticaria.

Methods: 14 patients with autoimmune urticaria (18–60 y-o., time since disease onset ranging from 6 weeks to 5 years), having positive autoserum test results (7 mm or more in 11 patients, 4.5–6.5 mm in 3 patients) were treated with intravenous immunoglobulin for 4 days (50 mL of 5% immunoglobulin solution per day). Intravenous immunoglobulin of a fourth generation, containing 99.1 to 99.2% monomeric IgG, was applied.

Results: The treatment resulted in the rashes regressing in 13 (93%) patients after 3 to 4 days of treatment. All of the patients showed reduced autoserum test results (one of them was absolutely negative) 6 months after the end of treatment. Our investigations have shown a complete absence of clinical manifestations of urticaria within 1 year.

Conclusions: Intravenous immunoglobulin, containing only monomeric IgG, has proven highly efficient in treatment of chronic autoimmune urticaria. The above-mentioned reduced autoserum test results suggest fourth-generation intravenous immunoglobulin's contribution to the pathogenesis of the disease.

X-LINKED AND COMMON VARIABLE IMMUNODEFICIENCY

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Long Term Follow-up of Patients with Common Variable Immunodeficiency (Cvid) in Rio De Janeiro, Brazil: Clinical Phenotypes and Prognosis

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Background: CVID comprises a variety of clinical phenotypes that may influence the prognosis of the disease. Our goal was to investigate the clinical phenotypes and prognosis of a series of patients with CVID.

Methods: We evaluated 11 patients with CVID, according to the PAGID criteria in long-term clinical follow-up (> 10 years). Most patients were on regular use of intravenous immunoglobulin (IVIg), provided free of charge by the government. Clinical evaluation was performed monthly and exams every 6 months to 1 year, including immunological evaluation, hematologic, biochemical, autoimmune, stool, urine analysis, chest CT, abdominal ultrasound and specific investigations of infectious diseases and malignancies, when needed.

Results: The average follow-up was 21.9 years (12–34). Among the 11 patients, the mean current age was 39.8 years (16 to 62), 73% were female and 82% white. The age at symptoms onset ranged from 4 to 31 years (mean = 18) and diagnosis occurred between ages 11 and 47 (mean = 28). Most patients (55%) had the phenotype of infectious complications only, 27% had infections and immune thrombocytopenic purpura and 18% had infections and solid neoplasias. The most common infections were recurrent sinusitis (100%), pneumonia (82%), giardiasis (36%) and tuberculosis (18%). None of the patients developed lymphoproliferative and / or inflammatory complications. With regard to immunological changes, we observed that 4 patients (36%) experienced an increase in CD8 T lymphocytes and inversion of CD4/CD8 ratio. Adherence to the use of IVIg was good in 50% of patients, fair in 38% and unsatisfactory in 12%. All patients have good quality of life, performing their routine activities of study, work and leisure.

Conclusions: In the population studied, the most frequent phenotypes were infectious complications or infectious complications + autoimmunity. Tuberculosis can be an important infectious complication in patients with CVID in endemic areas. The delay in the diagnosis of CVID, around 10 years, indicates the need to improve the diagnosis of PID in our country. With proper clinical management and good adherence to the use of IVIg, patients with CVID in developing countries may have survival and quality of life similar to those described in developed countries.

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Quality of Life in Patients with Common Variable Immunodeficiency in the Department of Allergy and Clinical Immunology—Centro Medico Nacional Siglo XXI

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Background: Common variable Immunodeficiency (CVIDs) is characterized by a deficiency in antibody production and also generates enormous morbidity of school absenteeism and dropout or cause layoffs. All chronic diseases affect quality of life of patients, in this particular case CVIDs. The use of instruments like the SF - 36 provides information about the patients' perception of their disease and its environment. The objective is to determine the quality of life of adult patients with CVID who receive replacement therapy through the use of SF-36.

Methods: We conducted a cross-sectional cohort study, which included all patients diagnosed with CVID in our hospital with approval from local research committee F-2011-3601-21. We analyzed the results with descriptive statistics and the SF-36 was used the method of Rand Group.

Results: Involving 11 patients with CVID, 4 men and 7 women, average age 30 years (18–53) years. The results show a reduction in quality of life of 65%, without gender difference. However in general we see that men are more affected the physical role 31% and women in the general health 40%, In menthal health assesment, we found that in both genders is more affected in Vitality 55%, and Role Emotional least 84.72%. In relation to physical health, both genders showed greater involvement in aspects of general health 45% and less area affected is physical function 68 %.

Conclusions: CVID patients show a significant deterioration in their quality of life. It's important to highlight that there are not statistically different variations in quality of life. But the general perception of gender does vary without establishing differences between mental and physical health.

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Prevalence of Common Variable Immunodeficiency in Adult Patients Specialty Hospital—Centro Medico Nacional Siglo XXI - Mss—Mexico City

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Background: Common Variable Immunodeficiency (CVID) is the most common primary immunodeficiency (IDP), occurs primarily in adults between the second to fourth decades of life, without gender predominance. It is characterized by concentrations of immunoglobulins (Igs) of at least 2

standard deviation (DS) of normal, recurring infections, some patients have autoimmune diseases and tumors, absence of isohemagglutinins and lack of production of antibodies (Ab) after vaccination and have excluded other causes of hypogammaglobulinemia.

Objective: Determine the prevalence of CVID in the Specialty Hospital—Centro Medico Nacional Siglo XXI, IMSS, Mexico City.

Methods: We included all patients with suspected diagnosis of CVID, clinical history, laboratory tests, determination of serum Igs and isohemagglutinins and were given a dose of gamma globulin 500 mg/kg/dose every 21 days. The results were analyzed with descriptive statistics. The protocol was approved by the local research committee.

Results: A total of 15 patients, 11 women and 4 men, mean age 34 years (± 11), 14 patients met all international standards and just only one patient has positive isohemagglutinins. The prevalence of CVID calculated according to the total population that is entitled in this hospital, 1, 520, 900, 1: 101, 393. In relation to the number of patients served by our service, the prevalence of 0.053% with a ratio of 1:2.533 right holders.

Conclusions: Our results show differences in relation to the published literature, prevalence in female sex ratio of 3:1, participating patients were diagnosed at the 34 years of average age, just only 2 patients were diagnosed before 20 years of age, unlike some of the international and national reports, we establish the definitive diagnosis according to international standards in 93% of cases evaluated. The prevalence of CVID obtained in our study is 1:101.393, higher than reported in international literature is 1:30.000 to 1:50.000, but similar to that reported in Spain in 1997 and Iran in 2006.

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Infections in 14 Patients with Common Variable Immunodeficiency, Retrospective Study

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Background: Common variable immunodeficiency is a heterogeneous syndrome of primary antibody production failure. It affects 1 in 10000 to 50000 individuals, and is the most frequent primary immunodeficiency producing relevant clinical symptoms in adults and children. The hallmark of this disease is recurrent bacterial infections, usually of the respiratory and gastrointestinal tract. Onset is mainly in children aged 1 to 5 years, adolescents aged 16 to 20 years, and adults (fifth decade).[1]

Methods: We assessed retrospectively recurrent infections in 14 patients with definitive diagnosis of CVID, for a period of 2 months through the review of their medical records.

Results: Ten patients were female (71.4%) and 4 were male (28.5%). The average age was 34 years. The average age of diagnosis of CVID was 27.5 years with an age range from 6 to 60 years. In 9 patients (64%) of the total studied CVID diagnosis was made in adulthood. All patients had a history of respiratory infection process in the following distribution: in 9 patients (64%) found a history of bronchiectasis, in 8 patients (57%) was found rhinosinusitis, and pneumonia; in 5 patients (35%) recurrent or chronic otitis media and one patient was a history of pulmonary tuberculosis. The lower urinary tract infection was found in 11 patients (78%), chronic diarrhea in 5 patients (35%), osteomyelitis in 1 patient.

Conclusions: Recurrent infections of the respiratory tract specifically low and high and / or gastrointestinal infections should lead to systematic evaluation in which the primary immunodeficiencies are included as CVID.

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Autoimmune Thrombocytopenic Purpura Associated with Common Variable Immunodeficiency

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Background: Common variable immunodeficiency (CVID) is a condition characterized by antibody deficiency, and therefore susceptible to recurrent pyogenic infections, cancer and autoimmune diseases. It is a heterogeneous syndrome in primary immunodeficiencies and clinically the most important is often diagnosed in adulthood. Autoimmunity occurs in 5% of the general population, in patients with CVID the percentage increased to 20 to 48%, cytopenias being the most common cause of autoimmunity in these patients. Autoimmune thrombocytopenic purpura and autoimmune hemolytic anemia are the most common autoimmune consequences, occurring in 5% to 8% of all patients with CVID. Some patients develop these disorders before the diagnosis of CVID.

Methods: We present the case of a woman of 45 year old, with a history of lower respiratory tract and urinary tract infections in recurrent Pulmonary Tuberculosis. Enter the program short-course treatment strictly supervised for pulmonary tuberculosis with appropriate response. Autoinmune thrombocytopenic purpura refractory to steroids (WWTP) for performing splenectomy.

Results: Anti DNA antibodies, anti nuclear, anti-protease, C. ANCA/PR3 antimieloperoxidasa, serology for hepatitis B, C, HIV negative. Serum immunoglobulins were as follow: IgG, 158 mg/dL (normal 700 to 1600), IgM, 55 mg/dL (normal 40–230), IgA, 36 mg/dL (normal 70–400), and, IgE, 38.7 IU/mL (normal 0–100) in more than 2 occasions with values below 2 standard deviations. CD4 T lymphocytes (19%) CD4/CD8 ratio (0.54).

Conclusions: Meets diagnostic criteria for Common Variable Immunodeficiency (CVID) and starting treatment with intravenous immunoglobulin at a dose of 400 mg/kg (every 21 days) with significant clinical improvement and has even managed to integrate into your daily activities. Today, he continues with danazol for WWTP. Therefore, CVID is necessary to consider in the differential diagnosis of autoimmune thrombocytopenic purpura and autoimmune hemolytic anemia in adults (1).

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Cvid: A Common but Still Underdiagnosed Disease

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Background: Among the more than 150 different forms of Primary Immunodeficiency Diseases (PID) the CVID is the most common symptomatic primary immunodeficiency, present mainly in adults. There is a failure of B cells to develop and differentiate into plasma cells; at consequent a reduction of the production of one or more isotypes of antibody can also affected Cell-mediated immunity. Common manifestations included recurrent bacterial infections, that typically involve the upper and lower respiratory tract. Some patients are highly prone to autoimmune manifestations, lymphoid hyperplasia, and tumors.

Methods: We presented 3 cases of CVID with a variety of clinical presentation, evolution and complications related to delayed diagnosis.

Results: A 34 year old male presented chronic diarrhea, weight loss, malnutrition and recurrent upper respiratory infections; digestive tract endoscopy and biopsy was reported with villous atrophy, chronic inflammation and low grade non-Hodgkin's lymphoma B cell. Unfortunately this patient refused the use of gamma globulin treatment, had a high morbidity, and finally the patient died. The case of a nurse with clinical manifestation of recurrent rinosinusitis and pneumonia, which was diagnosed as IDCV 17 years later, after she developed pulmonary bronchiectasis. Fortunately the disease is under control and she is actually under treatment with intravenous immunoglobulin. Finally, the case of a 44 year old female, who suffered from recurrent upper respiratory infections, additionally had a thyroid gland tumor associated which affecting the thyroid function.

Conclusions: In the 3 cases had low levels of all immunoglobulin as a hallmark. The clinician must be suspecting this condition in all adults with recurrent infectious disease who have gastrointestinal symptoms or who are detected a malignant disease. Early diagnosis and correct treatment are critical in preventing tissue damage, long-term sequelae and death. Replacement with intravenous gamma globulin and antibiotics are the mainstays in the management of these patients.

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Infections in Patients Diagnosed with Common Variable Immunodeficiency

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Background: Common variable immunodeficiency (CVID) is the most frequent clinically manifested primary immunodeficiency. It is characterized by recurrent infections due to defective immunoglobulin production. We aimed to evaluate the infectious diseases of 7 patients as premising symptoms for diagnosis of CVID.

Methods: All patients had a marked decrease in IgG levels (at least 2 SD below the mean values for their age), a marked decrease in at least one of the isotypes of IgM or IgA, a diagnosis of immunodeficiency at age >2 years, and no other cause of hypogammaglobulinemia.[1]

Results: Seven patients who were diagnosed with CVID are investigated for immunodeficiency reasons based on their recurrent infections. Diagnosis of CVID was made at a median patient age of 28 years (range: 16–72 years); of the patients, 6 (86%) were male. All patients were presented with recurrent upper respiratory tract infections (URTI). Additionally, infected bronchiectasis and chronic diarrhea were noted respectively in 3 patients (42.9%), and 2 patients (28.6%); 1 patient (12.3%) had pericarditis. None of them had malignancy.

Conclusions: URTI, pneumonia, and diarrhea are the most frequent initial complications of CVID. CVID often remains misdiagnosed for several years. Unusual length, recurrence, or severity of these infections or pneumonia should suggest the possibility of immunodeficiency and justify appropriate evaluation.

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Phenotypic and Functional Analysis of B Cells in Patients with Common Variable Immunodeficiency

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Background: Common variable immunodeficiency (CVID) is a primary antibody deficiency characterized by a decrease in antibody production and low or normal B cell numbers. To elucidate the clinical and immunological heterogeneity of this condition, we studied 13 patients diagnosed with CVID, examined the status of B-cell maturation in patients with CVID by analyzing IgD/CD27 expression, and we analyze the in vitro B cell differentiation to plasma cells.

Methods: T, B and NK cell populations was analyzed by flow citometry, expression of CD27 marker was determined to define B cell subsets; we also assessed molecules important for B cell proliferation and differentiation, such as TNFRSF13B (TACI), inducible costimulator (ICOS), CD154, CD20, ICOSL and BAFFR. For B cell differentiation assays, total PBMCs were cultured with CpG alone, or with SAC Cowan, Pokweed and CpG; flow cytometric analysis of plasmablast generation was perfomed after 7 days of culture.

Results: Reduced numbers of T and B cells was observed in CVID patients, this reduction was more prominent in adults than in children. One group of 8 patients showed a significant reduction in IgD+CD27+ memory B cells while 3 patients had similar percentage than the healthy control group. The IgD-CD27+ memory B cell population was low in 10 patients (<12%); while it was similar to the healthy control group in 2 of the patients. BAFFR expression in B cells was reduced in 4 patients. Finally, the differentiation to plasmablasts was reduced in patients, stimulation with CpG induced 18.5% of plasmablasts (SD = 12.5%) whereas it was 24% (SD = 8.3%) in healthy controls.

Conclusions: These results suggest that a combined defect in T and B cells may account for CVID, at least in some patients. On the other hand, the complete analysis of markers important for B proliferation and differentiation such as ICOS, CD40, CD154 and TACI can be a useful tool for understanding this heterogeneous disease. B cells from CVID patients fail to progress to IgD-CD27+ memory B cells and plasmablasts. Based on these facts, we hypothesize that one or more crucial signaling molecules is required to induce terminal differentiation into memory B cells, if defective, may cause CVID.

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X-linked Agammaglobulinemia: Report of 4 Cases of Mexican Patients at Civil Hospital of Guadalajara Dr Juan I. Menchaca

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Background: The X-linked agammaglobulinemia is a primary immunodeficiency featured by hypogammaglobulinemia, recurrent infections and low levels of circulating B Lymphocytes, caused by a mutation of the tyrosine kinase of Bruton (Btk). The aim of this work is to present clinical and laboratory evidence of 4 patients with high suspect to bear a Bruton's agammaglobulinemia.
Methods: We review medical records of 4 patients bearing a humoral immunodeficiency probably Bruton's agammaglobulinemia.
Results: Patient 1: 20 years old with IgG of 197 mg/dL, IgM 14.6 mg/dL, IgA 10 mg/dL, IgE 0 UI/mL and B cells 0.02%. He has a brother with hypogammaglobulinemia, 2 maternal uncles died with history of recurrent infections. Patient 2: 13 years old, with IgG 33.3 mg/dL, IgM 6.07 mg/dL, IgA 6.07 mg/dL, IgE 0.5 UI/mL and B cells 0.03%. Six maternal uncles and 2 aunts have died at early age. Patient 3: 6 years old, IgG, IgM, IgA and IgE not detectable and B cells 0.4%. One brother died as newborn. Patient 4: 6 years old, with IgG 33 mg/dL, IgM 98.7 mg/dL, IgA 6.67 mg/dL and B cells 2%. The IgM maintained elevated until the age of 4 years old, afterwards was undetectable. He had 2 maternal uncles that had died at early age. All of our patients have presented infections before 6 months of age such as otitis, pansinusitis, septic arthritis, mastoiditis, pneumonia. Two of them with pleural efusion and patient 4 with bronchiectasis and atelectasis.
Conclusions: Because of the clinical findings of our 4 patients, immunoglobulin levels, the low percentage of B cells, the early death of family members and all of them arer males, we consider that the molecular defect in our patients could be at Btk gene and the diagnosis most probable would be Bruton's agammaglobulinemia.

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Case Report: Hypogammaglobulinemia Induced by Oxcarbazepine

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Background: Case report: A 6 year old girl with history of motor learning disability of unknown cause in treatment with Oxcarbazepine since December 2008 for epilepsy.
Conclusions: No previous infection history, on July 2009 presents a septic shock secondary to *Haemophilus influenzae* pneumonia. During hospitalization blood exams reveal; low IgG (356 mg/dL) with normal IgA/IgM levels. T cell populations in normal range LTCD3: 74.9% (2476 cells/mm^3), LTCD4: 47% (1562 cells/mm^3), LTCD8: 28% (930 cells/mm^3), CD56: 22.9% (758 cells/mm^3) and B cell number frankly diminished CD19:1.1% (38 cells/mm^3 (normal values range 200–1600 cells/mm^3)). IVIG treatment was indicated. The diagnosis of common variable immunodeficiency (CVID) induced by Oxcarbazepine was proposed. According to literature reports this cases should be controlled by immunoglobulin monthly quantification, and they recover between 3 and 9 months after drug suspension. After IGIV therapy immunoglobulin quantification show: IgG 1041 mg/dL, IgA 78 mg/dL, IgM 103 mg/dL, with frankly IgG elevation. A second control after 2 months IGIV infusion shows IgG 834 mg/dL, IgA 54 mg/dL, IgM 75 mg/dL. The patient remains in good health with no infections after drug suspension. Her IgG levels and B cell (CD19) number returned to normal after 3 months (10.7% (271 cells/mm^3)). Posterior IgG controls are in normal range which shows a resolution of hypogammaglobulinemia.

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X- Linked Agammaglobulinemia and Moebius Syndrome, First Case Reported

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Background: To know the association between X-linked Agammaglobulinemia and Moebius Syndrome. The X-linked Agammaglobulinemia or Bruton disease, is characterized by the absence of B cells and decreased serum immunoglobulin. The defective gen codes a tyrosincinasa protein: Btk. Moebius Syndrome is a congenital facial palsy with impairment of ocular abduction, by a craniofacial dysmorphism and limb-abnormalities.
Methods: Review Medical Records in a patient with Diagnosis of Bruton Disease and Moebius Syndrome and review of cases in the literature. Case: Male patient, 15 years of age, a first borne from a normally evolved pregnancy, and no consanguinity data. There were some craniofacial dysmorphic features observed; severe lagofthalmus, lack of palpable lymph nodes and tonsils, difficulty swallowing, facial palsy, syndactyly, talipes equinovarus. Diagnosis is established as Moebius Syndrome by the department of genetics. Relatives have presented similar problems: 2 aunts and 2 uncles related to his mother had died prior to the first year of life with no specified cause. Almost since he became 3 years of age, has shown symptoms of rhinosinusitis, pneumonia, osteomyelitis in right knee caused by several pathogens as S. *aureus* and *H. Influenzae*, lack of weight and length, and multiple stays at the hospital. Serum IgG was 37.3 mg/dL, IgA $<$ 23 mg/dL, IgM $<$ 17.9 mg/dL, IgE $<$ 14.2 IU/mL. The total lymphocytes (cells/Microliter) were 3203; T lymphocytes 80%, CD8 44%, CD4 34%, ratio CD4/CD8 0.78, CD56 8%, CD19 0 %, CD20 2%, CD22 2%. Treatment begins with intravenous gammaglobulin in replacement dosage.
Results: According to review the literature and data base, Mendelian Inheritance in Man, from the Johns Hopkins University, there is not known association between Bruton Disease and Moebius Syndrome. However, we consider important to report the coexistence of these diseases in one single patient. The karyotype should be studies in order to determine in a more objective way the probable link between both.
Conclusions: Since there are not previous reports of the association between X-linked Agammaglobulinemia and Moebius Syndrome this might set the precedent for a better knowledge and its implications to the future.