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Poster Session Group III – Green

TPS 53 – Air pollution and moulds still as risk factors

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Immunological effects of ship diesel emissions in on-line exposed human bronchial epithelial cells

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Background: Ship diesel emissions contribute substantially to adverse health effects, especially in coastal regions and ports. Most of these effects are connected to inflammation. In this study composition and immunological effects of emissions from a ship diesel engine running either on modern diesel fuel (DF) or heavy fuel oil (HFO) were characterised.

Method: Human bronchial epithelial cells (BEAS-2B) were exposed in an air-liquid-interface exposure system to diluted HFO- and DF-emissions that were generated by a research ship engine. Whole-genome transcription analysis was performed using microarray technology. Simultanously, the composition of the emissions was comprehensively analysed.

Results: HFO-emissions contained more particles, metals like Vanadium, Nickel and Zinc and organic chemicals, whereas elemental carbon (soot) dominated DF-emissions. Monitoring of the cellular response revealed reactions especially in inflammatory, oxidative stress and protein synthesis pathways. Inflammation included TNFalpha-, IL-1-, IL-6, and TSLP-signaling and was associated with oxidative stress. It was stronger induced in HFO-treated cells. In contrast, DF evoked on whole-genome level a broader response, that included more general cellular processes like RNA and protein metabolism and that is probably caused by higher concentrations of elemental carbon in DF.

Conclusion: In conclusion, HFO- and DF-usage in shipping both caused harmful health effects that might influence immunological disorders. The currently promoted switching from HFO to DF without also eliminating elemental carbon-emissions may be not sufficient from a public-health perspective.

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Analysis of changes in airborne pollutant levels in response to nocturnal temperature controlled laminar airflow treatment

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Background: Black carbon (BC) and other particulate matter (PM) especially those <0.1 μm in size (nanoparticles), are the main drivers of pollution-related cardiorespiratory illness. Recent studies have shown that nocturnal temperature controlled laminar airflow (TLA) reduces inhalant PM exposure in a simulated environment. To assess the effect of TLA on inhalant PM exposure in the home, we evaluated indoor airborne BC and nanoparticle exposure, before and after a week of nocturnal TLA treatment. A second aim was to assess whether any reduction in nocturnal BC exposure, translated into a meaningful reduction in total BC exposure over 24 h.

Method: TLA devices (Airsonett) were installed for 1 week in the bedrooms of six volunteers living in polluted areas of London, UK. A personal MicroAethalometer AE51 real time sensor was used to measure BC exposure by mass, and a P-Trak 8525 sensor for nanoparticle exposure by number. Measurements were taken prior to and on the 7th day of TLA treatment.

Results: Nanoparticle counts fell significantly post-TLA use (median nocturnal nanoparticle count pre-TLA 6158 pt/cc, IQR 3065.3–8729.3; post-TLA 5 pt/cc, IQR 1–190.5, $P < 0.001$) with a 99% median reduction. Nocturnal BC exposure also fell significantly [mean (SD) pre-TLA 0.69 (0.84) μg/m^3; post-TLA BC 0.30 (0.60) μg/m^3, $P < 0.001$]. Total BC exposure over 24 h did not change significantly [pre-TLA 1.55 (7.92) μg/m^3; post-TLA 1.18 (5.63) μg/m^3, $P = 0.15$].

Conclusion: These results suggest that nocturnal TLA is unlikely to impact significantly on total 24 h BC exposure, but the implications of the profound effect on nocturnal nanoparticle exposure merit further investigation.

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Traffic-related air pollution is associated with allergic diseases in children

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Background: The relationship between air pollution and allergic diseases in children is not yet fully understood, with epidemiological data being a matter of debate. The aim of this study was to investigate the association between outdoor air pollution and current symptoms of allergic diseases in children.

Method: A nationwide cross-sectional survey was conducted in the first grade students from randomly selected 45 elementary schools. Prevalence of allergic diseases and information on various risk factors was obtained through the Korean version of International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire. All the children were examined by a pediatrician to determine the presence of eczema in their neck and flexural areas of both arms. Daily ambient concentrations of sulfur dioxide (SO_2), nitrogen dioxides (NO_2), ozone (O_3), carbon monoxide (CO), and particulate matter with an aerodynamic diameter of 10 μm or less (PM_{10}) were monitored from 235 monitoring sites throughout the nation. In this study, children who lived within 2 km from the nearest monitoring sites were selected and analyzed.

Results: Exposure to air pollutants was not related to the presence of symptom of atopic dermatitis (AD), allergic rhinitis (AR), or asthma within the last 12 months. The adjusted odds ratio (aOR) per increase of 10 ppb in 1 year average NO_2 was 1.278 for the presence of eczema on the day of survey (95% CI 1.049–1.556). For each increase of 0.1 ppm in 1 year mean CO, the aOR for the treatment for AR and asthma increased by 1.107 (95% CI 1.014–1.210) and 1.269 (95% CI 1.027–1.568), respectively.
Conclusion: Traffic-related air pollution such as NO_2 and CO is associated with current symptoms of AD, AR, or asthma in children.

1242
Effects of formaldehyde on allergic inflammation in ovalbumin-immunised mouse model

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Background: Formaldehyde (FA) is a common indoor air pollutant that has been implicated as a common cause of sick house syndrome and inducement of asthmatic symptoms. The present study utilised a mouse-asthma model to determine how FA affects allergic inflammation.
Method: BALB/c mice into five groups: Group 1, control; Group 2, ovalbumin (OVA)-immunised only; Group 3, OVA-immunised + 0.1% FA-inhalated; Group 4, OVA-immunised + 0.5% FA-inhalated; Group 5, 0.1% FA-instillated/inhalated. All of the groups were measured for Penh (enhanced pause) following a methacholin challenge. The total cells, eosinophils, and cytokines in bronchoalveolar lavage fluid (BALF) along with the mRNA and histological staining in lung tissue were measured.
Results: Penh level in groups 2–5 increased significantly compared with group 1 ($P < 0.001$). Group 5 also showed a significant Penh-level increase from 0 mg/ml ($P < 0.001$). In BALF, group 1 was the lowest in IL-4, IL-5 and IL-13, whereas groups 2, 3, and 4 increased steadily. Group 1 showed the highest concentration of IFN-γ, which was significantly lower in groups 2, 3, and 4. The IL-17 concentration was not consistent. The change in the level of real-time PCR mRNA in lung tissue was similar to that of the cytokines. IL-4 and IL-5 mRNA increased statistically ($P < 0.001$). However IL-10 mRNA ($P = 0.436$) showed no difference, and groups 2, 3, 4 and 5 showed significantly low levels of TGF-β mRNA compared with group 1 ($P < 0.001$).
Conclusion: It is possible to speculate that chemicals like FA can result in eosinophilia with the consequent airway inflammation and production of various inflammatory mediated factors. However, although the actual induction mechanism for immunoglobuline E increase remains unknown. It is possible that FA produces hapten that activates $CD4^+$ T cells. Further study to determine why the total IgE concentration increases is required.

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Air-pollution and respiratory sympthoms in children

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Background: Studies of school environment and related health diseases in pediatric population have been performed recently. The European Commission, through the Directorate General for Health and Consumer Affairs, funded the study on Health Effects of School Environment held in different European countries. Levels of air pollutants can be several folds higher exposures are prolonged. Since children spend a large part of the day in school environment, nationwide initiatives to evaluate such indoor air quality (IAQ) were developed.
Methods: The study protocol includes: one standardised questionnaire on school characteristics and IAQ policy completed by teachers, two standardised questionnaire derived from the International Study of Asthma and Allergy in Childhood questionnaire on characteristics of children one filled in by the pupils and the other by their parents, school environment assessments and non invasive clinical tests.
Results: Previous studies revealed that pupils exposed to an elevated level of indoor PM_{10} and CO_2 showed higher prevalence of all respiratory disorders than those exposed to lower level, significantly so for dry cough and as regards CO_2, also for rhinitis. The prevalence of dry cough significantly ($P = 0.001$) decreased with decreasing mean indoor levels of PM_{10} and CO_2.

1244
Is the sensitisation to *Alternaria alternata* manganese-dependent superoxide dismutase a risk factor for ABPA?

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Background: Allergic bronchopulmonary aspergillosis (ABPA) is a serious disease that may lead to pulmonary fibrosis and irreversible changes in lung function and was recently associated with a prior or concomitant sensitisation to *Alternaria* species. The sensitisation to a manganese-dependent superoxide dismutase (MnSOD) isolated from the pathogenic mould *Aspergillus fumigatus*, known as Asp f 6, is accepted as a specific marker for ABPA. In one of our previous studies on *Alternaria alternata* an IgE-reacting protein, homologue to Asp f 6, was identified. The aims of this study were to characterise the *A. alternata* MnSOD (Alt a MnSOD), to analyse its cross-reactivity with Asp f 6 and to evaluate its reactivity with IgE from ABPA patients sera.
Method: The complete coding region for Alt a MnSOD, was cloned by 5′ and 3′ rapid amplification of cDNA ends and PCR. The recombinant protein was produced in Escherichia coli and used in immunoblotting. Sixty-one sera from patients sensitised to *A. alternata* and two sera from patients with ABPA were used. Immunoblot inhibition experiments using *A. alternata* and *A. fumigatus* extracts were also performed.
Results: Recombinant Alt a MnSOD was expressed as a 26 kDa fusion protein. The investigation of the IgE-reactivity of Alt a MnSOD by immunoblot revealed that 7 out of 61 *A. alternata*-sensitised patients' sera (11.5%) reacted with the recombinant molecule. It was also verified that recombinant Alt a MnSOD was able to bind IgE from ABPA patient sera. The native proteins contained in the *A. alternata* and *A. fumigatus* extracts inhibited the IgE-binding to recombinant molecule.
Conclusion: Alt a MnSOD is a minor allergen of *A. alternata*. The findings that recombinant Alt a MnSOD was *in vitro* recognised by IgE antibodies from two ABPA patients and that it has cross-reactive IgE epitopes with Asp f 6, suggest that

sensitisation to Asp f 6 or to other cross-reactive fungal MnSOD should be carefully revised as a specific/risk marker for ABPA.

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Transaldolase allergen of *Fusarium proliferatum*

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Fusarium species are prevalent airborne fungi and recognised as causative agents of human atopic disorders. The purpose of this study is to identify and characterise important allergens of *F. proliferatum*. IgE-reacting *F. proliferatum* components were identified by immunoblot using serum samples from patients of respiratory atopic diseases. Characterisation of allergens and determination of IgE cross-reactivity were performed by cDNA cloning and expression and immunoblot inhibition studies. Our results showed that a 37.5 kDa IgE-binding component reacted with a goat anti-human transaldolase antiserum. The full-length cDNA of *F. proliferatum* transaldolase was cloned which contained 312 amino acid residues and showed sequence identifies of 73% and 61%, respectively, against *Cladosporium* and human transaldolase proteins. IgE-binding against the 37.5 kDa component of *F. proliferatum* could be inhibited by the purified recombinant *F. proliferatum* transaldolase protein. In addition, inhibition of IgE-binding against the transaldolase allergen from *C. cladosporioides* was detected by using the recombinant *F. proliferatum* transaldolase protein. Interestingly, IgE-binding against human transaldolase could also be inhibited by the recombinant *F. proliferatum* transaldolase in a concentration-dependent manner. In conclusion, a novel and important *F. proliferatum* transaldolase allergen was identified. In addition to IgE cross-reactivity between the *Fusarium* and the *Cladosporium* transaldolase allergens, IgE cross-reactivity between the *Fusarium* and the human counterpart transaldolase proteins was also detected which might contribute to atopic manifestations in the absence of exogenous allergen exposure.

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Basidiomycetes Coprinus and Ganoderma fungal spores in the ambient air of Vinnitsa, Ukraine

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Background: Atopic patients with respiratory allergy may react to spores from basidiomycete fungi. The most common basidiomycete spores seen in Vinnitsa air are Coprinus and Ganoderma. This study assesses the daily and seasonal patterns of Coprinus and Ganoderma spore distribution in Vinnitsa.
Method: Spore counts were obtained at Vinnitsa National Pirogov Memorial Medical University (VNMU) in 2009–2011 daily and in 2012–2013 bi-hourly using a Burkard trap at 25 m height above ground from March 1 to October 31.
Results: Ganoderma and Coprinus spores occur most in late summer and autumn typical of Basidiomycota. Two periods with intensive sporulation in early summer and in late autumn were noted for Coprinus with seasonal peaks in the second 10 days of June until the first 10 days of July except in 2012 when the peak was August 16 due to unusually warm weather. Ganoderma sporulation occurs from mid-summer to mid-September with peaks in the middle of August until the beginning of September. Spores from Coprinus during the season usually were 7–11 fold more numerous than from Ganoderma. The peaks for Coprinus ranged from 911 to 1374 while peaks for Ganoderma ranged from 136 to 204 spores per cubic meter. Daily distribution patterns showed the highest concentrations of both spore types from the 7 PM to 1 AM with reduction at mid-day, and highest concentrations at 9 PM.
Conclusion: Intensive sporulation in early summer and late autumn was noted for Coprinus while Ganoderma has most abundant sporulation from mid-summer to the mid-September. Coprinus has more intense sporulation with higher peaks with fungi spores both peaking from 7 PM to 1 AM daily. This data may assist in allergen avoidance for mold sensitised patients in Ukraine.

1248
Validation of an in house-developed ELISA for the quantification of Alt a 1

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Background: Alt a 1 is the major allergen in *Alternaria alternata*, one of the most important fungi associated with allergic diseases. Mold allergenic extracts show considerable heterogeneity, and thus accurate standardisation of these extracts using validated assays according to the EMA Guideline on Allergen Products is essential to guarantee their quality. The aim of this study is to validate a specific assay to quantify Alt a 1.
Method: The developed ELISA was based on a monoclonal antibody (1D6) used as capture and a biotin-labelled specific rabbit polyclonal anti-serum for detection. The studied analyte was the *A. alternata* IHRP using Alt a 1 purified from spent culture medium as standard. The studied parameters were repeatability, intermediate precision, accuracy, and limit of quantification. Alt a 1 content was also determined in six extracts to prove batch-to-batch consistency.
Results: The dose-response curves obtained with Alt a 1 revealed a sigmoid shape when plotted on a semi-logarithmic scale and was parallel to those obtained with the extracts. The analysis of repeatability gave a CV = 3.0% while in the intermediate precision analysis, none of the analyzed factors (analysts, antigen purified batches, monoclonal antibody and polyclonal antibodies) had a statistically significant effect on the outcome of the assay, with a confidence level of 95%. The assay fulfilled the requirement of accuracy after applying Student's *t*-test to the recovery results (t_{exp} = 2.550). The limit of quantification of the *A. alternata* extract was 177 ng/ml and complied with the requirements of precision (CV = 17.1%) and accuracy (relative error = 1.0%). Alt a 1 content among six batches of *Alternaria* extracts had a CV of 15%, proving the consistency of the manufacturing.
Conclusion: The validated Alt a 1 ELISA system provides consistent and repetitive results evaluating this major allergen in mass units and complements the biological standardisation of different manufacturing batches.

1249
Influences of environmental triggers and lifestyle on the development of allergic sensitisations

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Background: The number of patients suffering from allergic diseases has been increasing in the last decades, especially in industrialized countries. However, the underlying reasons for this development still remain unclear. The aim of this study is to investigate the influences of environmental triggers and lifestyle on the development of an allergic sensitisation.
Methods: The study was conducted within a randomized cohort of 450 Austrian pupils aged 13–19 years. Schools in different geographical regions were involved, enrolling subjects from rural, urban and alpine areas. Living conditions were surveyed with a detailed questionnaire. Demographic data, self-reported health status including allergies, and other lifestyle conditions (diet, sports, alcohol consumption and smoking) were requested from all participants. In addition, blood samples were collected from each subject and analyzed for IgE sensitisation using the ImmunoCAP ISAC system.
Results: The influence of the geographical region is evaluated regarding general health condition and the development of allergies. Clinically confirmed allergies were declared by 23% of the subjects. Fourty-two percent stated to suffer from any allergy including self-reported adverse reactions. IgE reactivity to 112 different purified allergens is categorized according to allergen sources and number of sensitisations and statistically correlated with data obtained from surveyed living conditions.
Conclusion: The study investigated both, allergic and non-allergic subjects of young age. Therefore, the comparison allowed the determination of positive and negative influence parameters for the development of an allergic sensitisation.

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Characterisation of mite allergens for house dust mite allergy therapy – specific IgE antibody reactivities to group 1 and group 2 allergens

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Introduction: The aim of this study was to investigate whether concurrent IgE reactivities to group 1 and group 2 allergens of *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* are based on cross reactivity or arises from independent sensitisation.
Methods: In total, 381 serum samples were tested for specific IgE to extracts of *D. pteronyssinus*, *D. farinae*, recombinant group 1 allergens rDer p 1.0105 S54G and rDer f 1.0107 N53W, and group 2 allergens rDer p 2.0101, rDer p 2.0114, rDer f 2.0106, rDer f 2 0108 and rDer f 2.0103. The IgE antibody levels were measured using extract-coated paper disks, purchased from Omega Diagnostics (Reinbek, Germany). Paper disks coated with Der p 1, Der f 1, Der p 2 or Der f 2 isoallergens were prepared at Allergopharma.
Results: Of these 381 sera, 318 sera had specific IgE to any of the test antigens, and 304 sera had IgE to any of the two group 1 and five group 2 isoallergens tested. Of these 304 sera, 232 (76.3%) had IgE to at least one group 1 allergen, and the majority (n = 182, 78.4%) reacted to both Der p 1 and Der f 1. Exclusive reactivity to Der p 1 and Der f 1 was observed in 36 (15.5%) and 14 (6.0%) sera, respectively. All these sera with exclusive IgE reactivity to either Der p 1 or Der f 1 had low specific IgE (EAST class $\leq$3) to these allergens. Of the 304 sera with IgE to any of the two group 1 and five group 2 allergens tested, 293 (96.4%) had IgE to any of the two Der p 2 and the three Der f 2 isoforms. Of those 293 sera 290 (99.0%) reacted to any Der p 2 isoform and 292 (99.7%) reacted to any Der f 2 isoform. 284 (96.6%) of these 293 sera had similar IgE levels (=identical EAST classes) to all five group 2 isoforms of both mite species.
Conclusion: The observed similarities in IgE reactivity patterns of group 1 and group 2 isoallergens irrespective of species indicate allergen cross-reactivity rather than independent, species-specific sensitisation.

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Proteomic analysis of the house dust mite allergen Der p 23 produced in *Pichia pastoris*

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Background: Recombinant forms of house dust mite (HDM) allergens are very useful compounds not only for the component-resolved diagnosis of HDM allergy, the development of new immunotherapeutic treatment but also for the characterisation of their allergenicity. The objective of this study is the production and characterisation of the recently identified HDM allergen Der p 23 using the *Pichia pastoris* expression system.
Method: Total mRNA from *D. pteronyssinus* were extracted and retrotranscripted to amplify the cDNA encoding mature Der p 23 by PCR. The amplicon was cloned into the expression vector pPICZαA. *P. pastoris* KM71 strain was transformed with the recombinant plasmid and rDer p 23 expression was subsequently induced by methanol. The recombinant allergen was purified to homogeneity by cation-exchange and gel filtration chromatographies. Proteomic analysis of rDer p 23 was performed using MALDI-TOF MS and nanoLC-MS.
Results: Mature rDer p 23 was successfully expressed under a secreted form following induction with 2% methanol at 30°C. Optimisation of the induction time evidenced that the highest expression level was reached after 48 h whereas protein truncated forms were clearly detected for longer induction period. MS analysis of purified intact rDer p 23 showed the presence of two disulfide bridges as well as several hexose residues ranging from 8 to 16 units. By contrast, truncations of rDer p 23 occured at the N-terminus residues T_{16} and E_{18}, leading to the loss of putative O-glycosylations sites (T_9–T_{11} and T_{15}–T_{17}). The absence of sugar residues in truncated rDer p 23 suggesting that intact rDer p 23 is O-glycosylated.
Conclusion: rDer p 23 produced in *P. pastoris* could be appropriate for future characterisation of its allergenicity but also for HDM allergy diagnosis as well as future recombinant allergen-based specific immunotherapy.

Poster Session Group III – Green

TPS 54 – Allergens – pollen, mould and others

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Comparing house dust mite sensitisation in Malagasy and Italian school-age children

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Background: Previous epidemiological studies showed a low prevalence of allergies in rural areas of Africa. House dust mite (HDM) is the most common allergen all over the world, with a high prevalence of hypersensitivity among children in scholar age from urban areas of western countries. Prevalence of hypersensitivity to HDM among Malagasy children is not known. Our aims was to assess HDM hypersensitivity prevalence among Malagasy children and to compare it with data from the same age group in Italy.
Method: It was a cross-sectional study. Children aged 6–10 years from a public school of Ambanja, a town in a rural area in the north of Madagascar, and children of the same age from a primary school in Udine, North-east of Italy were included. A convenience sampling was applied.

Every child underwent skin prick test (SPT) for Dermatophaoigodes Farinae (DF) and Dermatophaoigodes Pteronissis (DP) according to current EAACI procedural recommendations. The Malagasy children with SPT positivity were interviewed about the presence of allergic symptoms. Children with SPT positivity for DP, DF or both were classified as sensitised to HDM.
Results: A total of 617 children were included, 288 Italians and 329 Malagasy. The median age was 8 years and 6/12 (Italian group: 8 years and 3/12; Malagasy group: 8 years and 8/12). The prevalence of SPT positivity for HDM among Malagasy children was 6.6% (22/331), of which 5/22 had asthma and 8/22 had allergic rhinitis. In the Italian group 19% (57/288) were sensitised to HDM.
Conclusion: It shows that hypersensitivity to HDM in school-age children living in a rural area in Sub-Saharan Africa is much less common than in children of same age from an highly industrialized urban area of a western country, confirming previous data from literature. This emphasizes the importance of environmental factors in the pathogenesis of allergic diseases.

1253
Seasonal changes of domestic mite antigen concentrations in day-care centres in comparison to homes

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Background: For humans, mites are major sources of indoor allergens which induce asthma, rhinitis, dermatitis, and other allergic diseases. It was the aim of the study to quantify seasonal allergen exposure in day-care centres and in the children's homes.
Method: In 20 day-care centres in Germany floor and other surfaces were sampled four times per year with a vacuum cleaner to collect 1364 dust samples. In addition, in the day-care centres and in parallel in the children's and day-care workers' homes electrostatic dust fall collectors (EDC) were used to collect 1220 samples (619 in day-care centres, 601 in homes). All samples were extracted and analysed with an enzyme immunoassay for domestic mite antigens. The influence of season on allergen concentrations was analysed with mixed linear models.
Results: The domestic mite antigen concentrations vary significantly during the seasons. In autumn and summer in surface samples as well as on EDC higher allergen concentrations occurred than in winter and spring. Median concentrations in surface dust were in autumn 6.3 μg/g (0.46 μg/m^2), in winter 3.3 μg/g (0.19 μg/m^2), in spring 2.2 μg/g (0.17 μg/m^2) and in summer 3.9 μg/g (0.27 μg/m^2). Domestic mite antigen concentrations on EDC were on average in day-care centres higher than in homes. In day-care centres on the EDC tissues in autumn 10 ng, in winter 5 ng, in spring 6 ng and in summer 9 ng median antigen was measured. In homes in autumn 7 ng, in winter and spring 3 ng and in summer 6 ng were detected with the domestic mite antigen assay.
Conclusion: Higher median concentrations of domestic mite antigens were found in day-care centres than in homes. Mite exposure depends on the season: in autumn and summer the concentrations were nearly twice as high as in winter and spring.

1254
Technical evaluation of an allergen challenge theatre™

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Background: Allergen challenge chambers expose allergen-sensitive subjects to a predetermined concentration of allergen in a closed, controlled environment and provide a mechanism to induce clinical symptoms and measure the effect of medication.
Method: We performed a technical evaluation of the capabilities of the Red Maple Trials Allergen Challenge Theatre™. The theatre is a 4-zone facility holding up to 99 seats in a series of elevated rows. Grass pollen (*Phleum pratense*) is injected into the air supply and blown into the facility through ducts located across the top of the front wall. We measured grass pollen concentrations on impact samplers set at face level in five sections of a T-shaped quadrant. Concentrations were measured every 30 min for 150 min. Continuous pollen counts were also read by a laser particle counter (LPC) set to read particles >5 μm and positioned 5 ft above floor level. Light bulbs were placed at seated face height on the seats to simulate the heat presence of participants.
Results: The impact sampler pollen concentration for the theatre quadrant during the entire 180-min exposure was 3992 ± 975 grains m^3. Concentrations for the quadrant were consistent at each 30 min measurement with means ranging from 3648 to 4523 and SDs from 678 to 1105. Pollen concentrations were consistent in each of the five sections of the quadrant

over time with means ranging from 3112 to 5268 and SDs ranging from 308 to 926. Pollen counts measured by LPC remained consistent at 4000/m^3 during the experiment.

Conclusion: The Red Maple Trials allergen exposure theatre demonstrated the capacity to achieve and maintain a concentration of pollen grains at a magnitude consistent with the literature and associated with the ability to induce symptoms of appropriate intensity upon allergen challenge.

The use of a LPC provided a significant advantage by monitoring pollen counts on a continuous basis. Our chamber with a seating capacity of 99 places has the ability to evaluate large test groups at a time.

1255
Are domestic rats safe pets?

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Introduction: Domestic furred animals are a known cause for respiratory allergy symptoms, especially in sensitised individuals. The search for 'exotic' pets is increasing.

Case report: We report the case of a 40-year-old man with allergic asthma since childhood, medicated with inhaled fluticasone and salmeterol, who experienced progressive deterioration of bronchial symptoms over the last 6 months, particularly aggravated at home. In this period, he developed *de novo* recurrent daily symptoms of sneezing, watery rhinorrhea and nasal obstruction. The patient had acquired, 1 year earlier, 'domestic' rats, that were kept in a cage at the garage; he was responsible for taking care of the rats. On the initial physical examination he presented nasal congestion and a slight reduction of pulmonary sounds. Skin tests with aeroallergens were negative. Pulmonary pletismography revealed severe airflow obstruction (basal FEV1 of 48%) with significant reversibility (43% increase after bronchodilation), and an increased RV (153%) with normal TLC (98%). Skin prick tests against mouse and rat epithelium extracts (BIAL – Aristegui) were negative. The dose of inhaled corticosteroid was doubled; nasal topical corticosteroid and antileukotriene were added. The patient kept the animals and he manifested a cutaneous rash on contact with the rats 3 months later. Serum specific IgE against urine extract (EAST technique) was positive (12 kU/l). Molecular masses of the IgE binding bands (SDS-PAGE immunoblotting) were the same in both extracts, rat fur and urine: 66 (possibly albumin), 40, 27, 19, 15 and 13 kDa. Those results confirmed sensitisation to rat proteins so the patient removed the animals from home and maintained the treatment. Two months later, he improved greatly and the FEV1 value rose to 78%.

Discussion: The authors feel that this is their first case of sensitisation to this most uncommon domestic pet. The reported case highlights that these, like other animals can also be a cause for allergic clinical symptoms.

1256
Effect of dust storms on patients visits to a tertiary allergy centre

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Background: Dust storms are frequently occurring environmental phenomena in the Middle East. It is thought that the health effect of such storms is more prominent on patients especially suffering from respiratory allergies. In this study, we investigate whether such dust storms result in increased patients visits in a tertiary allergy centre in the State of Kuwait.

Methods: A total of three dust storms (Dated: April 30/2008, March 10/2009, and May 14/2010) were chosen. Those were named as dust storms according to Meteorological department at Civil Aviation. The dates of those dust storms were carefully chosen outside the allergy seasons, which are carefully measured in an aerobiology laboratory in the centre. Those days were classified as index days. We selected two comparison days for each index day, 7 days before the index days and 7 days after the index days. Also, we studied the effect on patients' visits 2–3 days after the events. Finally, we compared those days with the mean patients visits during a week that was neither preceded nor followed by a dust storm.

Results: Compared to the index dates, there were total of 258, 437, and 138 patients, respectively, visited the centre 7 days before the index days. New vs Follow-up were 27 vs 231, 16 vs 421, and 22 vs 116, respectively. There were a total of 750 patients presenting to the center 7 days after the index days in comparison to 833 patients presenting 7 days prior to the storms ($P = 0.48$). There were a total of 52 new patients presenting after the storms compared to 65 presenting before the storms ($P = 0.25$). There were a total of 698 follow-up patients presenting after the storm compared to 768 presenting before the storms ($P = 0.38$). Comparing to 2–3 days after dust storms, there were total of 924 patients seen ($P = 0.38$). In addition, there were no significant differences between the two groups neither in the new (65 vs 52, $P = 0.25$) or follow-up (116 vs 218, $P = 0.38$) patients. The average patients' numbers visiting the centre during two different weeks which were neither preceded nor followed by a dust storm (July 13–18/2008, and April 11–17/2010) were 209 and 292, respectively. The total number (501) did not differ significantly compared to the dust storm days in the same years (total = 574; $P = 0.47$).

Conclusion: In an allergy tertiary health care facility, dust storms in Kuwait are not associated with increased number of patients visits, whether new or unscheduled follow-up.

1257
Pre- and postnatal exposure to parental smoking and allergic disease up to adolescence

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Background: To examine the role of pre- and postnatal second hand tobacco smoke (SHS) exposure on asthma, rhinitis, and eczema development up to 16 years of age.

Method: A birth cohort of 4089 children was followed for 16 years. Information on parental smoking habits, lifestyle factors, and symptoms of allergic disease were gathered using repeated parental questionnaires. Generalised estimating equations assessed the overall and age-specific associations between SHS exposure and allergic disease at ages 1–16 years.

Results: Exposure to SHS *in utero* was associated with an overall increased risk of developing asthma up to 16 years (OR: 1.45, 95% CI: 1.15−1.83), but not for rhinitis or eczema. After additional adjustment for parental smoking throughout childhood, excess overall risks for asthma remained statistically significant. Moreover, a dose-dependent pattern with SHS was observed. Exposure to SHS during infancy was associated with an overall increased risk of asthma (OR: 1.23; 95% CI: 1.01−1.51), rhinitis (OR: 1.18; 95% CI: 1.01−1.39) and eczema (OR: 1.26; 95%

CI: 1.09–1.45) up to 16 years. When age specific associations were examined, the increased risks related to SHS exposure *in utero* or during infancy were mostly confined to early childhood for asthma and rhinitis, while the risk of eczema appeared greatest at later ages.

Conclusion: Our findings indicate that early SHS exposure, *in utero* or during infancy, influence the development of allergic disease up to adolescence. Excess risks for asthma and rhinitis were primarily seen in early childhood while those for eczema occurred at later ages.

1258
Maternal exposure to mainstream cigarette smoke affects lung function in murine offspring

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Background: *In utero* exposure to cigarette smoke is a major risk factor for enhanced asthma susceptibility in the offspring later in life (according to epidemiological studies). To understand the mechanisms underlying this phenomenon animal models are required. Therefore, we aimed to establish a murine model of prenatal cigarette smoke exposure that matches human findings.

Methods: Female mice were exposed daily to mainstream cigarette smoke or air during pregnancy starting from embryonic day (E) 2.5 until E17.5. At E18.5 offspring were delivered by caesarean section. Lung and body weights were documented at birth and body weights were further monitored until postnatal day 20. Inspiratory capacity (IC, FlexiVent) and airway hyperresponsiveness (AHR, Buxco) were measured in 3 and 8 week old pups. All analyses were stratified for sex.

Results: Maternal weight gain during pregnancy did not differ between smoke- and air-exposed animals after correction for litter size. *In utero* smoke exposure was associated with significantly impaired weight development. This reduction was more pronounced in female pups. At 3 weeks of age, the IC was decreased in smoke exposed offspring. Further, AHR was significantly enhanced in *in utero* smoke exposed 8 week old male pups after challenge with metacholine.

Conclusions: Our model of prenatal smoke exposure is in agreement with findings in humans where maternal smoking during pregnancy is associated with small-for-the gestational age offspring and impaired lung function. Therefore, our smoke model may be suitable to study the mechanisms underlying impaired lung function development and asthma susceptibility after prenatal smoke exposure. In the future, we will study epigenetic mechanisms (histone modifications and microRNAs), as they might act as modulators of gene expressions in critical developmental time points.

1259
Relationship between indoor air pollutant levels and residential environment in children with atopic dermatitis

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Background: This study aimed to investigate the relationship between indoor air pollutant levels and residential environment in children with atopic dermatitis (AD) living in Seoul.

Method: A total of 150 children with AD were included. Residential environment was assessed by questionnaires completed by the parents. To evaluate the level of exposure to the indoor air pollutants, concentrations of the indoor air pollutants including particulate matter (PM_{10}), formaldehyde, CO_2, CO, NO_2, Total Volatile Organic Compound (TVOC), benzene, toluene, ethyl-benzene, xylene, styrene, bacterial aerosols, and airborne fungi were measured

Results: A significant difference was exhibited in the levels of PM_{10} in case of visible fungus on walls ($P = 0.047$). It had relationship with the construction year of the house, moving to a newly constructed building within 1 year and formaldehyde level. With the use of artificial air freshener, the differences were found in the concentrations of TVOC ($P = 0.003$), benzene ($P = 0.015$), toluene ($P = 0.012$) and ethylbenzene ($P = 0.027$). The concentration of xylene was significantly high when oil was used as heating fuel ($P = 0.015$). Styrene exhibited differences depending on building type and its concentrations were significantly high in a residential and commercial complex building ($P = 0.005$). The indoor concentration of bacterial aerosols was significantly low with the use of air cleaner ($P = 0.045$). High CO_2 concentrations were associated with presence of domestic pets at home ($P = 0.003$). High NO_2, benzene concentrations were present in case of almost no ventilation ($P = 0.028$ and $P = 0.028$, respectively).

Conclusion: To alleviate AD symptoms, simple questions about residential environments concerning aspects such as visible fungus on walls and the use of artificial air freshener are helpful to assess the possibility of increased indoor air pollutant levels when direct measurement is not available.

1260
Biological monitoring of nano-sized particles in the airways of asthmatic children

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Background: Exposure to air pollution triggers and exacerbates airway inflammation. Particulate material (PM) in ambient air pollution is characterised by aerodynamic diameter as being coarse (PM 10, range 2.5–10 μm), fine (PM 2.5, range 2.5–0.1 μm) and ultrafine [nano-sized particles (NSP) <0.1 μm]. Animal studies have shown that inhaled NSP produce more inflammation than larger inhaled particles. Most of our knowledge on human exposure to PM is based on environmental monitoring. Our objective was to evaluate the effect of individual exposure to NSP on respiratory symptoms, respiratory function and airway inflammation in children.

Method: Children aged 6–18 years who were referred to the Pulmonary and Allergic Diseases Department for evaluation due to respiratory symptoms were recruited. After obtaining consent, their parents responded to a questionnaire on their child's symptoms. Spirometry, bronchial provocation challenge, induced sputum, and measurement of exhaled nitric oxide were performed. Exhaled breath condensate (EBC) was collected for analysis of NSP. This was carried out using the NanoSight Light Microscope LM20 by analyzing Brownian motion of the particles.

Results: Fifty-two children were included in the study. The total EBC particle count correlated with wheezing ($R = 0.28$, $P = 0.04$), breath symptom score ($R = 0.3$, $P = 0.03$), and sputum eosinophilia ($R = 0.64$, $P = 0.005$). The percent of EBC particles that were in the nano range size also correlated with wheezing ($R = 0.36$, $P = 0.007$), breath symptom score ($R = 0.33$, $P \leq 0.02$), and sputum eosinophilia ($R = 0.72$, $P = 0.001$).

Conclusion: Nanoparticle exposure is correlated with respiratory symptoms and airway inflammation in children.

1261
Phthalate exposure and atopic dermatitis in Korea

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Background: Phthalates are widely used in our daily lives, including flooring, toys, food wrapping, plastic ware, emulsifying agent, lotion and shampoo. Exposure to phthalates has been associated with allergic disorders. We hypothesized that phthalate exposure, assessed by urinary biomarker, would be associated with atopic dermatitis in Korean children and adolescents.
Method: The nationwide representative survey on the environmental health was conducted with 1820 children and adolescents aged 6–18 years in Korea. The information of atopic dermatitis was collected by the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire. Urine monobenzyl phthalate (MBzP), mono-n-butyl phthalate (MnBP), mono-2-ethyl-5-carboxypentyl phthalate (MECPP), mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP) were measured. All phthalate metabolites were adjusted with urine creatinine.
Results: Urine MnBP, MECPP, MEOHP and MEHHP levels were higher in subjects, who were diagnosed atopic dermatitis by doctor, than others who were not (*P*-value: 0.001 in MECP, <0.001 in MnBP, 0.001 in MEOHP, 0.012 in MEHHP, respectively). Also, urine MnBP, MECPP, MEOHP and MEHHP levels were higher in subjects, who had symptoms or treatment of atopic dermatitis during last 12 months, than others, who were not (*P*-value of symptoms or treatment during last 12 months: <0.001, 0.003 in MECP; 0.003, 0.005 in MnBP; 0.002, 0.009 in MEOHP; 0.009, 0.047 in MEHHP, respectively). But urine MBzP level was not presented statistically significant association with atopic dermatitis.
Conclusion: Phthalate exposure may influence the risk of development or symptoms of atopic dermatitis.

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1262
Effect of cigarette smoking on lipopolysaccharides (LPS)-induced lung inflammation mediated by neutrophils

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Introduction: Cigarette smoke plays a significant role in the pathogenesis of pulmonary diseases. Alveolar macrophages (AM) are known to play an essential role in lung defense. It is also known that Lipopolysaccharides (LPS) induces lung inflammation. We previously reported that CS inhibited the immune functions of AM. However, it is unclear that CS affects on LPS induced lung inflammation. In this study, we investigated whether CS affects the functions of AM and LPS-induced neutrophils.
Methods: C57BL/6 female mice were exposed to CS (20 cigarettes/day) for 10 days. The next day after expose to CS, mice were inhaled 60 μg/mouse of LPS by intranasal administration (CS-LPS). LPS was inhaled to non CS exposed mice (NS-LPS) as well as CS-LPS. After 1 day, bronchoalveolar lavage (BAL) cell was obtained by BAL. Expressions of TLR4, CD14 surface antigen in BAL cells were analyzed by FACS. Reactive Oxygen Species (ROS) productions of BAL cells were measured by FACS. Cytokines and NF-κB mRNA expressions of BAL cells were assayed by RT-PCR.
Results: BAL cells counts were significantly ($P < 0.001$) increased with LPS inhalation. BAL cells counts were not increased in TLR4 deficiency mice. BAL cells counts were not significantly difference between NS-LPS and CS-LPS. The number of neutrophils was significantly ($P < 0.01$) decreased in CS-LPS, whereas the number of AM was significantly ($P < 0.01$) increased in CS-LPS compared with NS-LPS. The percentage of TLR4 positive neutrophil or AM was significantly decreased ($P < 0.05$) in CS-LPS compared with NS-LPS. Moreover, the percentage of CD14 positive neutrophil or AM was significantly ($P < 0.01$) decreased in CS-LPS compared with NS-LPS. Hydrogen peroxide production from neutrophil was significantly ($P < 0.001$) increased in CS-LPS compared with NS-LPS but not difference in superoxide production. IL-1β, TNF-α, CXCL1 and NF-κB mRNA expressions of neutrophil were not difference between NS-LPS and CS-LPS.
Conclusion: Induction of neutrophils to lung was mediated with TLR4. TLR4 and CD14 positive percents of induced neutrophil by LPS were decreased by CS. Hydrogen peroxide production from neutrophil increased by CS. However, CS did not augment lung inflammation via LPS-induced neutrophils. These results suggest that the recognition for bacteria of neutrophil is inhibited by CS. This inhibition may be resulted in increase of pulmonary infection for bacteria or virus and cause to exacerbation by infection.

1263
Quality of life and capsaicin cough sensitivity in patients with airway symptoms induced by chemicals and scents – 12 years follow up

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Background: A previous study has shown that patients suffering from airway symptoms induced by chemicals and scents had lasting airway sensitivity and symptoms together with enduring increased capsaicin cough sensitivity and impaired HRQL. The aim of the current study was to continue following the patients regarding symptoms and HRQL, and to evaluate cough reactions to inhaled capsaicin.
Method: Sixteen patients (12 women), who had previously participated in a longitudinal study (5 years) all having airway symptoms induced by chemicals and scents, were followed for about a total of 12 years (range 8–13 years) with questionnaires, measurements of HRQL, and inhalation provocation tests with capsaicin.
Results: At the last visit, patients reported more severe symptoms with dizziness compared to the first visit, otherwise there were no significantly changes in severity of symptoms. Since the first visit, seven patients were granted a retirement pension, and one patient was granted a disability pension, whereas, three patients where periodically on sick-leave because of their symptoms, alone or together with other conditions. Regarding HRQL, the patients reported significantly fewer problems with pain, mobility, and paid employment at the last visit of the study compared to the first visit. There was a significantly improvement of capsaicin cough sensitivity between the provocation at the first year and year 5, and between the provocation at the first year and year 12, but the cough sensitivity remained unchanged between

years 5 and 12. At the very last visit, nine patients had increased capsaicin cough sensitivity in comparison to earlier set limits for capsaicin sensitivity.

Conclusion: Patients with airway symptoms induced by chemicals and scents represent an entity of chronic diseases, with persistent symptoms and unchanged sensory hyperreactivity. Probably, having the possibility to avoid noxious and irritating stimuli after retirement is followed by improved HRQL.

1264
Long term effect of acaricides pre-treated home furnishings on mite allergen exposure

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Background: Global allergen reduction were efficient on asthma symptoms in children. This study is aimed to assess the efficiency of three different acaricides incorporated in different textiles at 1 and 3 years.

Method: In protocol 1: 48 rooms were sampled and categorized into four groups:

A bedding items and carpet pre-treated with Actigard®;
B no change;
C only carpet pre-treated by Actigard®;
D only mattress pre-treated by Actigard®.

In protocol 2: 60 rooms with house dust mite were sampled and categorized into four groups:

A new bedding items;
B old bedding items;
C bedding items pre-treated by Microstop®;
D bedding items pre-treated by Greenfirst®.

Der p 1 and Der f 1 were measured in dust sample of carpet and mattress at day pre-selection (D-1), D0, 3 (M3), 6 (M3), 12 (M12), 24 (M24) and 36 months (M36). Der p 1 and Der f 1 in fabric of quilts and pillows were measured at D0, M12, M24, M36.

Results: In protocol 1: at the end of the first year, Der p 1 and Der f 1 levels in mattress dust for group A and D (1.55 μg/g for A and 2.54 μg/g for D) were significantly different from group B and C (26.71 μg/g for B and 28.78 μg/g for C). Der p 1 and Der f 1 in the carpet showed group D was significantly higher than A and C. But by observing it, group D was lower than B.

In protocol 2: the levels of mite allergen remained higher at all points in group B. No difference was found between group A, C and D during the first year. At year 2 and 3, group B had a higher level of mite allergen than the three others.

Conclusion: Change of bedding items and rugs for new items, even untreated, allowed a reduction of mite allergen concentrations at first year. In addition, acaricides treated items reduced mite reinfestation compared to untreated items at 1 year but also after 3 years.

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1265
Autoimmune urticaria and angioedema masquerading as aniseed allergy

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Background: Aniseed IgE-mediated hypersensitivity was previously reported. *Pimpinella anisum* (*Apiaceae* family) allergens are Pim a 1, a Bet v 1-like protein, and Pim a 2, a Bet v 2-like profilin.

Method: We evaluated a 40-year-old female with segmental vitiligo referred to our allergy clinic due to recurrent episodes of oral angioedema associated with intake of aniseed drink. She had a history of recurrent spontaneous wheals, but no non-steroidal anti-inflammatory drug hypersensitivity. Allergy *in vivo* testing was performed to Pan-European skin prick test panel for respiratory allergens and to spices and vegetables. Autoreactivity was assessed by the autologous serum skin test (ASST). We determined the serum specific IgE for the Europe inhalation profile and for pollen-associated food cross-reactions profile. Serum levels of specific IgE to recombinant components rBet v 1 and rBet v 2 were assessed by a novel multiparameter immunoblot test system (SPAC 1). Extended diagnostic tests for chronic spontaneous urticaria were additionally performed according to the new international guidelines.

Results: Skin prick tests to birch, mugwort and ragweed pollen, to aniseed, pepper, carrot, celery were negative. Specific IgE against anise, lovage, mustard, onion, carrot, cellery, rBet v 1 and rBet v 2 were not detected (<0.35 kU/l). This vitiligo patient presented positive ASST and was diagnosed with euthyroid Hashimoto′s thyroiditis due to high antibodies against thyroid peroxidase and normal thyroid-stimulating hormone levels. Serum IgG antibodies against *H. pylori* were detected, while anti-dsDNA and C4 levels were in normal range.

Conclusion: Aniseed IgE-mediated allergy was excluded in this patient with autoimmune recurrent urticaria and angioedema using *in vivo* and *in vitro* assessement for specific IgE to aniseed and other *Apiaceae* spices and vegetables, *Betulaceae* and *Asteraceae* pollen, and specific IgE to pathogenesis-related protein PR-10 and profilin.

1266
Molecular allergology approach in a patient with corn silk (*Stigma maydis*) infusion and pollen allergy

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Background: Female corn flowers (*Zea mays*, *Poaceae* family), produce corn silk or elongated stigmas, pollen grains being captured by trichomes located along them. Corn silk (*Stigma maydis*) extract is a traditional herbal medicinal product in many parts of the world.

Methods: We evaluated IgE sensitisation pattern to suggestive pollen allergen components in a 53-year-old Romanian man with seasonal allergic rhinitis, intermittent asthma and oral allergy syndrome to hazelnuts, presenting history of generalised urticaria rapidly after consuming tea of corn silk prepared by infusion. Skin prick testing was performed according to European standards, while serum levels of specific IgE to birch and Timothy pollen and their recombinant components were assessed by a novel multiparameter immunoblot test system (SPAC 1).

Results: Skin prick tests revealed positive reactions to pollen extracts of *Betulaceae* mix, *Fraxinus excelsior*, five grasses mix and four cereals mix, while for maize kernels the prick test was negative. Values for serum specific IgE against birch and Thimothy grass pollen were high and we detected specific IgE against rBet v 1, associated to genuine sensitisation to birch pollen and oral allergy syndrome to hazelnuts due to cross-reactivity between Cor a 1.04 and Bet v 1. Specific IgE to expansin rPhl p 1 revealed true sensitisation to grass pollen, while sensitisation to profilin rPhl p12 was not detected, neither to ribonuclease rPhl p 5. It is known that group 5 allergens are lacking in maize pollen. Specific IgE against polcalcins rBet v 4 and rPhl p 7 were additionally detected, these calcium-binding proteins being likely to cross-react with Zea m 7 from corn pollen and Fra e 3 from ash pollen.

Conclusion: Hypersensitivity reactions to ceremonial oral corn pollen use in native Americans were previously described, but we report a case of corn silk infusion and pollen allergy, thermostable pollen protein allergen components being probably involved.

1267
Decreased IgE-binding capacity of fungal and pet allergens upon treatment with positive and negative cluster ions

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Background: Proteins from proallergic fungi and pet skin flakes represent important indoor allergens in addition to those from house dust mite. The most effective way for prevention of allergic symptom is to remove and/or avoid from those airborne allergens. We have previously demonstrated that a novel air cleaning system using positively- and negatively-charged cluster ions (plasma cluster ions) impairs allergenicity of Japanese cedar pollen and house dust mite allergens. In this study, we sought to test whether treatment with plasma cluster ions can also inactivate fungal and pet allergens.
Methods: Crude antigen extract from *Aspergillus fumigatus* or a cat major allergen (Fel d 1) solution was nebulized in a cylindrical container equipped with ion-generation devices, and those ion-treated allergens were collected at the bottom of the experimental cylinder. IgE-binding capacity and major allergen content of the ion-treated samples were analyzed by enzyme-linked immunosorbent assay (ELISA) inhibition and sandwich ELISA, respectively.
Results: Treatment with plasma cluster ions significantly impaired IgE-binding ability of *A. fumigatus* allergens as compared with those of sham-treated counterparts. The ion-treatment also significantly decreased the amount of a major allergen Asp f 1 in the *A. fumigatus* extract. We also found that exposure with plasma cluster ions decreased IgE-binding capacity and protein amount of a cat major allergen Fel d 1.
Conclusion: These results suggest that plasma cluster ions are effective for inactivation of fungal and pet allergens.

1268
Usefulness of recombinants determination in poly-sensitised patients in the clinical practice in our geographic area (Murcia, Spain)

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Background: In the Mediterranean area where we work, most patients allergic to pollen are sensitised to several pollens. The use of recombinants has represented an improvement for both diagnosis and treatment in allergic diseases, especially in these patients.
Objective: To study some epidemiological data of poly-sensitised patients in our geographical area (Murcia) and to assess the efficacy of recombinant allergens determination in the management of these patients.
Patients and methods: All patients sensitised to three or more pollen and previously treated with immunotherapy, who came to Allergy Department for revision, were recruited. The inclusion period comprised from January 2011 to May 2012.

For the study, prick test with grasses, parietaria, olea and salsola pollens and determination of recombinant allergens (rPhl p 1, rPhl p5b, rOle e 1, rPar j 2 and nSal k 1) by Immuno-CAP were realised. We analysed the most important sensitiser pollens in this area.
Results: A total of 156 patients from 14 to 69 (mean 38.8) years old were studied, 74 (47.4%) were male. All of them suffered from rhinitis and 102 (65.38%) also from asthma. From the 156 poly-sensitised patients, 146 of them were sensitised to olea (93.59%), followed by 129 to grasses (82.69%), 110 to salsola (70.51%) and, finally 88 to parietaria (56.41%).

After *in vitro* study through recombinant allergens determination, previous ITE composition was modified in 77 patients (49.36%). In the posterior revision, 1 year after the change, we observed that 50 patients (64.94%) have clearly improved their allergic symptoms, whereas 27 patients (35.06%) have not.
Conclusions: Olea and grasses are the major sensitiser agents in our area.

Recombinants determination is effective in order to choice the immunotherapy composition.

1269
In-vitro atopy testing in Australia using a novel modified ELISA system – the FastCheckPOC® 20

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Background: Allergy and related diseases are an extensive and rapidly growing problem worldwide. Most allergy research is conducted with patients from temperate regions. Very little information is available about the performance of diagnostics in tropical regions, a vast geographic zone, already home to over 40% of the world-population. The two most commonly used methods for confirming allergic sensitisation are skin prick testing and measurement of allergen-specific IgE antibody. While both methods have similar diagnostic value, from a patient perspective point-of-care (POC) testing causes little disturbance and no potential harm, whilst immediate test results can initiate better patient management.
Method: This Australian study was an open intra-individual controlled performance evaluation to assess IgE specific to 20 allergen components of the FastCheck-POC® 20. The gold standard ImmunoCAP system (Thermo Fisher, Phadia) was used as a reference system. Semi-quantitative test results of all 20 allergens of the Fast-CheckPOC® 20 were read (30 min) and documented by three readers using a 5-level score. Results are compared to the quantitative ImmunoCAP (kU_A/l) results of the 20 allergens.
Results: The correlation study demonstrated across all allergens 91.8% Sensitivity, 80.2% Specificity and 81.7% Accuracy for either whole finger-prick blood or serum. Results varied slightly from one allergen to another, with the lowest correlation observed for hazelnut (f17).
Conclusion: The FastCheckPOC® 20 is an exciting and innovative new diagnostic POC for the identification of allergen specific IgE amongst Australian patients. With its inherent advantages of speed-of-result, it should prove to be a valuable alternative to traditional SPT and laboratory-based specific IgE tests. Current studies will guide the development of optimised allergen panels and reactivities to enable the application in a variety of populations and geographic settings such as the Tropics.

1270
Ragweed plants and pollen spreading in Parma, Northern Italy

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Background: Ragweed is an annual, anemophilous weed producing pollen extremely allergenic that represents a question of public health in countries where plants are abundant. In Italy most affected region is Lombardy, where ragweed is the first cause of pollinosis. In Parma, until 2007, the plant had been identified as sporadic. In our previous report, we described a significant increase in SPI (Seasonal Pollen Index) and in patients with positive SPT (Skin Prick Test) for ragweed pollen, with a significant increase of asthma. The aim of our study was to confirm pollen results until today and detect the presence of ragweed plants sources on the territory.
Method: Temporal variations in pollen seasons (start dates, end dates, duration of pollination, peak dates), were investigated as the number of days from January 1st (DOY); peak values as grains/m^3 and SPI as grains.
Results: From 1996 to 2013 there were significant trends in peak values and SPI, but in the last 2 years, we found a decrease in ragweed pollen (−57.75% 2012 vs 2011, −53.91% 2013 vs 2011).
Conclusion: In Parma, there is currently no evidence of the presence of *Ophraella communa*, which feeds on ragweed leaves and which has been probably associated to a decrease in the concentration of ragweed pollen in Lombardy during 2013. The survey work carried out on our territory has identified numerous sites spreading *A. artemisiifolia* L. (21), *A. coronopifolia* Torr. & A. Gray (15) and *A. trifida* L. (3). On the basis of these results and considering our previous results we expect a rapid increase of allergy to ragweed related to the *Ambrosia* spread on our territory.

1271
The major birch pollen allergen Bet v 1 binds lipids from birch and grass pollen but not from peanuts

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Background: Although the physiological role of the major birch pollen allergen Bet v 1 still remains elusive, it is thought to be responsible for transport or storage of fatty acids, flavonoids or cytokinins. Lipids accompanying or binding to allergens can be immunomodulating. We analyzed the ability of Bet v 1 to bind lipids from peanuts, birch and grass pollen. Furthermore, we tested the binding of non-oxidized and oxidized 1-palmitoyl-2-arachidonyl-sn-glycero-3-phosphocholine (PAPC), a naturally occurring phospholipid, to Bet v 1.
Method: Peanuts, birch and grass pollen were homogenized in cold methanol using a Percellys homogenizer. Lipids were extracted with chloroform. Lipid concentrations were determined by using the sulfo-phospho-vanillin method. rBet v 1.0101 (10 μM final concentration; 174 μg/ml) was incubated overnight at 4°C with 3, 15 and 30 μg/ml of lipid extracts, untreated PAPC and photochemically oxidized PAPC (OxPAPC). Lipid binding to Bet v 1 was monitored by adding 10 μM 1-anilinonaphthalene-8-sulfonic acid (ANS) and measuring the decrease of fluorescence at 484 nm after 5 min.
Results: Due to pre-incubation of Bet v 1 with lipids of both pollen species, a concentration dependent reduction of ANS binding was observed. As compared to Bet v 1 alone, Bet v 1 incubated with 30 μg/ml of birch or grass lipids showed 76% and 73% reduction of ANS fluorescence. Interestingly, this was exclusively observed for pollen but not for peanut lipids. In addition we showed that 30 μg/ml OxPAPC bound to Bet v 1 (reduction of ANS fluorescence by 72%), whereas non-oxidized PAPC did not.
Conclusion: In this study supported by the Austrian Science Fund SFB-F4608, we observed that lipids extracted from birch and grass pollen were able to bind to the hydrophobic cavity of Bet v 1. This might represent an important mechanism, by which pollen lipids, most likely oxidized phospholipids, may act as potential danger signals during the sensitisation phase.

	Mean	SD	R^2	Slope	SE	P	n
Start date (DOY)	214.83	21.52	0.00	0.08	1.01	0.94	18
End date (DOY)	266.33	14.76	0.04	−0.59	0.68	0.40	18
Duration (DOY)	51.61	20.17	0.03	−0.63	0.93	0.51	18
Peak value (grains/m^3)	43.00	31.98	0.29	3.21	1.27	0.02	18
SPI (grains)	292.50	225.54	0.50	29.74	7.50	0.00	18
Peak date (DOY)	240.94	8.22	0.01	0.15	0.38	0.71	18

[Ragweed pollen season]

1272
Detection of airborne allergen (Pla a 1) in relation to *Platanus* pollen in Córdoba, South Spain

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Background: Córdoba is one of the Spanish cities with the highest records of plane tree pollen grains in the air. Clinical studies have identified *Platanus* as a major cause of pollinosis. This fact provokes an important public health problem during early spring when these trees bloom. The objective of the study is to evaluate the correlation between airborne pollen counts and Pla a 1 aeroallergen concentrations in Córdoba to elucidate if airborne pollen can be accurate information to understand the behavior of allergenic symptoms.
Method: Pollen sampling was performed during 2011 and 2012 using a Hirst-type sampler. Daily average of pollen grains/m^3 was obtained following the methodology proposes by the Spanish Aerobiology Network. A multi-vial cyclone was used for the aeroallergen quantification. Allergenic particles were measured by ELISA using specific antibodies Pla a 1.
Results: The trend of *Platanus* pollen was characterised by a marked seasonality, reaching high concentrations in a short period of time. Airborne pollen and aeroallergen follow similar trends. The overlapping profile between both variables during both years shows that pollen and Pla a 1 are significant correlated with higher significant correlations coefficients during 2011 and for the Post-peak. Although some studies have found notable divergence between pollen and allergen concentrations in the air, in the case of *Platanus* in Córdoba similar aerobiological dynamics between pollen and Pla a 1 have been found. Allergenic activity was found only during the plane tree pollen season showing a close relationship with daily pollen concentrations. The pollen potency obtained was similar for both years of study.
Conclusion: The results of this paper suggest that the allergenic response in sensitive patients to plane tree pollen coincide with the presence and magnitude of airborne pollen.

1273
Recent trends in airborne pollen at Córdoba city, Southern Spain (Possible response to climate change and land uses)

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Background: Annual airborne pollen recorded in a place is usually strongly correlated with flowering intensity in that area and surroundings. It has been demonstrated that water availability is an important variable in flowering intensity. However, other parameters, mainly temperature and relative humidity, influence on plant reproductive development. But airborne pollen recorded in a place depends also on land uses.
Method: The present study has been performed in the city of Córdoba (South Spain). We have analyzed airborne pollen data from the last 15 years. Mediterranean climate is characterised by a high interannual variability in its meteorological patterns, showing climatic micro-cycles alternating wet and dry periods. The selected statistical technique for extracting the trend component of pollen time series has been the seasonal decomposition procedure by Loess method (STL). STL decomposes long time series taking into account small patterns, at short term, in data. It has been analyzed changes on land uses around the city (25 000 m radius and 50 000 m radius) during the period 1999 and 2007.
Results: Results show different trends depending on species. Some agronomical species, as *Olea*, show significant increasing trend, attributable to the increment on olive crop areas during last years in the area. On the other hand, ruderal species and other taxa related with strong anthropic activity, as *Rumex*, *Plantago* or Urticaceae, show significant decreasing trends, that could be related with recent changes in urban planning.
Conclusion: STL method has shown high effectiveness for extracting trend component of ecological time series, because the features of Nature present a wide range of possibilities and it can change quickly at short term.

1274
The allergenic relevance of defensin-like proteins from feverfew, mugwort and ragweed pollen

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Background: Pollen of weeds belonging to the *Compositae* family is an important source of allergy in Europe and Asia. Defensin-like proteins, Art v 1 and Amb a 4 are relevant allergens from mugwort and ragweed pollen. Although relevant in India, little is known about the major allergen of *Parthenium hysterophorus* tentatively named *Par h 1*. Thus, we sought to clone and produce recombinant *Par h 1* for immunological studies.
Method: Total RNA was extracted from *P. hysterophorus* pollen and the full-length cDNA sequence was obtained using a degenerated primer followed by 5′-RACE protocol. The mature sequence of Art v 1.0101, Amb a 4.0101 and *Par h 1* were cloned into a pET-based vector and expressed in *E. coli* Rosetta-gamiB pLysS. Purified proteins were analyzed by gel electrophoresis, mass spectrometry and circular dichroism. Sera from Austrian patients allergic to mugwort pollen were used for immunological analysis in ELISA.
Results: The entire coding region including the signal peptide corresponding to *Par h 1* was identified. The cDNA sequence translates into a 156 amino acid protein with a defensin domain fused to a proline rich region. The mature protein has a calculated molecular mass of 12 kDa and a pI of 5.33. Art v 1.0101 and Amb a 4.0101 were obtained in *E. coli*. Analogous protocols are used for the production of recombinant *Par h 1*. Mass analysis confirmed protein identities. Circular dichroism analysis of mugwort and ragweed allergens showed similar secondary structures. Analyzed patients' sera displayed sensitisation to Art v 1 and Amb a 4 and partial IgE cross-reactivity was observed.
Conclusion: We present for the first time the full-length cDNA sequence of the major feverfew allergen, Par h 1. The recombinant protein together with Art v 1 and Amb a 4 will enable to study sensitisation and IgE cross-reactivity of defensin-like allergens in large patients' cohorts from Europe and India.

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1275
Glycosylation is required for high quality recombinant allergens

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Cross-reactive carbohydrate determinants (CCDs) are the main common feature of all allergens. Although their clinical role is still debated, the presence and cross-reactivity of CCDs pose a significant challenge for allergy diagnostic. Indeed, if an IgE-based immune response has built against a CCD glycoepitope in an individual following exposure to an allergen, his serum will likely show cross-reactivity to various allergens bearing similar CCDs during diagnostic. This can lead to an inaccurate diagnostic as to the source of allergenicity.

In order to alleviate this potential inaccuracy, some have turned to *E. coli* as host for the production of allergens destined to diagnostic. Being a prokaryote, *E. coli* cannot perform the complex post-translational modifications that are the signature of many eukaryotic proteins. It is thus true that *E. coli* will produce allergens that do not bear CCD epitopes as CCDs are one of many post-translational modifications solely performed by eukaryotes. However, allergens produced by *E. coli* will also lack all the post-translational features that contribute to their immunogenicity and as a result, will often lack reactivity and this can also lead to erroneous diagnostic results. In light of this, it seems that making allergens in *E. coli* for the sole purpose of avoiding the presence of CCDs is too much of a compromise. Allergens made in *E. coli*, though devoid of CCDs, are still far from meeting the stringent essential requirements of diagnosis and therapy.

We have developed a recombinant plant-based system that can produce a broad range of allergens of all levels of complexity (i.e. Der p 1, Der p 2 or Der p 4). This proprietary system is rapid, convivial, high-yielding and low-cost (both operational and CAPEX). It produces allergens that are structurally and biologically identical to the same allergens from natural sources while avoiding cross-reactivity due to CCDs.

Poster Session Group III – Green

TPS 55 – Animal studies in asthma

1276
Preventive effect of galectin-9 on double-stranded RNA-induced airway hyperresponsiveness in an exacerbation model of mite antigen-induced murine asthma

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Background: Viral respiratory infection is the most common cause of acute asthma exacerbation in patients with stable asthma. The replication of most respiratory viruses requires the generation of double-stranded RNA (dsRNA), resulting in the activation of host immune responses. Synthetic dsRNA, polyinosinic-polycytidylic acid (PolyIC), mimics the effects of viruses in various cell types. To evaluate new therapies for mite antigen-induced chronic asthma, we developed an acute exacerbation model of mouse chronic asthma using mite antigen and PolyIC. We also examined the preventive effects of recombinant galectin-9 (Gal-9) on acute asthma exacerbation in this model.
Method: Airway hyperresponsiveness (AHR) was examined to evaluate the exacerbation of chronic asthma. To analyze airway inflammation, the numbers of inflammatory cells and concentrations of cytokines in the bronchoalveolar lavage fluid (BALF) were estimated by flow cytometry and enzyme-linked immunosorbent assay (ELISA), respectively. Concentrations of cytokines were determined in the culture supernatants of alveolar macrophages by ELISA.
Results: AHR was accelerated by intranasal administration of PolyIC in addition to mite antigen. Levels of cytokines that contribute to AHR, including interferon-ϒ, tumor necrosis factor-α, and RANTES (CCR5), and of Gal-9 in the BALF were elevated in this acute asthma exacerbation mouse model. Intranasal administration of recombinant Gal-9 reduced the PolyIC-induced AHR and levels of these cytokines in the BALF. Further, Gal-9 suppressed the production of cytokines induced by PolyIC in the alveolar macrophages.
Conclusion: Our findings demonstrated that exogenous Gal-9 suppressed dsRNA-induced AHR in an acute exacerbation model of chronic asthma in mice, and suggest that recombinant Gal-9 could be therapeutically effective for preventing acute asthma exacerbation.

1277
Efficacy of parthenolide on lung histopathology in a murine model of asthma

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Background: Parthenolide is the active constituent of the plant 'Tanacetum parthenium' (Feverfew) which has been used for centuries as a folk remedy inflammatory conditions. In this study we aimed to investigate the effects of parthenolide on histological changes in a murine model of chronic asthma.
Methods: Thirty-five BALB/c mice were divided into five groups; I (control), II (placebo), III, IV and V. All groups except the control were sensitised and challenged with ovalbumin. Sterile saline was administered instead of ovalbumine in control group. Mice in Group II (placebo group) received solvent of parthenolide dimethyl sulfoxide (DMSO), Group III received dexamethasone, Group IV received parthenolide and Group V received both dexamethasone and parthenolide via intraperitoneal route once daily in the last 5 days of the challenge period. Animals were sacrificed by an overdose of ketamin after 24 h from the last dose of the drug administration. Lung histology was evaluated by using light and electron microscopy. Levels of interleukin (IL)-4 and IL-5 were determined by ELISA.
Results: All histologic parameters except the number of mast and goblet cells improved in parthenolide group when compared with placebo. All parameters except basal membrane thickness and number of mast cells were improved significantly better in group receiving dexamethasone when compared with parthenolide group. Improvement of most of the histologic parameters were similar in Group III and V. Interleukin-4 levels were significantly reduced in parthenolide group when compared to placebo group, but IL-5 levels were similar in both groups.
Conclusion: We demonstrated that parthenolide administration alleviated some of the pathologic changes in asthma. But parthenolide alone is not efficient as dexamethasone therapy and parthenolide and dexamethasone combination also did not add any beneficial effect to dexamethasone treatment.

1278
Inadequate antioxidant response is associated with allergic sensitisation in mice and man

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Background: Oxidative stress has been reported to be associated with the pathology of allergic diseases but its role in the genesis of allergic development is not known. We investigated whether oxidative stress predisposes to allergic sensitisation, both in a mouse model for house dust mite (HDM) allergy and in a human longitudinal occupational allergy cohort.
Methods: C3H/HeJ and Balb/c mice were exposed intranasally to HDM extract with low endotoxin levels (3.14 EU/ml) for a period of 3 weeks. Four weeks later, mice were re-challenged and eosinophil recruitment, Th2 cytokine production, serum immunoglobulin, and lung histology were analyzed. Serum and PBMC from an occupational cohort of laboratory animal workers, taken at the start of their employment and after 2 years, were analysed for oxidative stress markers, antioxidant protein expression and neo-sensitisation against rodents allergens.

Results: Low-endotoxin HDM was not able to induce sensitisation in Balb/c. However, in C3H it induced eosinophil recruitment to the airways, Th2 cytokine production, peri-bronchial inflammatory infiltrates and specific immunoglobulins. Both Balb/c and C3H showed increased expression of oxidative stress markers in the lungs. However, the expression of anti-oxidant proteins HO-1, GPx-1 and Nrf2 were only increased in lungs of Balb/c. Antioxidant pre-treatment of dendritic cells from C3H inhibited the induction of CD40, CD80 and CD86 *in vitro*. In support of an association between poor control of oxidative stress and sensitisation, the animal laboratory workers that became sensitised to rodents after 2 years, expressed higher levels of oxidative stress markers and lower levels of antioxidant proteins at the start of their employment compared to those that did not become sensitised.
Conclusion: Our results strongly indicate that both in humans and mice an inadequate antioxidant response is associated with increased susceptibility to allergic sensitisation.

1280
Subcutaneous immunotherapy of allergen extracts from Humulus scandens pollen desensitises specific allergen-induced allergic asthma in mice

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Background: Subcutaneous immunotherapy (SCIT) was introduced into clinical practice early in the 20th century (Noon *et al*., 1911), but no animal model has been established to prove this. We hypothesised that abdomen subcutaneous injection of a high-dose of Humulus scandens pollen extracts may prevent IgE-related responses in Humulus scandens pollen desensitises specific allergen-induced allergic asthma in mice allergic asthma in mouse model.
Method: In the present study, we try to generate an allergic asthma model by sensitising and challenging balb/c mice with humulus pollen (HP) extracts. Besides, subcutaneous injection of HP extracts is also done to imitate desensitisation treatment in human. Lung function was assessed by Penh, cell accumulation was performed by HE staining, and mucus secretion was indicated by AB-PAS staining. Serum total IgE (tIgE) specific IgE (sIgE), IgG1 (sIgG1) and IgG2a (sIgG2a) levels were measured by ELISA. Same tests were carried out in the control group.
Results: The results indicated that SCIT not only prevented the airway hyperresponsiveness (AHR) in response to methacholine in a dose-dependent manner but also significantly elevated serum allergen-specific IgG2a, thus normalised the imbalance between the Th1 and Th2 response. HP Specific IgE, IgG1 and total IgE level showed no significant difference between model and desensitisation group. Finally, SCIT significantly reduced mucus secretion and inflammatory cell infiltration.
Conclusion: These data suggest that SCIT effectively improves specific allergen-induced inflammation and AHR in HP sensitised and challenged mice and provides a plat form for further investigation of allergic asthma therapy.

1281
The preventive effects of dietary galacto-oligosaccharides in a house dust mite-induced asthma model in mice

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Background: Allergic asthma is associated with the exposure to house dust mite (HDM). Characterised by a Th2 immune response, asthma leads to mucus hypersecretion, eosinophilic inflammation and airway hyperresponsiveness. Recently, there is an increased interest in using specific oligosaccharides as a novel strategy to prevent development or reduce symptoms in asthma.
Aim: We examined the effects of galacto-oligosaccharides (GOS) compared to the corticosteroid, budesonide, on the development of allergic asthma.
Method: BALB/c mice were intranasally (i.n.) sensitised with 1 μg HDM on day 0 and challenged i.n. with PBS or 10 μg HDM on days 7 till 11. From day −14 till 14 mice were fed a control diet or a diet containing 1% GOS. A separate group of mice were instilled *oropharyngeally* with budesonide (500 μg/kg) on day 7, 9, 11, and 13. On day 14 airway resistance was measured by applying increasing doses of methacholine in the airways of mice. Bronchoalveolar lavage (BAL) fluid and lungs were collected.
Results: HDM allergy resulted in airway hyperresponsiveness and a significant increase of leukocytes in the BAL fluid. Dietary intervention with 1% GOS decreased the total number of leukocytes in the BAL fluid, represented by a significant decrease in macrophage and eosinophil subsets. Budesonide treatment resulted in a significant decrease in lymphocytes, neutrophils and eosinophils. The 1% GOS diet significantly decreased airway hyperresponsiveness, whereas budesonide did not. Moreover, HDM allergy resulted in significantly enhanced levels of IL-6, -13 and -33 in lung homogenates. Both IL-6 and -13 were significantly decreased after budesonide treatment. Dietary intervention with 1% GOS significantly decreased IL-13, but not IL-6 and -33 levels in lung homogenates.
Conclusion: These findings show that 1% GOS has a preventive effect on the HDM induced influx of inflammatory cells and airway hyperresponsiveness, whereas budesonide only affects inflammatory cell numbers.

1282
A combination of fructo-oligosaccharides and *Bifidobacterium breve* M-16V suppresses airway resistance and inflammation in house dust mite allergic mice

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Background: Allergic asthma is strongly associated with exposure to house dust mite (HDM). Allergic asthma is characterised by eosinophilic inflammation, mucus hypersecretion and airway hyperresponsiveness. There is an increased interest in using specific non-digestible oligosaccharides (OS) and beneficial bacteria to prevent development or reduce symptoms in allergic asthma.
Aim: Study the effect of non-digestible fructo OS either alone or combined with *Bifidobacterium breve* M-16V (*BB*) on the development of HDM-induced allergic asthma in mice.
Method: BALB/c mice were intranasally (i.n.) sensitised with 1 μg HDM on day 0 and challenged i.n. with PBS or 10 μg HDM on days 7 till 11. From day −14 till 14 mice were fed a control diet or a diet containing a 1 w/w% 1:1 mixture of short chain fructo-OS (scFOS) and long chain fructo-OS (lcFOS) without or with *BB*. On day 14 airway resistance was measured by applying increasing doses of methacholine in the airways of mice. After sacrificing bronchoalveolar lavage (BAL) fluid and lungs were collected.
Results: Airway resistance was increased in HDM-allergic animals on a control diet. Dietary intervention with scFOS/lcFOS

reduced airway resistance in presence or absence of *BB*. HDM allergy resulted in an influx of leukocytes in the BAL fluid ($P < 0.001$), which was reduced by the scFOS/lcFOS/*BB* diet ($P < 0.01$). Dietary intervention with scFOS/lcFOS decreased BAL eosinophil numbers ($P < 0.001$) and neutrophils ($P < 0.01$), when *BB* was added also the lymphocyte ($P < 0.01$) and macrophage numbers reduced ($P < 0.05$). HDM allergy resulted in significantly increased levels of interleukin (IL)-6, IL-13 and IL-33 in lung homogenates. The scFOS/lcFOS/*BB* diets reduced IL-6 levels ($P < 0.05$).

Conclusion: These findings suggest that *B. breve* M16-V combined with scFOS/lcFOS has a beneficial effect on airway inflammation and hyperresponsiveness in HDM allergic mice.

1283
The effect of ursodeoxycholic acide on lung histopathology in a murine model of chronic asthma

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Background: Ursodeoxycholic acid (UDCA) is used to treat primary biliary cirrhosis, intrahepatic cholestasis and other cholestatic conditions. In previous studies, immunomodulatory properties of UDCA, such as suppression of immunglobuline production, suppression of cytokine synthesis by lymphocytes, inhibition of mast cell activation was shown. UDCA treatment was also reduced tissue eosinophilia in allergic airway inflammation of mice model. Using a murine model of chronic asthma, we investigated the effects of UDCA on airway histology and cytokine levels of asthmatic lung tissue.

Materials and methods: Twenty-seven mice were divided into five groups; I (control), II (plasebo), III (UDCA 50 mg/kg), IV (UDCA 150 mg/kg), and V Mice except control were sensitised by an intraperitoneal injection of ovalbumin with alum adjuvant and then challenged with an aerosol of ovaalbumin on 3 days of the week for 8 weeks beginning from the 21st day of the study. Lung histology was evaluated after treatment with peroral 50 and 150 mg/kg UDCA, dexamethazone and plasebo. Interleukin-4, IL-5, IL-13, NO levels were studied in lung homogenates and OVA spIgE level was studied in serum with ELISA. Immunohistochemical staining was done with matrix metalloproteinase-9 (MMP-9), vascular endothelial growth factor (VEGF), transforming growth factor beta (TGF-b), for evaluation of effect's of ursodeoxycholic acid on angiogenesis.

Results: In light microscopic evaluation 150 mg/kg UDCA group's subepithelial smooth muscle thickness, number of mast cells, number of goblet cells and epithelium thickness were significantly reduced compared with placebo group but results of group 50 mg/kg UDCA was similar with placebo group. The number of eosinophils in BAL decreased significantly in both UDCA treatment groups. There were significantly decreases of IL-4, IL-13, OVA spesific IgE levels in 150 mg/kg UDCA group compared with placebo group except for IL-5 and NO. All cytokine levels were decreased in 50 mg/kg UDC group compared with plasebo. Immunohistochemical analyses, only staining of MMP-9 was significantly decreases in 150 mg/kg UDCA group compared with placebo and 50 mg/kg UDCA group is similar with plasebo.

Conclusion: In our study we demonstrated that 150 and 50 mg/kg UDCA treatment decreases Th-2 sitokin levels and alleviated some of the histologic changes in chronic asthma. Furthermore, UDCA treatment has not too important effects on inhibition of angiogenesis in chronic asthma.

1284
Characterisation of a murine experimental allergic asthma model induced with *Dermatophagoides pteronissinus (Der p)* allergenic extract

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Background: The purpose of this study was to compare different modeling variants to obtain a mouse allergic asthma (MA) using house dust mite *Dermatophagoides pteronissinus (Der p)* extract.

Methods: BALB/c mice were i.p. immunised three times in 2 weeks interval with different doses of lyophilized *Der p* extract with $Al(OH)_3$. Eight weeks after the last immunisation mice were pulmonary challenged with *Der p* for 5 consecutive days by intranasal applications (INA) or aerosol administration (AA). Mice were divided into five groups:

Group 1 was immunised with 50 μg/mouse *Der p* and challenged by INA;
Group 2 was immunised with the same dose and challenged by AA;
Group 3 was immunised with 100 μg/mouse *Der p* and challenged by INA;
Group 4 was immunised with the same dose and challenged by AA;
Group 5 mice were intact (negative control).

Twenty-four hours after the challenge airway hyperresponsiveness (AHR) to methacholine was measured by whole-body plethysmography. Forty-eight hours after the challenge blood and bronchoalveolar lavage fluid (BALF) were collected for differential cell count and lung tissue was removed for histological examination. Serum anti-*Der p* IgE, IgG1 and IgG2a antibodies during sensitisation period and after the challenge were measured by ELISA.

Results: The highest level of serum *Der p*-specific IgE was observed in group 2. Serum levels of *Der p*-specific IgG1 and IgG2a in group 2 were substantially higher than other groups. AHR was maximal in groups 1 and 3. Elevated eosinophil count in BALF was observed in group 3. No significant differences were observed among groups in peripheral blood cell counts. Histological picture of allergic inflammation in lungs (peribronchial and perivascular infiltration with eosinophils and lymphocytes) was expressed in group 3.

Conclusion: These data suggest that immunisation with *Der p* in dose 100 μg/mouse and challenge by INA is acceptable for obtaining MA that can be suitable for studying of novel approaches in allergen immunotherapy.

1285
The effects of probiotics and PPAR-γ on the murine model of allergic asthma

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Background: Probiotics are normal inhabitants in the gastrointestinal tracts of man and are widely considered to exert a number of beneficial roles including immunomodulation, interference with enteric pathogens, and maintenance of a healthy intestinal microflora. In recent years, studies of probiotics have also confirmed their extra-intestinal effects, particularly for the prevention of allergic diseases. However, the anti-allergy mechanism of probiotics is still unclear.

Method: In the first part of this study, we continuous feeded of *Lactobacillus gasseri* (*L. gasseri*) PM-A0005 10^7 CFU/200 ml or 10^9 CFU/200 ml for 4 weeks in Der p-sensitised and challenged mice could prevent allergen-induced airway inflammation. In

the second part of study, we applied microarray analysis of the lung draining lymph nodes and mesenteric lymph node of mice to detect genes expression signal pathways and genetic profiling of immunological tolerance induced by *L. gasseri* PM-A0005. Thirdly, we have picked up one candidate targeted gene, peroxisome proliferator-activated receptor-γ (PPAR-γ), to study the beneficial effect of probiotics on the allergic induced airway inflammation.

Results: In the first part of this study, we found that significantl changes of airway hypersensitivity, TH_1 and TH_2 cytokine patterns, lymphocyte proliferations and immunoglobulin production between *L. gasseri* PM-A0005-treated and non-treated mice. In the second part of study,we found that there was significantly decrease of inflammatory and chemokines genes expression and increased of carbohydrate and lipid metabolism genes expression in the *L. gasseri* PM-A0005-treated mice as compared to non-treated sensitised and challenged mice. Finally, probiotics treatments PPAR-γ P456L mutant mice and wide type mice improved the lung inflammation after mite allergen sensitised and challenge.

Conclusion: Our results showed that PPAR-γ play important role in the inhibitory effect of allergen-induced airway inflammation in mice. And the anti-allergic effect on *L. gasseri* PM-A0005 may through activation of PPAR-γ to alleviate airway inflammation in allergen-sensitised murine model of asthma.

1286
The effect of sinomenine on lung histopathology in a murine model of chronic asthma

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Background: Sinomenine is an active compound isolated from *Sinomenium acutum*, which has been successfully used for centuries in the treatment of various disease. In a study, anti-allergic effect of sinomenine by inhibition of prostaglandine D2 and leukotriene C4 in mouse bone marrow-derived mast cells was shown, previously. Using a murine model of chronic asthma, we investigated the effects of sinomenine on airway histology and cytokine level of asthmatic lung tissue.

Materials and methods: Twenty-four mice were divided into four groups; I (control), II (plasebo), III, IV. Mice except control were sensitised by an intraperitoneal injection of ovalbumin with alum adjuvant and then challenged with an aerosol of ovaalbumin on 3 days of the week for 8 weeks beginning from the 21st day of the study. Lung histology was eveluated after treatment with peroral 100 mg/kg sinomenine, dexamethazone and plasebo. Interleukin-4, IL-5, IL-13, NO levels were studied in lung homogenates and OVA spIgE level was studied in serum with ELISA. Immunohistochemical staining was done with matrix metalloproteinase-9 (MMP-9), vascular endothelial growth factor (VEGF), transforming growth factor beta (TGF-b), for evaluation of effect's of sinomenine on angiogenesis.

Results: In light microscopic evaluation sinomenine group's subepithelial smooth muscle thickness and number of mast cells were reduced compared with placebo group. The number of eosinophils in BAL decreased significantly in groups receiving study drugs. There were significantly decreases of IL-4, IL-13, NO, OVA sp IgE levels in sinomenine group compared with placebo group except for IL-5. Immunohistochemical analyses, staining of MMP-9, VEGF, TGF-b were significantly decreases in sinomenine group compared with placebo.

Conclusion: In our study we demonstrated that 100 mg/kg sinomenine treatment decreases Th-2 sitokin levels and alleviated some of the histologic changes in chronic asthma. Additionally, sinomenine treatment has positive effects on inhibition of angiogenesis in chronic asthma.

1288
Quercetin theraphy in experimental asthma

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Background: Asthma is a chronic inflammatory disease characterised by reversible airway obstruction, airway inflammation and remodeling. Quercetin is a plant flavonoid present in many plants including broccoli, apples, berries,onions, and tea. It has anti-allergic and anti-oxidant properties. This study investigated the anti-inflammatory and anti-apoptotic properties of quercetin in a mouse model of asthma.

Method: Six to eight week old male BALB-C mouse diveded into four groups:

Group 1 (control group, $n = 6$),
Group 2 (ovalbumin induced asthma only, $n = 7$),
Group 3 (ovalbumin induced asthma + quercetin, $n = 7$), and
Group 4 (ovalbumin induced asthma + dexametazon, $n = 7$).

Ova spesific IgE levels analyzed with ELISA from serum, IL-4, IL-33, IL-25, IFN GAMA, TSLP levels analyzed with ELISA from broncholaveolar lavage, histological findings (basement membrane, epithelium, subepithelial smooth muscle thickness, numbers of goblet and mast cells) analyzed from lung tissue. IL-33, IL-25, TSLP, TUNEL and Caspase was also evaluted with immunstaining of lung tissues. Eosinophil counts also assesed in broncholaveolar lavage.

Results: In the quercetin treated group, the numbers of mast cells and goblet cells as well as the thickness of basement membrane, epithelium, and subepithelial smooth muscle layer were significantly higher when compared to asthma group ($P < 0.005$). Bronchoalveolar lavage cytokin levels (IL-4, IL-33, IL-25, IFN GA MA, TSLP) were lower in quercetin group compared to asthma group ($P < 0.005$). Immunohistochemical staining (IL-33, IL-25, TSLP, TUNEL and Caspase) were also showed that quercetin group has antiinflammatory and anti-apoptotic properties compared to asthma group ($P < 0.005$). Bronchoalveolar lavage eosinophil counts also lower in quercetin group compared to asthma group.

Conclusion: This study suggests quercetin as a potent anti-inflammatory therapy. Apoptosis must be kept in mind for the pathogenesis of asthma and drugs with anti-apoptotic properties can have an option for treatment.

1289
Cockroach allergen increases bystander allergen interaction with dendritic cells reduced by serine protease inhibitor

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Background: Protease inhibitors are potential therapy in allergic diseases. The present study was aimed to study the effect of protease inhibitor in adjuvanticity for allergic sensitisation.

Method: BMDCs from naive mice were pulsed with cockroach extract (CE) and OVA-alexa, incubated with AEBSF to study the interactions using FACS. To decipher the serine protease inhibitor role in allergen sensitisation, BALB/c mice were given intranasaly AEBSF before CE sensitisation or challenge or both. Airway resistance was evaluated in mice and sacrificed to collect BALF, blood and lung tissue.

Results: BMDCs pulsed with CE significantly increased the OVA-alexa uptake as compared to heat inactivated CE. BMDCs incubated with AEBSF further reduced the OVA-alexa uptake ($P \leq 0.001$) indicating its role in reduction of allergen uptake. Mice given allergen on sensitisation or challenge or both with AEBSF reduced the airway resistance. AEBSF given during sensitisation or challenge or both reduces total cell ($P \leq 0.05$, $P \leq 0.01$, $P \leq 0.01$) eosinophil (not significant, $P \leq 0.05$, $P \leq 0.01$) and neutrophil ($P \leq 0.05$, $P \leq 0.01$, $P \leq 0.01$) count, respectively in BALF. This is accompanied by reduction in IgE and IgG1 ($P \leq 0.01$) in treatment during sensitisation compared to treatment during challenge only ($P \leq 0.05$). The level of TNFα was also significantly ($P \leq 0.01$) lower in sensitisation as compared to CE immunised mice but not during challenge. AEBSF treatment also significantly ($P \leq 0.05$) increased the IL-12 secretion in all groups.

Conclusion: Serine protease inhibitor decreases the allergen uptake thereby reduces the inflammatory parameters.

Poster Session Group III – Green

TPS 56 – Autoimmunity

1290
Sjogrens syndrome – a case report

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Background: Sjögren's syndrome is the second most prevalent disease after rheumatoid arthritis. Might be primitive (rare) or secondary, most commonly associated with other autoimmune disease such as rheumatoid arthritis, lupus, dermatomyositis or primary biliary cirrhosis; and is characterised by lymphocytic infiltration of the exocrine gland. This disease touches mainly exocrine glands but may involve all organs and systems. The lacrimal and salivary glands are mostly manifested by xerophtalmia and xerostomia.
Method: We present the case of a female patient, aged 72 years, who comes in emergency unit with eye pain, myalgia, 'burning' mouth. Clinical examinations highlights injury with lack of substance in the mouth mucosa, arthralgia and proximal muscle weakness in scapular-humeral and the hip belt, Gottron papules on the dorsal face hand at the level of inter-phalangeal and metacarpal-phalangeal joints. The ophthalmology examination revealed no lacrimation, Schirmer test = 0, lack of conjunctiva and extreme thinning of the sclera in supero-temporal segment and a marginal corneal ulcer. Laboratory exams show normocytic hypochromic anemia; creatine kinase, serum aldolase and ESR increased, modified electromyogram, present creatinuria, positive antinuclear antibodies with nucleolar pattern, positive Anti Ro antibodies.
Results: The diagnosis is dermatomyositis overlap Sjogren's syndrome. Particularity of the case lies in the severity of ocular lesions in the right eye and the appearance of signs of distress in the left eye ocular surface after only 2 months, even under treatment.
Conclusion: The sufferance of ocular surface requires complex immunological investigation to support the diagnosis and initiation of suitable therapy.

1291
Recognizing lupus profundus: an insidious diagnostic challenge. A case report

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Background: Lupus Profundus (LP) is a variant of Lupus Erythematosus Panniculitis, a rare manifestation of Lupus Erythematosus consisting of deep subcutaneous inflammatory nodules or plaques, associated to overlying discoid lupus erythematosus. Because of some histological characteristics similar to panniculitides associated with autoimmune diseases, as well as to the subcutaneous panniculitis-like T-cell lymphoma, the correct diagnosis can be difficult. Therapy is based on antimalarial drugs and steroids.
Case report: At the age of 31, C.L. noted the appearance of a nodular lesion at the upper medial quadrant of right gluteus under a normal skin. Ultrasound showed an hyperecogen area (48 × 17 mm diameter) which at the subsequent MRI was interpreted as an angioma. After 8 months, because of the extension of the lesion and the appearance of erythema and scaling on the overlying skin, FNAB with cytological examination was performed. It showed an extended lymphoplasmacellular infiltrate compatible with a lymphoproliferative disease. The lesion was surgically removed. A reactive pattern with superficial ulceration was found at new histological analysis. After 1 year the patient was admitted to our Clinic for the appearance of a new lesion next to the previous one. The final diagnosis of LEP was based on:

1 ecographic evidence of subcutaneous thickening with edema and hyperemia;
2 increased flogistic values (ESR, CRP, hypergammaglobulinemia); the presence of anti-nucleus and anti-DNA antibodies.

Hydroxichloroquine was started. After 6 months, the lesion is stable.
Discussion: We report a case of LP which represents an insidious diagnostic challenge. This condition is rare and confounding for its histopatological features. Several histological and clinical criteria are helpful in assessing the autoimmune pattern, thus allowing to start treatment in the early phase and avoid the progression to atrophy.

1292
Macrophagic activation syndrome in adult-onset Still's disease: report of a complex case

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Background: Adult-Onset Still's disease (AOSD) is a systemic inflammatory disease characterised by spiking fever, evanescent rash, arthritis and multiorgan involvement. Macrophagic Activation Syndrome (MAS) is a potentially fatal complication of AOSD, as well as of several hematologic, infectious and immunologic diseases. It arises with continuous high fever, liver disfunction, hyperferritinemia, cytopenias and multiple organ failure.
Case report: Here we report the case of a 39-year-old woman with a previous diagnosis of Undifferentiated Connective Tissue Disease chronically treated with 16 mg metilprednisone per day. She was admitted to our clinic with intermittent fever, sore throat, weakness and joint pain. Blood examination showed increased inflammatory markers and LDH, neutrophilia, anemia. Infections were ruled out. Antinuclear antibody and rheumatoid factor were negative. At day 15 an episodic evanescent rash appeared, followed by further increase of fever up to 39.4°C. Fever turned into continuous, with a spike of 40.2°C. Platelets and WBC rapidly decreased with neutropenia, lymphocytopenia and monocytosis. Ferritinemia trygliceridemia and LDH respectively increased up to 13 500 ng/ml, 800 mg/dl, 7500 U/l. Liver disfunction, fibrinogen consumption and ESR decrease were detected, while clinically astenia worsened. Bone marrow aspiration revealed histiocytosis. CT scan showed diffuse lymphadenopathy and hepatomegaly. AOSD complicated by MAS was diagnosed and metilprednisone dose was increased to 32 mg/day with rapid decrease

of fever and gradual return of the laboratory parameters to the normal ranges.
Discussion: We diagnosed an AOSD complicated by MAS. Both AOSD and MAS are uncommon conditions, but MAS incidence is not so rare among AOSD cases. Since AOSD-associated MAS is often life-threatening, a prompt diagnosis is crucial in order to start an effective therapy.

1294
Antiphospholipid syndrome during pregnancy, plasmapheresis treatment

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The case report provides information on application of plasmapheresis (PP) in treatment of a woman born in 1974 with a diagnosed antiphospholipid syndrome. At the age of 20 (1994) she prematurely delivered (the 32th week of gestation) heavily handicapped daughter. 11 years later the antiphospholipid syndrome with high titres of antiphospholipid antibodies (APLA) and positive lupus anticoagulant was detected in connection with an extra-uterine pregnancy (2005). Three failed pregnancies were following in spite of an appropriate therapy with low molecular heparin (LMWH), aspirin and low dose prednisone: dead fetus delivery in the 20th week of gestation (2006), abortion in the 27th week of gestation (2007) and anembryomola (2012).

Therefore the repeated PP as the second-line treatment was applied. After the introductory cumulative PP administration (5 times every other day) 1 week PP interval was applied with reference to the APLA dynamics. On total the patient received 25 PP which led to a substantial decrease of APLA. The foetus development was monitored by regular USG investigations, we observed prospering growth at the lower limit of the growth chart. The pregnancy was finished in line with the schedule in the 36th gestational week by iterative Caesarean operation. The patient has delivered a healthy boy 2330 g/47 cm, APGAR score 10, 10, 10, Astrup in normal range. The baby was discharged together with its mother the 8th day after the delivery.

This case demonstrates justification of an experimental treatment in the case when conventional therapy (LMWH, aspirin, prednisone) fails.

1295
Analyses of hormonal status and anti-TPO autoantibody in patients with goiter disease

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Background: Many autoimmune diseases overlaps each other in symptoms, signs and mostly in immunological pattern by wich these deseases were developed. A lot of antibody were positive in two or more disease, and in oposite, some diseases share multiple autoantibodies. Autoimmune inflamation during long period cause malfunction of organ-specific tissue. That′s could become for a few months or for many years of durration. So, detection of patterns of developement of damaged tissue are of substantial importance for early detection and follow up of ilness. Goiter is very often caused by autoimmune paterns, but both extreme of hypo and hyperfunction could developpe.
Method: Patients with goiter, with or without clinical signs of thyroid disease were analyzed, during period of 1 year. Measurement of anti-thyreoperoxidase autoantibody (Anti-TPO) was performed using the enzyme immunoassay sandwich method, with which final fluorescent detection, known as 'ELFA method', combined a two-step method. Red blood cell count, leukocytes and thrombocytes cells were analyzed. Statistical analysis was completed by using software package Statistica for Windows, with multiple-correlation test and descriptive statistics.
Results: During period of 1 year 95 patients have been treated with goiter, 89 female and 6 male. Among them two patients have clinical and hormonal hyperthyreosis, and eight out of all have clinical and hormonal hypothyreosis. Hypothyreotic cases have lover level of hemoglobin and erythrocytes, but not in statistical significant level. No differences in general inflammatory status was detected. Anti-TPO was in statistical significant correlation with lower level of thyroid hormones.
Conclusion: Presence of anti-TPO could results in higher or lower levels of thyroid hormones, but much more frequent is lower one. Lower level of red blood cells count and no differences of general inflammatory status in eider extreme.

1297
Quality of life in hospitalised patients with systemic lupus erythematous (SLE) is not correlated with disease activity or damage

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Background: SLE is a systemic disease with major impact on patients quality of life.
Objective: To evaluate the impact of systemic lupus erythematosus (SLE) disease in terms of disease activity and damage on patients quality of life.
Methods: Prospective study on 42 hospitalised patients with SLE, diagnosed according to ACR criteria, mean age 51.42 years, 40 (95.23%) women, mean duration of the disease 12.3 ± 8.9 years. All the patients were evaluated with Lupus Quality of Life (LQol), a 34-item SLE specific, patient reported questionnaire, correlated with physician assessment of SLE disease activity (evaluated with BILAG 2004 flare considered when presented one BILAG A or two BILAG B and SELENA SLEDAI 2K >6 points) and presence of irreversible damage (SLICC/ACR ≥1). We used as statistics aseesment Pearson, ANOVA, multiple regression.
Results: Twenty-three (54.76%) patients presented disease activity on BILAG/SLEDAI evaluation; irreversible damage was present in 20 (47.61%) patients.

Ten (23.08%) patients reported severe affected QoL due to SLE (total score 34–67), 27 (64.28%) moderately affected (total score 68–135) and five (11.9%) mild affected (total score 136–170).

Moderate/severe affected Qol in SLE was significant present in the study group ($P < 0.001$). No significant correlation was found between disease activity or damage and Qol ($P = 0.67$, $P = 0.5$)
Conclusion: Moderate/severe affected Quality of life in patients with SLE is statistically significant but not correlated neither with disease activity or chronic damage.
Key words: Lupus Qol, disease activity, damage.

1298
Prevalance of allergic diseases in patients with Raynaud phenomenon

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Background: The Raynaud phenomenon (RP) is an exaggerated vascular response to cold or emotional stress. Cold is also a trigger factor for allergic diseases like asthma, vasomotor rhinitis and urticaria (cold urticaria, idiopathic urticaria, dermographism). The aim of the present study was to investigate the prevalance of allergic diseases in patients with primary and secondary Raynaud′s phenomenon.
Method: Consecutive 53 patients with Raynaud phenomenon who were followed in rheumotology department and volunteered for allergic evaluation, were evaluted between April 2013–September 2013. An additional 20 patients with rheumatic disease and without Raynaud phenomenon were included as control group. A questionnaire evaluating the presence of allergic diseases were applied to all patients. Depending on oral corticosteroid usage, either skin prick test or specific IgE (phadiatop) requested. Pulmonary function test and ice cube test were performed for all patients.
Results: Among the patients included in the study, 90.4% were women and 72.6% had RF. The most common rheumatic diseases were scleroderma and rheumatoid arthritis. Patients with vasomotor rhinitis (12.3%), dermographism (8.2%) and cold urticaria (4.1%) have had RF. Fifty three point four percent of all patients had at least one allergic disease. Having allergic diseases was associated with primary RF (OR = 9.24, 95% CI 1.05–81.05).
Conclusion: In conclusion, Raynaud′s phenomenon has been shown to be associated with cold related allergic disaeses such as asthma, vasomotor rhinitis, cold urticaria and dermographism. In addition, the frequency of allergic diseases in patients with rheumatoid arthritis was not less than the normal population.

1299
Humoral immunodeficiency in systemic lupus erythematosus (SLE)

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Background: Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune connective tissue disease. The aim of our study was to determine the incidence and etiology of humoral immunodeficiency in SLE patients.
Method: There were retrospectively evaluated 799 results of serum immunoglobulin levels (Ig) from 157 SLE patients fulfilling the revised ACR diagnostic criteria (1997) treated at the Department of Revmatology, University Hospital Hradec Kralove, Czech Republic in the years 2008–2013.
Results: The decreased Ig levels were diagnosed in 29/157 (18.5%), mostly of secondary etiology: decreased IgG level in 17/157 (10/17 nephropathy, 7/17 drug induced), IgA in 6/157 (2/6 selective IgA deficiency), decreased IgM 4/157, 1/157 SLE and common variable immunodeficiency (CVID) coincidence, and 1/157 prolonged severe hypogammaglobulinaemia after rituximab therapy in SLE patient with lymphoma history. These two cases required the initiation of regular immunoglobulin supplementation therapy because of clinical significance of immunodeficiency (recurrent sinopulmonary infections and severe *Campylobacter jejuni* sepsis). The increased Ig levels were detected in 54/157 (34.4%), mainly close to SLE diagnosis.
Conclusion: Antibody deficiency may occur in the field of SLE. Immunoglobulin levels should be checked to enable identification of deficiency monitoring and appropriate treatment. CVID should be suspected in any SLE patient with recurrent sinopulmonary infections in the absence of SLE activity and/or immunosuppressive treatment.

1301
Evaluation of clinical features and outcomes of 25 patients with granulomatosis with polyangiitis (Wegener′s) – a single-center study

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Background: Granulomatosis with polyangiitis (Wegener's; GPA) is characterised by systemic necrotizing vasculitis and granuloma formation, and mainly affects the upper and lower respiratory tracts and the kidneys. The aim of this study was to investigate the survival and contributing factors in patients diagnosed with GPA between 2000 and 2013 in Hungary.
Method: In our retrospective, single-center study, 25 GPA patients (mean age: 46.04 ± 12.51 years) were followed-up for 5.78 ± 3.36 years. We evaluated their clinical and laboratory data, assessed organ involvements and Vasculitis Damage Index (VDI) scores. Survival time and rate were assessed using Kaplan–Meier estimator; Cox regression was used to predict poor outcome of the disease.
Results: At disease onset among the patients, the most frequent organs involved were ear, nose, throat (ENT; 72%), lungs (68%) and kidneys (48%). ANCA positivity was present in 68% of all the patients. Three months after the disease onset, the mean early VDI score was 2.64 ± 1.29, which increased to 3.84 ± 1.91 at the end of follow-up. The overall 1-year survival rate was 92%, the 5-year survival rate was 72.7%, while the mean survival was 125.3 months.
Conclusion: The longer diagnostic delay, ANCA-positivity and male gender were prevalent in the group of patients with poor outcome.

1302
Clinical, imaging and laboratory-based definition of Takayasu arteritis progression parameters

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Background: Takayasu arteritis (TA) is an orphan idiopathic inflammatory disease. A major pitfall in TA studies is the absence of a reliable modality to describe TA evolution and activity. Morphological vascular progression represents a relevant clinical outcome, given the prognostic impact of cardiovascular complications. We thus used Magnetic Resonance Angiography (MRA) as the reference for the assessment of disease evolution and morphological progression and performed an exhaustive follow-up of patients with multiple MRA assessments. We verified if variables currently used in clinical practice as well as functional imaging data could predict the concurrent morphological progression.
Method: We enrolled 16 TA pts, for which 38 couples of MRA examinations performed within 24 months were available.

Morphological progression within each couple was defined as the occurrence of new lesion(s) or worsening of at least one of the pre-existing lesions. Wall contrast enhancement (CE) was expressed as the difference of CNR (Contrast to Noise Ratio) pre- and post- infusion of contrast medium.

Results: Morphological progression occurred in 18/38 couples of MRA, despite effective treatment selected based on the most recent information available in the literature. All variables commonly used in the clinical practice failed to predict TA progression, except for maximum neutrophils values and radiological progression in the year preceding the first MRA of each couple. Wall CE at the first MRA within each couple was not associated with progression at the following MRA.

Conclusion: Most clinical, laboratory and functional imaging variables currently associated with TA activity fail to predict the vascular progression. Since they reflect the activation of systemic inflammatory pathways, our data suggest that other inflammatory pathways contribute to the clinical outcomes of TA pts. Their identification, and as such the identification of more effective targeted molecular therapies represent a major unmet medical need.

Poster Session Group III – Green

TPS 57 – Rhinoconjunctivitis and rhinosinusitis

1303
Atopic comorbidities in allergic rhinitis patients – Allergybarometer study

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Introduction: In the Finnish Allergy Programme 2008–2018 we aim to allocate resources to manage and to prevent severe allergies. In order to find gaps in treatment of allergic rhinitis we carried out a survey of allergy symptoms, use of medication and health care services in Finland.
Material and methods: In this study, we examined atopic comorbidity, symptom severity and use of health care services in allergic rhinitis patients. Study population was determined as those seeking for allergy or asthma medication in pharmacies all across Finland in September 2010. The respondents were 692 patients with self-reported physician diagnosed allergic rhinitis and 422 with other atopic disorders, all aged from 5 to 75 years.
Results: 66% of the allergic rhinitis patients had also asthma, 37% allergic conjunctivitis, 37% atopic eczema, 35% food allergy and 6% reported anaphylaxis. Only 11% of the allergic rhinitis patients did not have any other atopic disease. Self-reported mean severity of allergy was 4.7 (SD 2.1) in allergic rhinitis patients and 2.9 (SD 2.6) in patients with other atopic disorders in scale from 0 (no symptoms) to 10 (severe symptoms; $P < 0.001$). Need for allergy medication (mean 3.5; SD 1.3) and nasal obstruction (mean 3.3; SD 1.2) were the most difficult worries and concerns in rhinitis patients in scale from 0 (not at all) to 5 (very much). Daily use of nasal corticosteroids was reported by 32% of the respondents with allergic rhinitis and 9% of those with other atopic disorders ($P < 0.001$); likewise, 45% of the respondents with allergic rhinitis used antihistamines daily and 14% of those with other atopic disorders.
Conclusion: Most of the allergic rhinitis patients (89%) had other atopic diseases emphasizing clinical outcome of atopy as being a syndrome rather than one single disease. Only 6% of the allergic rhinitis patients had visited emergency department in the last 12 months because of allergies.

1304
Relationship between rhinitis and respiratory symptoms in primary school children

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Background: There is a complex relationship between nasal and lower airway symptoms, independently of the diagnosis of asthma, particularly in children.
Method: To evaluate whether rhinitis is associated with symptoms related to lower airway involvement, as cough, wheezing and dyspnea, and whether this relationship is independent of asthma and allergy, we analyzed data collected using standardised parental questionnaire in all children ($n = 681$, M:F 0.99, mean age 8.2 years, range 6–10 years) of a primary school of Barletta (Italy), accounting for 12.5% of the whole primary school population.
Results: Rhinitis was reported by 25% of children, with no significant gender prevalence, while cough and wheezing were reported by 11.3% and 4.7%, respectively. Cough prevalence was significantly higher among children with rhinitis compared to children without rhinitis (31.8% vs 5.4%, respectively, $P < 0.0001$), as well wheezing prevalence, which was reported by 15.3% of children with rhinitis, compared to 1.4% of children without rhinitis ($P < 0.0001$). Physician diagnosed allergic rhinitis was reported by 11% of children, who showed a highest prevalence of cough and wheezing, compared to children with non allergic rhinitis (48.9 vs 25.8%, $P = 0.004$ and 29.8 vs 10%, $P = 0.002$, respectively). Physician diagnosed asthma was reported by 3.1% of children, who reported rhinitis in 61.9% and cough in 33.3%.
Conclusion: Rhinitis and cough, with and without wheezing, coexist in a substantial percentage of children, particularly those with allergic rhinitis, independently of the diagnosis of asthma.

1305
Self-medication in persistent rhinitis: overuse of decongestants in half of the patients

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Background: Patients with rhinitis often self-medicate with over-the-counter drugs, however this self-treating population has remained largely unstudied.
Objective: To characterise individuals self-medicating persistent rhinitis and to determine the prevalence of and risk factors for intranasal decongestant overuse within this population.
Methods: Cross-sectional observational study of individuals self-medicating persistent rhinitis (defined according to the Allergic Rhinitis and its Impact on Asthma guidelines). Participants ($n = 895$) completed a self-administered questionnaire to assess current symptoms, rhinitis medication and previous physician diagnosis. Intranasal decongestant overuse was defined as daily use for at least 1 year.
Results: The vast majority (95%) of subjects had moderate to severe rhinitis. Nasal congestion was the predominant symptom [median Visual Analogue Scale, 66 mm (interquartile range, 48–82)]. Sixty-five percent suffered from their current nasal problems since more than 5 years. About 80% had a physician diagnosis (mainly allergic rhinitis or rhinosinusitis). Intranasal decongestants (used by 70% of the study population), nasal saline (40%), intranasal glucocorticosteroids (30%) and oral decongestants (21%) were the most commonly used rhinitis products. Prevalence of intranasal decongestant overuse was high (49%), despite the fact that most of the patients (80%) were educated about the limit on duration of use. Use of intranasal glucocorticosteroids was inversely

correlated with being an overuser (odds ratio, 0.24; 95% CI, 0.17–0.35).
Conclusion: Half of individuals self-medicating persistent rhinitis overused intranasal decongestants, despite the fact that they were well educated about the limit on duration of use.

1306
Prevalence of allergic rhinitis to house dust mite at 1 year of age in a Chiba city birth cohort (interim analysis)

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Background: The sequential development of allergic diseases (beginning with food allergy and atopic dermatitis followed by asthma and allergic rhinitis (AR)) during early childhood is often referred to as the allergy March. But early onset of AR is poorly described, and it remains unknown about the prevalence of allergic rhinitis in young children.
Objective: We aim to elucidate the prevalence of AR at 1 year of age in Japanese population (inner-city birth cohort) and analyze the relationship between AR and allergic sensitisation to food allergens.
Subjects: Two hundred and sixty-nine infants in an inner-city birth cohort with atopic family history in Chiba, Japan.
Method: We determined serum levels of specific IgE to house dust mite (*Dermatophagouides pteronyssinus*: Der p), cat (*Felis domesticus*: Fel d) dander, cedar (*Cryptomeria japonica*: Cry j) pollen, egg white (EW), and milk at 1 year of age. AR was diagnosed with sensitisation to house dust mite, disease-specific questionnaire, and physical examination by otolaryngologists.
Results: Among 269 infants, 18 infants (6.7%) were sensitised to Der p. 24 (8.9%) had positive history of rhinitis symptom and positive finding by otolaryngologist examination, and five (1.9%) were diagnosed as AR. Among those five infants with AR, four infants were positive serum IgE to EW.
Conclusion: The prevalence of AR at 1 year of age in Japan is about 2%. It is suggested that sensitisation to food allergen may be involved related in to the development of AR to Der p.

1307
Epidemiology of elderly rhinitis in relation to atopy and living area

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Background: Rhinitis is a prevalent and significant medical condition in the elderly. However, contributing factors for rhinitis are largely unknown in the aged population. The aim of the present analysis is to explore determinants of rhinitis in elderly population samples from different living areas.
Method: The present study analyzed the characteristics of elderly persons from three different regions (rural, semi-rural, and urban), which were retrieved from two cross-sectional community population surveys in Korea. Rhinitis was examined in relation to various demographic or clinical parameters, such as residence area, age, gender, smoking, obesity, comorbidity, or atopy. Rhinitis was defined by structured questionnaires, and atopy was defined by the presence of inhalant allergen sensitisation in skin prick tests.
Results: A total of 1313 elderly persons were analyzed (rural, $n = 265$; semi-rural, $n = 193$; and urban, $n = 853$). Rhinitis was significantly more prevalent among urban resident elders (26.8%) than semi-rural (18.2%) or rural counterparts (11.5%); in univariate tests, male gender and diabetes mellitus also showed positive associations with rhinitis. Multivariate logistic regression demonstrated the strong independent associations between rhinitis and the urban residence. Atopy was also more frequent among urban elders (17.2%) than semi-rural (9.8%) or rural-living elders (6.0%), and in particular for indoor allergens such as house dust mites. However, rhinitis was mostly non-atopic, and the relationship between rhinitis and atopy was not significant in all of three study areas.
Conclusion: The present analysis provided epidemiological evidence that elderly rhinitis was less atopic but more significantly influenced by environmental factors such as urbanization.

1308
Patients' preferences in the therapy of pollen-allergic rhinoconjunctivitis – a discrete choice experiment

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Objectives: The increasing emphasis on shared decision making and patient-centred health care requires an intensive exploration of patient preferences. In the present study, patient preferences regarding treatment of pollen-allergic rhinoconjunctivitis (AR) were assessed using qualitative and quantitative methods.
Methods: Following a literature research, three focus groups with 27 therapy-naive pollen AR-patients were conducted in the qualitative pre-study to elicit quality criteria of therapies according to the patients. In the subsequent quantitative pretest ($n = 24$) and main study ($n = 527$) patient preferences for therapy characteristics were assessed and analysed using direct measurements with 18 items as well as a discrete choice experiment (DCE) with six characteristics with a positive and a negative pole each with eight pairs in an orthogonal fold-over design.
Results: Five hundred and twenty-seven pollen-allergic therapy-naive patients with a middle to high burden of disease (≥5 points on a 0–10 scale) completed the questionnaire of the main study. Of 58% were male and almost half of the participants were younger than 35 years (44%).

In the direct assessment (5-point Likert scale transformed to values from 0 to 100) the most relevant therapy characteristics out of 18 assessed were 'high probability of success', 'clear (min 50%) reduction of symptoms', 'low risk of heavy side effects', and 'reduction of complaints' with 85/86 points as the general mean value.

In the DCE 4196 choices were the base of the random effects model analysis. Most relevant for the patients' choices were 'mode of application (injection vs oral; self vs physician)' (coeff. = 1.74) and 'reduction of symptoms' (1.68) followed by 'broad spectrum of effects (>1 allergen)' (1.00). Less important were 'short period of recovery' (0.57) and 'long term effects' (0.25), all significant with $P < 0.01$. For the sixth parameter 'interruptions in treatment' (0.09) no significant effect was found.
Conclusions: The main result of the DCE is the high impact of characteristics of treatment flexibility (self-treatment, mode of application, short period of recovery) and reduction of symptoms for AR-patients. The quality of potential treat-

ments (existing or virtual) through the eyes of the patients can be assessed using this preference model.

1309
Discovering the trends in allergic diseases using google trends

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Background: Google Trends is a web-based surveillance tool to visualize the trends of searching specific queries by analyzing the temporal and spatial frequencies of Google search. Google Trends has proved to reliably predict the epidemics of influenza and dengue fever and offers a new insight in understanding for various social and scientific aspects. However, it has not been sufficiently studied yet in allergy.
Objective: To explore the trends of various queries for allergy on Google search.
Method and results: Google trends can visualize the variation of relative frequencies of searching queries over time series and by location. The queries on 'allergic rhinitis' and 'asthma' showed the repetitive seasonal variations each year, whereas the queries on 'food allergy' and 'atopic dermatitis' did not. The searching volumes about allergic rhinitis reached peak in April-May in Western Europe including UK and the United States. However, the reversal was observed in Australia, which the peak of searching volume has observed in November. The trends of allergic rhinitis has been highly correlated with the temporal variation of queries on 'seasonal allergy', 'hay fever', 'pollen', 'pollen.com' as well as 'antihistamines' such as claritin and zyrtec (all correlation coefficients >0.85 and all $P < 0.01$). In the US, the small peaks for searching queries on 'allergic rhinitis' and 'pollen count' were also observed in September, but these trends were not observed in UK. The frequency of searching 'ragweed' was 4-fold increase in September compared with that of July in US, which was not observed in UK.
Conclusion: Queries on allergic diseases analyzed using Google trends showed the distinct seasonal patterns and trends, but varied by location. Further studies comparing the trends of queries in Google with the real-world epidemiological data on various allergic phenomenons are needed.

1310
Prevalence trends and risk factors of rhinoconjunctivitis – two cross-sectional studies in Georgia

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Background: In recent decades, a large number of epidemiological studies investigating the change of prevalence of allergic rhinitis showed an increase in the occurrence of this disease. The aim of our study was to investigate prevalence, time trends and factors associated with rhinitis and rhinoconjunctivitis not related to acute infections in Georgia.
Method: The International Study of Asthma and Allergies in Childhood (ISAAC) surveyed children aged 6–7 and 13–14 years for symptoms of these conditions. Two centres were surveyed on two occasions (Phase Three and Phase Five) 9–10 years apart. In Phase Five, questions were included on environmental factors, which might be associated with rhinoconjunctivitis. We report findings related to symptoms of rhinoconjunctivitis among 11 513 Georgian children.
Results: Symptoms of rhinoconjunctivitis in the past year were reported in 4.5% (95% confidence limit: 4.0–5.0) of 6- to 7-year-old children and 9.0% (8.2–9.8) of 13- to 14-year-old adolescents in Phase Five compared with 2.5 (2.2–2.8) and 5.7% (5.1–6.3), respectively, in Phase Three. The association was found between symptoms and having the pets inside during the first year of life (OR, 95% confidence interval: 1.51, 1.12–2.04) at 6- to 7-year-old children and past year (1.35, 1.11–1.65) at 13- to 14-year-old adolescents, as well as self-reported truck traffic on the street of residence in both age groups (1.41, 1.10–1.80 and 1.53, 1.27–1.85 correspondently). Weaker associations were noted for antibiotic use and exercise. The diet factors that reduced risk of allergic rhinoconjunctivitis were consumption of fruit (0.77, 0.62–0.96), seafood (0.67, 0.44–1.00) and egg (0.74, 0.54–0.99) three times or more per week.
Conclusion: Our results confirm the increasing of prevalence of rhinoconjunctivitis and reveal some factors strongly associated with allergic rhinitis in Georgia. Further study of environmental factors is recommended.

1311
Suppressive effects of IL-8, ECP and total IgE in the tear of atopic keratoconjunctivitis by rebamipide eye drops

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Background: Rebamipide, a gastroprotective drug, has been reported to suppress gastric mucosal inflammation. In Japan, rebamipide eye drops have recently been approved for the treatment of dry eye disease. The purpose of this study was to evaluate the anti-inflammatory effects of rebamipide eye drops on atopic keratoconjunctivitis.
Methods: Eight eyes of four patients with atopic keratoconjunctivitis were instilled rebamipide eye drops four times daily. All four patients had dry eye with decreased tear-film break-up time. Before and after the treatment of rebamipide eye drops, tears were collected with Schirmer test papers and frozen until measurement of the cytokines. Normal healthy volunteers were also measured as control. IL-8, MCP-1, IP-10, and total IgE levels in the tears of these eyes were examined using cytokine bead assay, and the ECP levels in the tears were examined using ELISA.
Results: IL-8, ECP and total IgE, but MCP-1, IP-10, levels were significantly higher in atopic keratoconjunctivitis than normal controls, and IL-8, ECP and total IgE, but MCP-1, IP-10, levels in the tears of atopic keratoconjunctivitis patients decreased after treatment with rebamipide eye drops.
Conclusions: Our findings suggest that rebamipide eye drops might attenuate IL-8, ECP and total IgE levels in the tears of atopic keratoconjunctivitis patients. In addition to the treatment of dry eye, rebamipide eye drops may also be useful for the treatment of atopic keratoconjunctivitis.

1312
Impact of moderate/severe non-controlled allergic rhinitis on work and academic productivity in adults. ENERGY study

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Background: Factors that can influence on work or academic productivity and quality of life (QoL) of adult patients with moderate/severe rhinitis non controlled with symptomatic treatment have been scarcely studied. The aim of this study was obtain some data on that.
Method: Observational, multicenter and cross-sectional study. Allergic patients to pollens or mites whose principal activity included paid work or studies were recruited. It was carried out between March 2011 to March 2012.

For the evaluation of the impact of allergic rhinitis on QoL, work and academic productivity, ESPRINT-15 and WPAI + CIQ:AS questionnaires were used, respectively.
Results: Six hundred and eighty-three adult patients were recruited. The average age was 33.2 ± 10.3 years (51% females). The average evolution for AR was 10.8 ± 8.8 years. 48% had asthma and 65% conjunctivitis. 76% of the patients were being treated with AIT (IR/ml) for a mean time of 12.78 ± 14.20 months, the remaining did not received it. In case of academic/work performance, bivariate analysis showed the same picture as well as the multivariable analysis. It showed the benefits of AIT (Coefficients: −10.4 for work productivity lost, −11.9 academic performance). For the QoL assessment, the bivariate analysis identified these associated factor that influence negatively: visiting the allergist <3 times a year, having a persistent AR, a moderate/severe AR and not being under AIT. The multivariable analysis showed that AIT is the factor the most positive influence in QoL (Coefficients: −0.8 for workers and −1.1 for students).
Conclusion: The results of ENERGY study reflect for the first time that AIT (IR/ml) is the factor that more positively influence in work productivity, academic performance and QoL in adult patients suffering a uncontrolled moderate/severe allergic rhinitis.

1313
Allergic rhinitis frequently remains under-diagnosed: poorly-controlled AR imposes significant burden

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Background: Symptoms of allergic rhinitis (AR) include nasal congestion, rhinorrhea, sneezing, and ocular itching. Whereas poorly-controlled AR imposes substantial patient burden, including sleep disturbance, daytime fatigue, decreased cognitive functioning, impaired school and work performance, mood instability, and decrements in social functioning, treatment may mitigate AR-related burden. A small body of literature suggests that AR is under-diagnosed. Consequently, a segment of patients with undiagnosed AR who are appropriate for treatment may unnecessarily bear the burden of poorly-controlled AR.
Objective: To identify the percentage of patients with long-standing, clinically confirmed AR per clinical exam and skin prick or IgE test who previously have never received a physician-based AR diagnosis.
Method: Systematic literature review of original studies from 1960 to January 10, 2014 using MEDLINE terms: (underdiagnoses OR under-diagnosis OR undertreatment OR under-treatment OR practice variations OR practice patterns) AND (allergic rhinitis OR hay fever).
Results: Among 144 unique studies, 46 were included. Excluded were 98 (10 secondary sources and 88 not relevant). Of relevant studies, 17 pertained to patient, 22 provider, and 1 to environmental characteristics associated with having previously received a physician-based AR diagnoses. Six studies reported that 29–70.5% of patients with long-standing, clinically confirmed AR previously had not received a physician-based AR diagnosis (Table 1).

Table 1. Citations, population descriptions, and percentage of patients with clinically confirmed AR at follow-up who previously had never received a physician-based AR diagnosis.

Bachau, 20041	Western European adults 45%
Bunyavanich, 20092	Costa Rican children with asthma 70.5%
Larsen, 20133	Danish adults 43%
Nolte, 20064	Danish adolescents and adults 32%
Sazonov, 20095	European adults with asthma 18%
Sibbald, 19916	Adults with seasonal AR in London 29%

Conclusion: AR may be undiagnosed by physicians in approximately one- to two-thirds of cases.

1314
Prevalence of chronic rhinosinusitis in childrens with bronchial asthma

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Background: The purpose of the study was to evaluate alteration of sinus mucosa in selected patientswith pulmonary disease.
Method: The analysis of prevalance of chronic rhinosinusitis in 248 children 4–12 years old with various pulmonary diseases was made. The medical history of the patients was examined with the help of parents by some standard questionnares about the symptoms of present disease of previous E.N.T. disorders, previous treatments, the frequency of antibiotics administration pointing out the subjective symptoms: nocturnal cough, nasal obstruction, rhinorrhea, nasal congestio, oral breathing, nasal voice, hyposmia, postnasal drip, headache. After the inspection of the face and of the anterior cervical region we proceeded to systematic palpation of sinus points. This was followed by the specific E.N.T. objective endocavitary examination: narinoscopy, anterior rhinoscopy in two position: horizontal and oblique, examination of the oral cavity, posterior rhinoscopy, indirect laryngoscopy and otscopy. All patients underwent axial paranasal sinus computer tomography examination of paranasal sinuses to evaluate the status of paranasal sinus mucosa: swolen, liquid, cystic degeneration.
Results: In a group of 62 asthmatic chidren 21 (33.8%) had some alteration in sinuses. In another group children (n = 42) with other atopic diseases chronic catharal rhinosinusitis were observed in seven (16.6%) individuals, but in a group of the children with other non-atopic pulmonary diseases (n = 144), rhinosinusitis was found in only nine (6.25%) individuals. The correlation between the severity of asthma and prevalence of rhinosinusitis was found. In children with severe asthma the abnormality of sinuses were found in over 65% individuals.
Conclusion: Among young chidrens with bronchial asthma chronic rhinosinusitis can be found in 33.8% inividuals and iti is far more frequent than amng patients with other non-atopic pulmonary diseases (6, 25%).

1315
Skin prick test reactivity to aeroallergens among Egyptian patients with isolated allergic conjunctival disease

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Background: Allergic conjunctival disease (ACD) is a type of ocular allergy, which includes seasonal allergic conjunctivitis (SAC), perennial allergic conjunctivitis (PAC), and vernal keratoconjunctivitis (VKC). Usually, it is associated with allergic rhinitis but it may be observed as the only allergic sensitisation. There are almost no data about the pattern of sensitisation or prevalent aeroallergens among patients with isolated ACD in Egypt. We aimed to evaluate the prevalence of skin prick test positivity to common aeroallergens among Egyptian patients with isolated allergic conjunctival disease.
Method: This study included 75 patients with isolated ACD recruited from a tertiary Egyptian outpatient clinic. Skin prick test (SPT) was performed for all patients with a panel of 14 common aeroallergens. Total serum immunoglobulin E (IgE) was performed for all patients by ELISA.
Results: A positive SPT reaction was present among 32 patients (42.7%). The most prevalent aeroallergens among patients with ACD were mites and pollens (12% respectively), followed by grass (8%). Eight patients (10.7%) had SAC, 19 patients (25.3%) had PAC, and 48 patients (64%) had VKC. Prevalence of SPT positivity to indoor allergens was significantly more common among PAC (52.6%) than among SAC (25%) and VKC (16.7%), $P = 0.011$. Outdoor allergen sensitisation did not differ significantly between the three subgroups, $P = 0.614$. High IgE levels were observed among 62.5%, 73.7% and 66.7% of patients with SAC, PAC and VKC, respectively, with no statistically significant difference between them, $P = 0.806$.
Conclusion: Aeroallergen sensitisation is common among Egyptian patients with isolated allergic conjunctival disease. Accordingly, skin prick test should be included in the diagnostic workup of these patients.

1316
Drug induced rinitis: case series of 55 patients

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Background: Drug Induced Rhinitis (DIR), oral and topical, is a type of rinitis non-allergic, represents 6–9% of total rinitis. There are few references in the literatura of DIR, not being a well-known Adverse Drug Reaction (ADR) and sometimes it is not included in the summary of product characteristics.
Method:
Design: Case series, 55 patients with DIR, average age: 68.1 years (37–85); 36 females.
Scope: Allergy service, Hospital Central de la Defensa; Madrid.
Period: 1 March 2009–31 December 2013.
Main Variables assessed: demographic and clinical variables, diagnostic criteria, treatment, evolution, causal relationship between drugs and rinitis according to the modified Karch Lasagna algorithm.
Results: Drugs involved: contraceptives ($n = 2$); oxymetazoline ($n = 2$); alfa adrenergic agonist ($n = 1$); Angiotensin-Converting Enzyme Inhibitors (ACEI)/Angiotensin II Receptor Antagonist (ARAII)/Direct Renin Inhibitor (DRI; $n = 50$). More frequently involved drugs were enalapril (30 cases), valsartan (15 cases) and losartan (9 cases). Severity: Severe rinitis with anosmia ($n = 5$); moderate ($n = 50$). Average time evolution: 21 months (0.5–120). Re-exposure to drug ($n = 27$). Treatment: Drug withdrawal, achieving complete remission in all cases, in average time of 7.2 weeks (3–12 weeks). Causal relationship between drugs and rinitis were defined in 27 cases and probable in the rest.
Conclusion: Active drugs on the renin-angiotensin system ACEI/ARAII/DRI are the main cause of DIR. As they are widely used and they should be taken into account in moderate/severe persistent rhinitis. DIR is underdiagnosed considering the average time evolution, the physicians should include it in the differential diagnosis of rhinitis.

1317
Total antioxidant capacity of the diet in relation to allergic rhinitis at age 16 years

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Background: Dietary intake of antioxidants has been hypothesized to influence the development of allergic disease. Previous studies has examined dietary intake of specific vitamins and minerals. Total antioxidant capacity (TAC) aims to assess the cumulative and synergistic activity of all antioxidants present in diet. Our objective was to study the association between the TAC of diet and allergic rhinitis at age 16 years.
Method: The study was performed in the Swedish prospective birth cohort BAMSE. The TAC of the diet at age 8 years was estimated combining information from a food frequency questionnaire with a database of common foods analyzed with the oxygen radical absorbance capacity (ORAC) method. Dietary TAC was calculated by multiplying the average frequency of consumption of each food item by ORAC content (μmol Trolox equivalents) of age-specific portion sizes, and energy-adjusted with the residual method. Serum IgE levels of antibodies to airborne allergens were analyzed at age 16 years using Phadiatop. Rhinitis was defined as reported symptoms from eye/nose after exposure allergens (latest 12 months) or having received a physician's diagnosis of allergic rhinitis. Logistic regression was used to examine the association between dietary TAC (divided into quartiles) at age 8 years and rhinitis in combination with sensitisation to airborne allergens (phadiatop) at age 16 years (hereafter called allergic rhinitis) using as reference category children with no rhinitis and no sensitisation. In total, 2025 children were included in the analyses.
Results: The major contributors to dietary TAC were fruits (39.8%), juices and jam (15.8%), and whole grains (12.1%). Supplements were not included in the dietary TAC. The prevalence of allergic rhinitis at age 16 years was 24% ($n = 487$). A significant inverse association was observed for TAC and allergic rhinitis ($OR_{adj} = 0.69$, 95% CI 0.50–0.95 for highest vs lowest quartile, P for trend 0.038). The inverse association was diluted and no longer statistically significant after exclusion of chil-

dren who avoided fruits and/or vegetables due to allergic symptoms (n = 194).
Conclusion: In the Swedish birth cohort BAMSE, we observed an inverse association between the TAC of the diet and allergic rhinitis at age 16 years, although the association was diluted after exclusion of children who avoided fruits and/or vegetables due to allergic symptoms.

1318
Therapeutic effect of capsaicin nasal treatment in patients with mixed rhinitis unresponsive to intranasal steroids

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Literature is convincing regarding the efficacy of capsaicin nasal treatment in idiopathic rhinitis (IR). However, up to 50% of IR patients do not meet the strict inclusion criteria of the trials conducted so far. As a consequence, the efficacy of capsaicin is unknown in a significant number of IR patients that do not meet these strict inclusion/exclusion criteria. 'Mixed rhinitis' patients have more than one major etiologic factor involved in the mucosal pathology. We have no idea about the efficacy of capsaicin nasal spray in these patients nor about the time interval to seek a second application. We report here that capsaicin nasal spray is effective in a broader group of IR than the purely selected ones described before and that the time interval for seeking a second treatment is likely to be shorter in mixed rhinitis patients than in the strictly selected IR patients.

1320
Prevalence of allergic rhinitis in elderly patients of an allergy clinic in Niterói, Brazil

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Background: Rhinitis symptoms affect significantly the quality of life in elderly patients. Nevertheless, data from this disease in geriatric population is sparse. The aim of this study is to describe the prevalence of allergic rhinitis and the profile of sensitisation to aeroallergens in this population.
Method: Cohort study of patients with nasal symptoms assisted at Fluminense Federal University (UFF) Immunology Service in Niterói, Brazil and analyzis of the results of skin prick tests (SPT) performed between August 2013 and March 2014. Data were analyzed through Excel statistics tools.
Results: A total of 62 patients were evaluated, with a mean age of 51 year old (13–85 year old) and 51 female (82%). All patients had rhinitis symptoms and 19% had rhinitis and asthma associated. Regarding the SPT, 76% were negative. In 15 patients (24%) we observed positivity for at least one aeroallergen (93% to *D. pteronyssinys*, 80% to *B. tropicalis*, 13.3% to cat and 6.6% to dog). In the subgroup of patients ≥65 year old (15 patients), atopy was observed in only 13%, with positivity in SPT mainly to house dust mite, despite the high prevalence of rhinitis symptoms in this population (sneezing 73%, nasal itching 66% and nasal obstruction 46%).
Conclusion: Allergic rhinitis in elderly subjects of our cohort was observed in only 13%, wich draws attention to the possibility of other etiologies in this age group, including local allergic rhinitis.

1321
Monosensitisation to the tree of heaven *(Ailanthus altissima)* pollen in allergic rhinitis

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Background: Diagnosis of allergic rhinitis is based on clinical manifestations and positive results for SPTs or sIgE antibodies to aeroallergens. Negative results for SPTs and sIgE may lead to a diagnosis of NAR. Allergists are often called to evaluate patients with undetectable sIgE but clinical manifestations consistent with seasonal allergic rhinitis. Local nasal IgE production has been proposed as an explanation, but primarily sensitisation to rare pollens should be excluded. *Ailanthus alt*. is mainly anemophilous and blooms from April to June. Only multisensitisation has been described so far in *Ailanthus* pollen skin positive patients.
Method and results: We report two patients, manifesting seasonal (April–June) rhinitis symptoms, who were proved to be monosensitised to *Ailanthus* pollen.

Patient 1: a 38-year-old man with symptoms of rhinitis from April to June the last 10 years. He also presented symptoms of seasonal conjunctivitis but no asthma symptoms. After being tested negative for all common aeroallergens, an SPT with *Ailanthus* pollen extract was conducted as the patient suspected the tree as the causative agent of his symptoms. SPT induced a 10 mm wheal. A nasal provocation test showed sneezing, nasal pruritus and blockage with a 55% fall from baseline PNIF.

Patient 2: a 33-year-old woman with rhinitis symptoms during the same pollen season the last 5 years. SPT to *Ailanthus* provided a 5 mm wheal while no skin nor IgE reactivity were observed for common aeroallergens. Furthermore, a control group of 21 non atopic individuals was tested negative with the same pollen extract preparation.
Conclusion: To our knowledge, we report the first cases of monosensitisation to *Ailanthus* pollen. Diagnostic evaluation with *Ailanthus* pollen should be considered in patients with symptoms suggestive of seasonal allergy but negative results in SPTs and serum sIgE to all common pollen allergens, especially in areas where this tree is widespread.

1322
Micronized cellulose powder enhances and augments the effect of locally applied decongestant in patients with allergic rhinitis

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Background: Prolonging the contact time of locally applied drugs with the nasal mucosa would improve their efficacy. One way is to develop dosage forms containing mucoadhesive polymers like methylcellulose. An alternative would be to 'seal' the applied nasal drug with adhesive powder so that the formation of a gel layer could delay its clearance. The aim of our study was to document the feasibility of this approach with objective measures.
Methods: This double blind placebo controlled study was conducted in 40 subjects (mean age 35 years, 23 women) with persistant allergic rhinitis with prominent congestion. We randomized them to one puff oxymetazoline followed by either one puff of commercially available micronized cellulose powder (test treatment, TT) or lactose powder used as sham (reference treatment, RT). After the first application on Day (D) 1, peak inspiratory nasal flow (PNIF, l/min) was measured at minutes 0, 1, 2, 5, 15, 30, 60, 120 180, 240, 300 & 360, areas under the curve (AUC) were analyzed. After 1 week of regular b.i.d. treatment, the procedure was repeated on D8. Patients were followed up without regular treatment and baseline PNIF was measured on D15.

Results: Eighteen patients from each arm completed all three visits. AUCs at D1 showed superiority of TT, 56366.3 (mean) ± 3514.4 (SEM), over RT, 46818.5 ± 2847.3, $P = 0.042$. On D8 this difference was further enhanced: 60855.7 ± 3227.1 vs 49411.1 ± 2395.1, $P = 0.009$. Baseline PNIF rose for both treatments from D1 to D8, but further increased in TT on D15 reaching statistical significance: TT vs RT: 93.1 ± 5.4 vs 100.0 ± 7.3, $P = 0.354$ (D1); 135.6 ± 10.0 vs 124.2 ± 8.1, $P = 0.383$ (D8); 158.1 ± 10.9 vs 125.0 ± 6.6, $P = 0.013$ (D15).
Conclusion: Micronized methylcellulose powder enhances the decongestant effect of nasal oxymetazoline in patients with allergic rhinitis. One week of such regular treatment augments the nasal patency and this effect carries over for another week after its discontinuation.

1325
The prevalence of allergic rhinitis in Northern Turkey: a population based study and a comparison of allergic rhinitis and nasal polyp

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Background: The clinical diagnosis of allergic rhinitis (AR) includes the presence of clinical symptoms and laboratory evidence of immune response. However there are some difficulties to evaluate both of them in the prevalence study. Our aim was confirmed the prevalence of AR by clinical symptoms, clinical sign and skin test in Tokat Province in Northern Turkey.
Method: The present study was conducted April 2013 and August 2013 and designed as a part of the prevalence of chronic diseases in adults (over the age of 20) in Tokat Province (TEKHAP study). This wide variety epidemiological study has been planned population-based, cross-sectional. The targeted population was found 2635. The ENT specialist asked main symptoms allergic rhinitis and wanted to response the questions according to visual analog score (VAS). Then, nasal endoscopic examination and skin test was used.
Results: In the end of study, it was reached 2527 subject. The prevalence of AR was 2.9% in take account of clinical findings and confirmed skin test. Subjects were separated to three groups respect to age (20–39 age, 40–64 age and over 65). The prevalence of AR was 4.3%, 2.6% and 0%, respectively and an important difference statistically was in between groups ($P < 0.05$). The prevalence of nasal polyp (NP) was found 3.3% (according to age groups, 1.65%, 4.2% and 4.8%, respectively ($P < 0.05$). Interestingly, never of subjects with allergic rhinitis had NP.
Conclusions: The study given our AR prevalence 2.9% regarding to both clinical symptoms and positive skin test and, AR was disease younger adult. Also NP prevalence was found 3.3% and, NP was disease elderly population compared to AR. It is noted that the patients with AR were not polyp positive. The present study was demonstrated that AR and NP have same prevalence in difference age.

1327
Therapeutic management of chronic maxillary sinusitis

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Background: Chronic maxillary sinusitis (CMS) in adults is a significant problem of the health due to its frequency. It is caused by chronic inflammation of the nasal and sinus lining for over 3 months and may be preceded by an acute episode. The aim is to present 36 cases with CMS with allergic etiology and their therapeutic management.
Method: The diagnosis of all cases was based on typical signs and symptoms, X-ray examination, CT scan of paranasal sinuses, nasal endoscopy and skin-prick tests or RAST to confirm the allergic elements of chronic symptoms. The surgery was applied in all cases with CMS non-responsive to medical treatment (antibiotics, oral antihistamines, intranasal steroids and nasal decongestants). In 16 cases we performed endoscopic sinus surgery (ESS) via the canine fossa. External surgical approach Caldwell-Luc procedure was performed in the rest 20 cases.
Results: Follow-up ranged from 1 to 3 years with a median of 2.5 years. External procedure remove all the diseased mucosa with the hope that new healthy mucosa will regrow. Endoscopic sinus surgery revealed no recurrence. Allergic CMS has a good prognosis after surgery and post-operative steroid treatment. Long-term topical steroids control relapses and prolonged follow-up was required.
Conclusion: The therapeutic management of CMS included external approach or combined endoscopic procedures in order to ensure best results. Endoscopic sinus surgery is the gold standard therapy for CMS non-responsive to conservative treatment.

1328
The CO_2 laser surgery for chronic hypertrophic rhinitis

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Background: The aim of the study is to present the efficacy of CO_2 laser surgery in the treatment of chronic hypertrophic rhinitis. The CO_2 laser surgery of hypertrophic inferior turbinates is a treatment of choice in allergic and non-allergic chronic rhinitis, refractory to local and general conservative treatment.
Method: A group of 68 patients, 28 males and 40 females, aged 18–55 year old, main age 25.3, with chronic hypertrophic rhinitis refractory to medical treatment were treated by CO_2 laser surgery. We used the specially hand-pieces single-laser spot technique. Shrinkage of the mucosa with subsequent scarring can be observed during the laser procedure. It is important to keep intact mucosal island between the lasers spots, from which rapid reepithelialization can originate. The pre and postoperative control included anterior nasal rhinoscopy, nasal endoscopic examination and evaluation of subjective symptoms related by the patient: nasal obstruction, rhinorrhea, sneezing, nazal itching. The follow up was performed at 1, 6 and 12 months after surgery.
Results: The surgery was performed under local anesthesia, with no pain or bleeding. Healing was complete in 3–4 weeks. The subjective findings reported by the patients after the CO_2 laser surgery were classified as excellent, good, fair and no change. One month after the laser surgery, the subjective results revealed excellent and good results in 81% cases. Long term results at 12 months showed 87.5% excellent and good results.
Conclusion: The CO_2 laser surgery is the best option in bilateral inferior turbinate hypertrophy with significant advantages: excellent haemostasis, minimal postoperative discomfort, rapid wound healing and low grade morbidity.

1329
Idiopathic eosinophilic parotitis: a case report

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Background: Eosinophilic parotitis is characterised by recurring bilateral parotid swelling caused by obstruction of salivary outflow by plugs rich in eosinophils. It's a rare disease whose etiology and pathophysiology remain poorly understood. Massage by compressing the salivary glands, antihistamines and steroids should be considered for treatment. A new case of eosinophilic parotitis is reported only responded to treatment with montelukast.

Method: A 50-year-old woman presented recurrent bilateral parotid gland swelling for the past 8 years. Over time his symptoms progressed, featuring daily swelling, itching and pain. Her medical history was unremarkable and she had no history of atopy. Her symptoms were not associated with food or drugs.

Results:

- A skin prick test with aeroallergens, food and pan-allergens (LTP, profilin and polcalcine) was performed, with negative result.
- Total IgE was 5.27 kU/ml.
- Serum levels of specific IgE (CAP) against food, latex and parasites (Anisakis simplex, Echinococcus granulosus y Ascaris lumbricoide) were negative (< 0.35 kU/ml).
- Complete blood examination, immunological study including autoantibodies, serology test against microorganism and chest X-ray, were normal.
- A computed tomography (CT) scan reveated diffuse swelling of both parotid glans.
- In pathological anatomy showed that the mucous plugs from Stensen's duct contained numerous eosinophils.
- Cytology of nasal discharge no eosinophils were observed.
- Microbiological examination of plugs revealed normal bacterial flora.

After starting treatment with montelukast (10 mg/day) parotid inflammation decreased and symptoms disappeared.

Conclusion:

We report a new case of eosinophilic parotitis, of unknown etiology, that responds to treatment with montelukast.

Clinical efficacy of montelukast suggests cysteinyl leukotrienes involvement in this pathology.

Poster Session Group III – Green

TPS 58 – Hereditary angioedema – best practice

1331
A pilot study on the role of stress and emotional processes in the variability of hereditary angioedema (HAE) in childhood and adolescence

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Background: Hereditary Angioedema (HAE) is characterised by remarkable clinical variability and unpredictability of attacks. Previous studies suggested that stress and emotions can trigger HAE attacks. We carried out a study on 11 patients aged 4–17 years as well as their parents, to explore the connection between psychological factors and clinical symptoms of HAE.
Methods: We examined the psychopathological risk of the patients, the connection between stress and illness and how the parents interpret the causes of the attacks. The Child Behaviour Check-List (CBCL) questionnaire was administered to 11 parents to evaluate the psychopathological risk. The young patients completed the Coddington Life Events Scale (CLES) to assess the level of perceived stressful events. Finally, semi-structured interviews were administered to the parents to explore their interpretations of the factors responsible for the onset of the attacks.
Results: On the CBCL scales more than one half of the patients achieved critical scores: five patients in the *syndrome scale* (3 of them in thought disorders); six patients in the *scales dsm-oriented* (anxiety and somatic complaints); six of them in the activity scale (*competence scale*). In the CLES 10 patients out of 11 were above the normal levels of stress, but frequency of attacks was not proportionally increased. The interviews show that 10 families out of 11 consider emotions to play a part in the expression of HAE, even if interpretation of them as symptoms, triggers or consequences of HAE differs between families.
Conclusion: This pilot study confirms a connection between emotional and stressful factors and the onset of HAE attacks, even though a larger study is needed. The perception of stress in patients with HAE is above the norm and the recognition of the role of emotions is constant. These dimensions do not correlate sistematically with the variablility of the symptoms. It is likely that processes of *emotion regulation* play a role in the onset of the attacks.

1332
Hereditary angioedema – from genotype to phenotype

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Background: Hereditary Angioedema (HAE) is an autosomal dominant disease caused by mutations on the C1-inhibitor (C1INH) gene. Among the more than 250 known mutations is the missense mutation p.Arg444Cys, typical of type II HAE (HAEII). Apparently there is no genotype/phenotype correlation. No studies on Portuguese population so far. We aimed to report the mutation frequency on the C1INH-gene in two families (F1, F2) with HAEII and a possible genotype/phenotype correlation.
Method: We analyzed the clinical, laboratorial and genetic study of two families with HAEII followed at HSM's Immunoallergology department (IA-HSM). Genetic studies were performed by bidirectional sequencing of the eight exons of C1INH gene's, using PCR in more than 1700 sequencing reactions analyzed with SeqScape V.2 at CHC. The genotype/C1INH function correlation was evaluated by *t*-test (SPSS).
Results: F1: 5 generations with 101 individuals, 35 patients (34.65%) with HAEII, 28 (80%) followed at IA-HSM.22 (78.57%) with genetic study, mean age 47, 13 M 9 F; 18 (81.82%) harbored the isolated mutation p.Arg444Cys. In this group the mean C1INH function was 39% and 15 (83%) presented a moderate/severe phenotype. This mutation associated with others was identified in 4, mean C1INH function 9%; all presenting the same phenotype.

F2: 4 generations with 23 individuals, 9 (39.13%) with HAEII, 6 (26.09%) followed at IA-HSM. Four (66%) with genetic study, mean age 46, 3 M 1 F, all presenting the isolated mutation p.Arg444Cys, mean C1INH function 23.75% and all presenting a moderate/severe phenotype. There was a significant difference in C1INH function between the different groups (0.278; $P < 0.01$).
Conclusion: Both families with HAEII harbored the missense mutation p. Arg444Cys. Diagnosis based on the disease-causing mutation in these two families offers advantages, as it can be performed quickly and reliably, and answers the concerns about the disease in descendants. It appears that associated mutations cause a more severe phenotype.

1333
Clinical features and genetic analyses of type III hereditary angioedema patients

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Background: Hereditary angioedema (HAE) is a well defined autosomal dominant trait presented as Type I, Type II or Type III HEA. Our aim was to determine the prevalence of Type III HAE patients among all HAE patients and to analyze the clinical features and the genetic alterations in F12 gene.
Method: Type III HAE patients were selected among all HAE patients after detailed history, clinical examination and normal C1 INH, C4 levels and C1 INH function tests. Clinical symptoms and their durations, the duration of diagnosis, family history and the clinical treatments were assessed. All of the 14 exons of F12 gene (NM_000505.3) including the flanking regions were amplified and sequenced by sanger sequencing (ABI 3500).
Results: Twelve patients out of 80 HAE patients (15%) were diagnosed as Type III HAE. The longest duration of symptoms and diagnosis were 30 and 4 years, respectively. Two of the patients didn't have a family history for the disease. While six of these patients were receiving danazole prophylaxis, one patient was on prophylaxis

with C1 INH extract and four patients were having C1 INH only during their attacks.

One patient was treated with tranexamic acid. Genetic analyses were carried out in nine patients. Analysis of the sequencing chromatograms revealed a disease associated mutation in only one patient. This patient found to carry heterozygous c.983C>A resulting to the replacement of threonine at 328 by lysine (p.Thr328Lys) in exon 9. Another found to carry heterozygous c.G1027C resulting to the replacement of alanine at 343 by proline (p.Ala343Pro) in exon 10. Thr328Lys mutation identified in our patient was already reported as causative to HAE III, p.Ala343Pro was associated with FXII deficiency in one Japanese male.

Conclusion: The diagnosis of Type III HAE is relatively difficult and genetic analyses do not seem to contribute to the diagnosis in every patient. Therefore large population based analyses are needed to evaluate the significance of genetic alterations.

1334
A novel mutation at the C1 inhibitor gene, G345W, as the cause of hereditary angioedema in a Turkish family

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Background: Hereditary angioedema is an autosomal dominant disease, caused by deficiency of the C1 inhibitor protein, leading to recurrent episodes of angioedema. HAE is caused by mutations affecting the C1 inhibitor gene, SERPING1, resulting in low levels of C1 inhibitor (Type I HAE) or normal levels of ineffective C1 inhibitor (Type II HAE). More than 200 mutations in C1 inhibitor gene have been reported.

Objective: We aimed to analyze clinical features of a large family with an index case of HAE and to determine the disease-causing mutation at the C1 inhibitor gene in this family.

Method: Totally 124 person (60 male, 64 female) were screaned in two villages on the basis of an index case with HAE. One hundred and sixty-five subjects were interviewed and The frequency and severity of symptoms were scored from zero to eight. C4 and C1 esterase inhibitor protein (C1-INH) levels vere measured in 124 person. C1 esterase inhibitor activity was measured in all patients with low C4. We investigated for mutation at the C1 inhibitor gene in four patients with HAE, and one patient without HAE. Genomic DNA was extracted from peripheral blood. Complete sequencing of the coding region of the SERPING1 gene was carried out.

Results: Low C4 levels were found in 42 persons. There were 35 patients with C1-INH deficiency. We have identified a novel mutation at the C1 inhibitor gene, G345W. Interestingly, while three patients with type I HAE were positive for G345W mutation, one patient with HAE Type2 had no defect in the SERPING1 gene. Our HAE Type1-Index case displayed SERPING1 G345W mutation at two alleles. Moreover two patients (HAE Type1) displayed SERPING1 G345W mutation at one allel. Finally, one healthy person without HAE had no defect in the SERPING1 gene.

Conclusion: The present study provides evidence to link a novel genetic mutation, G345W, to the development of hereditary angioedema in a large HAE family from Turkey.

1335
Glucocorticoid polymorphism in patients with hereditary angioedema due to C1-INH deficiency

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Background: Hereditary angioedema (HAE) caused by C1-inhibitor (C1-INH) deficiency (HAE-C1-INH) is a rare, autosomal dominant disorder. In the absence of C1-INH, uncontrolled activation of the kinin system results in the excessive release of bradykinin. This leads to edema-formation, which may be associated with stress. To understand the role of stress in edematous attacks, our aim was to evaluate the cortisol levels of HAE-C1-INH patients. With the purpose of determining their sensitivity to glucocorticoids, we screened the study population for glucocorticoid receptor (GR) polymorphisms. Further, we studied their occurence in the whole HAE-C1-INH population.

Method: We measured cortisol levels during attacks as well as during symptom-free periods in 36 HAE-C1-INH patients. We screened 139 HAE-C1-INH patients for glucocorticoid receptor polymorphisms. Statistical analysis was performed.

Results: Cortisol levels were significantly higher during attacks than in symptom-free periods ($P = 0.004$). The magnitude of the elevation of cortisol levels did not show significant correlation with attack severity, attack location, or antigenic C1-INH levels.

There were no significant differences in the allelic frequencies of the BclI, N363S and 9-beta polymorphisms between HAE-C1-INH patients and healthy controls (160 healthy, unrelated Hungarian adults). A significant association was detected between carrier status for the 9-beta polymorphism and cortisol levels measured in symptom-free periods in HAE-C1-INH patients.

Conclusion: Cortisol levels were higher during attacks than in symptom-free periods. This might have reflected the effect of a stressful situation, such as of the attack itself, on the patients' neuroendocrine system. The allelic frequencies of GR polymorphisms in the HAE-C1-INH population were the same as in the control population. In 9-beta polymorphism, cortisol levels were significantly lower, and this indicates decreased sensitivity to glucocorticoids.

1336
Early Presentation of clinical hereditary angioedema (HAE) symptoms in a neonate

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Background: Timely diagnosis of hereditary angioedema (HAE) is challenging particularly in children. The barriers include lack of awareness of HAE, communication barriers, diagnostic testing involving young children, and broad differential diagnoses for symptoms of HAE. Consequently, there has been no definitive study on the age of onset of clinical symptoms of HAE in children. This lack of awareness can result in reduced quality of life due to untreated or improperly treated symptoms, significant delay in diagnosis, and/or misdiagnosis which can result in unnecessary tests, treatments, and procedures. Current literature suggests that the mean age of onset is in the second decade of life, which is worsened by puberty, estrogen containing contraception, or estrogen hormone replacement therapy, but symptoms can also be present under 1 year. Here we present a case report of a child not previously diagnosed with clinical symptoms of HAE but born from a mother with type I HAE.

Method: The obstetrician was asked to test cord blood for C1-INH and C4 protein quantities. Parents were requested to monitor the child for symptoms and pictures were taken to document any clinically suspicious edema and/or rashes. Repeat laboratory testing was done after 1 year of age.

Results: Cord blood results show C1-INH <0.12 (0.21–0.39) g/l and C4 0.08 (0.07–

0.30) g/l. At 9 months, the child's mother noted slight periorbital edema, which was documented with pictures. At 14 and 18 months, the child developed a rash on her torso and arms that resembled erythema marginatum, both episodes were documented with pictures.

Conclusion: Clinical symptoms of HAE can begin as early as 8 months without any triggers. Parents and clinicians need to be vigilant to ensure properly diagnosed HAE to optimise the quality of life for these young patients and their families. We emphasize that high index of clinical suspicion of HAE should begin even in the early neonatal period.

1337
Different forms of HAE prophylaxis

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Several forms of prophylactic treatment for HAE are possible. We have used in our angioedema center three forms of prohylaxis:

1 Short term prohylaxis before surgery,
2 Long term prohylaxis and
3 On demand prohylaxis.

We used for the three prohylaxis forms following drugs: Icatibant in short term prohylaxis and on demand propyhlaxis, C1 inhibator contentrates in all prohylaxis forms. All prohylaxis treatment forms were successful.

Patients with short term prohylaxis were treated with icatibant or C1 INH 30–60 min pre surgery, 2 h post-surgery and 12 h post-surgery. In long surgeries with more than 2 h or large blood-loss an additional application of icatibant or C1 INH was given. Long term prohylaxis was possible with Ruconest, Berinert and Cinryze. We have used all C1 INH options in long term prohylaxis. Patients get two times in the week the C1 INH concentrates for 12 weeks. Our results demonstrate here a significant reduction of angioedema attacks.

1338
Disease severity in hereditary angioedema due to C1-inhibitor deficiency

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Background: Hereditary angioedema due to C1-inhibitor deficiency (HAE-C1-INH) is a rare autosomal dominant disorder characterised by recurrent subcutaneous and/or submucosal angioedema. The prevalence, severity, and the location of the symptoms are variable. Our retrospective study investigated the changes of disease severity over a lifetime.

Method: Among 143 C1-INH deficient individuals (79 females and 64 males, including 11 symptom-free individuals), we studied 118 patients whose drug regimen remained stable during the study. The annual number of attacks (ANA) and plasma derived nanofiltrated C1-INH concentrate consumption (pnfCC) were determined and compared with the time of symptom onset. To detect any difference in disease severity during life, we stratified the subjects into 3–3 age groups of males and females. The ANA and individual attack types, as well as pnfCC were compared among these subsets. In 17 patients followed up for 15 years, ANA and pnfCC were analyzed in 5-year periods.

Results: ANA and pnfCC were higher with an early onset of initial symptoms ($P = 0.0076$, $P = 0.0271$). In 20- to 40-year old women, ANA ($P < 0.001$), and individual attack types (subcutaneous $P = 0.002$, abdominal $P = 0.002$) occurred in higher numbers and followed a more severe course than in males, this was mirrored by pnfCC ($P = 0.0131$). In male patients aged 20–40 years, ANA – including that of abdominal episodes- was lower than among the 10- to 20-years old ($P = 0.0199$ and $P = 0.0428$) and also among the 40- to 60-years old ($P = 0.0132$ and $P = 0.0098$). There were no significant differences among the age groups of females. During the 15-year follow-up, the number of abdominal attacks increased, but only in patients 10–25 years old interval ($P = 0.008$).

Conclusion: The earlier the initial symptoms occur, the more severe the course of the disease will be. The disease follows a more severe initial course in women aged 20–40 years than in males of matching age. We could not detect any consistent, unidirectional change in the natural course of the disease during a lifetime.

1339
Management of risk medical and surgical procedures in patients with bradykinin mediated angioedema

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Introduction: It is known the risk of angioedema associated with surgery or even minor invasive or surgical procedures in patients with bradykinin mediated angioedema (BK-AE), no systematic data on the risk of angioedema in patients without prophylaxis have yet been published. Our study analyzes angioedema (AE) events after risk medical or surgical interventions in our series of patients with BK-AE.

Methods: A retrospective, descriptive study was performed. All the patients with BK-AE followed at Allergy Department from Hospital Universitario La Paz were included. Demographic data, type of intervention, short term prophylaxis (STP), long term prophylaxis (LTP) and treatment of acute AE attacks were collected. Dental-oral procedures were excluded.

Results: One hundred and forty-one patients with BK-AE were included, Two hundred and eleven risk interventions had been performed in 88 patients (39 male/49 female). Seventy three patients had hereditary angioedema (HAE) type I, one patient HAE type II, nine patients HAE without C1-inhibitor deficiency (HAE-nC1-INH), and five patients acquired angioedema with C1-inhibitor deficiency (AAE-C1-INH). STP was performed before 67 procedures and patients were receiving LTP during 38 procedures. Drugs used as STP were: plasma-derived human C1 esterase inhibitor concentrate *(pdhC1INH)* (56), attenuated androgens (AAs) (4) and icatibant acetate (7). STP + LTP had been performed in 33 procedures (Group A), STP without LTP in 34 procedures (Group B), LTP without STP in five cases (Group C) and no prophylaxis (no STP, nor LTP) in 139 procedures (Group D). AE was developed after three procedures (2.16%) in three different patients from Group D. One patient had HAE type I (facial wart excision) and two patients had HAE-nC1-INH (thyroidectomy; caesarean section). No AE occurred after any procedure from groups A, B and C.

Conclusions: In our study AE following risk medical or surgical procedures in patients with BK-AE was only observed in patients not receiving STP, neither LTP.

1340
'Angioedema Emergency': a 24/7 phone call service in France

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Background: Hereditary angioedema (HAE) is a rare disease that can be life-threatening whenever acute attacks reach the upper airways. Today specific treatments can save patients from a fatal asphyxia as long as the diagnosis is made on time and actions are promptly managed. As referent medical doctors for hereditary angioedema, we are facing many requests for expert advice for the care and diagnosis of this disease. The 'CREAK', French National Reference Center of Angioedema, multi-sites, certified in 2006 within the Rare Diseases National Plan, has established a 24/7 phone call service since 2012.
Method: During the last 6 months, daily records of each phone call have been completed with the following informations: physician data (name, location, medical department, specialty), patient data (name, diagnosis if known, symptoms, medical history), and expert guidance (diagnosis refinement, therapy, and other further instructions).
Results: The call rate grew to an average of three calls per day as of December 2013. About 82% of them came from emergency room or intensive care, 2% from gynecology-obstetric departments, 9% from private physicians: all calls resulting from 40 French geographic departments. Diagnosis and advices were about: 30% for HAE patients, 40% for drug induced angioedema (mainly ACE) and 20% for chronic urticaria. Two of three of request calls were advices and support about upper airway edema with specific treatment decision given in 70% of these cases. Decision of a medical visit to the nearest reference site within a reasonable delay (5 days to 1 month) occurred in 90% of cases.
Conclusion: The implementation of a 24/7 phone call service brings an efficient daily and country wide 'remote expertise' to support local physicians facing HAE patients or patients not already diagnosed. It allows the healthcare professionals to benefit from expert advice directly aimed at their patient care. It improves medical assistance across the whole country, including overseas locations.

1341
Findings of a clinical response survey in patients with hereditary angioedema

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Introduction: Hereditary angioedema (HAE) is an autosomal dominant, inherited condition characterised by recurrent swelling attacks affecting the face, tongue, extremities, and gastrointestinal, genitourinary, and laryngeal regions. This study aimed to evaluate patient perceptions of the value and benefit of therapy for the prevention of angioedema attacks.
Methods: Patients with HAE completed a survey of 18 items evaluating the importance of attack frequency, severity, and duration, in addition to other quality-of-life factors. The US Hereditary Angioedema Association conducted the survey during phone calls to 50 patients randomly chosen from the US HAEA database.
Results: Most patients (88%) agreed that reduction in attack frequency is important to them [rating of 8–10 (1 = not important; 10 = extremely important)]; without treatment, the median reported number of attacks was 10.5 in a 3-month period. A 50% decrease in attacks is meaningful to 76% of patients, and 58% of patients believe that a reduction of at least 1 attack/month is clinically meaningful. Most patients (92%) stated that reduction in attack severity is important, and 86% of patients agreed that a reduction of mild attacks is meaningful. The median reported duration of attacks without treatment was 3 days, and 90% of patients thought that a reduction in duration of attacks is important. Patients generally agreed on the importance of improvements in quality of life (88%); absence from school/work (86%); and impact on physical activity (94%), leisure and recreation (86%), and social/emotional relationships (92%). Quality of life was reported as the single most meaningful way to measure effectiveness of a medicine to prevent attacks by 48% of patients.
Conclusion: HAE patients expect a preventative therapy to decrease the burden of disease by reducing attack frequency, severity and duration, as well as contributing to the improvement in their quality of life.

1342
Findings of a clinical response survey in physicians caring for patients with hereditary angioedema

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Introduction: Hereditary angioedema (HAE) is an autosomal dominant, inherited condition characterised by recurrent swelling attacks involving the upper airway (face, tongue), extremities and, gastrointestinal and genitourinary regions. This study evaluated clinical parameters that could be potentially meaningful to physicians in determining the value of preventative medication for patients with HAE.
Methods: Nine clinical experts who treat patients with HAE completed a survey consisting of 14 items that evaluated the importance of attack frequency, severity, and duration, in addition to other quality-of-life factors, such as absence from work/school, quality of life, and impact on social/emotional relationships.
Results: Respondents reported that the single most clinically meaningful parameter in determining the value of prevention for patients with HAE was a reduction in the number of moderate to severe attacks (67%) followed by an improvement in quality of life (33%). In addition, 88% of respondents stated that a reduction in the number of moderate to severe angioedema attacks per month was important [rating of 8–10 (1 = not important; 10 = extremely important)]. The majority of physicians (56%) considered a $\geq 30\%$ reduction in monthly attack frequency to be clinically meaningful, as well as a reduction of ≥ 2 attacks during a 3-month clinical trial treatment period. All respondents considered a reduction in the number of mild attacks to be clinically meaningful. In general, physicians agreed on the importance of improvements in quality of life (100%); absence from work/school (89%); and impact on physical activity (78%), leisure and recreation (78%), and social and emotional relationships (89%).
Conclusion: When assessing the value of prevention for patients with HAE, physicians prioritize a reduction in the number of angioedema attacks as being clinically meaningful and relevant.

1343
Long-term prophylaxis of HAE with danazol in China

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Background: Danazol is the most commonly used and effective drug for long term prophylaxis of hereditary angioedema (HAE). However, systematic study on the administration and dosage of danazol in Chinese patients with HAE was limited.
Objective: Our aim is to provide long term prophylaxis data of the effective dosage for Chinese patients.
Method: This study retrospectively analyzed 74 HAE patients continuously being treated with danazol. All the clinical data were obtained from medical record files.
Results: Danazol can completely avoid attacks at daily dosage of 600 mg for 95.94% of patients, 400 mg for 77.02%, 200 mg for 21.62% and <200 mg for 16.22%. 1.35% of patient got partially controlled with danazol 600 mg daily, 17.57% with 400 mg daily, 55.41% with 200 mg daily and 18.91% with <200 mg. For the maintaining dosage, 55.41% of patients can get free from attacks at danazol 200 mg per day, 5.40% at 200 mg for 5 days a week, 13.51% at 200 mg for 3 days a week and 2.70% at 200 mg for 2 days a week. All the parameters (C1-INH antigen, C4 and CH50) increased at different degree during the treatment. The efficacy of danazol was independent from the age of onset, severity and the levels of C1-INH and C4.
Conclusion: Danazol 400 mg per day should be recommended as the initial dosage and 200 mg daily or less was effective for control of HAE attacks.

1344
Severe side effects in 22 patients with hereditary angioedema using different dosage of danazol – how to switch to other treatment regimen?

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Background: Hereditary angioedema (HAE) is caused by functional deficiency of C1-inhibitor (C1-INH). C1-INH deficiency manifests as spontaneous, often acute, recurrent non-allergic cutaneous and subcutaneous swelling attacks, usually involving the face, throat, abdomen and extremities.

Avoiding acute swelling attacks in HAE patients is the primary goal of treatment. For long-term prophylaxis, attenuated androgens (e.g. danazol) are used. However, the use of danazol raises general concern, since it is associated with multiple side effects, it is not recommended for children, and is also contraindicated in pregnant women.
Methods: All patients aged >18 years with HAE were enrolled. Data were obtained from patient diaries, patient histories and other medical documentation. Danazol was used as short-term and long-term treatment (median: 11.25 years; range: 0.5–23.5 years). The primary endpoint is the detailed characterisation of adverse drug reactions using different dosage of danazol (<200 mg–1000 mg/day).
Results: Twenty-two patients were recruited, of whom 13 were women and nine were men. The mean age was 41.8 ± 10.1 and 35.8 ± 7.3 years for female and male patients, respectively. All patients under danazol treatment experienced at least one adverse drug reaction. Common adverse events (AEs) were depression, increase of transaminases, headache, increased body weight, amenorrhea, virilization and hypertension (range: 23–77%). Liver adenoma was identified in two patients (9%). We observed adverse drug reactions even with low doses (<200 mg/day).
Conclusion: All HAE patients, who are under danazol therapy, should be monitored closely, because of several side effects also under low dose (<200 mg/day) treatment. From our experience androgens have to be stopped, but can't be stopped immediately – not to put the patients on risk. Tapering down androgen dosage over weeks is necessary during emplacement of a new therapeutic regimen.

1345
C1-esterase inhibitor antibodies in a patient with type 1 hereditary angioedema

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Background: Angioedema due to C1-inhibitor (C1-INH) deficiency may be either hereditary or acquired. Acquired angioedema can complicate lymphoproliferative disease.
Methods: To present a patient with genetically confirmed type 1 hereditary C1-INH deficiency (HAE) who developed C1-INH autoantibodies and lymphoproliferative disease.
Results: A 75 year-old female, who had recurrent episodes of angioedema since the age of 2 years and a family history of sudden death was diagnosed with HAE on clinical grounds at 35 years of age. She was treated with tranexamic acid without benefit but her clinical course was stable on intermittent danazol. At the age of 69 she was diagnosed with autoimmune thyroiditis and seropositive rheumatoid arthritis. At the age of 71 she was found to have serum paraprotein on routine blood tests. One year later she started to experience frequent episodes of angioedema affecting her tongue, throat, pharynx and larynx with associated breathing difficulties. She needed several hospital visits for administration of C1-INH concentrate. She was found to have low C1q levels and positive anti-C1-INH antibodies. She was started on Icatibant and Tranexamic acid and was clinically stable. One year later she was diagnosed with non-Hodgkin lymphoma and received chemotherapy. Sequencing of the SERPING1 gene confirmed hereditary C1INH deficiency with a muatation in exon 8 resulting in a frame shift that causes premature termination of 15 codons downstream.
Conclusions: A sudden symptoms flare in our patient with longstanding HAE was caused by antibodies against her residual CI-inhibitor on the background of low C1q and the development of a paraprotein, She had developed acquired C1 inhibitor deficiency, in addition to her HAE, leading to frequent angioedema and clinical deterioration. Acquired C1 inhibitor deficiency superimposed on HAE is a rare cause for increased attack severity, and should be considered in patients in whom no other cause can be found.

1347
Hereditary angioedema-induced acute pancreatitis: a case report

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Background: Hereditary angioedema (HAE) is a rare, autosomal dominant inherited disease. The cause is a quantitative or qualitative congenital deficiency in C1 inhibitor. Typical symptoms include recurrent and unpredictable attacks of angioedema involving the extremities, gastrointestinal tract, genitourinary system, face

or upper airways. Although abdominal attacks are a common complaint in HAE, very few cases of acute pancreatitis have been reported so far.

Case presentation: A 14 years old woman was admitted to the emergency medicine with a 1 day history of abdominal discomfort and vomiting. She had a 11 year history of HAE. The diagnosis was confirmed after a review of the clinical presentation and assessment of the reduced Cl esterase inhibitor antigen level (9.7 mg/dl) and C4 compleman level (4.3 mg/dl). Abdominal examination revealed mild tenderness to palpation without guarding or rebound tenderness was noted in the epigastric quadrant. Other system examinations were normal. Abdominal ultrasound showed no cholelithiasis and no bile duct dilation, pancreatic head and body size was minimally increased. Laboratory studies revealed leukocytosis and elevated amylase (2796 U/l) and lipase (835 U/l) levels, with normal liver enzymes and function: Other laboratory values were all normal. The patient was treated with 1000 U of plasma-derived C1-INH but there wasn't relief of symptoms. The patient′s diagnosis were considered HAE-induced pancreatitis. Oral intake was withheld, and the patient was put on intravenous fluids, patient controlled analgesia, and nasogastric decompression and continued on proton pump inhibitor treatment. On hospital day 15, the patient's clinical status showed marked improvement along with normalisation of the pancreatic enzymes.

Conclusion: This case is about the complication of a rare disease. Abdominal pain is known to be gastrointestinal manifestation of HAE, but acute pancreatitis is uncommon as a complication of HAE. We suggest that physicians should be aware of this rare comlication in HAE.

1348
Delayed diagnosis of hereditary angioedema: a case report of 39 years of misdiagnosis and inadequate treatment

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Background: Hereditary angioedema (HAE) is a rare disease that usually manifests during childhood and is characterised by recurrent episodes of swelling in various body tissues. Delay in diagnosis of HAE is common due to ambiguous pathology and low awareness of the disease among health-care professionals.

Method: This is the case of a 42-year-old woman with a long history of misdiagnosed, untreated or inadequately treated HAE symptoms, including gastrointestinal attacks, facial swelling, and swelling of the airway.

Results: First symptoms of airway obstruction occurred at an age of 3 years following a myringotomy. Between 3 and 12 years of age, the patient suffered gastrointestinal attacks with each common cold and facial swelling after a visit at the dentist. With onset of menstruation the attacks became more frequent (1–2 times monthly). Visits at the dentist triggered facial swelling and airway obstruction. Subileus and free peritoneal fluid were diagnosed repeatedly. Between the age of 3 years and 41 years, the patient underwent numerous medical assessments and interventions including MRT, nuclear spin tomography, ERCP, gastrointestinal endoscopies, endoscopic papillotomy, capsule endoscopy, several hernia repair surgeries, pancreatic surgery, and repeated abdominal adhesiolysis, but the cause of the symptoms could not be identified. At the age of 41, the patient experienced facial swelling, airway obstruction, and difficulty swallowing after a visit at the dentist and C1 inhibitor deficiency was suspected. Two months later, 39 years after the manifestation of first symptoms, the diagnosis of HAE was confirmed.

Conclusion: Early diagnosis could have prevented the patient from inadequate treatment and unnecessary interventions, and could have facilitated appropriate treatment not only of painful gastrointestinal attacks but also of potentially fatal airway obstruction. This underlines the importance of raising the awareness of HAE among health care professionals.

1349
A case of recurrent angioedema in a 12-year-old girl

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Introduction: Hereditary angioedema (HAE) is a rare autosomal dominant disease that is often difficult to diagnose.

Case presentation: Twelve-year-old girl had recurrent episodes of swelling of extremities and face without urticaria and pruritus, since 2 years of age. Her symptoms worsened over 24 h, and then resolved over the next 48 h. Despite no relieve, she used antihistamines and corticosteroids. Trigger factors of acute edema were trauma, cold weather, and mental stress. None in her family suffered from the same symptoms. Even though her sister – 8 year old – had a facial angioedema once in life time, her C1INH antigenic and functional level were tested normal (27.5 mg/dl, and 90.25%). She was diagnosed after an episode of angioedema of the head and face for which she was seen in the nephrology department of our institution. The level of serum C4 was 3.0 mg/dl, C1INH antigenic level was 7.2 mg/dl, C1INH functional level was 9.5%, complement (C) 1q level was normal. C1-INH concentrate was recommended in case of acute attack and for short term prophylaxis.

Conclusion: This hereditary case is interesting as it points out that C1q level should be assessed in the differential diagnosis of acquired and hereditary angioedema with lack of positive family history.

Poster Session Group III – Green

TPS 59 – Hereditary angioedema – clinical aspects

1350
Tranexamic acid as long term prophylaxis in angio-oedema: safety and efficacy in 47 patients

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Background: Angioedema (AE) is a clinical syndrome characterised by localised swelling lasting several hours. The swelling is often recurring and can be lethal if it is located in the laryngeal region. Much progress has been made recently in the treatment of acute episodes, but no consensus has been reached on a maintenance treatment.
Method: We have performed a national retrospective observational study to assess the use of tranexamic acid (TA) as maintenance treatment for non-histaminergic AE (hereditary AE (HAE) or idiopathic non-histaminergic AE).
Results: From the 1st of October 2012 to the 31st of August 2013, records for 64 cases were collected; 37 of these were included (12 patients with HAE with C1-inhibitor deficiency, 6 with HAE without C1-inhibitor deficiency, and 19 idiopathic non-histaminergic AE). When treated with TA, over 6 months, the number of attacks was reduced by 75% in 17 patients, 10 patients showed a lower level of reduction, 10 had the same number of attacks, and in no instance were symptoms increased. No thromboembolic events were observed, and the main side effects were digestive in nature.
Conclusion: Thus, TA, which is well tolerated and inexpensive, appears to be an effective maintenance treatment for some patients with HAE or idiopathic non-histaminergic AE.

1351
Pasteurised nanofiltered C1-inhibitor concentrate (pnf C1-INH, Berinert) for prophylaxis of attacks in hereditary angioedema (HAE): results from an ongoing registry

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Background: An International Berinert® registry (clinicaltrials.gov identifier NCT01108848) was started in 2010 to collect real-life data on the use and safety of pnf C1-INH for any indication. The prophylactic use and the breakthrough hereditary angioedema (HAE) attacks for short-term (STP) and long-term prophylaxis (LTP) were assessed among others.
Method: Reasons for and outcomes of pnf C1-INH use by any patients, including treatment of HAE attacks or prophylaxis, were captured retrospectively or prospectively. STP was defined as a single prophylactic application of pnf C1-INH. LTP constituted two or more consecutive prophylactic infusions with the period of 7 days or less between infusions.
Results: A total of 1582 prophylactic pnf C1INH infusions (49.5% of all infusions) were reported in 43 (31.9%) patients; the vast majority (97.6%) were given at patients' homes by self-administration or with help of their parents/caregivers. Mean prophylactic dose was higher among patients with prospectively collected data (1254 infusions, 18.2 IU/kg) than retrospectively collected data (324 infusions, 13.2 IU/kg). Eight patients (18.6%) reported 215 adverse events (AEs) after 1493 prophylactic infusions (rate per infusion: 0.14), 9 of which were mild, 206 moderate and none severe. Most frequent AEs included nausea and constipation, sinusitis, arthralgia, and back pain and were not causally related to pnf C1-INH. In 25 STP patients, breakthrough HAE attacks occurred within 7 days after 6/34 (17.6%) infusions. LTP with frequency of infusions between once and twice a week was observed in 18 patients for a total of 185 patient-months. The rate of HAE attacks on LTP was 0.4 per patient-month.
Conclusion: Real-life clinical data demonstrate that self-administration of pnf C1-INH is the preferred method of injections among the Berinert Registry patients for prophylaxis and acute HAE treatment. pnf C1-INH was safely and effectively used for STP and LTP therapy in HAE patients.

1352
Icatibant for laryngeal hereditary angioedema (HAE) attacks: patient/attack characteristics, reinjection rates and symptom outcomes across three open-label extension studies

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Background: Icatibant demonstrated efficacy for the treatment of hereditary angioedema (HAE) attacks in the controlled phases of the For Angioedema Subcutaneous Treatment (FAST)-1 (NCT00097695), FAST-2 (NCT00500656) and FAST-3 (NCT00912093) studies. In the open-label extension (OLE) phases, most attacks were treated with one injection, regardless of patient age, sex, body mass index, prior attack frequency, HAE type, attack location or severity. Here, we investigate reinjection needs and outcomes for potentially fatal laryngeal attacks.
Method: After the controlled phases of FAST-1, -2 or-3, adults with HAE type I or II could enter the OLE phases to receive up to three injections of icatibant 30 mg per attack, at ≥6-h intervals. Reinjection rates for laryngeal attacks (laryngeal or pharyngeal symptoms) were analysed by patient/attack characteristics (severity defined by investigator global assessment). Patient-assessed severity of 'difficulty swallowing' and 'voice change' symptoms (absent, mild, moderate, severe, very severe) was recorded before and 2 and 4 h after treatment. Patient-assessed perceived time of initial symptom improvement was also recorded.

Results: Of 110 laryngeal attacks (n = 52 patients), 25 (22.7%) were mild, 50 (45.5%) moderate and 35 (31.8%) severe. There were 101 (91.8%) attacks treated with one injection, 8 (7.3%) with 2 injections, and one (0.9%) with 3 injections. Reinjection needs did not appear associated with patient age, sex, HAE type or attack severity. Laryngeal symptoms were generally absent/mild by 4 h (difficulty swallowing 82/110 attacks; voice change 89/110 attacks). For icatibant-treated first laryngeal attacks, patient-assessed median (95% CI) time to initial symptom improvement was 0.6 h (0.5–0.9; n = 66 attacks).
Conclusion: Most laryngeal attacks were successfully treated with one icatibant injection, irrespective of patient/attack characteristics. Laryngeal symptoms were generally absent/mild by 4 h after treatment.

1353
Body-weight adjusted dosing of C1-esterase inhibitor for optimal treatment response in acute attacks of laryngeal edema in hereditary angioedema

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Background: Laryngeal attacks of hereditary angioedema (HAE) can be life-threatening and immediate treatment response is of clinical importance. Two plasma-derived C1-esterase inhibitors (pdC1-INH) are approved for treating HAE in the EU. However, two different dosing regimens of pdC1-INH are licensed: a body weight (bw) adjusted dosing with 20 IU/kg (Berinert) and a fixed dosing with 1000 U (Cinryze). We thought to explore the clinical evidence for the efficacy of different dosing regimens of pdC1-INH for the treatment of acute laryngeal attacks.
Method: Data from an open-label, prospective study (I.M.P.A.C.T.2) with 16 HAE patients treated with 20 IU/kg pdC1-INH for acute laryngeal attacks were compared with historical data from a hospital database (20 patients treated with fixed doses of 500 or 1000 IU). For comparison between the weight-adjusted dosing and the fixed dosing the variable 'time to first symptom relief' (TSR) for laryngeal attack was assessed by Wilcoxon test and Kaplan–Meier curves.
Results: No significant difference in TSR was observed between fixed doses of 500 vs 1000 IU. The mean TSR (95% CI) was 41.5 min (38.6; 44.3) in the fixed-dose group and 23.4 min (18.5; 28.3) in the bw-adjusted dose group. A significant difference between the two dosing groups for the time to 1st symptom relief was shown (P < 0.0001, Wilcoxon test). The Kaplan–Meier curves for TSR for individual HAE attacks showed that the 20 IU/kg bw adjusted dosing group had a higher percentage of attacks with lower times to first symptom relief than the fixed- dosing group regimen (500 or 1000 IU).
Conclusion: Body weight-adjusted dosing of pd-C1INH with 20 IU/kg pdC1-INH provides faster treatment response in acute laryngeal HAE attacks compared with fixed dosing with 500 or 1000 IU.

1354
Long term follow-up of a hereditary angioedema patient treated with attenuated androgens

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Background: Hereditary angioedema (HAE) is a rare disorder usually diagnosed before adolescence and with positive family history in most cases. Attenuated androgens is one of the recommended prophylactic treatment options, but long-term use may be associated with severe adverse reactions, like hepatic, metabolic and tromboembolic diseases.
Method and results: We present a case of a 64 years old woman with complex allergic pathology and chronic comorbidities, presented to Allergology Department for recently onset deep venous thrombosis of lower limb. She was diagnosed with hereditary angioedema type I at age 52, after reported almost 30 years personal history of recurrent facial and peripheric angioedema, considered allergic. No family history suggesting HAE was recognised. After confirming diagnosis of HAE with constant low antigenic level of C1INH, the prophylactic treatment with attenuated androgens (Danazol) was started, with initial dosage 100 mg daily for 6 months, then reduced to 50 mg, continously for 12 years. Pacient associated chronic urticaria aggravated by aspirin, ischemic heart disease with sequelar inferior miocardial infarctus, chronic nodular thyroiditis and mild hepatic cholestasis. After having initiating the treatment with Danazol, the patient has never experienced angioedema episodes and no other symptoms possibly related to HAE. The deep venous thrombosis of lower limb was confirmed by Doppler ecography and oral anticoagulation has been started before hospitalisation. The repeted dosage of C1INH confirmed significant lower plasma level, with normal complement fractions.
Conclusion: We considered the actual trombotic disease as complication of attenuated androgens, but long-term favourable efficacy and safety profile recommended continuation of this treatment for HAE prophylaxis.

1355
Hereditary angioedema with normal C1INH without FXII mutations: description of a family

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Background: HAE with normal C1INH (HAE-nC1INH) was first described in 2000 in women and in relation with estrogens. Later on, new cases were described and affected men were reported. This type of HAE is thought to be caused by factor XII mutations although they are not present in all patients with HAE-nC1INH.
Method: A 55-year-old man presented an acute episode of airway edema without evident cause. His father and brothers had a history of repeated episodes of angioedema.

Clinical history and analytical studies were done: antigenic and functional

Patient	Age	Angioedema	C4 g/l (0.1–0.45)	C1INH (Antigenic) g/l (0.15–0.34)	C1INH function (%)	*F12* gene mutation
Father	76	Multiple episodes of face and genitalia	0.53	0.39	101	ND
Son 1	56	Multiple labial and peripheral; one laryngeal	0.32	0.27	104	Not present
Son 2	53	Multiple labial episodes	0.27	0.32	ND	Not present
Daughter	41	Multiple labial episodes, one lingual	0.29	0.30	101	Not present

*[Clinical Data]

C1INH, C4 and study of mutations in exon 9 of the *F12* gene.

Results:

In all cases symptoms began in adult life, trauma had no influence and abdominal episodes were absent. The episodes of angioedema were slowly progressive and lasted 3–4 days. The only woman affected had no increase of angioedema in two pregnancies or with estrogenic contraceptives. They were unresponsive to antihistamines (ANTIH1) and a partial influence of antihypertensive drugs (ACEI/ARB) was found. The fifth member (a 37-year-old man) could not be studied, but he suffered also peripheral bouts of angioedema.

Conclusion: A family with HAE-nC1INH without factor XII mutations is described. The clinical picture suggests they are bradykinin dependent and does not support an 'estrogen-dependent' angioedema. Laboratory analysis did not show complement abnormalities or mutations on *F12* gene. Other potential genes involving bradykinin metabolism should be involved in the pathogenesis of this type of HAE.

1356

Health-related quality of life (HRQoL) in patients with hereditary angioedema (HAE) receiving nanofiltered C1 inhibitor (C1 INH-nf) for prophylaxis: results of a randomised, placebo-controlled, cross-over study

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Background: We evaluated the HRQoL of patients with HAE receiving C1 INH-nf as preventive therapy or for the acute treatment of attacks.

Method: Patients ≥6 years old with ≥2 attacks/month were eligible for this randomised, placebo-controlled, cross-over study in the US. Patients received 1000 U C1 INH-nf or placebo every 3–4 days for 12 weeks and then crossed over to the other treatment arm for a second 12-week period. All patients could receive open-label C1 INH-nf (1000 U) for the acute treatment of attacks. Patients completed the SF-36 V1.0 survey before the first treatment period and at the end of both periods. Least-square (LS) mean differences (C1 INH-nf minus placebo) and 95% CI in norm-based SF-36 scores at end of treatment period are from a mixed-model ANOVA with a period effect, a treatment effect, and adjustment for the baseline score.

Results: Of 22 patients evaluated for efficacy, 16 completed SF-36 surveys for both treatment periods. At baseline, mean physical and mental component summary scores were 36.4 and 49.9, respectively (US general population = 50). At treatment end, LS means in all domain and summary scores significantly favored C1 INH-nf (table). Social function and bodily pain had the greatest magnitude difference.

Conclusion: Routine prevention of angioedema attacks with C1 INH-nf was associated with more favorable HRQoL outcomes relative to C1 INH-nf dosed for the acute treatment of individual angioedema attacks in the absence of routine prevention.

1357

Safety and efficacy of C1 esterase inhibitor for acute attacks in children with hereditary angioedema less than 12 years of age

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Background: In Europe, CINRYZE® [C1 esterase inhibitor (human); C1 INH-nf] is approved for acute treatment and prevention of angioedema attacks in adolescents and adults with hereditary angioedema (HAE). This post marketing study evaluated a dose range of C1 INH-nf in children experiencing an acute angioedema attack.

Methods: This multicenter, open-label study was conducted at six US sites in subjects 2 to <12 years of age and ≥10 kg of body weight with a confirmed diagnosis of HAE. Subjects received a single IV administration of C1 INH-nf within 8 h after onset of symptoms according to weight categories. The primary endpoint was the onset of clinical relief within 4 h after start of treatment.

Results: Nine consecutively enrolled children (8 female, 1 male; median age 9 years, range 6–11 years) were treated according to weight categories: three (10–25 kg) received 500 U, three (>25 kg) received 1000 U, and three (>25 kg) received 1500 U. The primary endpoint was achieved in all nine treated children. Anatomic attack locations were abdominal in five, extremity in three and facial in 1. Median time to beginning of relief of symptoms was 0.5 h (range 0.25–2.5); median time to complete symptom resolution was 13.6 h (range 1.6–102.3). Functional C1 INH levels increased in all subjects; six had levels ≥0.7 U/ml. There were no significant laboratory abnormalities or changes in vital signs. The only AEs were mild nausea and diarrhea in a 6-year-old girl with an abdominal attack, which were considered related and resolved without additional treatment within 1 day.

Conclusion: Intravenous administration of single doses of C1 INH-nf 500 U (in subjects 10–25 kg), and 1000 and 1500 U (in subjects >25 kg) for the acute treatment of an angioedema attack was effective and well tolerated. Lower doses may be considered based upon the PK and efficacy profile in this study and exposure comparisons to the adult population.

1358

Mutational spectrum of the C1 inhibitor gene in a cohort of Italian patients with hereditary angioedema: description of nine novel mutations

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Background: Hereditary angioedema (HAE) is an autosomal dominant disease

Physical Component Summary	6.55 (1.48, 11.62)	$P = 0.015$
Mental Component Summary	8.70 (1.67, 15.72)	$P = 0.019$
Physical Function	4.33 (0.42, 8.24)	$P = 0.033$
Role Physical	7.51 (1.49, 13.53)	$P = 0.018$
Bodily Pain	11.35 (4.35, 18.34)	$P = 0.004$
Social Function	11.44 (3.88, 19.00)	$P = 0.006$
Mental Health	8.23 (0.94, 15.52)	$P = 0.030$
Role Emotional	6.09 (0.39, 11.78)	$P = 0.038$
Vitality	8.88 (1.32, 16.44)	$P = 0.025$
General Health	5.17 (1.71, 8.63)	$P = 0.006$

*[LS mean differences (95% CI) in SF-36 scores].

due to mutations in the C1 inhibitor gene (C1NH) that affects protein synthesis (HAE type I) or function (HAE type II).
Method: In 45 subjects affected by HAE diagnosed through clinical features and C1 inhibitor deficiency from the south of Italy (38 with type I and seven with type II HAE), the whole *C1NH* coding region was screened for mutations by direct DNA sequencing. A severity score based on clinical manifestation, age at disease onset and need for long-term prophylaxis was used to investigate possible genotype-phenotype correlations.
Results: A series of 22 different mutations was identified: nine missense (40.9%), five nonsense (22.7%), six frameshift (27.3), one small deletion (4.5%) and one splicing defect (4.5%). Nine *C1NH* mutations have not been previously described. No correlation was found between C1 inhibitor function level and severity score or age at first attack. Moreover, there was no correlation between different types of mutations and clinical phenotype.
Conclusion: The number of different mutations identified highlights the heterogeneity of C1 inhibitor deficiency and supports the hypothesis that HAE clinical phenotype is not strictly related to the type of mutation but rather depends on unknown factors.

1359
Treatment of ACE-inhibitor-related angioedema with icatibant: a case series

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Background: Angioedema occurs in 0.1–0.7% of patients treated with ACE-inhibitors (ACE-I), with potentially serious consequences requiring immediate attention. At present there are no specific drugs for the treatment of ACE-I-related angioedema. Icatibant might represent a potential treatment for this condition; however, additional reporting of cases which document the use of icatibant in this setting appears necessary. We report here a series of 13 cases of ACE-I-related angioedema successfully treated with icatibant.
Case series: Thirteen Caucasian patients with ACE-I-related angioedema involving face, lips and/or upper airways were treated at five Emergency Departments (ED). Other causes of angioedema were ruled out. Eleven patients had already experienced ACE-I-related angioedema. The median time to complete resolution of the previous attacks was 51 h (range: 15–60).

At the ED, all patients received standard therapy based on corticosteroids, antihistamine drugs, and/or adrenaline. Due to the lack of response to standard therapy and the worsening and severity of symptoms, all patients received one injection of subcutaneous icatibant (30 mg). Following icatibant administration, all patients experienced improvement of the symptoms. The median time from onset of clinical symptoms to injection of icatibant was 4 h (range 3–8). Symptom relief was objectivated at 30 min (range 15–90) after icatibant administration. A complete resolution of symptoms after icatibant administration was observed at 5 h (range 2–10).

None of the patients received tracheal intubation or tracheotomy, and all patients were discharged within 24 h from admission. No relevant adverse events were reported. Before discharge all patients were instructed to discontinue ACE-I, and received a different antihypertensive drug.
Conclusions: This case series supports the effectiveness of icatibant in improving symptoms of ACE-I-related angioedema in patients refractory to standard treatment.

1360
Icatibant treatment for acute attacks of acquired angioedema due to C1 inhibitor deficiency

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Background: Acquired angioedema due to C1 inhibitor deficiency (AAE-C1-INH) is a rare condition characterised by recurrent edema and an underlying non-genetic deficiency of C1 inhibitor. AAE-C1-INH may be associated with benign or malignant lymphoproliferative diseases. The acquired lack of functional C1 inhibitor can give rise to excessive accumulation of bradykinin, resulting in acute edema attacks. The investigational use of icatibant, a selective bradykinin B2 receptor antagonist, in patients with AAE-C1-INH is reported.
Method: In this observational study, eight patients (five women, three men) with AAE-C1-INH received 30 mg icatibant subcutaneously (one injection per attack) for a total of 131 acute attacks of AAE-C1-INH comprising 52 facial swellings, 32 peripheral swellings (30 swellings of the extremities and two genital swellings), 44 abdominal attacks and three tongue swellings. Times between attack onset, icatibant administration, first relief of symptoms and complete relief of symptoms were recorded.
Results: Data are reported as mean ± SD. The time between attack onset and icatibant injection was 0.6 ± 0.5 h. First symptom relief following the injection occurred at 0.8 ± 0.5 h for all attacks. The total duration of treated attacks was 12.6 ± 4.7 h for facial swellings, 13.3 ± 11.1 h for abdominal attacks, and 25.4 ± 9.3 h for peripheral swellings. The total duration of untreated attacks was 65.5 ± 17.2 h for facial swellings, 63.8 ± 14.4 h for abdominal attacks, and 76.8 ± 12.5 h for peripheral swellings. One facial and two genital swellings required further treatment. The most frequent adverse events were generally mild injection site reactions that all resolved without intervention.
Conclusion: The investigational use of icatibant for acute attacks of AAE-C1-INH in the reported cases appears to be generally well tolerated with reported patient improvements.

1361
High dose of plasma derived C1 inhibitor (pdC1INH) to control disease activity and protein hypercatabolism in a symptomatic patient with hereditary angioedema due to C1 inhibitor deficiency (C1-INH-HAE)

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Background: C1-INH-HAE is characterised by symptom recurrences that vary form a few per year to several per week. Symptomatic patients may have poor response to therapies.
Method: We describe the case of a female patient (74 years), with very frequent HAE attacks (>1/week) for several years. Prophylactic regimens with danazol, tranexamic acid and plasma derived C1-INH up to 2000 IU three times a week were not effective in reducing the need for on demand therapy. Infusions of pd-C1INH resulted in minimal (<40% of normal) and short lasting (<4 h) increase in C1-INH plasma levels. No anti-C1-INH antibodies were detectable in the patient's plasma. We hypothesized that infused pdC1-INH was rapidly consumed by activated target proteases and that daily infusions of 3000 IU of pdC1-INH (Berinert) would be able to achieve normal levels of C1-INH activity, associated with symptom relief.
Results: At baseline C1-INH function, C4 and C1q were below detection limits and cleaved high molecular weight kininogen

(HK) was 60%. After 3 consecutive days with pdC1-INH 3000 IU the 24 h post-infusion C1-INH function was >70% and the patient was switched to 3000 IU three times per week for 5 weeks. At day 4, C4 and C1q were within the normal range; on day 9 cleaved HK returned to normal (≤30%). During this phase 48 h post-infusion C1-INH activity was >40%; all other parameters remained normal and the patient had no angioedema recurrences. From weeks 6 to 9, the patient received pdC1-INH 2000 IU twice per week. Forty-eight hours post-infusion C1-INH activity values were <30%, C4 reduced to 60%, C1q remained normal, cleaved HK reverted >40%: the patient became symptomatic with need for repeated on demand treatments.

Conclusion: Our study demonstrates that highly symptomatic C1-INH-HAE patients rapidly catabolize pdC1-INH probably due to hyperactivated target proteases. A high dose treatment regimen with pdC1 INH in these patients can restore normal C1-INH catabolism and achieve symptom control.

1362
Exploring the cost and burden of illness of hereditary angioedema in England

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Background: Hereditary angioedema (HAE) is a rare disease causing episodic, potentially life-threatening attacks of oedema. This study aims to define the burden of HAE in England from NHS and patient perspectives as published data are limited.

Method: A cross-sectional, retrospective study of the economic and humanistic burden of HAE (type I/II) using three data collection methods

1 Hospital Episode Statistics secondary care database analysis (all episodes 2011–2012).
2 The Health Improvement Network primary care database analysis (all interactions 2011–2012).
3 Subsequent research in five secondary care centres (4 England, 1 Scotland) collecting information from >100 adult patients via medical records (past 2 years), patient self-completion questionnaires and centre interviews is ongoing.

Results: For HAE patients admitted to hospitals in the past 2 years for any reason (n = 1383) the direct cost to the NHS was £1619 per-patient-per-year vs £362 for matched controls (excluding hospital drug costs e.g. HAE specific medication, $P \leq 0.05$), giving an incremental cost of £1257 per HAE patient-per-year. Hospital admissions were more frequent for HAE patients (69% vs 21% for control, $P < 0.05$) with more bed days than controls (3.02 days per annum vs 0.95 for control, $P < 0.01$). The primary care cost (including HCP interactions and non HAE-specific drug costs) was £1102 for HAE patients (n = 112) vs £689 for controls giving an incremental cost of £413 per HAE patient-per-year. In total, HAE patients incurred an additional cost to the NHS of £2 308 807 or £1699 per-patient per-annum, not including costs for HAE-specific drugs. Due to limitations associated with current diagnostic and procedure coding, these costs may be underestimated.

Conclusion: This is the first comprehensive UK HAE burden of illness study. Although rare, HAE presents a burden to the NHS, related both to increased secondary and primary care costs relative to controls. These findings will be further investigated with results of the ongoing patient-perspective research.

1363
Cost-minimization of innovative C1-inhibitor self-administration strategies in Hereditary Angioedema

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Background: Replacement therapy with plasma-derived C1-inhibitor (pdC1INH) is used to treat acute Hereditary Angioedema due to C1-inhibitor deficiency (HAE) attacks. This treatment is usually administered intravenously in healthcare settings. Recently pdC1INH self-administration training programs were made available for patients with HAE. The aim of this study was to compare the economic impact of two alternative administration strategies for the treatment of HAE attacks. Economic evaluation was performed considering both the payer (Italian National Health System) and the social perspective.

Method: Seventeen patients who decided to switch to self-administration were interviewed before and 12 months after the beginning of the home therapy. The interviews allowed to collect data about the number and type of hospitalisation, the number of primary care emergency room visits, the number and type of treatment, the number of missed days of work/school, as well as other cost-generating relevant factors. We considered, in the payer perspective, only the medical costs while in the social perspective both medical and non-medical costs. The total costs per-capita of the two alternative strategies were calculated, by referring to scientific evidence and official data (such as DRGs, hourly labour costs, etc.).

Results: The self-administration strategy generates sensible savings amounting to a total of €25.313 per year, of which €15.078 may be ascribed to the payer perspective. On a per-capita basis, the total savings amount to €1.489,of which €887 are related to the payer perspective. The self-administration strategy results in an average saving of 90% compared with the health professional administration strategy.

Conclusion: Self-administration strategy is less expensive than health professional administration both in the payer and the social perspective. This economic evaluation model indicates the beneficial economic impact of implementing pdC1INH self-administration programs.

1364
Successful pregnancy outcome after treatment with C1-inhibitor concentrate in a patient with hereditary angioedema

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Introduction: Management of hereditary angioedema (HAE) in pregnancy is important as the possibilities for complications. We present a HAE patient with recurrent attacks during pregnancy, but uncomplicated labour under C1-inhibitor (Cl-INH) concentrate prophylaxis.

Case presentation: Twenty-eighty-year-old woman was admitted with recurrent attacks of abdominal pain and swellings of extremities and face without urticaria from early childhood. There was no history of angioedema in her siblings, but parents' history was unknown since they were dead years ago. She was diagnosed type I HAE with low levels of serum C4 (3.31 mg/dl, normal: 10–40 mg/dl), C1INH antigen (<2.80 mg/dl, normal: 18–32 mg/dl), and C1INH function (<1%, normal 70–132%). As she grew older, frequency and severity of her swellings increased. Long term prophylaxis was indicated with at least one attack in a week, and she was initially started on tranexamic-acid with no response. Afterwards she was improved with Danazol for 6 months. But when she

got married, the treatment was switched to C1-INH concentrate as needed therapy, and used 500 U of C1-INH concentrate for short term prophylaxis approximately once every week. She subsequently presented with positive pregnancy test, and got persistent swellings. Long term prophylaxis was started and her angioedema episodes were relieved with 1000 U C1INH concentrate per week. She received C1-INH concentrate during delivery, and was discharged with no complications. Finally the patient and baby are healthy in lactation period with 500 U of C1-INH concentrate as needed therapy.

Conclusion: Plasma derived C1INH concentrate is a safe therapeutic drug in HAE for pregnancy and delivery, as well as lactation period.

1366
Tongue edema, a case report

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Background: Angioedema is defined as recurrent episodes of skin or submucosal tissues with digestive symptoms or airway edema. It can put in danger patients life. This disease is infradiagnoses because it can go unnoticed. Hereditary angioedema It is transmitted by dominat autosomic way. Incidence: 1:50 000 three types: I (85%) quantitative deficiency, II (15%) qualitative deficiency and type III less frecuent, Diagnosis by clinical and lab tests (C1INH concentration, activity and C4).

Method: A 27 year old woman with recurrent episodes of tongue edema for 1 year. Personal precedents: Diabetes insulin dependent, hipotyroid, and hormonal contraception with estrogens. Familiar precedents: cousin with angioedema. Clinical course: episodes of tongue edema monthly unpredictable and with different intensity. In one ocassion mechanical intubation was required. Symptoms were not controlled with epinefrine, corticoids or C1IHN concentration. Lab tests were normal and genetic study was negative to FXII.

Results: Symptoms were controlled with icatibant (antagonist receptor of bradykinin). Preloaded syringe of 30 mg than patient can auto-administered subcutaneously when needed.

Conclusion: It is an Hereditary angioedema with normal C1INH and genetic study unknown. Scientific community must be alerted.

Classification of Non histaminergic angioedema.

A) With C1INH deficency (Hereditary or Acdquired),
B) With normal C1INH (Hereditary- with FXII mutation or unknown, Acdquired- medicaments or idiopathic).

1367
Type I hereditary angioedema clinical debut in a 72-years-old female patient

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Background: Hereditary angioedema (HAE) is an autosomal dominant disease caused by a deficiency in functional C1-inhibitor. Symptoms typically begin in childhood and worsen around puberty.

Patient and methods: A 73-year-old female patient has been suffering frequents episodes of edema at face, lips and tongue with mild difficulty in breathing and swallowing since November 2012. When symptoms started she was receiving treatment with an angiotensin-converting enzyme inhibitor (ACEi). Her father's sister had also suffered angioedema. We realised the analytic screening for HAE obtaining a low value of C4 (3.44 mg/dl). We amplified the study of complement obtaining low values of quantitative C1-inhibitor (20.2 mg/dl) and functional C1-inhibitor (55%). Few months later we repeated the study of complement with similar results, although the functional value of C1-inhibitor was 44%. Normal results were obtained for C1q, C2 and C3. She has three daughters and a son who have never suffered from angioedema. Three of them show normal quantitative and functional values of C1-inhibitor, but a 44 years-old daugther shows repeated low values of C4 and quantitative and functional C1-inhibitor.

For some months the patient continued suffering frequents attacks in spite of have stopped the treatment with the ACEi and was treated in two occasions with Icatibant. In September 2013 we decided to start a therapy with an attenuated androgen because of the frequency and severity of the attacks. She started to take 2 mg of stanozolol every 8 h. Two months after begining this therapy the patient has not suffered new attacks.

Conclusion: We present a patient suffering from a type 1 HAE. The particularity of this case is the old age of the patient when symptoms appeared for the first time. We also underline that the patient's daughter has not suffered until now symptoms suggestive of HAE in spite of reduced values of quantitative and functional C1-inhibitor.

1368
The traumatic effect of angioedema attacks in patients with hereditary angioedema

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Background: Hereditary angioedema (HAE) is an uncommon and a serious life-threatening disorder which is presented with swelling episodes on extremities, face and trunk and may cause intense feeling of helplessness and being terrified and appears to the person to occur from out of the blue. In our study, traumatic effect of angioedema attacks on mental health was researched in patients with Hereditary angioedema.

Method: In this study, 25 patients who were diagnosed as HAE and followed up by Istanbul Faculty of Medicine Allergy outpatient clinic were inclueded. Semi-structured interview form, The Impact of Events Scale-Revised (IES-R), Beck Depression Inventory, Beck Anksiety Inventory were applied to each patients.

Results: \Sixty percentage (15) of 25 patients who concented to participate were female. The mean age was 36.9 ± 14.1. 80% (20) of patients reported that they experienced the perception of life threat and for 12% (3) this was an ongoing problem. Beck Depression Inventory mean score of the entire group was 8.9 ± 8, Beck Anxiety Inventory mean score was 11.4 ± 8.7. The mean score of intrusion (reexperiencing the event) for angioedema attack was 8.8 ± 7.9, mean score for avoiding was 8.4 ± 6.6, increased arousal (hypervigilance) mean score was 7.5 ± 5.6. Patients who experienced laryngeal edema during attacks had higher scores of intrusion, avoiding and increased arousal according to the patients who didn't experienced, but these scores were not statistically significant. The scores of intrusion ($P = 0.04$) and increased arousal ($P = 0.03$) were statistically significant and all of IES-R subscale scores were high in HAE patients with depression.

Conclusion: In patients with HAE, anxiety and depression scores were founded higher than general population and the susceptibility of traumatic effect were more common in HAE patients with psychiatric symptoms. In this context, control and management of the presence of psychiatric symptoms is required for therapeutic alliance and having a healthier work, social and family life in these patients.

Poster Session Group III – Green

TPS 60 – Immunodeficiency I

1369
Perceived reduced (Immune) resistance, sleep and daytime functioning

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Background: Changes in immune functioning can have an impact on sleep and health. The current survey was conducted to explore the relationship between perceived reduced (immune) resistance, sleep, and daytime functioning.
Methods: A survey among Dutch young adults (18–35 years old) collected information on perceived immune function (i.e. resistance) and its relationship with sleep quality and duration. SLEEP-50 subscales of sleep apnea, insomnia, circadian rhythm disorder, and daytime functioning were completed, and scores of subjects reporting reduced resistance were compared to those reporting a normal health status.
Results: The survey was completed by $n = 574$ Dutch young adults (mean age 22.3 years old, 68.5% women). Of them, $n = 209$ subjects (36.4%) reported reduced resistance. They were significantly older (22.5 vs 21.9 years old, $P = 0.024$), smoked more cigarettes per day (1.8 vs 0.7 cigarettes, $P = 0.001$) and consumed more alcohol per week (10.5 vs 8.1 drinks, $P = 0.009$) when compared to subjects that reported a normal health status.

Only few of the subjects ($n = 13$, 2.2%) could be classified as having a sleep disorder. Overall, the groups did not differ on total sleep time, but sleep quality was rated significantly lower in those reporting reduced resistance (6.8 vs 7.2, $P = 0.0001$). In line, significant differences in sleep scale scores were found between subjects with normal and reduced resistance. Relative to those reporting a normal health status, subjects with reduced resistance reported significantly higher scores ($P = 0.0001$) on sleep apnea (2.6 vs 3.6), insomnia (5.1 vs 6.8), and circadian rhythm disorder (2.1 vs 2.7). Subjects with reduced resistance also reported significantly poorer daytime functioning (5.4 vs 7.6, $P = 0.0001$).
Conclusion: Perceived reduced (immune) resistance is associated with sleep disturbances and impaired daytime functioning.

1370
Investigation of T_{REG} cells in DOCK8 immunodeficiency

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Background: DOCK8 immunodeficiency is a rare human immunodeficiency that gives rise to susceptibility to a limited range of viral infections (human papilloma virus, herpes virus and molluscum contagiosum) as well as frequent sino-pulmonary infections. The patients also have significant allergic disease, increased levels of IgE and a significant rate of hematological and non-hematological malignancy.[1,2] Previous work carried out in ENU-mutant mouse models of DOCK8 immune deficiency, have shown abnormal immune synapse formation in both B and T cells[3,4] but no clear mechanism for the specificity of the infections, nor the presence of allergic disease, have been found. Decreased or dysfunctional regulatory T cells (T_{REG}) are associated with hyper-IgE, eczema and allergy in a number of primary immunodeficiencies such as IPEX syndrome (*FOXP3* mutations), Omenn's syndrome and Wiskott Aldrich syndrome.[5]
Method: Thymic and splenic T_{REG} cells from the previously described DOCK8$^{pri/pri}$ mice[3] were quantitated by flow cytometry. T_{REG} cell numbers and development were also assessed by flow cytometry in mixed bone marrow chimeras and in DOCK8$^{pri/pri}$ mice carrying a transgenic T cell receptor specific for a hen egg lysozyme peptide.
Results: The number of T_{REG} cells in the spleen of DOCK8$^{pri/pri}$ mice was similar to wildtype mice, consistent with the finding of normal numbers of T_{REG} cells in the peripheral blood of patients with DOCK8 immunodeficiency. The number of T_{REG} cells in the thymus of DOCK8$^{pri/pri}$ mice, however, was reduced and there was evidence of a decrease in both thymic and splenic DOCK8$^{pri/pri}$ T_{REG} cells in the presence of competition from wildtype T_{REG} cells in the mixed bone marrow chimera mice. Initial analysis of thymic development of T_{REG} cells indicates a defect in the precursor stage.
Conclusion: DOCK8 deficiency in mice is associated with a defect in thymic T_{REG} cells.

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1372
Immediate adverse systemic reactions with intravenous immunoglobulin treatment in adult primary immune deficiency patients

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Background: Intravenous Immunoglobulin (IVIG) is used as replacement therapy in patients with primary immune deficiency (PID). The most common side effects are nausea, vomiting, fever, sweating, myalgia and headache. Life-threatening anaphylaxis may also occur with the infusion of IVIG in panhypogammaglobulinemia or selective IgA deficiency patients. In this study, primary immune deficiency patients treated with IVIG in our clinic between 2012 and 2013 were evaluated in terms of immediate adverse reactions to IVIG treatment retrospectively.
Method: Patients who were diagnosed as primary immunodeficiency and treated with IVIG were evaluated.
Results: We retrospectively analyzed 13 patients (7 male, 6 female) who were diagnosed as PID and treated with IVIG aged between 17 and 69 years in 2012 and 2013 in our clinic. A total number of 159 infusions were given. Nausea and vomiting occurred in two infusions in a female patient; infusions were stopped and treated symptomatically. The treatments were completed successfully after reducing the infusion rate. No side effects were observed in other infusions.

Conclusion: Accurate and early diagnosis of humoral immune deficiency, and administering IVIG improve the quality of life, reduce morbidity and prevent economic losses. The patients with immune deficiency should be evaluated and treated by an experienced clinical immunologist. Evaluating each patient before IVIG treatments can prevent possible side effects.

1373
Warning signs in primary immunodeficiency diagnosis

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Background: Primary immunodeficiencies (PID) are common, but under diagnosed diseases. The Jeffrey Modell Foundation developed warning signs to help physicians identify PID. The aim of this study was to evaluate ten warning signs application in an outpatient reference center in Southern Brazil.
Method: Cross-sectional study applying ten warning signs in patients followed in a reference center for PID treatment between 1994 and 2013. Warning signs were adapted by experts to Brazilian reality based on the original by Jeffrey Modell Foundation.
Results: Forty five patients with PID were evaluated; 32 (71.1%) had humoral deficiencies, 7 (15.6%) immunodeficiency associated to genetic syndrome, 3 (6.7%) congenital phagocyte defect, 1 (2.2%) SCID and 2 (4.4%) unclassified. Forty four (98%) showed one or more warning signs. The more frequently warning sign was two or more pneumonia within 1 year (71%); next was four or more new ear infections within 1 year (32%); then, 1 or more severe systemic infection (27%), recurrent intestinal infections/chronic diarrhea (27%) and a family history of PID (20%).
Conclusion: PID are common and underrecognised by health professionals. Suspicion is essential to diagnosis and ten warning signs have been a helpful tool to investigate patients for PID.

1374
Main pathogenic mechanisms of respiratory diseases in frequently ill children

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Background: Bronchopulmonary pathology remains one of the most urgent problems of pediatrics. Despite multiple research papers on this problem, diseases of the respiratory system, continue to worsen, recur and swich to a chronic form, and it is observed mostly in frequently ill children (FIC).
Method: The aim of our study was to identify the pathogenic mechanisms respiratory diseases in FIC. To this end, were examined 340 FIC with respiratory diseases. Patients were examined in the acute period of the disease and in the period clinical remission. In a study of children use of the following methods: number of CD3-cells, CD4-cells, CD8-cells, CD19-cells by flow cytometry, the content of serum immunoglobulins A, M, G by immunodiffusion methods of G. Manchini, IgE- by ELISA, the content of cytokines IL-1beta, TNF-alpha,IL-2, IL-6, IL-8 -by method immunochemiluminescence (IMMULITE system), IFN-gamma and the level of substance P – by ELISA. State of hemostasis was studied using TEG method Hartert.
Results: Our results show that in the acute period of the respiratory disease,reduced the level of cellular immunity, marked imbalance of humoral immunity. By the marked in cytokine status increase proinflammatory cytokines. In acute period of the disease is marked as raising the substance P and blood clotting. The high correlation between the immune system including cytokine status, substance P and hemostatic system. We found that the clinical remission of respiratory diseases in FIC is not accompanied by a normalisation parameters of the immune system, cytokine status, substance P and hemostatic system.
Conclusion: High level of proinflammatory cytokines in the period of clinical remission, reflect ongoing inflammation, which is associated with persistence of the infection agent.

1375
Congenital IL-12R1β receptor deficiency and thrombophilia in a girl homozygous for an *IL12RB1* mutation and compound heterozygous for *MTFHR* mutations: a case report and literature review

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Interleukin-12 (IL-12) plays an important role in the production of interferon gamma (IFN-γ) from T and natural killer (NK) cells and is essential for protection against intra-macrophagic pathogens such as *Mycobacterium* and *Salmonella*. Here, we described a 16-year-old girl who had disseminated *Mycobacterium tuberculosis complex* (MTBC) infection, retroperitoneal fungal abscess, and superior mesenteric-portal vein junction thrombosis. We found a homozygous mutation in exon 12 of the *IL12RB1* gene, which caused complete IL-12Rβ1 deficiency. We also found compound heterozygous mutation (C677T and A1298C) in the *MTFHR* gene, which encodes methylenetetrahydrofolate reductase. This is the first case report of a primary immunodeficiency associated with a genetically determined venous thrombosis.
Keywords: IL-12R1β receptor deficiency, retroperitoneal fungal abscess, superior mesenteric-portal vein junction thrombosis, methylenetetrahydrofolatereductase, thrombophilia.

1376
A case of XMEN syndrome presented with severe auto-immune disorders mimicking autoimmune lymphoprolipherative disease

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The magnesium transporter 1 (MAGT1) is a critical regulator of basal intracellular free magnesium (Mg^{2+}) concentrations.

Individuals with genetic deficiencies in MAGT1 gene have CD4 lymphopenia, chronic viral infections, and defective T-lymphocyte activation causing clinical features with magnesium defect, EBV infection and neoplasia (XMEN syndrome). Herein, we report a patient with XMEN syndrome, with presented CD4 lymphopenia, chronic CMV infection, Guillain Barre Syndrome (GBS), and Hodgkin lymphoma, which caused by a novel hemizygous mutation in exon 4 of the MAGT1 gene (c.555dup).

1377
Atypical severe combined immunodeficiency caused by a novel homozygous mutation in RAG1 gene in a girl who presented with pyoderma gangrenosum: a case report and literature review

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Severe combined immunodeficiency (SCID) is a heterogeneous group of inherited defects involving the development of T- and/or B-lymphocytes. We report a female with atypical severe combined immunodeficiency caused by a novel homozygous mutation at cDNA position 2290 (c.2290C>T) in exon 2 of the RAG1 gene. The patient presented with bronchopneumonia, pyoderma gangrenosum (PG), pancytopenia and splenomegaly. She presented to us with pancytopenia and splenomegaly at the age of 11. Her condition was complicated by PG on left lower ankle at the age of 12. She experienced bronchopneumonia at the age of 15. She was diagnosed with RAG1 deficiency at the age of 16. Her immunological presentation included leucopenia and diminished number of B cells.

1378
A case report: Wiskott Aldrich syndrome accompanied with multipl food allergies

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Background: Wiskott Aldrich syndrome is a rare X-linked recessive disease characterised by eczema, thrombocytopenia, immune deficiency, secondary infections, autoimmune disease predisposition and increased risk of malignity. Wiskott Aldrich syndrome has a variable disease severity depending on the genotype.
Case: A 5.5 year old boy who had eczematous eruptions for 5 years admitted to our hospital. He had thrombocytopenia ranging between 17 400 and 100 000/mm^3. There were no consanguity between the parents and no other relatives suffering from such a disease. He didn't have developmental and growth delay. He had eczematous eruptions on his face, hands and arms. In laboratory findings total IgE was 1948 ku/l and specific IgE was 2.93 ku/l and allergy to egg, milk, gluten, fish, soya beans and nuts was found. While his IgE level was in normal range, IgA level was high and IgM level was low. His clinical findings regressed with elimination diet and local treatment. He had only two times pneumonia and two times otitis media in his life and he had upper airway infection once a year.

Total WAS deletion was found when he was detected because of thrombocytopenia and eczema. He had no autoimmunity or cancer at that time.
Conclusion: Wiskott–Aldrich syndrome (WAS) is a disorder that may clinically appear in a wide variety of symptOms; from mild eczema and infection to severe, life threatening infections, resistant eczema, autoimmunity disorders and concomitant malignancies. Type of mutation can effect clinical appearance of the patients. Our case is the second in the literature with absance of WASP gene. As reported in the former case, our patient also had a clinical score of 3. Our case is significant with clinical symptoms accompanied with multipl food allergies and total absance of WASP gene, second in the literature.

1379
Treatment of acute hereditary angioedema attacks with recombinant C1 inhibitor during pregnancy – a single case experience

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Background: Hereditary angioedema (HAE) is rare disease characterised by C1 esterase inhibitor (C1-INH) deficiency resulting in recurrent angioedema attacks. The treatment of pregnant HAE patients is problematic, since none of drug used.
Method: We present our clinical experience with recombinant C1-inhibitor (rhC1-INH) in the repeated treatment of acute attacks of HAE during pregnancy. RhC1-INH is an analogue of human C1-INH and is obtained from the milk of rabbits expressing the gene encoding for human C1-INH. The amino acid sequence of rhC1-INH is identical to that of endogenous C1-INH.
Results: The patient, now 22-year-old women, presented at age 10 with clinical and laboratory symptoms of HAE. Before pregnancy the patient was treated prophylactically with tranexamic acid. Prophylaxis used before the pregnancy had to be discontinued resulting in increase of the attack in the second trimester. During the entire pregnancy there were eight potentially life-threating upper airway attacks. They were successfully treated with 50 U/kg rhC1-INH. All attacks responded within 4 h after administration rhC1-INH. The Cesarean section was performed in 39th week of pregnancy. The patient received 500 U of plasma derivated human C1 inhibitor concentrate immediately before surgery, without any complications. The newborn was healthy with birth weight 3370 g.
Conclusion: This is the first case-report showing the use of rhC1-INH in treatment of acute HAE attacks pregnant women, in our experience this approach was effective and safe.

1380
Recurrent malignant lymphomas in a patient with recessive DOCK8 gene defects

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Background: Most forms of autosomal recessive (AR) hyper IgE syndrome (HIES) are caused by loss-of-function deletions and mutations in the DOCK8 gene. These patients are prone to develop recurrent (viral) infections, autoimmunity and malignancies, probably related to impaired B cell, T cell and NK cell development.
Method: We present a patient with AR-DOCK8 gene defects who developed both non-Hodgkin's lymphoma (NHL) and Hodgkin's lymphoma (HL).

Patient is a 24 year old woman who had a history of eczema and recurrent pulmonary infections complicated by bronchiectasis. She had an impaired vaccination response and was treated with IVIG. At the age of 19 she developed a large cell B-NHL, stage IV. At the age of 22 she developed HL (stage I) and had recurrent disease at the age of 23. The course of disease was further complicated by systemic herpes, molluscum contagiosum, condylomata accuminata, autoimmune hemolytic anemia and listeria meningitis.
Results: Laboratory investigations; increased $CD3^+$ T cells; 4.1×10^9/l (0.7–2.1×10^9/l), $CD8^+$ T cells were increased; 2.9×10^9/l (0.2–1.2×10^9/l). Naive, memory and effector T cells were respectively; 7.2, 20.7 and 72.1% of the $CD8^+$ subset. $CD4^+$ T cells numbers were normal. Pre- and during malignancy normal $CD16.86^+$ $CD3^-$ NK cells; resp. 0.12×10^9/l and 0.2×10^9/l ($0.1–0.5 \times 10^9$/l). B cell subsets as % $CD19^+$ gate, naive ($IgD^+/CD27^-$); 1291 cells/υl (57–447), marginal zone/natural effector B cells; 41 cells/μl (9–88), memory B cells (IgD^-CD27^+); 11 cells/μl (13–122). All IgM^- B cells were class switched. Genetic analysis revealed heterogenous gene defects; deletion in exon 2–11 and c.5386C>T p.(Arg1796) mutation. Genetic analysis of both parents confirmed recessive inheritance.
Conclusion: We present a case with AR-HIES with normal NK cell numbers during course of disease, increased $CD8^+$ and naive mature B cells numbers, low B memory cells, severe infections and recurrent malignant lymphomas.

1381
Immunophenotype of the cellular component of the immune system in patients with primary agammaglobulinemia and IVIG replacement therapy

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Background: Regular introduction of immunoglobulins improves the quality of patients' lives right up to elimination of clinical signs of agammaglobulinemia. The question of activity of other links in immune system during replacement therapy IVIG still remains unanswered The aim of research – studying of ripening, activation and differentiation of immune cells in the dynamics of replacement therapy IVIG.
Methods: The analysis of dynamical observation after patients with CVID (7) and XLA (5 people) who did not have any clinical response of PID in a month's period before treatment and during the process of observation (1 year).
Results: The process of maturation of T-lymphocytes of the patients with X XLA was activated before the therapy with a change of differentiation to $CD8^+$ cells with an evident lytic potential ($CD3^+$-92 ± 3%; $CD8^+$-51 ± 2%, of which 86% Gr+), the expression of activation markers increased ($CD8^+$ HLA DR^+-3 ± 0.2%) on the background of lowering of suppression qualities ($CD3^+$ $CD4^+$ $Foxp3^+$-0.3 ± 0.03%). During the period of observation the activation potential of $CD8^+$ T-lymphocytes lowered to normal rate and the quantity of $CD3^+$ $CD4^+$ $Foxp3^+$ rose to 2.8 ± 0.08%. Nevertheless the focus of differentiation towards the prepotency of $CD8^+$ subpopulation remained the same ($CD8^+$-50 ± 3%). The patients with CVID before the therapy had their changes of differentiation focus and maturation of T-cells at the same level as patients with XLA, but it was less evident ($CD3^+$-83 ± 4%, $CD8^+$-43 ± 3%) with more significant activation potential $CD8^+$ cells (100% Gr+). The decrease of suppression qualities ($CD4^+$ $Foxp3^+$-0.2 ± 0.05%) and increase of expression of activation markers ($CD8^+$ $HLADR^+$-2.1 ± 0.09%) were identical to XLA. Within half a year's period activation and regulation potential of T-lymphocytes restored to the level of the control group. Moreover their differentiation and ageing did not undergo any changes within the year of observation.
Conclusions: Normalisation function humoral component does not effect the ageing and the focus of differentiation of cell potential, but followed by changes of it's regulation and activation potential. Compinsatory processes effector qualities of T-cells are more obvious among the patients with CVID, which immuneregulatory and functional potential recovers faster.

1382
The use of non-specific immunostimulators in children with recurrent respiratory tract infections. Critical review

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Background: Children suffering from recurrent respiratory infections are often subject to excessive use of so called 'immune-stimulating enhancements'. On the other hand, evidence base behind these preparations is usually lacking and no peer-reviewed studies are available that support claims made by 'immune-booster' supplements. Nevertheless the parents are strongly persuaded by media advertisements and pressure their pediatricians and family physicians to prescribe these formulations. Therefore, an evidence-based review of currently available immunostimulatory products for children with recurrent respiratory infections was strongly needed.
Method: Here, we critically analyze most of the marketed immuno-active drugs, including:

- herbal and vitamin preparations,
- dietary supplements,
- trace elements,
- homeopathic remedies,
- cod liver oil,
- inosine pranobex,
- Ecchinacea,
- bacterial lysates,
- zinc preparations, and
- probiotics

as well as some behavioural factors that can influence functioning of the immune system:

- sleep habits,
- physical activity,
- psychological stress,
- dietary regimes.

Results: A detailed list of possible and evidence-based interventions was prepared.
Conclusion: The vast majority of preparations are founded upon no reliable scientific knowledge. We also postulate that patients presenting with recurrent respiratory tract infections, should be evaluated

for an underlying immune deficit, including careful history and rational diagnostic testing. However, the history should focus on the environment of the patient, and behaviours that may negatively influence immunity.

1383
Frequency and pattern of sinopulmonary complications in primary immunodeficient patients

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Background: We aimed to determine the frequency and pattern of sinopulmonary complications in patients with primary immunodeficiency (PID).
Method: Data was obtained from Kuwait National Primary Immunodeficiency Disorders Registry which included patients diagnosed between January 2004 and December 2013.
Results: A total of 202 patients were registered during the study period as follow: combined immunodeficiencies (32.1%), well-defined syndromes with immunodeficiency (22.2%), predominantly antibody deficiencies (17.3%), diseases of immune dysregulation (15%), Phagocytic defects (7%), complement deficiencies (4.4%) and autoinflammatory disorders (2%). A total of 295 sinopulmonary manifestations were observed in 127 patients (63%). 53.2% of the manifestations were among the presenting symptoms while 46.8% occurred after establishing the PID diagnosis. Sinopulmonary manifestations were more common in patients with predominantly antibody deficiencies (2.3 manifestations/patient) followed by patients with combined immunodeficiencies (1.75 manifestations/patient). Pneumonia was the most common manifestation (108 episodes affected 80 patients), followed by otitis media (81 episodes affected 59 patients), bronchiectasis affecting 28 patients (13.8%) and asthma affecting 22 patients (11%). There is significant statistical association between the occurrence of pneumonia, otitis media and bronchiectasis and PID categories while there is no such association between asthma and PID categories. Microbial organisms were isolated during 46 pneumonia episodes (CMV and PJ were the most common). Other less common manifestations are sinusitis (12 pts), interstitial lung diseases (6 pts), pulmonary nodules (4 pts), LIP (2 pts) and aspiration pneumonia (2 pts). There were 57 deaths during the study period. Twenty four deaths (42%) were due to pulmonary complications as follow: pneumonia (16 cases), pulmonary hemorrhage (6 cases) and aspiration pneumonia (2 cases).
Conclusion: Sinopulmonary complications are common in PID patients. They can be serious and continue to happen even after proper treatment is initiated.

1384
Management of CVID patients in the Central Bohemia

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The common variable immunodeficiency (CVID) is the most common primary immunodeficiency characterised by impaired immunglobulin production and immune dysregulation. The chronic and recurrent infections and their consequences are a typical manifestation of this disease. In addition there is a higher risk of autoimmune disorders, lymphoproliferative or granulomatous diseases and malignancies.

In our study we analysed the data of 40 patients obtained from the medical records and the patients′ questionnaires. This data was also input into the Czech Primary Immunodeficiency Deficit (PID) Registry. We aimed at the period before the dignosis of CVID- onset of the symptoms and their characteristics, and at the course of the disease – effect of the therapy, occurence of the related complications. At the end we compared our data to the similar studies performed.

The chronic and recurrent upper and lower respiratory infections were the most frequent first manifestation for our CVID patients, but we observed developed chronic lung disease or autoimmune disorder as well. For the most of them the diagnosis of CVID was made with a significant delay.

An intravenous or subcutaneous imunoglobulin replacement therapy, eventually a combined therapy with an antibiotic prophylaxis, was initiated in all the patients. We achieved significant reduction of the severe infections.

Besides chronic lung disease, the most common complications were autoimmunity disorders, especially autoimmune thyroiditis, trombocytopenia, hemolytic anemia. On other hand we revealed two patients with insuline dependent (type 1) diabetes mellitus and CVID. Only a few case reports have been published with such association. In addition we also observed a higher risk of allergy for those patients.

Successful management of CVID patients is based on a prevention and a consistent treatment of infections with sufficient immunoglobulin replcement and/or antibiotic therapy, a prevention and an active screening of CVID related complications. Such approach can significantly improve the prognosis of CVID patients and the quality of their life.

Poster Session Group III – Green

TPS 61 – Immunodeficiency II

1386

Combine interferon- and immunotherapy in the treatment of immunocompromised children with different recurrent and latent herpesviral infections associated with recurrent acute respiratory infections

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Background: The treatment of Imunocompromised children suffering from different recurrent and latent herpes viral infections (HVI) associated with recurrent acute viral respiratory infections (ARVI) is a very difficult problem.
Method: We have studied 27 immunocompromised children (both sex, age 5–8 years) who had suffered from different recurrent and latent HVI and recurrent ARVI (from 6 to 24 episodes a year). We had studied clinical and anamnestic data, PCR and sulfur diagnostics for detection of HVI HSV1/2, CMV, EBV, HHV6), fIFN status (serum IFNα and IFNγ) and immune system (T – and humoral chain, neutrophlic granulocytes (NG), natural killers (NK).
Results: All patients had disturbance of IFN status (low levels of serum IFNα and IFNγ) in 100% of cases. Combine immunodeficiencies took place in 89.1% of cases. Patients were randomized in two groups. Patients of group 1 received system and local therapy with recombinant IFNα2-viferon (1 Mln IU with further reduction of dose for 2.5 months) and for recovery of the T chain three 10-day courses of isoprinosinum with a break for 2 weeks. For patients of group 2 viferon and isoprinosinum were used, similar group 1, and additionally they got two 10-day course of licopid in days free from isoprinosinum. In both groups were achieved a high clinical effects: the number of acute episodes of HSV1/2 was decreased in 9.0 fold in group 1 and in 5.5 fold in group 2. The number of children with replication of herpes viruses in both groups decreased and herpes viral proteins were detected in one biomatherial: in saliva or the nasal cavity. The level of ARVI was decreased in 12.6 fold in group 1 and in 16.8 fold in group 2. The reconstruction of immune system had more than 85% all of patients. The recovery of number and functional activity of NG were showed in group 2. The level of IFNα was increased in both groups in 100% of cases.
Conclusion: Combine interferon- and immunotherapy created for both groups of pattents had demonstrated high clinical and immunological effects. At the same time the levels of serum IFNα had increased in both groups, and the restoration of NG was happened only in patients of the group 2 who received additionally licopid.

1387

Adaptive Immune defect in a rare phagocytic disorder: leukocyte adhesion deficiency III with a novel missense mutation in *FERMT3*

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Background: Leukocyte adhesion defect type III (LAD-III), a rare phagocytic disorder, is caused by mutations in FERMT3, leading to functional defects of integrins. The main clinical features are related to phagocytic dysfunctions. Although integrins are present on the surface of T and B lymphocytes, defects in adaptive immune functions have only been demonstrated by *in vitro* experiments.
Method: We identified a patient with LAD-III caused by a novel FERMT3 mutation. Flow cytometric analysis of T and B cell subset, and lymphocyte proliferation assays were performed. Peripheral blood mononuclear cells (PBMCs) and purified T-cells were used for lymphocyte proliferation assays. Genetic analysis was performed by exome sequencing.
Results: The patient had low immunoglobulin levels and impaired lymphocyte proliferation to antigens in addition to classical features of LAD-III which included persistent leukocytosis and impaired platelet aggregation. Flow cytometric analysis revealed low percentages of class switched memory B cells ($CD27^+$ IgD^-IgM^-), marginal zone-like B cells ($CD27^+$ IgD^+ IgM^+), $CD27^-$ memory B cells ($CD27^-IgD^-$), and plasmablast ($CD24^-CD38hi$). Lymphocyte proliferation against PPD and tetanus was impaired using PBMCs, but not with purified T-cells. This suggests that the adaptive immune defect s is caused by impaired T cell interactions with antigen-presenting cell (APC), and not by intrinsic defects in T-cell signaling. The patient demonstrated significant clinical improvement with IVIG treatment, emphasizing the importance of adaptive immune defects in LAD-III.
Conclusion: Adaptive immune defect was identified in a rare phagocytic disorder, LAD-III. The proposed mechanism is related to the interaction between T-lymphocyte and APC. In the management of this type of phagocytic disorder, the status of adaptive immunity should be evaluated and emphasized.

1389

Clinical and laboratory manifestation in nine patients with selective IgM deficiency

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Background: Selective IgM deficiency represents a relatively rare primary immune disorder of unknown pathogenesis, characterised by marked decrease of IgM, but not of other immunoglobulin isotypes. Clinical manifestation is variable including recurrent infections and/or occurrence of autoimmune, allergic or malignant diseases.
Patients and methods: Clinical and immunological manifestation of nine adult patients with selective IgM deficiency, defined as IgM <0.20 g/l, referred to our department over an 18-year period were evaluated.
Results: The cohort consists of nine adult patients, four males (aged 22–65 years at the time of diagnosis) and five females (aged 49–66 years). Four patients had

undetectable serum levels of IgM (<0.05 g/l), while in five patients IgM level ranged from 0.09 to 0.18 g/l. On referral three patients presented with susceptibility to infections (upper respiratory tract infections, pyoderma), eight had type-one hypersensitivity diseases (allergic rhinoconjunctivitis, urticaria and asthma), three had systemic autoimmune diseases (2× Sjögren's syndrome, 1× systemic lupus erythematosus). All patients had protective levels of anti-tetanic and anti-pneumococcal polysaccharide antibodies. Surprisingly three of them had normal isohemagglutinin levels. Five patients had decrease of IgG subclasses: two patients in IgG1 (3.54, 3.08 g/l), two patients in IgG2 (1.02, 0.77 g/l), four patients in IgG4 (<0.08 g/l). Besides the three female patients with systemic autoimmunity, other two male patients showed positivity of antinuclear antibodies. All patients had normal numbers of B-cells, including presence of surface IgM^+ B-cells. In one patient the progression to panhypogammaglobulinemia with thymoma (Good's syndrome) was observed.

Conclusion: Clinical manifestation of selective IgM deficiency is variable. Besides mild clinical immunodeficiency, also other immunopathological diseases, both allergic and autoimmune, seem to be increased. The mechanism leading to this association remains to be elucidated.

1390

The phenotypic characteristics of subpopulations of neutrophils and monocytes – partners's myeloid phagocyte system, expressing the same membrane markers, in deep preterm newborns with congenital pneumonia

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Background: Myeloid phagocyte system (MFS) include neutrophil granulocytes (NG), monocytes (MON) circulate in the peripheral blood and work in inflamed tissues. (Silva, MT, 2010). The normal functioning of MFS is an essential element of anti-infectious protection.

Method: We had studied 14 very preterm infants with gestational age from 25 to 32 weeks, weighing from 930 to 1900 g, with severe congenital pneumonia on a background of respiratory distress syndrome. The control group consisted of 20 healthy term infants with gestational age – 38–40 weeks, weighing 2880–4370 g. For detection of different subpopulations of NG and MON we investigated simultaneous expression of molecules CD64, CD16, CD32, CD11b using four-color flow cytometric study. Density of expression of each membrane molecule of NG and MON measured using MFI. Adequate statistical analysis was performed.

Results: In patients with congenital pneumonia total leukocyte count was reduced ($P < 0.01$). The level of NG was reduced too ($P > 0.05$). The number of MON in patients did not differ from control ($P > 0.05$; p2 >0.05). 92.8 ± 1.8% healthy newborns had a subpopulation of $CD64^-CD16^+CD32^+CD11b^+$NG. This subpopulation was decreased in patients. Expression molecules CD11b and CD32 was, respectively higher compared with the control, CD16 did not differ from controls (p1 < 0.01; p2 < 0.001; p3 > 0.05). MON with phenotype $CD64^-CD16^+CD32^+$ CD11b consist 7.39 ± 3.0% in the control group. This subpopulation in patients was decreased in 2.8–3.3 times.

The density of expression CD16, CD32, CD11b risen significantly in pneumonia specially, CD16 ($P < 0.001$). In healthy newborns $CD64^+CD16^+CD32^+CD11b^+$ NG was minor (1.51 ± 0.6%). The number of NG with this phenotype increased in 27 times in patient with pneumonia ($P < 0.001$). Significant reduction, the density expressed membrane CD16, in contrast to increasing the density of CD32 and CD11b took place (p1 < 0.01; p2 < 0.001). The amount of $CD64^+CD16^+CD32^+$ $CD11b^+$MON was 23.7 ± 4.7 in healthy newborns. In patients with pneumonia the number $CD64^+CD16^+CD32^+CD11b^+$MON and density of CD64 did not change (p1 > 0.05), but the density of CD16, CD11b, CD32 was increased (p1 < 0.001; p2 < 0.001).

Conclusion: The obtained data indicate significant differences in the remodeling phenotypes of subpopulations NG and MON with the same equipment of receptors, that may lead to immunodeficiency in deep preterm infants with severe congenital pneumonia.

1391

Successful treatment of immune thrombocytopenia by rituximab in a patient with common variable immunodeficiency

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Background: Patients with common variable immunodeficiency (CVID) are at high risk of developing autoimmune hematological disorders like immune thrombocytopenia (ITP) and/or autoimmune haemolytic anaemia. Although this may seem a paradox, immunosuppressive drugs are used to treat ITP associated with CVID. Rituximab is a *chimeric monoclonal* anti-CD20 antibody that has been used for the treatment of B-cell lymphoma, rheumatoid arthritis and also primary autoimmune cytopenias in patients with CVID. In this report, we describe a response to rituximab treatment of steroid resistant ITP in a patient with CVID.

Cases: A 36-year-old woman who was diagnosed as selective IgA deficiency at 2 years old. After a traffic accident she had began to suffer from chronic diarrhea and also decreased serum *IgM and IgG levels* were *found* 13 years ago. She was diagnosed with CVID and *began receiving* monthly intravenous immunoglobulin (*IVIG) therapy*. *After the IVIG replacement therapy*, her platelet count dropped to 7000/mm^3. ITP was *resistant* to *steroid therapy*. She then started receiving rituximab at a dose of 375 mg/m^2, once weekly for 4 weeks. Therapy was well tolerated and no significant infections were seen. Her platelet count was found to be 121 000/mm^3 1 month later from initiating rituxumab.

Conclusion: *CVID* is often *associated* with recurrent infections and autoimmune manifestations, of which ITP is one of the most common. ITP results from Increased platelet destruction due to dysregulations of B and T cell homeostasis.

Treatment options ITP include corticosteroids, immunesupressive agents, intravenous immunoglobulin and splenectomy. Rituxumab is an alternative therapeutic option for CVID patients with CVID and ITP together who are resistant to first line treatments by taking into account that opportunistic infections may increase.

1392
Cyclosporin a effectively treated erythrodermia and lowered total eosinophil counts in an infant with Omenn syndrome

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Omenn Syndrome is an autosomal recessive combined immunodefiency characterised by generalised erythematous skin rash, enlarged lymph nodes, hepatosplenomegaly, severe susceptibility to infections, eosinophilia and hyper-immunglobulin E. Three months old girl was admitted to our hospital with a history of recurrent sepsis. Her physical examination revealed severe erythrodermia, hepatosplenomegaly, lymphadenopathy and failure to thrive. Laboratory findings revealed leukocytosis, lymphocytosis with high CD3 T cells, high CD4/CD8 ratio and absence of CD 19 B cells, high eosinophil count,and low immunglobulin levels. Heterozygote RAG1 gene mutation was shown. She suffered from itchy, scaling, icthyosiform erythrodermia and protracted diarrhoea. Cyclosporin A treatment up to 10 mg/kg effectively resolved erythrodemia and lowered total eosinophil counts. She gained weight during treatment. In this patient, stem cell transplantation at 16 months of age has been planned. The rate of complication until stem cell tranplantation is high, so we emphasize that cyclosporin treatment might improve the prognosis of these patients until cure is established.

1395
Is allergenic sensitisation profile associated with immunologic and allergologic events after a kidney transplantation?

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Background: Th1/Th2 immune profile of kidney transplanted patients may be associated with post-transplant outcome. The aim of the study was to determine if pre-transplantation allergenic sensitisation profile was associated with the occurrence of immuno-allergic events in kidney transplanted patients.
Methods: We included kidney transplanted patients from the University Hospital of Reims (France). All patients were explored by skin prick tests and specific IgE detection for environmental and health care components allergens before transplantation. We retrospectively analyzed the relationships between the results of systematic skin prick tests and specific IgE performed previous transplantation and post-transplantation immunologic events (rejection, allo-immunisation), post-transplantation opportunist infections and cancer.
Results: Eighty eight patients were included, mean aged 54 years. A cutaneous and/or biological sensitisation was found in 25% of the patients. Sixty eight immunological events were described, including 22 transplant rejections, 30 *de novo* anti-HLA immunisation, 9 opportunist infections and 7 cancers. One patient acquired a food allergy. Patients sensitised and not sensitised did not differ in terms of allergic events (5% vs 0%), rejection (25% vs 21%), *de novo* anti-HLA antibodies (41% vs 36%), rates of lymphocytes $CD4^+$, $CD8^+$, $CD19^+$ subpopulation, number of opportunist infections (9% vs 11%) and cancer (0% vs 11%).
Conclusion: Pre-transplantation allergenic sensitisation profile is not associated with post-transplantation immuno-allergic events in our study. Allergenic pre-transplantation exploration should be adapted to interview and allergic history of patients.

1397
Unrelated umbilical cord transplant in 75 primary immunodeficiency patients: a single centre experience

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Background: Hematopoietic stem cell transplantation (HSCT) is the curative treatment for many PID. Umbilical cord stem cell transplantation (UCSCT) represent good alternative for PID who requires HSCT with no suitable HLA-matched donor available. A retrospective analysis of 75 PID patients who underwent unrelated cord blood stem cell transplantation in our institution since it's started in 2003 to December 2012 which is considered as one of the largest single-center study. We examined UCSCT outcomes including engraftment, GVHD, transplantation related mortality (TRM), complications and the impact of different variable on these outcomes.
Method: In total 75 PIDs patients underwent 76 UCSCT at King Faisal Specialist Hospital and Research Center in Riyadh between January 2003 and December 2012 are included in the study. Related cord blood stem cell transplantation, familial hemophagocytic lymphohistiocytosis and congenital neutropenia were excluded.
Results: Seventy-five Primary Immunodeficiency Disease (PID) patients received 76 UCSCT in single centre between 2003 and 2012 in Saudi Arabia; SCID, $n = 44$, Non-SCID ($n = 31$) includes Griscelli Syndrome seven 13, Wiskott Aldrich Syndrome 7, Leukocyte Adhesion Deficiency -1 4, Chediak Higashi Syndrome 3, Bare Lymphocyte Syndrome 2), Chronic Granulomatous Disease 2. Myeloabaltive Conditioning was used for 45 pts Reduced Intensity Conditioning RIC in 26, TBI in one while four patients with no conditioning. Disease free survival was 55% (24/44) for SCID with mean follow up 52.5 months higher with RIC and 61% (19/31) for Non-SCID with mean follow up 66.6 months. Cumulative incidence of grade 3–4 Acute GVHD at day + 100 days were 4.5% for SCID and 9.6% for Non-SCID, and that for Chronic GVHD 36% for SCID and 13% for Non-SCID.
Conclusion: UCSCT represents worthy option for patients with PIDs who lack full match related donor with good outcome.

Poster Session Group III – Green

TPS 62 – Immunotherapy – AIT clinics III

1398
Patient supervision in a dose range finding trial using a timothy grass (*Phleum pratense*) pollen allergoid preparation

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Background: We performed a double-blind, randomized, placebo and actively controlled study to investigate the dose response relationship of a *Phleum pratense* allergoid preparation for subcutaneous specific immunotherapy (SCIT) in patients suffering from allergic rhinoconjunctivitis ± bronchial asthma. To assess safety and tolerability, patients were monitored for lung function and vital parameters for up to 6 h after each injection. An independent Data Safety Monitoring Board assessed the safety data.
Method: Adult patients (FAS $n = 98$) were randomised to one of five groups. Three groups received nine pre-seasonal subcutaneous injections of the *Phleum pratense* allergoid in different doses: standard dose group ($n = 18$), threefold lower ($n = 20$), and threefold higher than standard dose ($n = 18$). The active comparator group ($n = 22$) was treated with standard dose of a 6-grasses allergoid. Twenty patients received placebo. Covering the entire period of interest, long-term safety assessments 15 min, 30 min, 1, 3, and 6 h after injection were performed. These included peak expiratory flow rates (PEF), vital signs and local reactions (diameter in mm) at injection site.
Results: After drug administration, the values of PEF, systolic blood pressure, diastolic blood pressure, heart rate and respiratory rate for patients in all treatment groups remained in normal ranges during the observational periods at all visits. Median size of the local reactions 30 min after injection of medication ranged from 0.0 to 6.5 mm (low dose), 0.0 to 5.0 mm (standard dose), 0.0 to 5.0 mm (high dose), 1.0 to 8.0 mm (active comparator), and remained constant at 0.0 mm in the placebo group. There were no serious adverse events during treatments.
Conclusion: During the supervision period no changes in vital signs occurred in all treatment groups. All doses of the *Phleum pratense* allergoid, even at the threefold higher than standard dose level, showed a favourable safety profile.

1399
Satisfaction with sublingual immunotherapy in allergic rhinitis treatment: dependence on some clinical factors – real life study

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Background: There are many trials on the efficacy of sublingual immunotherapy in patients with allergic rhinitis, but studies on satisfaction are insufficient. Satisfaction is especially relevant in long – term treatment such as sublingual immunotherapy. The aim of the study is to evaluate some factors that can determine the satisfaction with sublingual immunotherapy of patients with allergic rhinitis.
Method: Sixty-nine adults (males – 39/56, 52%) with allergic rhinitis were included in this prospective study. The patients were divided into three subgroups, on the base of duration of the complaints till the initiation of sublingual immunotherapy (SLIT): up to 4 years – 19; 5 to 9 years 26; more than 8 years – 24. Twenty-one patients were treated by SLIT for house dust mites and another 49 – for 5 Grasses/4 Cereals. Severity of the disease and overall treatment satisfaction (using visual analogue scale) and quality of life (measured by Rhinoconjunctivitis Quality of Life Questionnaire) were established at baseline and after 3 years of SLIT.
Results: Significant differences were established at baseline and after 3 years of sublingual immunotherapy for severity of allergic rhinitis (mean values: 7.14/3.07); quality of life (2.93/0.99) and overall treatment satisfaction (4.56/7.58)/($P < 0.01$). It was established that overall treatment satisfaction did not depend on gender, duration of complaints and type of SLIT ($P > 0.05$). Significant correlation between severity of the disease and quality of life after 3 years of SLIT and overall satisfaction was established ($P < 0.01$).
Conclusion: Our prospective study had shown that overall treatment satisfaction with SLIT in patients with allergic rhinitis appeared to be associated with severity of the disease and quality of life.

1400
Frequency of immunotherapy with cupressus arizonica pollen in patients of our immunotherapy unit

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Background: The Cupressus arizonica (CA) pollination period extends from January to March in Madrid area (Spain), acting as a trigger of rhinoconjunctivitis and asthma symptoms. We aimed to analyse patients receiving immunotherapy (IT) with arizonica pollen in our IT Unit.
Methods: We included 216 patients 5 to 67 years-old attended in our IT unit. All of them have been diagnosed of pollen induced rhinitis/asthma and have received pollen immunotherapy from March, 2012 to August, 2013. Total IgE and specific IgE to Cupressus arizonica were measured by ImmunoCAP (ThermoFisher Scientific).
Results: We included a total of 97 patients (44.9%) that received CA pollen IT. The remaining 119 received other pollens (grass, olive, plane tree). There were more women than men in both groups (56.3% women vs 43.7% males without arizonica in contrast to 56.7% vs 43.3% with arizonica) with no statistically significant difference between them. According to the diagnosis, rhinoconjuctivitis was the most frequent symptom observed in 60 patients (61.9%), followed by rhinoconjunctivitis and asthma in 37 patients (38.2%) in the CA group. It is observed that asthma has a similar frequency in regard to the group without arizonica (40.3% vs 38.2%). We observed higher level of total IgE in patients without arizonica IT (IgE = 377) in contrast to CA group (IgE = 296.6), with a non-statistically significant result ($P = 0.06$).
Conclusion: The 44.9% of pollen allergic patients attended in our IT Unit received vaccines which included Cupressus arizonica pollen. It is noteworthy that 38.2% of these patients had asthma. Therefore we consider the CA as a relevant pollen

causing allergic symptoms in patients attending our IT unit.

This study is the output of a clinical fellowship awarded by the EAACI in 2013.

1401
Systemic reactions in patients receiving cluster immunotherapy: a prospective study

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Background: Allergen specific immunotherapy (IT) is currently the only disease modifying option for patients with respiratory and venom allergies. Cluster IT is a good alternative to the conventional schedule as it shortens the build-up phase, increases patient compliance and reduces costs; yet, it is still not widely used because of the fear of side effects. We aimed to study the tolerance of cluster IT in real life practice.
Method: We collected prospectively data from all the patients who received the updosing shots of cluster IT from August 31st to December 5th 2013 at the IT Unit of the Allergy Department of Hospital Clinico San Carlos. Detailed information including demographics, allergy history, skin prick test, total and specific IgE, allergen composition of the vaccine, manufacturer, type of reaction (if any) and treatment received, were recorded.
Results: A total of 100 patients were included, 51 males and 49 females, mean age 28.8 years (range 5–70 years). They received 557 injections and reached maintenance dose in 1–4 weeks. All patients had respiratory allergy (rhinoconjunctivitis ± asthma) except one patient who had hymenoptera venom allergy. Ninety six patients received pollen IT. There were five systemic reactions (SR) in four patients, mean age 36.5 years (range 5–62), all females ($P = 0.045$), accounting for a frequency of 4% and 0.9% of all patients and doses, respectively. Three of the SR were delayed and two immediate (grade 1 and 4). The composition of the vaccines included grass pollen in two patients, grass + cypress and grass + olive pollens in one patient each. Adrenaline was administered in two occasions, and no patient needed hospitalisation. IT was stopped in the patient with two SR. We did not find any specific factor associated with SR.
Conclusion: Our results suggest that cluster immunotherapy can be well tolerated by the great majority of patients, but it should be administered in expert clinics.

1403
Combination of immunotherapy, systemic and local antinflamatory treatment for skin atopic dermatitis

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Background: In recent years, atopic dermatitis is a disease with increasing occurrences. The presence of the disease can range from early childhood to mature, elderly adults. To successfully treat atopic dermatitis, it is necessary to not only proficiently diagnose the patient, but to outline imperative patophysillogical and immunological mechanism involved in the pathogenesis of the disease. Several mechanisms and clinical presentation of atopic dermatitis overlap with other immunological diseases. Therefore, treatment should include local and general care to decrease immunological responses from recurring exposure and contact with environmental allergens.
Method: Patients with atopic dermatitis, presented as eczema, were treated with local anti-inflammatory steroid (bethamethason 0.01% ointment) every other night as well as systemic steroid (prednisolone) in early phase of treatment with gradually decreasing daily doses up to 30 days. After positively responding to skin diagnostic procedures including an intracutaneous test, total IgE level in the blood, and specific IgE level for allergens, subcutaneous immunotherapy was administered to the patients. Statistical analysis was performed using software Statistica for Windows.
Results: During follow up, 1 year after diagnosis, 58 patients were treated, 37 female of them being female and 21 male. Subcutaneous immunotherapy (SCIT) was performed as follows: after initial dose and weekly increase in dose, the satisfied weal was obtained. Next, we administered equivalent doses, one per week for 2 weeks and thereafter monthly. After 1 year of treatment patients were reassessed. The success of the immunotherapy was evaluated by the improvement of the local eczema as well as general impact of therapy for satisfaction of patients (Health Related Quality of Life-HRQL). Satisfactotory local status was reached after 3–4 weeks of treatment (average days 24.2 SD 3.5). Maintenance dose of prednisolone was 10 mg, two or three times a week (average 22.45 mg a weekly, SD 3.4). Out of all the patients, 52 displayed considerable and continuous improvement of local skin eczema and HRQL satisfaction scores.
Conclusion: The combination of local and systemic treatments of eczema results in better therapeutic success with minimal or no adverse effects, in comparison to isolated, singular treatment or either.

1404
Impact of moderate/severe non-controlled allergic rhinitis on academic performance in children and in the work productivity of the patient''s caregivers. ENERGY study

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Background: Although allergic rhinitis is the leading cause of consultation in the allergist's office, its impact on the academic productivity has been understudied to date as well as the impact in the work productivity of patient's caregivers. The aim of this study was obtain some reliable information about this subject.
Method: Observational, multicenter and cross-sectional study. Allergic patients to pollens or mites whose principal activity was studying were recruited. The trial was carried out between March 2011 to March 2012.

Evaluation of the impact of allergic rhinitis on academic productivity was done by use of WPAI + CIQ:AS questionnaire.
Results: One hundred and eighty-six children were recruited. The average age was 13.77 ± 1.54 years (range: 12–17; 38% females). The average evolution for allergic rhinitis was 5.66 ± 3.4 years. 55% had asthma and 65% conjunctivitis. 84% of the patients were being treated with AIT (IR/ml) for a mean time of 12.28 ± 14.61 months, the others did not received it. Children declared to lose 0.60 ± 2.10 h of class/week due to allergic related problems and the caregivers 0.48 ± 1.15 h of work/week.

Academic performance loss was associated with two variables (bivariate analysis): history of atopy in the family and not

being under treatment with AIT. From the point of view of the caregivers no variable is associated with their work productivity loss.

The multivariable analysis pointed out that being under treatment with AIT is the factor that most positively influences the academic productivity in children (Coefficients: −12.9 for productivity lost, −9.5 for regular activities impairment).

Conclusion: The results of ENERGY study reflect for the first time that AIT (IR/ml) is the factor that most positively influences the academic productivity in children patients suffering an uncontrolled moderate/severe allergic rhinitis.

1405
Epidemiological data of patients with moderate/severe non-controlled allergic rhinitis attending the allergist office. Energy study

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Background: Although allergic rhinitis is the leading cause of consultation in the allergist's office, detailed clinical profile of non-controlled patients with moderate/severe allergic rhinitis and its impact on the academic/work productivity is still scarce. The aim of this study was obtain some reliable information about this subject.

Method: One hundred and fifty-five allergy specialists participated in a multicentre, observational, epidemiological, questionnaire-based study. Each investigator had to recruit six patients over the age of 12 that were currently studying or working. The impact of allergy rhinitis on their principal activity was obtained by use of WPAI + CIQ:AS questionnaire.

Results: Of the patients recruited, 683 were adults and 186 children. 48% were female. The mean ± SD days a week that they study/work was 5.17 ± 0.83 days spending 7.04 ± 2.02 h each day. These four diagnosis methods were used in more than 50% of patients: clinical records, prick-test, total IgE and specific IgE. 21.2% were allergic to mites (mainly Dermatophagoides), 30% to pollens (mainly grasses and/or olive) and 33.5% to both of them. 69.9% had a persistent rhinitis, 86.5% a moderate/severe rhinitis (ARIA classification), and 49.7% had concomitant bronchial asthma. The disease duration was 8.7 ± 7.9 years. Just 18.4% of patients reported that their symptom status had improved or greatly improved since the beginning of the condition, whereas the remainder qualified their symptom status as equivalent (27.9%), worse (47.1%) or much worse (6.6%). 77.9% were using AIT (72.5% AIT expressed in IR/ml) for 12.67 ± 14.28 months.

Adult patients reported losing 0.72 ± 1.99 h of work in the last week due to allergic impairment, children were losing 0.60 ± 2.10 h of school in the last week. The work/academic productivity loss was rated as 1.93 ± 2.29 and 1.65 ± 2.13, respectively (0–10 scale, 10 being the worse scenario). AIT is the factor that most positively influences productivity in this study.

Conclusion: Allergic rhinitis definitely impacts the principal activity of the non-controlled patients no matter they were in an academic or working environment. Absolute data of absenteeism and presenteeism could seem no very alarming in this study, probably because the fact that 77.9% of patients were on AIT for nearly 1 year on average.

1407
Factors associated with early, local side effects of allergen-specific immunotherapy

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Background: Allergen specific immunotherapy is one of the most effective tools in modern allergology, but it remains largely underutilised in certain countries and regions due to concerns about it′s potential adverse reactions. While early local side effects are considered to be of little clinical significance, they can notably decrease patient′s quality of life and adherence to treatment. Our objective was to assess the incidence and risk factors of early side effects in patients undergoing specific allergen immunotherapy.

Method: Seven hundred and eighty-eight immunisations administered to 578 subjects randomly chosen from patients undergoing SCIT in outpatient clinic were analyzed. Immediate reactions 30 min following the injection were recorded and compiled with medical histories to build a database.

Results: 78 (9.9% of injections) local adverse reactions (erythema, swelling and itching) were observed. None of the events developed into systemic allergic reaction. Univariate analysis showed similiar incidence and severity of adverse events in males and females, with younger patients having significantly more frequent reactions (mean age 25.6 vs 32.4 years). An increased incidence of side effects was noticed in patients treated with Phostal compared to other products (16.4% vs 6.2%), as well as in those receiving house dust mite extract compared to other allergens (14.7% vs 8.4%). Lower frequency of side effects was associated with vaccine 1 (1.7% vs 12.3%), tree pollen (6.4% vs 11.5%) and grass pollen (5.8% vs 14%) compared to other extracts. Multivariate analysis using logistic regression revealed that young age [below 15 years; odds ratio (OR) = 17.23; $P < 0.001$] and treatment with vaccine 2 (OR = 2.21; $P = 0.017$) were main factors significantly associated with increased risk of local immediate reactions during specific immunotherapy.

Conclusion: Allergen immunotherapy is a safe procedure, but further studies are required to accurately identify it′s risk factors to further increase it′s safety.

1408
Disease-modifying properties of SQ-standardised grass SLIT-tablets and long-term cost-effectiveness

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Background: Grass allergy immunotherapy (AIT) tablets for sublingual use (SLIT-tablets) are effective in reducing symptoms and need for medication. The economic analysis of AIT treatment is based on the assumption that the additional cost of AIT in the short term is balanced by long-term return on patient quality of life. Hence, in order to estimate the cost-effectiveness of AIT, extrapolation of clinical trial data is the standard method. However, long-term effectiveness depends on the ability of the specific AIT to modify the underlying nature of the disease. The study objective was to assess the potential of disease modifying effect (DME) of SQ-standardised Grass SLIT-tablets on long-term cost-effectiveness.

Method: Based on data from a 5 year clinical trial showing disease modifying effect for 2 years after end of treatment (GT-08, SQ Grass SLIT-tablet, ALK, Denmark), we established a Markov state model of allergic rhinoconjunctivitis and estimated long-term societal cost and QALYs. Uncertainty around DME of AIT was explored by estimating two scenarios: (i) Only the SQ-standardised grass SLIT-tablet allergy immunotherapy tablet product is available and compared to symptomatic treatment; (ii) Two available grass SLIT-tablet products are compared, differing in DME potential. We applied cost from a German societal perspective and used a

15 year time-horizon as the basis for the analysis.
Results: Grass SLIT-tablets are cost-effective compared to symptomatic treatment when the product is disease modifying (ICER < 15 000 €/QALY). Applying the model assuming no DME of therapy, the ICER increases to a level above 50 000 €/QALY. Comparison of two grass SLIT-tablet products shows that the drug cost savings associated with pre-/co-seasonal regimen, cannot balance the loss of efficacy if the product is not disease-modifying.
Conclusion: When assessing the cost-effectiveness of AITs the level of evidence for disease-modifying properties should be considered comparing products.

1409
The impact of sublingual immunotherapy on asthma control level and the life quality

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Background: Allergic asthma and allergic rhinitis are some of the most common forms of atopic diseases. Allergen-specific immunotherapy still remains the only method of pathogenic therapy. The aim of our work was to evaluate the effects of sublingual allergen-specific (SLIT) therapy on the level of asthma control and the life quality level of patients with allergic asthma and sensitisation to pollen of trees.
Method: There were included 37 patients in open prospective study, who have proved allergy to tree pollen. Every patient had a skin prick tests, which were positive to pollen of a birch, alder or hazel. All of the patients had diagnosis – mild and moderate asthma. We evaluated the control level by ACT test and ACQ-5 test, quality of life was measured by SF-36 and average dose of inhaled corticosteroids (ICS; in terms of beclomethasone) before and after SLIT were also evaluated. We used the standardised allergens by index of reactivity.

Patients were divided into two groups, which were comparable by a control level, asthma severity, gender and sex. The first group had 18 patients, their mean age was 28 ± 3.4 years. This group received SLIT to birch, alder and hazel allergens. The second group had 19 patients and they did not receive SLIT, their mean age was 32 ± 4.5 years.
Results: We observed significant difference in the average dose of ICS at the first group at the beginning of the study in comparison with the end point of the research: the average initial dose was 513.15 mg per day and after SLIT the average dose became 355.22 mg per day ($P < 0.05$). There was shown better effect in patients with severe asthma. Comparative analysis of the parameters of the groups showed significant differences between them in FEV1 data, ACQ-5 and ACT – test results. Patients of the second group in comparison with the first group had significant differences in the FEV1 results of questionnaires ACQ-5 and ACT tests and average doses received ICS. We observed significant differences between two groups in all parameters of the life quality level ($P < 0.05$).
Conclusion: Our study showed significant improvement of asthma control and quality of life among patients after SLIT in comparison with the patients who did not receive immunotherapy. Better results of SLIT were shown among patients with moderate asthma.

1410
Gammaplex 5% IVIG reduces adverse events in patients unable to tolerate 10% IVIG

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Background: IVIG is very well tolerated. However, a subpopulation of patients does not tolerate a high concentration product. Systemic adverse events (AEs), such as headaches, fatigue, fever and muscle aches often make the 10% IVIG solution intolerable. Administration of immunoglobulin subcutaneously often leads to fewer systemic AEs but it requires weekly infusions and most patients experience infusion site reactions.
Methods: We performed a retrospective chart review of 12 patients switched to a 5% solution of IVIG from a higher concentration due to the occurrence of non-serious AEs. The number and severity of adverse events occurring between 5% IVIG and 10% IVIG (headache, fatigue, nausea, arthralgia, muscle spasms, pain) were evaluated as well as trough levels of IVIG.
Results: Severity of adverse events with the 5% IVIG infusions was generally of 1+ or 2+ in nature vs the 2+, 3+ and 4+ severity reported with the 10% infusions. Severity of six common AEs was reduced with a switch to a 5% concentration without compromising infection-preventing trough levels of IgG.
Conclusion: The 5% IVIG was better tolerated in patients previously having side effects with a higher concentration making a reduced concentration IVIG a valid alternative for patients who poorly tolerate infusion with a 10% solution. Investigation of the mechanism responsible for better tolerability with 5% IVIG vs 10% is required.

Poster Session Group III – Green

TPS 63 – Immunotherapy – AIT clinics IV

1411
Economic evaluation of allergen immunotherapy for seasonal allergic rhinitis

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Background: We aim at modelling cost-effectiveness (CE) of alternative treatments of allergic rhinitis and identifying appropriate data needed for a complete assessment. Standard treatment (ST) provides partial temporary improvement, and allergen immunotherapy (AIT) sustained efficacy, but at a higher cost and with minimal treatment duration of 3 years. A new desensitisation with a 5-injection/2-month treatment would improve patient compliance if proven safe and efficacious.
Method: We develop a simple economic model to assess the CE of treatments as the cost per QALY gained by different AIT regimens vs ST alone. The model considers costs from different perspectives and accounts for level of severity and nature of allergy (seasonal/perennial). The model takes into account the progression of symptoms in spite of ST, as well as a dropout rate in the course of multi-year AIT. Only direct costs of treatment, including patient time consumption, are considered. Dealing with multi-year effects, a discount rate is used to calculate the present value of costs and QALYs. One-way sensitivity analysis on uncertain parameters is performed to assess the robustness of the results.
Results: We first focus on seasonal allergy and European countries. Based on published available data, expert opinion and outcome of the first trial run with short AIT, we evaluate incremental cost effectiveness ratios (ICER), for different scenarios. ICERs appear to be lower with short AIT compared to conventional AIT (24 000€ vs 40–47 000€), with an even larger difference when dropout is considered. These initial results will help specify the data to collect in the future Phase III trials.
Conclusion: Results presented should be regarded as indicative in view of assumptions required to overcome the present lack of data. Additional data from adequately designed trials will improve robustness of the results.

1412
Prospective Adherence to Specific Immunotherapy in Europe (PASTE) study: the enrollment of patients in Greece

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Background: PASTE study aims in evaluating patients' adherence to Allergen Immunotherapy (AIT) for allergic respiratory diseases and hymenoptera venoms, across different European countries. An EAACI Task Force has been formed for this purpose with eight partecipating countries. Hereby data from the enrollment of the Greek patients, regarding demographic data and type of sensitivity, are presented.
Method: Inclusion criteria were adult age (>18 year old) and the eligibility for AIT. Patients' enrollment started on October 2012 and ever since data are updated every 4 months. Study is expected to end in 3 years.
Results: A total of 322 patients (mean age: 33.8 year-old, 64.3% males) were recruited in allergology departments at NHS hospitals (69.3%) and private practices. Patients had been suffering from allergic rhinitis (259), conjunctivitis (138) and/or asthma (134). 50.6% reported symptoms lasting for more than 5 years. Most common airborne sensitivities were to grasses (136), to weeds (114), to Olive (96) and to house dust mites (89). AIT was prescribed for Grass (134), Parietaria (127), Olive (89), Cypress (8), Dermatophagoides (82), Alternaria (19) and cat (3). Subcutaneous AIT for airborne allergens is performed in 178 patients, while 49 are receiving sublingual drops (39) or tablets (10). Fifty-two patients had positive allergy tests to venoms; to honeybee (39) to Vespula spp (14) and to Polistes spp (6). Finally, venom immunotherapy was prescribed at 39 bee-allergic, at 12 Vespula-allergic and at six Polistes-allergic patients.
Conclusion: Most patients have had symptoms long before starting AIT. The majority of the patients were receiving AIT for aeroallerges subcutaneously. Grass is the main airborne allergen causing respiratory allergies in Greece, followed by Parietaria and Olive. Honeybee is the commonest insect for venom allergy in Greece. Since PASTE includes data from countries with different longitudes, useful conclusions will be extracted.

1413
Satisfaction with AIT (ESPIA questionnaire). From validation to reference values

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Background: The design, development and validation of a satisfaction questionnaire (ESPIA) for patients under AIT treatment was an interesting working area as far as there were already some instruments measuring the satisfaction with the treatment of certain illnesses (diabetes, eczema…), but not for AIT.

ESPIA questionnaire has been developed in three phases: I, Item generation; II, Item reduction and III, Questionnaire validation. The whole process lasted 3 years, more than 700 patients were involved and the results was a 16 items questionnaire.

One step beyond is to obtain the reference values for the interpretation of the questionnaire (ESPIA-IV).

AIT duration	<12 months AIT or 1 precoseasonal cicle					
AR frequency	Intermittent			Persistent		
Nasal symptoms (intensity)	Mild	Moderate	Severe	Mild	Moderate	Severe
n	112	105	95	108	108	104
Mean	75.8	67.4	55.3	68.9	61.3	56.8
DE	18.3	20.5	25.5	22.0	23.4	24.8
Cronbach alpha	0.93	0.95	0.96	0.96	0.96	0.96

Method: A longitudinal multicenter cross-sectional study was carried out in Spain. Two hundred allergologists recruited 1200 patients. The patients' sample had to be as heterogeneous as possible, therefore, patients were treated with any kind of allergen immunotherapy in terms of composition, via and manufacturer.

To ensure that a sufficiently representative sample would respond to ESPIA, 12 quotas were defined on the basis of the following variables: type of allergic rhinitis (2 variables), time using allergen immunotherapy (2 variables) and nasal symptoms intensity (3 variables).

Results: All the quotas have been completed since 1312 adult patients were recruited. The average age was 34.4 ± 11.7 years (54% females). 42.7% of the patients had concomitant asthma. Allergy diagnosis was done 40.7 ± 45.7 months before this study. ESPIA questionnaire score (0–100, being 100 the maximum level of satisfaction) was statistically higher in patients with more than 12 months of AIT ($P < 0.001$), in patients with intermittent rhinitis ($P < 0.001$) and in patients with mild nasal symptoms ($P < 0.001$). Satisfaction data of patients with <12 months of AIT is shown in the following table:

Conclusion: ESPIA questionnaire is a valid tool potentially useful for monitoring patient's satisfaction with AIT, the reference values obtained can be used in clinical practice to evaluate individual scores and assign the patient to the corresponding reference group.

1414
Systemic adverse reaction of specific immunotherapy in a child with allergic rhinitis

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Background: Specific Allergen Imunotherapy is one of the most effective forms of therapy available in the specialty of allergy. Subcutaneous immunotherapy (SCIT) has proven efficacy in allergic rhinitis and asthma, but it requires regular injections at a clinician′s office and carries the risk of potentially serious systemic allergic reactions in response to the treatment itself. The most common systemic reactions were respiratory reactions, occurring in up to 46%. General symptoms (such as headache, fatigue) occurred in up to 44% of patients and were usually mild or unspecified.

Results: A 10-year-old male patient with a history of allergic seasonal rhinitis have started allergen immunotherapy with grasses (chenopodium sunflower three Graminess dactilus glom secale cer phleum prat poa prat), which he was sensible. At the first flacon patient did n't have adverse reaction, but at the second one he had dyspnea, cough immediately after subcutan injection and was hospitalised for 3 days with complete resolution of symptoms. Five-days later at the young boy had cranial and facial edema, nasal congestion, lost of conscience, so for the second time he was hospitalised. CT-scan resulted with left sphenoidal sinusitis, nasal culture was infected with Moraxella chatarralis, the patient began an antibiotic therapy with Clarythromycin, cefixime for 3 weeks. After this episode the patient change the immunotherapy and took LoFarma pollen immunotherapy. At the first and second flacons everything was at normal course with a little local adverse reaction, so antihistamines before the injection was prescribed and 5 h after subcutan immunotherapy began headache, abdominal pain and lost of conscience. RM resulted normal, heart echo and EEG also. The patient get hospitalised for the second time and was decided to interrupt immunotherapy. At the consult after 4 months the young boy was healthy, but with symptomatic allergic rhinitis.

Conclusion: In conclusion, we present a case with systemic reaction of immunotherapy in a pollen sensitisation patient. Although immunotherapy is considered a good treatment for allergic rhinitis with good results to symptoms, sometimes adverse reaction may threat the live.

1415
Prospective Adherence to Specific immunoTherapy in Europe (PASTE) survey – 1 year on

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Background: Prolonged administration is required in order for allergen immunotherapy (AIT) to induce long-term immunological and clinical effects. Therefore, adherence is very important. However, there is currently limited data available on AIT adherence outside of clinical trials i.e. in real-life clinical practice.

Methods: This EAACI Immunotherapy Interest Group endorsed survey aims to prospectively evaluate adherence to sublingual and subcutaneous immunotherapy in adults with allergic respiratory diseases and hymenoptera venom allergy in a 3 year period in real life practice across different European countries. In addition, it will explore the reasons for lack of adherence and discontinuation of treatment.

Results: A total of 1367 participants are currently enrolled from eight countries: Czech Republic, Georgia, Germany, Greece, Italy, Poland, Portugal and Spain. Average age is 35.12 years with the majority (54.13%) being male. 82.14% are treated for allergic rhinitis, 43.91% for allergic conjunctivitis, 37.49% for asthma and 14.76% for hymenoptera venom allergy. 50.77% of participants suffered with the condition for over 5 years prior to receiving immunotherapy. 82% are treated by the subcutaneous route while 18% with sublingual drops or tablets. The main allergens treated include grass pollens 33.87%, house dust mite 32.25%, Parietaria 15.06% and 15.28% hymenoptera venoms. Twelve months after follow up of the participants started 11.1% have missed on average two doses in 4 months whilst <2% of participants have discontinued treatment.

Conclusion: This survey has so far provided useful information on the practice of immunotherapy in different European countries. The participants will continue to be followed up 4-monthly for a total of 3 years in order to assess adherence and explore the reasons for non-adherence or

discontinuation of treatment. This is hoped to provide useful information for modifying clinical behaviours and attitudes towards AIT in order to improve adherence wherever possible.

1416
Full symptom control in patients with allergic rhinoconjunctivitis induced by birch pollen treated with sublingual allergen immunotherapy (AIT) in real-life medical practice

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Background: The aim of this non-interventional study was to document the impact of a sublingual immunotherapy with a birch pollen extract (Stallergenes, France) on symptom severity and use of symptomatic medication as well as tolerability in patients with birch pollen-induced allergic rhinoconjunctivitis (RC) over 2 years of treatment in real-life medical practice. Here we focus on the subgroup of all patients who completed the entire study period and describe those patients achieving full symptom control.
Method: This open, prospective, non-controlled, multicenter study including 716 patients (409 female, 300 male; mean age: 38 ± 16) was conducted in Germany over two consecutive birch pollen seasons. 365 of the patients completed the entire study period and were considered in this analysis.

Allergic symptoms were analyzed as combined scores of severity [scale: 0 (none)–3 (severe)] and frequency [scale: 0 (none)–4 (very often)]. In the combined RC score, the severity of rhinitis and conjunctivitis were pooled.

Fully controlled patients were defined as patients with a rhinitis and conjunctivitis score of lesser degree of severity (max. mild) after the second year of treatment.
Results: According to the definition, 74.2% (271) of all patients who completed the study were fully controlled after 2 years of AIT. The RC score decreased in fully controlled patients from a mean value of 3.49 ± 1.78 to 1.76 ± 1.33 during the first year (Y1) and to 1.17 ± 0.78 during the second year (Y2) of treatment. The asthma score decreased in fully controlled patients with asthma from a mean value of 3.71 ± 0.99 to 1.72 ± 1.39 during Y1 and to 1.08 ± 1.21 during Y2.

During the birch pollen season preceding AIT, 83% of the fully controlled patients had used symptomatic medication. This rate dropped to 58% during Y1 and to 38% during the Y2. AIT with birch pollen extract was well tolerated in fully controlled patients with an incidence of adverse events of 6.6% during the 2 years of treatment.
Conclusion: In the management of patients treated with AIT, adherence plays an important role. The results of our study indicate that patients who are most adherent to therapy benefit most in terms of symptom control. A remarkable number of the adherent patients (74%) treated with birch pollen AIT achieved a very good symptom control after 2 years of treatment.

1417
Sublingual allergoid immunotherapy for mites in the prevention of recurrent respiratory infections: a prospective real life study

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Background: The bidirectional relationships between respiratory infections and allergy have been object of wide research. Therapies targeting the immune system potentially modulate the response to pathogens and allergens. Recurrent respiratory infections (RRI), characterised by at least three episodes of fever, loco-regional inflammation, cough, asthma and wheezing without severe lung function impairment, are quite common during winter season in children and adults sensitised to house dust mites (HDM).
Method: A real life study was conducted in patients allergic to HDM and affected by RRI, during four consecutive winter seasons to compare the effects of different treatments in reducing allergy symptoms, respiratory infections, days of antibiotic therapy, school/work absence, nasal inflammation, bronchodilators and nasal steroids use, lung function and disease progression. After a run-in season, patients were randomized to 6 months of cetirizine 10 mg daily, or probiotic preparation (lactobacillus and streptococcus thermophilus), or mixture of lyophilized bacterium lysate, or a mixture of phytotherapic agents, or to 12 months of sublingual immunotherapy with HDM monomeric allergoid tablets (1000 UA/week).
Results: One hundred and sixty-two patient (5–58 years) concluded the study. After 3 years of treatment, allergy symptoms were largely inferior in the group treated with SLIT (-73.6%) in respect to cetirizine (-46.2%), probiotic (-36%), phytotherapic agent (-18%) and lysate (-18.9%). Respiratory infections were reduced of 75.9% under SLIT, 61.4% with probiotic, 55% with phytotherapy, 45% with cetirizine and 7.1% with lysate. In respect to other treatments, SLIT reduced more largely the use of antibiotics, days of school/work absence, use of symptomatic medications, nasal eospinophils, bronchial reactivity and asthma worsening.
Conclusion: SLIT with HDM monomeric allergoid is a useful tool for the management of allergic patients suffering from RRI.

1418
CONtraindications to Specific ImmunoTherapy (CONSIT) survey

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Background: The contraindications to allergen immunotherapy (AIT) Task Force has been formed in the framework of EAACI, in order to implement current guidelines. Besides the extensive review of the existing literature an online survey was designed to gather information on whether allergists perform AIT in cases of conditions or concomitant diseases that are considered contraindications.
Method: A SurveyMonkey online questionnaire was sent to all EAACI members. It addressed demographic data of the physicians and their experience (expressed in number of patients treated with any condition) and their opinion on treating AIT-eligible patients with concomitant 'contraindicated' diseases or conditions. Based upon different existing guidelines, 17 contraindications were studied. A 3-grade scale was used to express the effect of AIT in terms of safety: 'no problem', 'minor' or 'major' problems. Respiratory allergen (SCIT, SLIT) and venom (VIT) AIT were addressed separately. Doctors

were invited to provide additional commends.

Results: Totally 7124 emails were sent and 2068 (29%) were opened. Finally 520 questionnaires were collected and analyzed. 38 473 patients had been treated although presenting a potential AIT-contraindication. Most common 'contraindications' that received AIT were: previous anaphylaxis in the course of AIT, children under 5, controlled severe asthma, ACE inhibitor- and beta-blocker-therapy. Having faced a patient with a concomitant disease/condition differentiated the answers. Major problems were infrequent, with higher ratio problems occurring in patients with severe asthma (9.1%). SLIT resulted to be the modality with weaker degree of contraindications. Interviewed doctors commended on the individual assessment of risk-benefit ratio in each patient, especially in VIT.

Conclusion: Although the number of patients reported was very high, the participation to the survey was less than expected. Doctors using SLIT are less restrictive with its use in contraindications, than using other AIT modalities. VIT tends to have lower contraindication ratios than SCIT.

1419
A comparison of the relative clinical impacts of sublingual allergen immunotherapy tablets and symptomatic drugs in grass-pollen-induced allergic rhinoconjunctivitis

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Background: In the absence of robust, large-scale, head-to-head clinical trials of sublingual immunotherapy (SLIT) formulations and symptomatic medications in seasonal allergic rhinitis (SAR), the treatment modalities can be indirectly compared by calculating the 'relative clinical impact' (RCI, defined by the World Allergy Organization as $100 \times$ (clinical $\text{score}_{\text{Placebo}}$ – clinical $\text{score}_{\text{Active}}$)/clinical $\text{score}_{\text{Placebo}}$). However, methodological factors in clinical trials of SLIT may lead to underestimation of the effect size.

Method: After selecting double-blind, placebo-controlled trials of five-grass and single-grass pollen SLIT tablets or symptomatic medications with at least 100 participants in the smallest treatment arm, we calculated the RCI from the post-treatment or season-long nasal symptom scores, total symptom scores or (for some SLIT studies) the Average Adjusted Symptom Score (AAdSS) or combined symptom-medication scores.

Results: Twenty-eight symptomatic medication trials and ten SLIT tablet trials were selected for meta-analysis and calculation of the RCI. Based on the RTSS or the combined score, the RCIs for SLIT tablets in SAR ranged from −16% to −30%. In the tertiles with the highest AAdSS in four studies of five-grass pollen SLIT tablets, the weighted mean (range) RCI was −37.1% (−26% to −45%). These values were thus similar to or even greater than the values for symptomatic drugs (−3% to −26% for second-generation H1-antihistamines, −7% to −54% for nasal corticosteroids and −3% to −10% for montelukast).

Conclusion: In the absence of head-to-head clinical trials, the RCI method for indirect comparison of the effect size in high-severity tertiles in SLIT trials constitutes a good approximation of the conditions encountered in a symptomatic drug trial. In moderate-to-severe SAR, grass pollen SLIT tablets appear to have a greater RCI than second-generation H1-antihistamines and montelukast and much the same RCI as nasal corticosteroids.

1420
Allergen immunotherapy in allergic rhinitis: efficacy and impact on quality of life

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Background: Our aim was to evaluate the effectiveness of subcutaneous allergen immunotherapy with the symptom scores (RSS), visual analog scale (VAS) and medication scores (MS) and the impact on quality of life with rhinoconjunctivitis quality of life questionnaire (RQLQ) in allergic rhinitis patients sensitised to different allergens. Also the development of new sensitisations and asthma during the immunotherapy were determined.

Method: Allergic rhinitis patients sensitised to at least one common aero-allergen who completed a three or 5 year period of allergen immunotherapy in our outpatient clinic between 2002 and 2013 were enrolled in the study and patients with allergic rhinitis who received only medical treatment were chosen as the control group. Patients were separated in two groups according to sensitisation patterns including pollens or house dust mites. All patients were evaluated before immunotherapy, in the first and the fifth years of treatment and 2 years after the treatment.

Results: Mean follow-up period was 7.38 ± 1.13 years (6–12 years). Nine out of 92 patients who completed 5 years of treatment revealed relapse in long term follow up. MS in the fifth year was significantly lower in the immunotherapy group than the control group ($P < 0.001$). In addition, 1 out of 80 patients was diagnosed as new asthma (%0.10), while four out of control group (4/24:16.6%) developed new asthma during treatment (17.2%, $P < 0.001$). In the immunotherapy group significant improvements in VAS, RSS, MS, RQLQ scores were seen at the end of the treatment when compared to the begining ($P < 0.001$). New sensitisation was detected in seven patients including four mites and three pollens in immunotherapy group.

Conclusion: This recent study showed that SCIT is an effective treatment in patients with allergic rhinitis in terms of symptom and medication scores and it improves the quality of life scores and also prevents the development of new asthma.

1422
AAAAI membership experience with allergen immunotherapy (AIT) safety in patients with special medical conditions varies according to practice characteristics

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Background: Little data exists on (AIT) in patients with specific medical conditions. Results of a large survey among practicing allergists were presented last year. We here present sub-group analyses.

Methods: A survey (Surveymonkey®) was sent out to all AAAAI members in and outside US to explore their experience with AIT in patients with specific medical conditions. We analyzed sub-group differences with Pearson's ×2-tests (95% CI, $P < 0.05$).

Results: Response rate: 21.1% ($n = 5148$). Practices: 86–14% US-outsideUS; 44% urban, 51% suburban and 5% rural; 31% academic; 54% had clinical experience >16 years; small, middle and large practices equally represented. 97.8% dosed within Practice Parameter dosing intervals. More high dosing in medium + large

practices ($P = 0.006$) and >11 years working experience ($P = 0.0006$). Equal % of high dosing in academic/non-academic or urban/rural. Starting immunotherapy during pregnancy is generally considered a contra-indication (CInd); experience with such patients is very low. Physicians in urban centers consider ′continuing AIT once a patient gets pregnant′, severe asthma, hypertension, coronary artery disease, arrhythmias and cerebrovascular disease more frequently a CInd for AIT, than allergists working in sub-urban/rural clinics ($P < 0.001$). Consequently, these allergists have much more experience than urban centers with AIT in this kind of patient ($P < 0.008$). Physicians in academic centers consider certain medical conditions a CInd for AIT much more frequently than non-academic centers (depending on condition: $P = 0.03$ to $P < 0.00001$). Consequently non-academic allergists have more experience with AIT in patients with certain medical conditions than academics ($P = 0.027$ – $P < 0.00001$, exceptions: solid organ transplantation or HIV). Physicians with a practice experience of 11–15 years more often contraindicate AIT in severe asthma and cerebrovascular disease. Physicians working longer in practice (11 + years) contraindicate IT more in patients after BM transplantation, with HIV or auto-immune diseases. Physicians of small clinics (<100 patients on AIT) considering many of the medical conditions more often a CInd for immunotherapy ($P = 0.002$ to $P < 0.00005$). Allergists from medium and large clinics have much more experience with AIT in patients with almost all medical conditions ($P = 0.003$ – $P < 0.00001$).

Conclusion: Allergists with more experienced in AIT consider severe asthma, cerebrovascular and autoimmune diseases more often a CInd to AIT.

1423
The impact of physician–patient communication on the prescription and perception of allergen immunotherapy

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Background: Treatment adherence is critical for the efficacy of long-term treatments such as allergen immunotherapy (AIT). Patient education/knowledge (based on good physician–patient communication) are important determinants of adherence. We investigated physicians′ reasons for (not) proposing AIT and allergic patients′ perceptions of AIT when the latter was proposed.

Methods: We surveyed a total of 1486 allergy specialists and 4866 patients with a physician-diagnosed respiratory allergy in 13 countries: France, Germany, Italy, Spain, Australia, Slovakia, Czech Republic, Poland, Turkey, Russia, Argentina, Brazil and China. Via online questionnaires, physicians were questioned about their caseload, prescription of AIT and other treatments, reasons for AIT non-prescription and AIT acceptance levels. Patients were questioned about symptoms, care pathways, treatment and their impression of AIT left by statements made to them by their physician.

Results: The frequency of prescription of AIT to eligible patients varied from 61% (France) to 20% (Turkey). When an allergy specialist decided not to recommend AIT in an eligible patient, the most frequently cited reasons were anticipated poor compliance (49% of physicians), lengthy treatment (34%) and patient preference (34%). Contraindication to AIT was rarely mentioned (3%). On the basis of information provided by the physician, patients had the impression that AIT would enable better quality of life (81%), entail long-term treatment (80%) and effectively control their symptoms (76%); effectiveness in treating the underlying allergy itself was only cited in fourth position (68%).

Conclusion: The physician′s preconceived ideas about AIT (notably poor anticipated adherence) reduce the frequency of prescription to eligible patients. Poor physician–patient communication (including misunderstanding about treatment benefits) may prevent eligible patients from receiving AIT. This ‘communication gap’ requires further investigation.

Poster Session Group III – Green

TPS 64 – Infection & allergy

1425
A case of apparent allergy and hypereosinophilia treated with antiparasitic therapy

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Background: Infections from parasites, particularly from *Toxocara canis*, may present with symptoms of allergy unresponsive to standard drug treatment. Here we report the case of a patient diagnosed and treated for allergic asthma whose symptoms disappeared after antiparasitic therapy.
Methods: The patient was a 44 year-old male with no family history of allergy and no significant pathologies. In October 2008 skin tests were positive for grass pollen, birch pollen and dust mites, spirometry results showed a small airway obstruction and hypereosinophilia (20.5%) was detected. Due to worsening symptoms and new spirometry results with a FEV1 value of 56%, in addition to treatment with formoterol/budesonide, we added prednisone 25 mg for 5 days. At the following check-up, the patient showed an improvement in asthma symptoms, but eosinophilia had risen to 41.1%. Tests for IgE antibodies to *T. canis* using ELISA and Western blot were prescribed.
Results: Both *in vitro* tests were positive for *T. canis*, thus treatment with Albendazole 400 mg 1 tablet twice a day for 5 days was prescribed and repeated after 20–50–80 days. After 6 months, asthma was well controlled, using formoterol/budesonide only as needed. Eosinophils had dropped to 13.3%, the Western blot was negative and ELISA showed a decreased value. After 12 months, the patient′s asthma continued to improve, the eosinophils were 12.7% and ELISA was further decreased. At the final check-up (September 2010), the patient used drugs for asthma and rhinitis only when exposed to birch and grass pollen, eosinophils had fallen to 6.3%, ELISA was negative and the spirometry was normal.
Conclusions: This case confirms recent literature on *T. canis* infection presenting as allergic asthma. Hypereosinophilia, often linked to parasitic infections, and the failure of standard allergy treatment, suggest searching for *T. canis*. For patients who test positive, antiparasitic therapy can lead to significant clinical improvement of asthma.

1426
Atopy as a risk factor for lower respiratory tract infections in children

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Background: Lower respiratory tract infections are a common pathology, especially actual for young children. These can be severe what require hospital treatment. It is important to study the risk factors of lower respiratory tract infections including atopy because it is significantly.
Method: Analysis of 200 case histories of children under 5 years who admitted to hospitals in Novosibirsk with acute infection of the lower respiratory tract. 39% of patients had acute bronchitis, 43%-obstructive bronchitis, 18%-community-acquired pneumonia.
Results: Logistic regression showed risk factors for lower respiratory tract infections which leads to hospitalisation in children. Along with patient age (OR = 1.6, 95% CI 1.3–2, $P < 0.0001$), visit them to day care attendance (OR = 0.3, 95% CI 0.08–0.8, $P = 0.02$) significant criterion proved a atopic diseases whose frequency in groups was 47.4%, 66.3% and 47.2% respectively. 71.2% of children had atopic dermatitis, 24.3% – food allergy. It has proved influence of allergic diseases on the development of acute bronchitis (OR = 2.2, 95% CI 1.1–4.2, $P = 0.019$), obstructive bronchitis (OR = 2.2, 95% CI 1.2–4.1, $P = 0.016$) and community-acquired pneumonia (OR = 2.2, 95% CI 1.2–4.1, $P = 0.02$).
Conclusion: Atopic diseases in children are a risk factor for acute lower respiratory tract infections which requires treatment in hospital.

1427
Use of antibiotics during pregnancy increases the risk of acute otitis media in early childhood

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Background: Antibiotics during pregnancy have been shown to increase the risk of immune-mediated diseases like asthma. We hypothesized that antibiotics during pregnancy could influence children's risk of acute otitis media (AOM).
Method: Children were included from the Copenhagen Prospective Study on Asthma in $Childhood_{2010}$ ($COPSAC_{2010}$) prospective unselected birth cohort of 700 children. AOM episodes were registered by the parents in a daily diary at age 0–3 years. Detailed information on maternal antibiotic prescriptions during pregnancy filled at the pharmacy was obtained and verified longitudinally with the women. COX proportional hazard regression analyses were performed, where the dependent variable was first time of AOM. Hazard ratios were adjusted for gestational age, maternal age and education, household income, maternal asthma, smoking, older siblings and perinatal antibiotic treatment.
Results: Forty-nine percentage of the children had one or more episodes of AOM. The prevalence of antibiotic use was 36% during pregnancy.

The overall prevalence of AOM if the mother received any antibiotics during pregnancy was 57% compared to 45% in women without antibiotic intake; adjusted hazard ratio (aHR) 1.36; CI, [1.08–1.71], $P = 0.008$. The same was present for antibiotics for respiratory tract infection; aHR 1.48; 95% CI, [1.14–1.92], $P = 0.003$; and for antibiotics for urinary tract infection; aHR 1.37; 95% CI, [1.06–1.78], $P = 0.016$. The association was independent of pregnancy trimesters.
Conclusion: Risk of AOM in early childhood is associated with maternal intake of antibiotics during pregnancy.

1428
Infection rate of *Chlamydia pneumoniae* in patients with chronic cough

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Background: Persistent cough has recently been found to be associated with *Chlamydia pneumoniae* infection. We aimed to investigate the infection rate of *C. pneumonia* in adult patients with chronic cough.
Method: We recruited 68 patients with persistent cough lasting in excess of 3 weeks, who visited Kangdong Sacred Heart Hospital from January 2010 to August 2010. On the first visit, chest and paranasal sinuses radiography, skin prick test of common allergens, and induced sputum samples for *C. pneumoniae* were performed in all of patients. Further evaluation for diagnosis included a methacholine provocation test and eosinophil counts in induced sputum.
Results: The most common cause of chronic cough was upper airway cough syndrome (UACS) (26.5%), followed by eosinophilic bronchitis (20.6%) and cough variant asthma (16.2%). Idiopathic chronic cough was the cause in 33.8% of patients. The mean duration of cough was 11.7 months. *Chlamydia pneumoniae* was isolated by polymerase chain reaction (PCR) from one patient who had upper respiratory air way syndrome.
Conclusion: *Chlamydia pneumoniae* appears to have a minor role as a cause of chronic cough in patients.

1429
Efficacy of procalcitonin-guided antibiotic therapy in children with pneumonia

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Background: We aimed to use procalcitonin (PCT), which is elevated in bacterial infections, as a biochemical marker in pediatric patients diagnosed with viral pneumonia to reduce the use of antibiotics in patients with viral pneumonia.
Method: The subjects were 108 pediatric patients diagnosed with viral pneumonia who were treated at the Chungnam National University (CNUH) and the Soonchunhyang University hospital (SCH) between November 1 and December 31, 2012. The patients were divided into two groups: the group that was treated according to the PCT guidelines (group A, CNUH), and the group that was treated based on their clinical symptoms without using the PCT guidelines (group B, SCH). In all patients, PCR examination was done to test for viruses, and the age, gender, fever duration, frequency of antibiotics use, length of hospital stay, serum WBC, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) at the time of admission were compared. Patients with positive sputum, blood, urine cultures, mycoplasma antibody and co-existing or underlying disease were excluded from this study. The PCT guidelines used in group A suggested antibiotics not to be used in patients with serum PCT levels below the cut-off value, 0.11 ng/dl, antibiotics to be used based on other clinical and laboratory findings in those with PCT levels between 0.11 and 0.5 ng/dl, and antibiotics to be used in those with PCT levels above 0.5 ng/dl.
Results: Of the 108 patients (male/female = 1.40:1) in this study, 47 belonged to group A (M/F = 1.44:1) and 61 belonged to group B (M/F = 1.35:1). Thirty-five and 60 patients had RSV in groups A and B; 2 and 0 adenovirus, 0 and 1 coronavirus, 4 and 0 parainfluenza virus, and 1 and 0 influenza virus respectively, showing no significant statistical difference. Fever duration was significantly longer by 2.5 days in group A (3.7 ± 2.5 days) rather than group B (1.2 ± 0.5 days) ($P < 0.001$). There was no significant difference the length of hospital stay ($P = 0.191$), whereas the frequency of antibiotic use was significantly lower in group A (22%) rather than group B (90%) (OR = 0.033 (0.011–0.098), $P < 0.001$). Serum WBC ($P = 0.013$) and ANC ($P < 0.001$) were significantly higher in group A rather than group B, but there was no significant difference in CRP ($P = 0.238$).
Conclusion: The use of the levels of serum PCT for treatment of patients with viral pneumonia showed that antibiotic use based on serum PCT levels can be a useful tool to reduce the overuse of antibiotics.

1430
Antibody response to recombinant of *Aspergillo fumigatus* in patients with chronic obstructive pulmonary disease

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Background: The complexity of the antigenic structure of *Aspergillus fumigatus* and the varying host immune responses determine the severity of the clinical conditions. Studies have evaluated different combinations of recombinant allergens for diagnostic use in Aspergillus allergy. The mycetes arrive in the pits for inhalation and the presence of *A. fumigatus* in bronchial lumen causes an allergic response in the airways and lung parenchyma causing acute pneumonia. It is found between the main responsible of forms chronic lung in situations of high risk infectious favoring the role of fungus such as pathogens. In the Department of Respiratory Medicine patients with chronic obstructive pulmonary disease, COPD, were tested for the specific IgE of the *A. fumigatus* with the test system ImmunoCap of Phadia S.r.l. of Thermo Fisher Scientific. The respiratory disease COPD is a disease that develops slowly, over the years, characterised by a blockage of the airways that causes a limitation of the air stream is not completely reversible and represents one of the main causes of chronic morbidity and mortality in the world. Studies have evaluated different combinations of recombinant allergens for diagnostic use in Aspergillus allergy.
Method: This study was conducted in patients suffering from COPD by dosing for IgE antibodies to the native allergen of the *A. fumigates*. When it's positive were dosed to check on the various components available: Asp f 1, Asp f 2, Asp f 3, Asp f 4, Asp f 6.
Results: The results obtained show that the 60% of the patients with COPD are negative at screening with the native allergen of *A. fumigates*, the 25% of serum positive they are negative to recombinant used. In routine when the allergen *A. fumigatus* native is positive you are running as a test reflex Asp f 4 and Asp f 6. However, in these patients we have different results of recombinants positive from patient to patient and Asp f 1 has more frequency of the other (about 70%) and some of these patients are negative to Asp f 4 and/or the Asp f 6.
Conclusion: On the basis of the results obtained is in progress, for the patients enrolled, clinical history insights to highlight any special characteristics for differences and clinical therapeutic correlated to the diversity of positivity. Then currently the patients/customers positive to the allergen native of *A. fumigatus*, without distinction to pathology, are necessary to evaluate all the recombinant available.

1431

Hypersensitivity vasculitis – two different cases same presentation!

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Background: Hypersensitivity vasculitis (HV) is a histopathologic term commonly used to denote a small vessel vasculitis. A cause is not found in as many as 50% of patients. HV may manifest clinically as cutaneous disease only or it may manifest as skin disease with involvement of other organs.

Method: Two cases of HV, with the similar skin presentation but with two completely different causes.

Case no 1: 74 year-old with an 8 year history of a recurrent tender, non-blanching, palpable, purpuric rash involving her lower limbs. A diagnostic punch biopsy revealed a leukocytoclastic vasculitis. Laboratory investigations confirmed normal full blood count, renal, liver and thyroid function with an absence of microscopic haematuria and red cell casts on urinalysis testing. Chronic hepatitis C virus infection was confirmed by enzyme immunoassay and reverse-transcriptase polymerase chain reaction. The patient was treated with intermittent use of potent topical steroids which controlled exacerbations of her cutaneous vasculitis and prevented progression to ulceration.

Case no 2: A woman aged 24 years with a 1 week history of rapidly enlarging, almost asymptomatic, vesicobullous, haemorrhagic, and necrotic lesions on the buttocks and lower limbs. A biopsy specimen was also taken from the border of one lesion and the results of light microscopy and direct immunofluorescence exam confirmed the clinical diagnosis of vasculitis. The eruption had not been heralded or accompanied by any constitutional upset. Cultures grew colonies of Neisseria gonorrhoeae from the cervix. The patient started penicillin therapy, to which the isolates showed highly susceptible, and although results were constantly negative, the diagnosis of disseminated gonococcal infection was made.

Conclusion: On one hand HV may be acute and self-limited or chronic and on the other hand the prognosis for hypersensitivity vasculitis is good when no internal involvement is clinically present.

Poster Session Group III – Green

TPS 65 – Management of asthma II

1433

Once-daily tiotropium Respimat® as add-on to at least medium- to high-dose ICS, with or without LABA, improves lung function in patients with symptomatic asthma, independent of allergic status

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Background: A substantial number of patients have symptomatic asthma despite treatment according to guidelines. Several studies have confirmed that tiotropium Respimat®, a once-daily long-acting anticholinergic bronchodilator, improves lung function in symptomatic patients receiving at least medium-dose ICS ± LABA (Kerstjens et al. NEJM 2012;367:1198–207; Bateman et al. JACI 2011;128:315–22). Here we examine whether the atopic and/or allergic status of patients in these trials influenced their response to tiotropium Respimat®.

Method: Two 48-week trials of tiotropium Respimat® 5 μg (PrimoTinA-asthma®: NCT00776984, NCT00772538) in patients (n = 912) on high-dose ICS + LABA; two 24-week trials of tiotropium Respimat® 5 μg and 2.5 μg (MezzoTinA-asthma®: NCT01172808, NCT01172821) in patients (n = 2100) on moderate-dose ICS. Pre-planned analyses (pooled populations) were performed in two subgroups defined at baseline as total serum IgE ≤ or >430 μg/l or blood eosinophils ≤ or >0.6 × 10^9/l or clinical judgement of allergic status (no or yes).

Results: Tiotropium Respimat® 5 μg or 2.5 μg improved peak and trough FEV_1 vs placebo (Table) independent of IgE, eosinophil count and clinical judgement.

Conclusion: Once-daily tiotropium Respimat® as add-on to ICS or ICS + LABA in patients with moderate to severe symptomatic asthma reduces airflow obstruction, apparently independent of their atopic and/or allergic status.

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Omalizumab management beyond clinical trials: the added value of a network model

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Background: Omalizumab is effective and safe in severe allergic asthma, as showed by several trials. Limited Italian data on omalizumab management in real-life are to date available. Moreover few published works have focused on the impact of omalizumab on lung function and on asthma comorbidities. We aimed at evaluating these clinical outcomes in a real-life setting.

Method: We created a collaborative network (NEONet – North East Omalizumab Network) involving nine Allergy and Respiratory referral centres for severe asthma placed in the North-East of Italy. Patients demographic and clinical data were entered into a common study database shared by all the participating physicians. A preliminary retrospective analysis was performed.

Results: The mean treatment duration was 22.97 months (SD:16.55). A significant improvement of the study population mean FEV_1 was observed (from 2.04 to 2.54 l, $P < 0.001$), independently of the treatment duration ($P = 0.072$) and the baseline severity of bronchial obstruction ($P = 0.108$). The proportion of major (need for Emergency Department visits or hospitalisation) and minor (need for oral steroids) exacerbations-free patients at the time of evaluation was significantly higher compared with the baseline ($P < 0.001$). Before the omalizumab treatment 82% of patients suffered from allergic rhinitis and at the time of evaluation 4% recovered completely. In the remaining 78% a trend towards less severe symptoms, according to the ARIA classification, were recorded ($P = 0.002$). The clinical efficacy of omalizumab in terms of lung function improvement ($P = 0.442$) and exacerbations ($P = 0.618$) was independent from the

Adjusted mean difference for tiotropium Respimat® from placebo (ml)		IgE ≤/>430 μg/l	Interaction P value[a]	Eosinophils ≤/>0.6 × 10^9/l	Interaction P value[a]	Clinical judgement no/yes	Interaction P value[a]
PrimoTinA-asthma®	n[b]	336/377		654/175		335/516	
Tiotropium Respimat® 5 μg	Peak $FEV_{1(0\text{-}3\ h)}$	148/102	0.742	115/58	0.7021	76/130	0.2114
	Trough FEV_1	127/89	0.6209	103/52	0.7542	94/91	0.4099
MezzoTinA-asthma®	n[b]	356/610		769/201		349/624	
Tiotropium Respimat® 5 μg	Peak $FEV_{1(0\text{-}3\ h)}$	168/193	0.9677	170/240	0.2375	180/189	0.6233
	Trough FEV_1	139/152	0.8437	137/182	0.5148	138/153	0.6727
MezzoTinA-asthma®	n[b]	364/614		779/203		349/635	
Tiotropium Respimat® 2.5 μg	Peak $FEV_{1(0\text{-}3\ h)}$	197/237	0.9677	236/176	0.2375	243/213	0.6233
	Trough FEV_1	167/188	0.8437	185/158	0.5148	209/164	0.6727

[a]For treatment × subgroup interaction; [b]Values for active and placebo groups combined.

presence and the severity of upper respiratory comorbidities.

Conclusion: This work represents the first NEONet activity report. Our findings, based on an homogeneous population sample (coming from a well-defined geographical and environmental district), confirm omalizumab efficacy and provide some new insights concerning: – the impact of omalizumab on lung function and on nasal comorbidities; – omalizumab efficacy in patients with upper airways comorbidities. The network approach, under a prospective view, allows creating a large uniform database, by means of a standardised shared tool for data collecting, and joining a multidisciplinary expertise.

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Anxiety and depression in patients with bronchial asthma treated with Alprazolam

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Background: Twenty-five patients with bronchial asthma who also show sings of anxiety and depression have been examined. They have been treated with Alprazolam for 3 weeks. The therapeutic efficiency of Alprazolam has been measured by the Zung scale after the treatment. Psychosomatic complaints of the patients have declined significantly after the treatment. According to the data from our previous studies, 87.5% of the patients with different allergic diseases have shown anxiety, and 45% – depression.

Method: The symptoms of anxiety and depression have been measured by the Zung scale before and after the treatment.

Results: The results after 3-week-treatment with Alprazolam are in three degrees: lack of any effects, good effect, or reducing the symptoms, and excellent effect when the anxiety and the depression have been eliminated.

Altogether, of the twenty patients with anxiety symptoms who have been observed, 3 patients have endured no effect. Excellent effect in overcoming the anxiety symptoms has been accomplished in eight of the patients. Fourteen patients have shown good effect, their anxiety symptoms reduced. After the treatment there were no patients with great anxiety symptoms. From the observed patients with symptoms of depression five have experienced no effect. Four patients have shown excellent effect, and 16 patients have shown a good one – milder depression. Altogether, the patients who showed good and excellent effects on their anxiety symptoms are 22. Those whose depression is influenced satisfactorily and excellently are 20. Secondary effects that are recognised in the course of the treatment with Xanax are sleepiness with five patients, general weakness −1, dry mouth −1, which has not caused cessation or change in the dose of the medicine.

Conclusion: Alprazolam influences a high percentage of the anxiety-depression symptoms and has been accepted very well.

1438
Correlations of bronchodilator reversibility and exhaled nitric oxide with bronchial hyperresponsiveness in adolescence: Isle of Wight birth cohort study

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Background: Airway reversibility test and exhaled nitric oxide are used in management of asthma in clinical practice. Given the diverse pathophysiology of asthma, how do these tests correlate with bronchial hyperresponsiveness? We aim to look at the correlation of fractional exhaled nitric oxide (FeNO) and bronchodilator reversibility (BDR) with bronchial hyperresponsiveness (BHR) in adolescents with asthma.

Method: The Isle of Wight cohort is a population based birth cohort of adolescents born in 1989/90 (n = 1456). Participants have been followed up through childhood and at 18 years. At 18 years 19.9% (234/1306) had asthma, 65.4% (153/234) underwent methacholine bronchial challenge test, 45.7% (107/234) had BDR and FeNO was analysed in 48.3% (113/234). Methacholine bronchial challenge test, BDR and FeNO (hand held Nitric Oxide analyser; Niox-Mino) were measured following ATS/ERS guidelines. Continuous variables; DRS (Dose response slope) for BHR for, FeNO and BDR (change in FEV1) were used for correlation analysis. Asthma was defined as physician diagnosis plus current wheeze or on current treatment. Stratified analysis was carried out in groups on and not on any corticosteroid (inhaled/oral) treatment.

Conclusion: BDR correlates to BHR and can be helpful particularly where bronchial challenge is not possible (resources/patient factors). FeNO only correlates to BHR in corticosteroid naïve patients with asthma; corticosteroid treatment dampens the airway inflammation thus influencing correlation of FeNO with BHR.

Table Correlation of reversibility (BDR) and exhaled nitric oxide (FeNO) with bronchial hyperresponsiveness (BHR).

BHR	BDR Correlation (n)	BDR P value	FeNO Correlation (n)	FeNO P value
Whole cohort	0.306 (524)	<0.001	0.321 (553)	<0.001
Asthma	0.523 (103)	<0.001	0.421 (107)	<0.001
Asthma on steroid	0.598 (47)	<0.001	0.424 (52)	0.002
Asthma not on steroid	0.733 (19)	<0.001	0.522 (20)	0.018

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Clinical-functional effectiveness of different regimens of basic treatment in severe bronchial asthma patients

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Objective: To compare the effectiveness of different regimens of basic treatment on clinical symptoms, lung volumes and airway resistance in severe bronchial asthma patients.

Materials and methods: Thirty severe asthma patients ($FEV_1 < 50\%$), male – 12, female – 18, in the age 37–75 years poorly controlled with high doses of inhalative steroides after 2 weeks run-in period (daily doses 1000 μg of fluticasone propionate) were randomized 1:1 to receive (fluticasone propionate 500 μg + salmeterol 50 μg) (ICS + LABA) BID (I group), or (ICS + LABA) BID + tiotropium bromide 18 μg OD (II group) during 2 months period. Data of bodyplethysmography and spirography (MasterLab, Erich Jaeger) were studied before the beginning and after 2 months of treatment.

Results: At the end of the 2nd month of treatment in the I group significant decrease night awakenings because of asthma from (1.91 ± 0.13) till (1.46 ± 0.11) and daily symptoms from (1.91 ± 0.11) till (1.39 ± 0.10) ($P < 0.01$) was noted. In I group total asthma score and use of rescue medication had tendency to decrease. In II group – there was a significant ($P < 0.01$) decrease in both total asthma score from (6.2 ± 0.6) till (2.8 ± 0.5), and use of β_2-agonists PRN – from (3.9 ± 0.6) till (1.5 ± 0.4). In the I group it was tendency to improvement of FEV_1 [(48.8 ± 3.4)–(53.8 ± 5.2)], while in II group significantly increased FEV_1 from (42.4 ± 4.1) till (59.3 ± 4.8) ($P < 0.05$) and FEF_{25} from (23.3 ± 2.4) till (36.2 ± 4.1) ($P < 0.05$).

Conclusion: Introduction of tiotropium bromide to the basic treatment in severe asthma patients, not controlled on high doses of ICS + LABA provides additional clinical-functional benefit.

1440
Immunological effectiveness of statines in complex therapy of severe persistent bronchial asthma patients

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Aim of the investigation: To study immunological effectiveness of atorvastatin in complex basic therapy (fluticasone propionate/salmeterol 50/500 BID) in severe persistent bronchial asthma (BA) patients.

Materials and method: Forty-six patients with BA were divided against the results of local immunity study into 3 groups: I group – with predominantly neutrophilic type of inflammation: male – 5, female – 11, in the mean age (57.9 ± 2.5) years; II group – with predominantly eosinophilic type of inflammation: male – 2, female – 13, age (53.8 ± 2.5) years; III group – with mixed type: male – 8, female – 7, in the age (57.8 ± 1.8) years.

During first 4 weeks patients were treated with fluticasone propionate/salmeterol (250/25) – 2 BID and salbutamol PRN with further addition of 10 mg of atorvastatin once daily for next 4 weeks period.

Results: After 1 months of studied therapy content of neutrophils in sputum in I group patients decreased from (37.0 ± 6.6) % till (21.1 ± 2.6) %. Activity of oxygen dependent methabolysm of granulocytes in sputum in I group patients decreased, IL-8 decreased from (418.9 ± 46.2) to (200.0 ± 42.4) pkg/ml, ($P < 0.05$)/In II group was noted decrease of IL-8 from (368.2 ± 61.7) to (279.3 ± 48.2) pkg/ml ($P < 0.05$). In III group there were not significant changes vs initial level.

Conclusion: Addition of atorvastatin to ICS + LABA in basic therapy of severe asthma patients rendered more expressive anti-inflammatory effect.

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Treatment efficacy and clinical practice with omalizumab in Spain after five years of experience: the eXpert-5 study

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Background: Significant amount of data on omalizumab efficacy and safety has been compiled after 5 years from the approval for the treatment of asthma in Spain. The aim of this study was to identify and describe the patterns of use of omalizumab in current clinical practice in Spain.

Method: Retrospective, multicenter, nationwide study based on the review of medical records from patients with severe allergic asthma and other serious and long-standing immunological diseases, treated with omalizumab between January-2006 and September-2011.

Results: 464 patients were enrolled: 63.8% were female and mean age (SD) was 45.6 (19.3) years. Omalizumab was prescribed for: asthma (84.5%), chronic urticaria (5.6%), food allergy (5.2%), atopic dermatitis (2.4%) and allergic bronchopulmonary aspergillosis (1.7%). Atopy was present in 67.9% of the patients. The disease was considered as severe in 76.7%. Average time-length of the disease was 16.9 (12.8) years. The main reasons to start omalizumab were: lack of efficacy with conventional (93.1%) or alternative therapy (22.0%), or the appearance of adverse events with previous prescriptions (18.5%). Average time between treatment iniciation and response evaluation was 16.2 (12.7) weeks. The overall efficacy of omalizumab was rated as good/excellent in 64.4%. The best therapeutic responses were observed in food allergy (87.5% good/excellent), chronic urticaria (80.7% good/excellent) and asthma (63% good/excellent). Efficacy was evaluated considering several items: clinical improvement (87.7%), disease control (77.6%), reduction of disease exacerbations (72.2%) and quality of life (33.4%).

Conclusion: Omalizumab was mainly prescribed for the treatment of severe asthma but it was also used in other serious and long-standing immunological diseases. Treatment with omalizumab appears as a good therapeutic option for all the evaluated indications.

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Changes in blood eosinophila during omalizumab therapy as a predictor of asthma exacerbation

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Background: Omalizumab is a monoclonal anti-immunoglobulin E antibody developed for the treatment of severe allergic asthma. The number of exacerbations used as a parameter of omalizumab therapy efficacy may be insufficient in many cases due to the relatively short time period till first evaluation (16 weeks). Therefore it is advisable to look for parameters of more prognostic value while continuing omalizumab therapy. Aim of the study was to evaluate usefulness of analysis changes of blood eosinophilia after 16 week of omalizumab therapy as a predictor of asthma exacerbations.
Method: The study was conducted on a group of 13 patients with severe persistent allergic asthma treated with omalizumab. Blood eosinophil counts were measured before and after 16 weeks of anti-IgE therapy. On the base of percentage of eosinophilia decrease (>50% or < 50% of the initial value) patients were divided into two groups. Analysis of asthma exacerbation rate during 12 months and time to first exacerbation were performed.
Results: In the group with high decrease of blood eosinophil counts (Group 1) we showed statistically significant lower asthma exacerbation rate in 12 months compare with the group with low decrease of blood eosinophil counts (Group 2) ($P = 0.02$). We also observed the tendency to longer time to first asthma exacerbation in Group 1 compared to Group 2 ($P = 0.06$).
Conclusion: Our results showed that decrease in blood eosinophila during omalizumab therapy can be a predictor of asthma exacerbation. Evaluation of changes in blood eosinophil count should be taken into the consideration, while estimating response to anti-IgE therapy in patients with severe allergic asthma.

1443
Critical pathway of acute asthma attack for the emergency center: patients' outcomes and effectiveness

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Background: Early recognition and treatment of acute asthma attack is important before asthma attack becomes worse. For the early and successful management of asthma attack, we developed critical pathway (CP) of acute asthma attack for emergency center (EC).
Method: We started Acute Asthma Attack Assessment and Treatment (4AT) CP on April 1st 2012. Included patients are adolescents and adults older than 15 years who visits EC for dyspnea and wheezing. Initial assessment was done using peak expiratory flow rate (PEFR), oxygen saturation using pulseoximetry, chest X-ray and laboratory tests. Once 4AT CP is activated, starts inhalation of oxygen, repetitive administration of short acting beta-2 agonist at intervals of 30 min, and injection of systemic corticosteroid. After 2 h, re-assessment of the patients' symptom, lung sound, PEFR, and oxygen saturation were done. And make decisions whether to admit or discharge.
Results: Until January 10th 2014, 62 patients enrolled. 7 (15%) patients hospitalised for asthma and 40 (85%) patients discharged to home. One patient was enrolled twice. Dyspnea of 15 (24.1%) patients was due to heart failure, myocardial infarction, aortic dissection, anaphylaxis, chronic obstructive lung disease and pneumonia rather than asthma. One patient came after already managed by other hospital. 6 (12.8%) patients were followed up patients of our Allergy-Asthma clinic, 28 (59.6%) patients were from other hospitals and 13 patients (27.7%) were newly diagnosed asthma. Among the discharged 40 patients, 23 (58%) patients revisit the clinic for evaluation and management for asthma and 11 (28%) patients revisit other hospital, but 6 (15%) patients did not. We call back to the lost 6 patients but three patients never reached, two patients had no insight of importance of regular management of asthma and only one patient promised to revisit our clinic. Mean time from EC arrival to 4AT activation was 32.57 ± 29.05 min and activation to position decision was 254 ± 302 min.
Conclusion: 4AT CP was successful for management of acute asthma attack. But 15% of discharged patients never show up at outpatient clinic. We need more patient education for importance of daily management of asthma before attacks occur.

1444
'ioEasma', an integrative framework for addressing the relationship between asthma control and mental health issues in children and adolescent

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Background: Asthma is a leading chronic condition among youth, causing disability as well as direct and indirect health-related costs. To enhance the level of asthma control among youth, there is a need to address medical, social, and psychological issues associated with asthma.
Method: A questionnaire was administered to patients, ages 5–18 years old, to allow clinicians to identify health adversities and determine the best therapeutic interventions. Patients involved in bullying or experiencing psychosocial problems were referred to the psychosocial intervention.
Results: In 2012–2013, 343 children were enrolled in the study. Fifty- three percent ($n = 181$) were identified as needing an intervention. Of these, 80% progressed through the clinical process and participated in a motivational interview. Twenty-nine patients participated in the psychosocial intervention. Asthma control levels were relatively poor at baseline: controlled (34.5%), controlled with daily therapy (17.2%), uncontrolled (50%), cough symptoms (20.7%). Also, a variety of psychosocial conditions were reported at baseline: psychopathological disease (62%), internalized disorder like depression or anxiety (48.3%), externalized disorder like aggression (13.8%), ADHD (0.03%) and mild cognitive impairment (0.03%). All patients were bullied, mocked, and suffered aggressive gestures, insults, and social exclusion. An increase in asthma control was documented after three clinical visits: controlled (79.9%), uncontrolled (13.8%), and coughing (10.3%).
Conclusion: Comorbidities exist among neuropsychiatric disorders. Thus, a multidisciplinary and integrative approach is needed to treat asthma patients. The combination of clinical care and behavioural and educational intervention increased the level of asthma control.

1445
Omalizumab reduces asthma exacerbations among responders at 28 weeks: the INNOVATE study

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Background: Omalizumab, an anti-IgE monoclonal antibody, has demonstrated effectiveness in reducing the frequency of exacerbations in patients with severe allergic asthma. In practice, patients recommended for long-term use are responders identified by the physician's global evaluation of treatment effectiveness (GETE) tool after 16 weeks of therapy. Therefore, we report here the effect of omalizumab on exacerbation rates and emergency visits in patients evaluated as responders in the INNOVATE study.
Method: INNOVATE was a randomized, placebo-controlled, double-blind study that determined the effect of omalizumab on asthma exacerbations. Patients with uncontrolled severe allergic asthma were randomized to receive omalizumab or placebo for 28 weeks. Rates of protocol-defined clinically significant exacerbations, severe exacerbations and emergency visits were evaluated *post-hoc* in responders to omalizumab vs placebo controls at week 28.
Results: Overall there were 419 primary intent-to-treat patients in the study. 118 (56%) of 209 patients who received omalizumab were assessed as responders. The rate of clinically significant exacerbations and severe exacerbations, adjusted for the pre-study imbalance in exacerbation history was significantly reduced by 61.9% ($P < 0.001$) and 76.7% ($P < 0.001$) respectively compared with all patients on placebo ($n = 210$). There was a 76.2% ($P < 0.001$) reduction in the rate of total emergency visits in omalizumab responders compared with the placebo group
Conclusion: A significant improvement in the rate of clinically significant and severe exacerbations was evident among responders to omalizumab add-on therapy. Total emergency visits were also significantly decreased. As a responder evaluation tool, GETE helps identify those who benefit from omalizumab.

1446
Obesity-asthma phenotype; effect of obesity on asthma course in adults

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Background: Obesity-asthma phenotype has become an increasinglycommon situation in our practice. Asthma in obese patients is often characterised as severe and poorly controlled diseaseThe mechanisms behind poor asthma control in obese subjects remain unclear. We aimed to determine the effect of obesity on asthma control in a group of adult patients
Method: Subjects with diagnosis of asthma who admitted to our clinic were included to this study. BMI and asthma control status of the patients were evaluated. BMI values at the time of diagnosis were also collected from the patient files and the difference between basal and current BMI values were calculated. Effect of obesity and weight gain on asthma control were investigated.
Results: Study population consisted of 218 patients (29 male/189 female), 79.3% of the patients were aged between 35 and 65 years. In 67.4% of the patients, disease duration was more than 10 years. Fifty one (51.4)% of the patients were obese, 30.3% of them were overweigt and 18.3% were normal weight. BMI values were higher in females than males both at the time of diagnosis and current evaluation. Comorbid diseases such as HT, DM, OSAS and GERD became much more frequent with the increase of the BMI. Obesity ratio increased as the disease duration got longer. Asthma control was lower in obese and overweight patients despite optimal treatment. In 55.5% of the patients, BMI was constant during the follow up period, and asthma control was higher in this group of patients. BMI was stable in 81% of the patients who were in remission.
Conclusion: In our study, asthma control was worse and frequency of comorbid diseases was higher in obese patients than the others. We think that obesity and presence of comorbide conditions complicated control of asthma. We suggest that weight loss may improve asthma course, in the light of our finding that weight gain caused a decrease in asthma control in the follow-up period.

1447
Singlon® (montelukast) in control of mild persistent bronchial asthma for children

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Background: Research aim – to generalise the first experience of Singlon® (montelukast) application for children with mild persistent bronchial asthma in Belarus.
Method: 9 children 6–12 years old (6 boys, 3 girls) with mild persistent partly controlled asthma were observed. They have not been getting any anti-inflammatory medicines during previous 3 months. Average duration of disease – 3.5 year. All patients have been taking Singlon® 5 mg one time per day during 3 months. The dynamic of level of control of asthma and dynamic of indexes of spirometry were estimated monthly according to therecommendations of ICONPA, 2012. In the beginning and in the end of course of therapy the general and biochemical blood tests were carried out. The monitoring of Singlon® tolerance was been conducted.
Results: By the end of 3 months' therapy of Singlon® control of flow of disease has been attained for all patients. The positive dynamics of indexes of function of the external breathing has also been attained. The level of eosinophilia has slightly decreased in the analysis of blood. Indexes of biochemical blood test has been without a negative dynamics. The good Singlon® tolerance has been registered.
Conclusion: The first experience of Singlon® (montelukast) application testifies to its efficiency in control of mild persistent bronchial asthma and good tolerance. The further accumulation of experience of application of Singlon® will allow to present the extended data about his place in control of bronchial asthma for children.

1448
The association of serum vitamin D and vitamin D related gene polymorphisms with asthma control parameters in asthmatic children: a prospective one-year study

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Background: There is scarce data about the role of vitamin D(vitD) levels on long term control of asthma in relation to seasons and other confounders. The aim of this prospective study was to determine the association of serum vitD levels and vitD related gene polymorphisms(VDRGP) with clinical and allergic outcome measures through all the seasons among 7–17 year old asthmatic children.
Method: The study included 30 patients with chronic asthma who were evaluated every 3 months for 12 months duration. Also, 30 healthy children were enrolled for comparative analysis of VDRGPs (VDR, GC, CYP2R1, CYP27B1, CYP27A1, CYP24A1). At each visit the children were evaluated by a questionnaire inquiring

about previous 1 months' health and lifestyle factors related to vitD and asthma, asthma control test(ACT), spirometry and bronchial provocation test. Also, serum vitD, vitD binding protein (VDBP) and allergic parameters were simultaneously sampled. The relation between mean annual and seasonal levels of vitD and major outcomes such as ACT, atopic markers, lung function tests(LFT) and bronchoprovocation were evaluated. The effects of VDRGPs on vitD levels and asthma control were also analyzed.

Results: Significant positive linear correlations were detected between the mean levels of vit D at winter, summer and spring samples and ACT scores. The highest correlation was observed for winter values (r: 0.606, $P < 0.001$). In pooled data analysis, vitD levels showed a positive correlation with ACT scores and FEV1% pred values and a negative correlation with body mass index (BMI), VDBP, serum IgE, and bronchodilator reversibility (Table 1). Multivariate regression analyses revealed that the mean of annual vitD level was significantly and positively associated with ACT score, and FEV1% pred value and negatively with serum IgE level, after adjusting for age, sex, BMI, inhale corticosteroid (ICS) use, daily sun exposure, VDBP and VDRGPs. Genetic analyses showed that VDR fokI polymorphism F allel was significantly higher in asthmatic group than controls(OR:2.97 CI: 1.2–6.8), but VDRGPs were not related to vitD levels or ACT scores.

Conclusion: This study revealed that serum vitD levels significantly affected asthma control measures, LFTs and IgE levels independent from age, gender, BMI, ICS use and daily sun exposure.

Table 1. The correlation between vitamin D level and asthma control test, allergic parameters, spirometric indices and bronchial provocation response in pooled analysis

OUTCOME	UNADJUSTED β(P)	ADJUSTEDβ(P)
Asthma control test score	0.43 (0.037)	0.48 (0.023)
FEV1%	0.51 (0.04)	0.62 (0.034)
FEV1/FVC	0.31 (0.56)	0.26 (0.32)
MMEF %	0.18 (0.27)	0.12 (0.41)
FVC %	0.22 (0.48)	0.31 (0.67)
Bronchodilator response %	−0.38 (0.02)	−0.41 (0.08)
Serum IgE	−0.47 (0.008)	0.47 (0.007)
Absolute eosinophil count	−0.11 (0.12)	−0.13 (0.28)

1449
Montelucast vs inhaled corticosteroids in the treatment of mild persistent asthma: compliance and asthma management

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Background: The reason for the choice leukotriene receptor antagonists as a stand alone treatment of mild persistent asthma is not only their proven effectiveness, but in some cases priority patients. What will be prescription observe the patient mild persistent asthma: a tablet or inhaled medicines?

Method: Within 6 months we have seen 68 patients with allergic asthma (adults and adolescents) 36 of which (1 group) received low doses of inhaled corticosteroids and 32 persons (2 group) received montelucast (Synglon® Gedeon Richter) 10 mg per day. In both groups of patients, asthma combined with allergic rhinitis (AR), while 22 patients of the 1st group were appointed intranasal corticosteroids, in the 2nd group intranasal corticosteroids were not appointed. Results of the therapy were evaluated on the level of asthma control test (ACT), the severity of symptoms of rhinitis, quality of life the scale compliance consisting of 12 issues and also we are proposed visual scale compliance (VSC) of adherence from 0 – 'I never taken this medicine' to 10 – 'I never missed receiving this medicine'.

Results: At a high level of compliance in both groups correspond to well asthma control that is correlated with the improvement of the quality of life. Most patients in both groups (61.7% and 66.4%) was recorded full or partly controlled asthma, but the average ACT score in the second group was significantly higher – 23.6 points (17.8 points in the first group). The study demonstrated a significantly higher adherence to basic therapy tablet form from 5.1 by VSC (scale compliance – 12.1) in the first group to 8.8 (scale compliance – 18.6) in the second. However, low compliance corresponded to the significantly lower level of asthma control and quality of life. We assume that the level of asthma control in the second group above in connection with the greater adherence to therapy. Preference pill form gave patients with mild persistent asthma even in the absence of difficulties with the technology for inhalation, as well as patients with concomitant AR.

Conclusion: So, in our observation compliance with montelukast was higher that may be associated with a traditional form of medicine delivery and the persisting alerted relation to steroid therapy in patients with mild asthma. The proposed VSC simple and reliable for the determination of patient adherence therapy.

1450
Inhaled long acting beta agonists prescription for asthma in pre-school children

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Background: Several studies have demonstrated the efficacy of inhaled long acting beta agonists (LABA) associated to inhaled steroids (ICS) in the treatment of uncontrolled asthma, however few have characterised their use in preschoolers. In Portugal, only one study has specifically reviewed drugs used in allergic disease in this age group.

Objectives: Characterisation of LABA prescription for asthma, in pre-school children from an allergology outpatient unit.

Methods: Revision of clinical files of children aged ≤6 years old, with asthma phenotypes, seen in a reference allergology consultation with asthma in a total of 238 patients, consecutively observed by the authors from January to June 2012. The data collected included sex, age, comorbidities and prescriptions with respective daily dosage.

Results: A total of 56 prescriptions for LABA (23.5% of children with asthma phenotype) were registered. The only prescribed was salmeterol and always in combination with fluticasone. Off-label use was shown in 30.4% of these patients for use below the authorized age of 4 years old. All presented with severe asthma not controlled on ICS with or without anti-leukotriene (ALT). The remaining children were treated with varying combinations of LABA, ICS and ALT and one child had no maintenance therapy.

Conclusions: In this age group, the lack of studies makes comparisons difficult and most of them are not aimed at pre-schoolers. Similar studies show the use of LABA varying from 10% to 22% although they focus mainly on children over 5 years old. Current guidelines state that these inhaled

drugs should always be used in conjunction with an inhaled corticosteroid and national authorizations restrict their use to children 4 years old and above. Due to insufficient clinical trials and the need to symptom control, their off-label use becomes more common at younger ages. Additional studies in this age group could further evaluate the safety and efficacy of their use in children.

1451
The new non-medicamental methods of therapy of bronchial asthma in children

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Introduction: One of the common allergic diseases in children is bronchial asthma (BA). The possibilities of application of non-drug therapy and combination of physiotherapeutic methods with standard schemes of treatment are very great. One of the new directions in treatment of BA is an application of noninvasive device 'ASTER'.

Aim: To establish the effectiveness of exposure to non-thermal intensity and ultrahigh frequency electromagnetic radiation (device 'ASTER') in children with BA for the purpose of increase of efficiency of basic therapy of BA without increase in drug loading.

Methods: 131 patients aged 6 to 17 years with BA have been divided into 2 groups. Children of both groups have not reached control over disease within last 4 weeks before the inclusion of study. Sixty-nine patients of group I who received basic therapy with inhaled corticosteroids (ICS) have been divided into 2 subgroups (IA and IB) depending on used medication. In subgroup IA 31 children received combination fluticasone/salmeterol. In subgroup IB 30 children received fluticasone, 8 patients – beclometasone. All patients from group I used a device 'ASTER' in addition. Sixty-two children who received only therapy by ICS have been included in group II.

Results: The amount of day and night symptoms, the requirement of use of beta2-agonists decreased more in group I in comparison to group II ($P < 0.05$). FEV1 increased on 14.5%, 10.87% and 8.02% in subgroups IA, IB and in group II accordingly by the end of 1 month of treatment. Indicators of the test of the control over asthma (ACT-test-Asthma Control Test) were better in subgroups IA and IB as compared to group II.

Conclusion: Device 'ASTER' application in combination with basic therapy allowed to reach faster and high level of control over disease, has led to significantly faster decrease of frequency and severity of symptoms of BA, to improvement of pulmonary function, in comparison with use of ICS only.

Poster Session Group III – Green

TPS 67 – Milk and egg allergies

1452
Extreme thrombocytosis in an infant with cow's milk protein allergy

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Background: Thrombocytosis is regularly observed in the context of allergy. It is involved in the inflammatory cascade and it is usually reported to be mild ($<700 \times 10^3/mm^3$). To our knowledge, extreme thrombocytosis [platelets (PLT) $>1.000 \times 10^3/mm^3$] has not been reported in food allergy in children. Thrombocytosis has been suggested to be the result of IL-6 mediated megakaryopoiesis by TPO. Furthermore, platelet activating factor (PAF) could also contribute to entertain the inflammatory state as it is supposed to be related to the increase of histamine. We report an infantile case of milk protein induced allergy who presented with extreme thrombocytosis and growth retardation.

Case report: A 2-month-old baby presented with intense vomiting/regurgitations and crying/abdominal pain. The infant had also dropped his weight from the 50th (birth and 1st month of life) to the 10th percentile. The baby was breast fed during the 1st month of life. A blood analysis revealed an extreme thrombocytosis (PLT $1.094 \times 10^3/mm^3$) with no associated anemia that was confirmed by microscope analysis. Platelets were normal as volume and width were concerned as well as their functional activity. Extensive investigation was negative for bacterial and viral infections and for systemic diseases. An extensively hydrolyzed milk formula was initiated at day 4 of hospitalisation. At day 14 the baby had a 50 g/day gain weight and the blood analysis revealed a slight decrease of platelet count at $846 \times 10^3/mm^3$. At day 46, however, an amino acid based formula was initiated, due to insufficient amelioration of the patient; vomiting, regurgitations and abdominal pain persisted while the baby remained in the 10th percentile of weight. IgE levels were slightly increased [7.9 kUA/l (normal values n.v.: 0–7.2 kUA/l), PLT:$766 \times 10^3/mm^3$, Hct :33%]. At day 56 the baby had a further clinical amelioration, though PLT remained increased ($810 \times 10^3/mm^3$) and IgE increased at 9.7 kUA/l. Lactose intolerance test and skin prick tests for milk allergy were negative. At day 70 all symptoms had been resolved though thrombocytosis persisted (PLT $641 \times 10^3/mm^3$) and RAST for cow's milk turned out to be positive at 0.15 kU/l (n.v. < 0.1).

Conclusion: Early diagnosis of milk protein allergy is essential to early initiate appropriate treatment. Co-existence with extreme thrombocytosis should not mislead the diagnosis. This is of paramount importance in order to avoid further complications and unnecessary examinations.

1453
Utility of cow's milk specific IgE in predicting outcomes of oral challenge test in Korean children with IgE-mediated milk allergy

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Background: We intended to validate the previously established diagnostic decision points to predict the outcome of oral challenge test in Korean children with IgE-mediated cow's milk allergy.

Method: In this prospective study, 225 children older than 12 months of age with suspected IgE-mediated cow's milk (CM) allergy were enrolled. The total IgE and levels of IgE antibodies specific for CM were measured by immunoCAP (Pharmacia, Uppsala, Sweden). The diagnosis for IgE-mediated CM allergy was confirmed by an open oral food challenge (OFC). Sensitivity, specificity, positive and negative predictive values and the positive and negative likelihood ratios were calculated for CM-specific IgE in confirmed CM allergy.

Results: Two-hundred and twenty-five patient's mean age 41.0 ± 35.2 months (range, 12–204 months), 138 (61.3%) participants were male. Twenty-three percent (52/225) of milk challenge were assessed as positive, which is IgE-mediated milk allergy was confirmed. The median concentration of CM-sIgE antibodies was 16.1 kU_A/l (IQR 5.73–32.37) in OFC- positive group and 0.30 kU_A/l (IQR 0.09–0.99) in OFC-negative group. There was statistically significant differences in the level of sIgE antibodies against CM between OFC-positive group and OFC-negative group ($P < 0.0001$). The sensitivity and positive predictive values of previously established decision values for cow's milk-sIgE antibodies were relatively low in Korean children. The relationship between sensitivity and specificity were further explored by ROC curves, yielding acceptable areas under the curve, 0.95. The CM-specific IgE concentration indicating a 92% risk of reaction was 22.9 kU_A/l.

Conclusion: The Diagnostic Decision Points for IgE-mediated CM allergy were different from those values in the US studies. The specific IgE level for the diagnosis of IgE-mediated CM allergy should be re-evaluated in each region and each race.

1454
Hydrolysis and peptide profiling crucial for the choice of hypoallergenic milk protein formula suitable for tolerance induction and primary prevention of allergic sensitisation

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Background: Hypoallergenic cow's milk-based formulas containing protein hydrolysates are usually used to prevent reactions in cow's milk allergic infants. Early exposure to small immunogenic and tolerance-inducing peptides is further suggested to prevent allergy development.

In this study, we compared the hydrolysates from two whey protein sources, both potentially containing small immunogenic fractions, in their capacity to prevent early sensitisation to cow's milk proteins (CMP).

Method: Five-Week old naïve C3H/HeOuJ mice were treated with two whey protein sources (Whey 1 and Whey 2, as positive controls for oral tolerance induction) or their corresponding hydrolysates (WH1 and WH2, respectively) prior to sensitisat-

ion. Mice were then sensitised orally with Whey 1 or Whey 2 mixed with cholera toxin as adjuvant. One week after the last sensitisation, mice were intradermally and orally challenged with whey protein. Clinical symptoms such as anaphylactic shock and body temperature were determined. Furthermore, serological analysis of allergen-specific IgE and IgG1 and mouse mast cell protease 1 (mMCP-1) were performed.

Results: Prior exposure to whey protein prevented the development of clinical allergic symptoms as no anaphylactic shock and drop in body temperature were observed in those groups. Both hydrolysates were not able to prevent allergy development to whey, however, WH1 tended to lower mMCP-1. By contrast, pretreatment with WH2 resulted in significantly more whey-IgE and mast cell degranulation. The same pattern was observed for whey-IgG1 levels.

Conclusion: Whey protein prevented the development of clinical symptoms of allergy, reflecting the expected tolerance induction. Reduction in size of CMP in hydrolysates might be sufficient for secondary (challenge) prevention, but potential differences in the characteristics of the resulting peptides might determine whether a hydrolysate will possess tolerogenic or allergenic capacities further highlighting the necessity of proper peptide profiling.

1455
Skin prick test and milk-specific IgE threshold values in the diagnosis of cow's milk allergy

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Background: Cow's milk allergy (CMA) is one of the most frequent food allergies in children, and its clinical and laboratory findings may influence the prognosis of the patients. Challange tests are expensive, time consuming, troublesome and have high risk for anaphylaxis. Skin prick test and f2 treshold values for he diagnosis of CMA is very important. The aim of our study was to determine the diagnostic threshold values of SPT and f2 according to challange test as the gold standard.

Method: We evaluated the results of the patients with CMA in our clinic for this purpose. Oral provocation tests, SPT and f2 were performed in patients. Patients were evaluated in two groups.

Group A (*n*:94): IgE-mediated CMA patients with positive oral challange test.

Group B (*n*:65): suspected CMA patients with challange test. Statistically using ROC curves were determined threshold values for f2 and SPT.

Results: In the study, 159 patients were evaluated. Patients aged between 45 days and 15 years, 58% were male, 25% were negative for SPT and 12% were for negative f2 values at Group A. The groups didn't differ in the diameter of histamine in SPT (*P*:0.54). Skin prick test's CM enduration diameter was 9.1 ± 7 mm in Group A and 2 ± 3.3 mm in Group B (*P*:0.00); f2 value 21.7 ± 40 ku/l for group A, 4.1 ± 8.2 ku/l in Group B (*P*:0.00). SPT and f2 threshold levels did not differ significantly by age. 95% Positive predictive values were for SPT and f2 10 mm and 26.3 nku/l, respectively. Challange test taken as the gold standard diagnostic power of the SPT(AUC: 82.5%), according to f2 (AUC: 71.8%) was significantly greater.

Conclusion: The diagnosis and monitoring of cow's milk allergic patient, especially for physicians who can't make challange test, according to age groups, clinical laboratory testing is essential to determine the laboratory threshold values.

1456
A compilation of oral food challenge data in cow milk allergic children to an extensively hydrolyzed casein-based infant formula

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Background: Hypoallergenic formulas are subject to recommendations and/or regulations regarding testing to support use in patients with cow milk allergy (CMA). Testing for hypoallergenic status should be sufficient to project with 95% confidence that 90% of CMA subjects will not react to the product (e.g. 0/29, 1/46, 2/61, 3/76, 4/89 challenges). The aim of this project was to analyze published and unpublished food challenge (FC) data for a specific extensively hydrolyzed casein-based infant formula from work sponsored by the manufacturer to confirm that these recommendations can be supported.

Method: 97 subjects (2.9 ± 0.3 year) with documented IgE-mediated CMA received a double-blind, placebo-controlled FC (DBPCFC) ($n = 40$) or a DBFC ($n = 57$) of Similac® Alimentum® (ALIM) (Abbott Nutrition [AN], Columbus OH). For DBPCFC in 29 subjects, 8 g freeze-dried ALIM was added to 100 ml placebo (Nutramigen® liquid [NUTR], Mead Johnson Nutritionals, Evansville, IN). For the remaining DBPCFC subjects, the current formula (NUTR or soy) was used as placebo and was mixed with ALIM. For DBFC, ALIM served as the placebo for milk and/or soy challenges.

Results: Ninety-three of 97 challenges to ALIM were negative. Of the remaining 4 challenges, 3 were positive to ALIM. The 4th challenge, in a subject with anaphylaxis to CM, was labelled 'inconclusive'. The subject reacted to NUTR and NUTR with ALIM (both with flavoring). Twenty-eight of 29 challenges to NUTR were negative and 1 was 'inconclusive' as it was impossible to ascertain if the reaction was to NUTR or flavoring.

Conclusion: These data, some previously reported (Sampson et al. *J Pediatr* 1999; Oldaeus et al. *Pediatr Allergy Immunol* 1991; Borschel et al. *Clin Transl Allergy* In press), support hypoallergenic labeling for ALIM and document that with 95% confidence, ALIM was tolerated by 90% of individuals documented to be CMA.

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1457
The assesment of clinical and immunological tolerance in children with cow's milk allergy

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Background: Food allergy is an increasing problem in developed countries. Because of the physiologic development of digestive tract and immune system the youngest children are especially predisposed to cow's milk allergy. Developing tolerance to harmful food is a complex process affected by different factors. The aim of the study was to assess clinical and immunological tolerance acquisition in children with cow's milk allergy.

Methods: The clinical evaluation was based on the result of challenge with low-lactose cow milk. The study involved 214 children, aged between 1 and 14 years, with diagnosed cow's milk allergy, treated with milk-free diet for a period of 12 months to 5 years ($X - 2$ years). The immunological evaluation was performed in 40 patients and based on the assessment of Tr cells ($CD4CD25^{high}$) by the flow cytometry and the concentration of IL-10 and TGF-β in serum using ELISA test. The immunological parameters were assessed twice: before the introduction, and after discontinuation of elimination diet. The control group consisted of 15 children without allergic diseases.

Results: The results of the study revealed that 62.6% of the examined children acquired tolerance to cow's milk. The percentage of Tr cells ($CD4CD25^{high}$) was increased in children who acquired tolerance in comparison to patients with persistent allergy and control group. IL-10 concentration in serum was significantly lower in children with negative result of food challenge in comparison to control group. The concentration of TGF-β in children who acquired tolerance was significantly higher in comparison to children with persistent allergy.
Conclusion: The results of the study showed that most of properly diagnosed and treated children acquired tolerance to cow's milk. Food challenge should be performed in children with food allergy to verify the need to continue the elimination diet. The immunological parameters used in the evaluation of milk tolerance acquisition characterised the limited usefulness.

1458
Dietary and weaning habits in cow's milk allergy: a case series of 20 infants

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Background: Cow's milk allergy (CMA) is the most common food allergy in infants in the UK. It requires a special weaning diet with strict exclusion of all forms of cow's milk. Previous research indicates diet during infancy may affect eating habits later in childhood. In food allergic children, fussy eating can be nutritionally problematic as it further limits the variety of an already restricted diet. The aim of this study is to determine early eating habits in this population.
Method: Recruitment took place at routine appointments at a secondary care allergy clinic on the Isle of Wight, UK. All infants aged between 8 and 24 months consuming a cow's milk free diet were invited to take part. Parents completed questionnaires about their child's food allergy history, dietary intake and eating habits.
Results: 20 infants were recruited. The mean age was 14.7 months. All had a history strongly suggestive of CMA. Two had a positive skin prick test to cow's milk. Eleven were consuming an amino acid based formula, four were consuming an Extensively Hydrolysed (EH) casein formula, four were consuming an EH whey formula and one was breastfed. The mean age for initiation of a specialised formula for CMA was 17 weeks. The mean age for introduction of weaning solids was 20 weeks. Eighty percentage of infants had been breastfed, with a mean duration 3.5 months. 25% were taking a vitamin D supplement. 100% of parents reported they paid 'a great deal' of attention to healthy eating. A food frequency questionnaire of 77 typically eaten baby foods indicated 39% of all listed foods, 67% of sweet foods, 37% of fruits and 18% of vegetables had never been eaten. Scores for fussy eating and neophobia were within the normal range.
Conclusion: Initiation, duration of breastfeeding and age of introduction of solid foods in this case series are similar to national UK data of healthy infants. Uptake of vitamin D supplements is suboptimal. All parents were concerned about healthy eating, with infants consuming few sweetened foods.

1459
Differential responses in allergen-specific IgG subclasses during oral immunotherapy for severe egg allergy

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Background: Oral immunotherapy (OIT) can induce desensitisation or tolerance in patients with severe food allergy, yet precise mechanisms for the efficacy have not been fully understood. Changes in allergen-specific antibodies in response to OIT may give us an important clue to dissect the mechanism. Although specific IgE and IgG4 levels have been widely investigated, information regarding other IgG subclasses and IgA in OIT is still to be needed. We have established a new microarray technique of high-density antigen immobilization using high-density carboxylated arms on silicon or glass slide protein chip that enabled highly sensitive specific antibody assays of any immunoglobulin allergen class/subclass.
Method: We measured the levels of egg (egg white, ovalbumin and ovomucoid)-specific IgE, IgA and IgG subclasses in sera from 24 egg allergy children who received rush OIT by using high sensitive allergen microarray and correlated the results with clinical outcomes.
Results: Egg-specific IgE gradually decreased during the course of OIT for 12 months. Conversely, egg-specific IgG4 increased during the course. Egg-specific IgG1, IgG3 and IgA significantly increased right after the rush phase, then decreased during the maintenance phase. Egg-specific IgG2 levels changed in the similar way with IgG4. Most of the patients successfully acquired desensitisation/tolerance to egg. In patients who failed to achieve desensitisation status, no elevations in the levels of egg-specific IgG subclasses during the OIT were observed.
Conclusion: Egg-specific IgG subclass levels differentially changed in parallel with the clinical course of OIT, which may reflect a feature of immune responses induced by OIT.

1460
Utility of egg white specific IgE in predicting outcomes of oral challenge test in Korean children with IgE-mediated egg allergy

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Background: We intended to validate the previously established diagnostic decision points to predict the outcome of oral challenge test in Korean children with IgE-mediated egg allergy.
Method: In this prospective study, 273 children older than 12 months of age with suspected IgE-mediated egg allergy were enrolled. The total IgE and levels of IgE antibodies specific for egg white (EW) were measured by immunoCAP (Pharmacia, Uppsala, Sweden). The diagnosis for IgE-mediated egg allergy was confirmed by an open oral food challenge (OFC). Sensitivity, specificity, positive and negative predictive values and the positive and negative likelihood ratios were calculated for EW-specific IgE in confirmed egg allergy
Results: Two-hundred and seventy three patient's mean age 40.3 ± 33.5 months (range, 12–199 months), 161 (58.9%) participants were male. Nineteen percent (52/273) of egg challenge were assessed as positive, which is IgE-mediated egg allergy was confirmed. The median concentration of egg white-sIgE antibodies was 16.7 kU_A/l (IQR 5.13–33.72) in OFC- positive group and 0.38 kU_A/l (IQR 0.08–1.54) in OFC-negative group. There were statistically significant differences in the level of sIgE antibodies against egg white between OFC-positive group and OFC-negative group ($P < 0.0001$). The positive predictive values of previously established decision values for egg white-sIgE antibodies were low in

Korean children. The relationship between sensitivity and specificity were further explored by ROC curves, yielding acceptable areas under the curve, 0.92. The EW-specific IgE concentration indicating a 90% risk of reaction was 27.6 kU_A/l.
Conclusion: The Diagnostic Decision Points for IgE-mediated EW allergy were different from those values in the US studies. The specific IgE level for the diagnosis of IgE-mediated EW allergy should be re-evaluated in each region and each race.

1461
Evaluation of antigenicity of two types of egg powder used as confectionery and cooking materials and possible use as a standard food for oral egg challenge test

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Background: Manifestations of food allergy symptoms induced by exposure to an allergen mainly depend on the amount and antigenicity of the allergen and the level of allergen-specific IgE in serum. To evaluate the relationship between the result of oral food challenge (OFC) and specific IgE levels both in identifying the offending allergen and in confirmation of allergen tolerance, standardisation of OFC material is needed.
Method: To standardise OFC material for egg allergy diagnosis and management, two types of commercially available egg powders used as confectionery and cooking materials were evaluated – dried whole egg powder as an alternative for raw hen's eggs, and frozen cooked egg powder as a substitute for cooked hen's eggs. Using sandwich ELISA, the antigenicity of the two egg powders was evaluated by performing quantitative assessment of ovalbumin (OVA) and ovomucoid (OM) levels in four lots of dried whole egg powder and 23 lots of frozen cooked egg powder.
Results: There was a large variation in the amount of OVA among 23 lots of frozen cooked egg powder, ranging from 5.34 to 295 mg/g. On the other hand, there was a minimal variation in the amount of OM among 23 lots. A tendency to have a small variation in OVA and OM levels was observed for the frozen cooked egg powder lots purchased at the same time. Regarding dried whole egg powder, there was a minimal variation in the amount of OVA and OM among four lots, and these amounts were almost equivalent to those of raw hen's eggs.
Conclusion: Dried whole egg powder can be used as a standard OFC material in evaluation of patients with egg allergy. As for frozen egg powder, there was a minimal variation among lots purchased at the same time. As every lot consists of 1 kg of egg powder, several kilograms of frozen cooked egg powder containing almost identical amount of OVA can be used to prepare a standard egg OFC material. These results will be further evaluated in a multicenter prospective study in Japan (IPAD3 g).

1462
Oral allergic syndrome due to egg ingestion in an adult subject: a case-report

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Background: Egg allergy is one of the most common forms of food allergy in childhood. Generally it has a good prognosis and is expected to resolve in the majority of children by school age, apart from in patients with a high ovomucoid sensitisation. Clinical presentation of egg allergy is varied: anaphylaxis, food protein-induced enterocolitis syndrome, atopic dermatitis and eosinophilic oesophagitis. In literature oral allergy syndrome due to egg ingestion in adulthood is not described.
Case report: A 18 y.o. girl reported, in the last 6 months, itching and burning of the lips, mouth and throat immediately after ingestion of raw and partially baked egg with spontaneous resolution, without other systemic symptoms associated. She denied previous history of egg and other food allergy; she had no symptoms of rhinitis, asthma nor atopic dermatitis.
Method: Skin prick tests for common inhalant allergens, suspected and common food allergens were performed (Stallergenes, France; Alk-Abellò, Denmark); serum specific IgE (ImmunoCAP, Phadia) were also measured.
Results: Skin tests resulted positive for grass and olive tree pollen, egg white (6 mm), yolk (5 mm), ovalbumin (12 mm), peach (4 mm) and shrimp (4 mm); prick tests with chicken meat (Stallergenes) and birth feathers (Alk-Abellò) were also performed with negative results. Specific serum IgE for egg white and ovalbumin (Gal d2) resulted positive (1.56 and 2.25 KUA/l respectively). A mild positivity was found also for yolk (0.21 KUA/l), Pru p3 (0.16 KUA/l), shrimp (0.16 KUA/l). Negative results were observed for ovomucoid (Gal d1) and tropomyosin (Pen a1).
Conclusion: Here we described a rare case of isolated oral allergic syndrome due to egg ingestion devoloped in adult age, due to ovoalbumin sensitisation without allergic reactions related to ingestion or inhalation of other bird products. Concomitant food and pollen sensitisations were not clinically relevant at the moment, but in our opinion follow-up is mandatory.

1463
Masks egg for hair: to proscribe?

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Background: Egg is one of the foods with greater allergenic potential. Allergic reactions triggered by the ingestion of egg are responsible for a significant proportion of episodes of food anaphylaxis. In most cases, this sensitisation occurs mainly during the first 2 years of life. The egg allergy with adult onset is rare and mostly described in young adults.
Case report: We describe the case of a female patient, caucasian with diagnosis of asthma and allergic rhinitis since the age of 62, without prior history of food allergies. At 67, after applying hair mask containing only raw egg, immediately began feeling unwell, red eyes, eyelid edema and urticaria at the site of contact with the egg. Thereafter, whenever she ate egg, she started immediate complaints of rhinoconjunctivitis, more exuberant with raw egg. Five months later, after eating pineapple mousse (with raw egg), she initiated complaints of wheezing, sneezing, and dyspnea. No history of exposure to birds, nor occupational to egg.
Methods and results: Immunologic studies showed positive skin prick-tests to common aeroallergens. Skin prick-tests with commercial extracts of egg and its components and determination of specific IgE levels (sIgE) (ImmunoCAP, Siemens-Phadia) were performed:

- Prick-tests with commercial extracts – wheal ø (mm)
  - Egg white 6
  - Egg yolk 6
  - Ovoalbumin 6
  - Ovomucoid 6
- sIgE – (KU/l) (Class)
  - Egg white 4.0 (3)
  - Egg yolk <0.35 (0)
  - Ovoalbumin 6.9 (3)
  - Ovomucoid 1.4 (2)
- Conclusion

Egg allergy with adult onset is uncommon and rare in the elderly. The development of the first symptoms after skin contact with proteins of egg is even less

frequent. We wonder if the first symptoms in this patient, would not be triggered by cutaneos absorption of undigested allergens in a known atopic background.

1464
Prediction of tolerance achievement in children with hen's egg allergy

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Background: The diagnosis of food allergy relies on oral food challenge. Therefore, it must be performed to ascertain whether a child recovers from egg allergy. However, oral food challenge is expensive and not without risk. Therefore, there is a growing interest in simple markers that may predict the resolution of egg allergy in children. We studied whether negativization of positive skin prick test reactions to egg white or egg yolk may be useful for identifying children who became tolerant to hen's egg.
Methods: Seventy-five children with hen's egg allergy and positive skin prick test to egg were followed. They periodically underwent skin prick test to egg components. Children were assigned to two groups. Twenty-three children whose skin prick test results to egg became negative were included in the patient group; 52 children with positive skin prick test to egg in the control group. Then, all children underwent oral egg challenge to assess tolerance.
Results: Oral egg challenges gave positive results in 4% of 23 children with negative skin prick test reactions to hen's egg and in 25% of 52 children who had positive skin prick test reactions to egg ($P < 0.03$). Skin prick test results to egg white and egg yolk showed high sensitivity (0.92) and negative predictive accuracy (0.95), but poor specificity (0.36) and positive predictive accuracy (0.25).
Conclusions: The assessment of skin prick test response to egg may be helpful in predicting which children will acquire tolerance to egg.

1465
Omalizumab and egg desensitisation in the outpatients office

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Background: Egg desensitisation protocols are included recently as a new therapeutic options in Allergy Units. Egg sensitised patients are considered a high risk patients and needed hospital observation during desensitisation protocols. The main objective was to complete an egg desensitisation protocol with the adyuvant use of omalizumab under outpatients setting in patient with persistent egg allergy.
Method: We present a 8 year-old girl with a confirmed diagnosis of severe persistent anaphylaxis to egg. No other atopic conditions were present. No controlled challenges were performed by the clear clinical history as minimal unwanted contacts with dairy products (even traces) were able to elicit immediate systemic symptoms. Diagnostic work-up showed a total IgE of 154 UI/l with specific IgE (kU/l) to egg white: >100; egg yolk: 52.9, ovomucoid 57.3, and ovoalbumin: >100. A total cumulative dose of Omalizumab 600 mg (300 mg every 2-weeks) was only administered 4 weeks prior to desensitisation. No pre-treatment with systemic steroids and/or antihistaminics were used. Clinical follow-up was strictly observed during the whole protocol. On the first day, the proposed rush schedule with dehydrated egg white (OVO-DES^R, Nutrición médica) included dosing up (every 30 min) with both diluted (1/100–1/10) and undiluted first dose up to a maximal dose of 4 mg. This daily manteinance dose was also weekly rised up to a maximal dose of 3600 mg according patient tolerance.
Results: A final dose of 3600 mg (equivalent to a complete raw egg) was reached in 9 weeks. Only local mild adverse reactions were observed at the first day of raising dose, controlled with oral antihistaminic medication, and no corticosteroids or adrenaline was needed either.
Conclusion: The inclusion of Omalizumab in the food desensitisation protocols could play a role as a usefull adyuvant tool specially in those patients with a high risk of anaphylaxis who require to be managed in the outpatient office. Further studies are needed to evaluate the optimal duration of Omalizumab in long-term food desensitisation.

1466
Oral immunotherapy in severe milk, peanut or egg allergy in adults – preliminary results

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Background: There is evidence of efficacy of oral immunotherapy in severe food (milk) allergy in children but information on adults is lacking. In comparison with pollen immunotherapy, oral food immunotherapy is associated with adverse reactions more often. Generally adverse reactions associated with oral immunotherapy are mild. However, there are occasional and unexpected more severe systemic reactions. There is a growing interest in oral immunotherapy treatment in severe food allergy also in adults.
Method: The diagnosis of peanut allergy is verified with positive symptom history, skin prick test and allergen specific IgE antibodies. In addition, food allergy is verified with an allergen specific challenge test (double blind in peanut and egg allergy, open in milk allergy). Simultaneously other allergies are allowed. Intermittent mild asthma, and mild and moderate persistent asthma are tolerated and treatment with inhaled steroids and other asthma medication is also allowed. Quality of life and patient history data is collected by questionnaires. All patients undergo a spirometry with a bronchodilatator test, exhaled nitric oxide and a methacholine challenge before and a year after oral immunotherapy. If the test results are diagnostic for asthma, the patients are treated with asthma medication before oral immunotherapy treatment is started. After escalating doses of allergen during the first phase of oral immunotherapy, the treatment is continued with the highest tolerated maintenance dose until 1 year of therapy.
Results: In these preliminary results we describe the results of oral food immunotherapy treatment in those patients that have received oral food immunotherapy treatment for either milk or peanut or egg allergy.
Conclusion: Oral immunotherapy might be an alternative treatment instead of total avoidance in some patients but further experience is needed. According to previous knowledge in children, obtained tolerance fades away if the immunotherapy is completed.

Poster Session Group III – Green

TPS 68 – Asthma: genetics, biomarkers and management

1467

Validation of the Epworth Sleepiness Scale, Berlin, STOPBANG questionnaires and American Society of Anesthesiologists checklist as screening tools for obstructive sleep apnea in patients with chronic obstructive pulmonary disease, asthma and cardiovascular diseases

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Background: Obstructive sleep apnea (OSA) is a common medical condition and may lead to life threatening problems if it is left undiagnosed. This study was conducted to evaluate the Epworth Sleepiness Scale (ESS), Berlin, STOP-Bang questionnaires and the American Society of Anesthesiologists (ASA) checklist for screening OSA in patients with COPD, asthma and CVD.
Method: The study was performed on 180 patients, 60 COPD, 60 asthmatics and 60 patients with CVD without previously diagnosed OSA were recruited subjects completed the Questionnaires. The scores from the ESS, Berlin, STOPBANG questionnaires, and ASA checklist were evaluated.
Results: In the COPD, asthma & CVD groups, the mean ages were 61.5 ± 4.8, 45.6 ± 7.1 and 58.8 ± 8.5 respectively. Of 180 screened patients (30%, 70%, 20% and15% of COPD), (32%, 55%, 37% and 35% of asthmatic) and (70%, 35%, 60% and 49% of CVD) were respectively classified as being at high risk of OSA by the ESS, STOP BANG, Berlin questionnaires, and ASA checklist. The risk of OSA increased up to age 65 years. A significant number of obese individuals (58%) were at high risk for OSA. Those whose questionnaire scores indicated a high risk for OSA were more likely to report subjective sleep problems, a negative impact of sleep on quality of life, and a chronic medical condition than those who were at lower risk.

The ESS score was highly significant in the cardiac patients in comparison to the COPD and asthmatic patients. The Berlin questionnaire show very high risk among the cardiac followed by the COPD and lastly the asthmatic patients. In STOP-BANG questionnaire demonstrate significant difference between the cardiac with the COPD and asthmatic patients existed. ASA checklist show high risk among the cardiac, asthmatic and COPD.
Conclusion: Berlin & STOP-Bang Questionnaires are quite reliable to determine which patient need further evaluation of OSA followed by ASA checklist then ESS.

1468

Delayed response to omalizumab in severe allergy asthma

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Background: Omalizumab is indicated for the treatment of patients with severe allergic uncontrolled asthma despite optimal therapy. The assessment of the treatment efficacy must be done every 16 week from the first administration of the drug. We presented a case of a man with lack of response after 16 week, becoming in a late responder.
Method: A 47 year old with a history of severe steroid-resistant asthma and rhinoconjuntivitis since 1996. His treatment was Salmeterol- Fluticasona 50/500 μg/twice daily, Salbutamol 3–4 times/day, Tiotropium bromide 18 μg/day, Montelukast 10 mg and Dezaflacort 30 mg (15 day every month). He had had many severe exacerbations with hospitalisation. Positive skin prick test and specific IgE for pollen of grasses and weeds, total IgE: 556.9 IU/ml and body weight: 93 kg. Normal blood test and immune-rheumatogical tests. Spirometry showed a pattern ventilatory of FEV1: 1.45 (71%), FVC: 3 (67%), FEV1/FVC: 48.23. A physical examination on the chest revealed hissing sounds during expiration. Computed Tomography did not find anomalies. The patient was selected as suitable for additional treatment with Omalizumab, administered subcutaneously in a dosage of 450 mg every 2 week.
Results: During the first year of treatment, he did not show improvement. We found lack of response to Omalizumab, with compromised respiratory functions (FEV1: 1.87 (52%), FVC: 3.5 (79%),(FEV1/FVC:53.29) and poorly controlled asthma. Asthma Quality of Life Questionnaire score (AQLQ) of 3.6 point and the Asthma Control Test (ACT):17. We decided to continue administering the drug. At 52 week, he began to see amazing improvement in the symptoms (ACT: 24 and AQLQ: 0) and in spirometric test (FEV1: 3 (85%), FVC: 4.5 (102%),(FEV1/FVC:67.14). This made it possible for us to gradually reduce the inhaler treatment and stop systemic steroid.
Conclusion: In this clinical case is the extremely delayed symptomatological response to the Omalizumab in 52 week. In the literature was reported a case with late-reponse to the 48 week after a long period of apparent resistance to treatment. Maybe explain the delayed response that he remodeling of the bronchial was requiring longer time to improve. We need more studies to identify this fenotypes.

1469

Two cases whereby a heavy persistant allergic asthma controlled by omalizumab and allergic bronchopulmoner aspergillosis co-exist

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Introduction: Hereby two cases will be presented to you. They involve a diagnosis of ABPA that was being treated with steroids and later on switched to omaluzimab (Anti-Ig E) treatment due to serious side effects caused by steroid treatment.

CASE 1: A 48 years-old male (E.B), an asthmatic since 35 years, diagnosed as ABPA 5 years ago, had been under steroid treatment for the last 5 years when he was referred to us. Despite the ongoing steroid treatment, he had serious symptoms and the asthma was not under control. He had a history of applying to an emergency service with asthma attacks for a minimum of four times a year and osteoporosis had developed due to long term steroid use. According to modified dose regimen, we started omalizumab 600 mg once every 14 days. When this patient came back for follow up 14 days following the first dose administration, he was observed to be free of all of the previous

symptoms, FEV1 value had increased by almost 100%, ACT had increased to %25. The steroid treatment that had been going on for 5 years was discontinued. Due to the positive response of the patient to the initial treatment of 16 weeks, we are still continuing the new regimen.

CASE 2: A 52 years old woman (FK), an asthmatic for 25 years, had been applying to emergency services with astma attacks for a minimum of 10–12 times per year, and had been taken to in-patient wards frequently. She was diagnosed as ABPA, and an initial treatment of systemic steroid and oral itraconazole was begun. Myopathy and osteoporosis developed in the course of this treatment and steroid was discontiued with tapering. Itraconazole, too, had to be discontinued due to disturbances in liver functions. Omalizumab 225 mg treatment, once every 14 days was begun, which controlled the disease. The patient is still under this treatment.

Result: In conclusion, Omalizumab can be adviced as a treatment option in ABPA when needed.

1470
A case with esophageal achalasia misdiagnosed as asthma

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Achalasia is an esophageal motility disorder characterised by obstruction of the distal esophagus and subsequent dilation of the proximal esophagus, and is considered to be a rare disorder in children. Eleven years old girl wasadmitted to our hospital with 1 year history of dyspnea on exertion and chronic cough that worsened at night. She was treatedwith high dose inhaled corticosteroid, leukotriene inhibitor and proton pump inhibitors. She was not responsive to any of these medication. She also complained of dysphagia to solids and occasionally regurgitation of food. Her physical examination was completely normal. Her chest X-ray was olso normal except mild mediastinal enlargement. Narrowing of esophagus at the esophagogastric junction was seen in barium oesophagogram. Chest computed tomography showed an over dilated esophagus. Esophageal achalasia was also confirmed with the results of esophageal manometry and upper gastrointestinal endoscopy. She went under Heller myotomy.

This case was received with asthma medication. We suggest, achalasia should be considered differantial diagnosis of childhood asthma.

1471
Is it really asthma?

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Objective: Confirmation of the asthma diagnosis is the first step in the management of severe asthma. Four cases, referred to our clinic with diagnosis of severe asthma, however diagnosed as another disease, will be presented.

Case 1: Forty-one-year-old female was consulted with a diagnosis of severe asthma. She has been treated with high dose inhaled steroid, long acting beta-2 agonist and montelucast for 10 years. Despite treatment, in the past year, she had many emergency visits. In her spirometry, severe obstruction pattern was detected. Thoracic tomography revealed tracheal stenosis in a long segment. Bronchoscopy confirmed the stenosis. We referred the patient to thoracic surgery department.

Case 2: Thirty-one-year-old male referred to our clinic for uncontrolled asthma despite optimal asthma treatment. Tomography revealed high density endobronchial lesion in lower lobe. The patient was evaluated with bronchoscopy. In bronchoscopy we detected bone like foreign body, however could not able to remove the object because of granulation tissue. This patient was also referred to thoracic surgery department.

Case 3: Thirty-four-year-old female patient has been followed as asthma for 6 months, and referred for uncontrolled asthma. Endobronchial lesion was detected at the intermediate bronchus level in thoracic tomography. Bronchoscopic biopsy was reported as carcinoid tumor. Lobectomy was performed.

Case 4: Thirty-four-year-old female was consulted for the evaluation for anti-IgE treatment. She has been followed as asthma for 15 years. Despite high dose inhaled steroid, long acting beta-2 agonist and montelucast, patients had many emergency visits and systemic steroid use. The patient's spirometry test revealed fixed obstruction pattern. In the thoracic tomography irregularity was detected in trachea. The patient is evaluated with bronchoscopy and biopsy is reported as tracheopathia osteochondroplastica.

Conclusion: In difficult to treat asthma cases, confirmation of the diagnosis is vital.

1472
Pulmonary hamartoma as a differential diagnosis of wheezing – case report

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Background: Benign tumors affect the lungs in less then 1% of neoplasm cases. Pulmonary hamartomas represent 77% of all benign lung tumors and they are more frequent in male adults and between the 4th–6th decade of life.

Method: We report the case of a 65 year old caucasian non-atopic female who complained of daily wheezing, dyspnea and dry cough, triggered by exercise, with 7 years of evolution. The symptoms began after a respiratory infection and resolved spontaneously. Neither night-time awakenings or general symptoms were present. One year before, she started inhaled indacaterol 150 micrograms/day, prescribed by her attending physician, without relief of symptoms. Personal and family background were irrelevant.

Results: On physical examination abnormal pulmonary sounds were found (wheezing at the apex of the right lung). Laboratory tests (hemogram, hepatic, renal function and immunological study) were normal. Spirometry revealed a moderate to severe obstructive ventilatory syndrome with a negative bronchodilator test. On chest X-ray an opacity was visible in the apex of the right lung. Chest CT Scan showed an endobronchial lesion in the right main bronchus with 2 cm of diameter, accompained by atelectasis of the upper lobe. Bronchoscopy revealed an endobronchic, mobile and smooth mass with multilobulated appearance that almost occluded the entry of right main bronchus. Pathologic exam was consistent with chondroid pulmonary hamartoma with normal cytologic and microbiologic bronchoalveolar lavage. The patient underwent surgical lobectomy successfully.

Conclusion: The differential diagnosis of wheezing includes several pathologies. Asthma stands out as the most likely diagnosis in most cases, but many other diseases must always be considered, including tumors.

1473
Polymorphisms within IL-4 receptor alpha and STAT6 are associated with increased risk of asthma in a Saudi Arabian population

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Background: IL-4Rα rs1805010 and rs1801275 SNPs have been found to be significantly associated with asthma susceptibility in different ethnic groups; some STAT6 SNPs, including rs324011 and rs324015, have also been associated with asthma predisposition and/or IgE levels. Risk evaluations of IL-4Rα and STAT6 SNPs in association with asthma have never been evaluated in Saudi Arabian populations. We investigated whether IL-4Rα (rs1805010 and rs1801275) and STAT6 (rs324011 and rs324015) polymorphisms are associated with asthma in a population of asthmatic patients from Saudi Arabia.
Methods: Saudi Arabian patients with documented history of severe asthma ($n = 320$) and healthy subjects ($n = 350$) were recruited. Allelic and genotype association to asthma was assessed for IL-4Rα and STAT6 polymorphisms using nucleotide sequencing.
Results: Genotype frequencies were analyzed by testing distinct genetic models, either adjusted or not for covariate gender. The IL4Rα rs1801275 SNP A/G-G/G genotypes, but not the A/A genotype, were significantly associated with asthma predisposition (OR = 0.47; 95% CI = 0.31–0.72; $P < 0.001$*; dominant model); IL4Rα rs1805010 SNP was also significantly associated with asthma (OR = 0.62; 95% CI = 0.39–0.99; $P = 0.043$*). Similarly, for STAT6 rs324011, odds were significantly higher that homozygous T/T genotype could be associated with asthma; contrariwise, STAT6 rs324015 genotypes were not significantly associated with asthma, according to this analysis (genotype A/A: OR = 0.70, 95%CI = 0.29–1.70, *P*-value = 0.43; recessive model).
Conclusions: The minor allele, G, of IL-4Rα rs1805010 and rs1801275 SNPs, and the corresponding A/G and G/G genotypes were significantly associated with asthma predisposition in asthmatic patients from Saudi Arabia; STAT6 rs324011 T/T genotype was also significantly associated with asthma predisposition, whereas rs324015 genotypes were not.

1474
A polymorphism of IL-17A (G-197A) increases the risk of neutrophilic asthma in Ukrainian adults

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Background: IL17A is located on 6p12.1 the genomic region which has been reported to be associated with neutrophilic asthma. An association of the IL-17A (G-197A) SNP in adults with neutrophilc asthma patients is not as of yet known.
Methods: Sixty-one persistent asthma patients with neutrophilic phenotype of asthma were assessed. Inclusion criteria were $FEV_1 < 65\%$ of predicted and induced sputum neutrophil count > 75%. Diagnosis of asthma was performed according to GINA 2012 guidelines. The control group included 83 non-atopic volunteers. The single nucleotide polymorphism of the IL-17A (G-197A) was detected by PCR. The exact Fisher test was performed to determine the distribution of genotypes according to the Hardy-Weinberg equilibrium. Logistic regression was used to calculate odds ratios (OR). Patients and volunteers provided written informed consent for the genetic study.
Results: In neutrophilic asthma patients, the GG genotype was detected in 25 patients, GA in 31 and AA in 5; while in the control group GG in 20, GA in 45, and AA in 18. The allele frequencies were 66% ($n = 81$) for the G allele and 34% ($n = 41$) for the A allele in the neutrophilic asthma cases, 51% ($n = 85$) for the G allele and 49% ($n = 81$) for the A allele in the controls. The risk of neutrophilic asthma was significantly higher in patients who carry the G allele (OR = 1.883, CI = [1.161–3.053], $\chi^2 = 6.64$, $P = 0.01$).
Conclusion: IL-17A (G-197A) polymorphism is associated with adult neutrophilic asthma in the Ukrainian population. Analysis of associations with this unique polymorphism may lead to further understanding the etiology of neutrophilic asthma.

1475
Investıgatıon ORMDL3 and GSDMB gene expressions which affect childhood asthma and its fenotypical characteristics and their functional effects

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Background: Most common associated genes in the pathogenesis of asthma are GSDMB and ORMDL3 genes. In this study of childhood asthma, the relationship between exhaled breath nitric oxide (FeNO), asthma control test (ACT), asthma control level (ACL), asthma control questionary (ACQ), asthma severity (AS) and ORMDL3 and GSDMB gene expression is aimed to be investigated.
Method: In this study, 59 asthmatic and 38 control group children were diagnosed. Patients′ demografic data about asthma was learned. Eosinophil count, pulmonary function test, reversibility testing, exercise challenge test (ECT), allergy skin test results, GSDMB ORMDL3 normalised gene expression levels (ΔCq values) of cases were determined. ACT and ACQ were applied to patients and ACL, AS and FeNO levels were determined.
Results: Positive correlations between FeNO levels and ACT scores ($r = -0.538$, $P = 0.0001$) and between FeNO levels and percent change in FEV1 ($r = 0.302$, $P = 0.020$) were observed. It is determined patients with asthma have 1.83 higher fold change (FC) ORMDL3 ΔCq values. It was observed that patients with bronchial hyper-responsiveness have, at least, 14 FC higher ORMDL3 and GSDMB ΔCq values. This increase was significant in GSDMB gene ($P = 0.012$). There is a positive correlation between GSDMB ΔCq values and maximum FEV_1 change percentage ($r = 0.289$, $P = 0.046$). When FeNO levels of patients with ≤25 ppb and with >25 ppb were compared it is obseved that a borderline difference was avaliable ($P = 0.051$). The relation between ORMDL3 ΔCq values and ACT scores revealed a negative correlation ($r = 0.418$, $P = 0.003$).
Conclusion: ORMDL3 and GSDMB gene expression levels in childhood asthma could lead to the emergence of different phenotypes. Especially, significant relationships between bronchial hyper-responsiveness in FeNO levels and ACT scores have been found.

1476
The associations between CHI3L1 polymorphisms and adult asthma in Taiwan

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Background: A genome-wide association study uncovered *Chitinase 3 like 1* (*CHI3L1*) as a candidate gene for asthma susceptibility. *CHI3L1* has been shown to be associated with Western European and American populations, and with atopy in Korean populations. However, asthma-associated polymorphisms remain unknown for the Chinese Han population.
Methods: We enrolled adult asthmatic patients and 1:1 age-sex matched community-based controls in southern Taiwan and tested if *CHI3L1* polymorphisms were related to genetic risks for asthma in the Chinese Han population.
Results: Risk ratios of the *CHI3L1* rs1538372 C allele (OR = 1.27, 95% CI: 1.10–1.46) and rs10399931 G allele (OR = 1.21, 95% CI:1.05–1.40) were significantly associated with asthma in Chinese Han populations. Predictive values of forced expiratory volume in 1 s (FEV1, %) and of forced vital capacity (FVC, %) decreased in conjunction with the increase in YKL-40 levels among *CHI3L1* rs1538372 CC and rs10399931 GG carriers, respectively.
Conclusions: Our data suggest that *CHI3L1* polymorphisms (rs1538372 and rs10399931) are associated with asthma and lung function, and plasma YKL-40 levels mediate the effect of *CHI3L1* polymorphisms on asthma severity in the Chinese Han population in Taiwan.

1477
Altered patterns of CD14$^+$ monocyte differentiation and cytokine production in subject with asthma

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Background: Circulating fibrocytes are increased and transformed to myofibroblasts in severe asthma with chronic airflow obstruction and remodeling. Monocytes are the up-stream source of macrophages and fibrocytes. To find an effective and new marker for severe asthma, we investigated circulating fibrocyte and macrophage polarization and the relationship to asthma severity and control status in adult asthmatics.
Method: Adult asthma patients (n = 133) with clinical data and age-matched controls (n = 152) were included prospectively. Circulating fibrocyte and macrophage polarization-related surface markers were evaluated by flow cytometry. We also investigated macrophage polarization-related cytokine and chemokine levels in supernatant of isolated monocytes by ELISA.
Results: Percentage of circulating macrophage (defined as PM-2K$^+$ on cell surface) was lower in asthmatics with higher M1- but lower M2b-polarization that was correlated with asthma severity, control status and change of lung function. The M2b polarization marker was statistically different between groups of mild/moderate and severe/very severe asthmatic patients. Most of M1- and M2-related cytokine and chemokine expression in supernatant of isolated monocytes were lower, but TGF-b1 was higher in asthmatic patients and also correlated with the declined lung function, asthma severity and control status. The frequency of fibrocyte was higher in asthma patients and positive correlated with poor lung function, but negative correlated with percentage of circulating macrophages. The additional recombinant TGF-β1 increased fibrocyte numbers, but suppressed PM-2K$^+$ percentage in the monocyte-derived fibrocytes and macrophage culture process *in vitro*.
Conclusion: Autocrined TGF-β1 altered patterns of CD14$^+$ monocyte differentiation to fibrocyte and macrophage and could be a marker in asthma.

1478
Biomarker for eosinophil and T-cell recruitment induced by interleukin-13 as a therapeutic target for allergic asthma tested in human precision-cut lung slices

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Background: Novel therapeutic strategies are required for patients with severe asthma. On molecular level interleukin IL-4 and (IL)-13 are considered as key cytokines of airway inflammation and hyperresponsiveness in the pathogenesis of asthma. IL-13 and IL-4 as key cytokines in asthma share the same dimeric receptor complex of IL-4Rα and IL-13Rα1. Targeting the soluble IL-13 or IL-4Rα subunit can be novel anti-inflammatory therapeutics. Precision-cut lung slices (PCLS) of human lung tissue display human microanatomy and functionality of the respiratory tract and were used as a *ex vivo* tissue model for evaluation of new biopharmaceuticals.
Method: PCLS were prepared from human lungs. Cytokine release and airway hyperresponsiveness were measured after incubation of PCLS with 1–100 nM IL-13. Antagonists were assessed in presence of IL-13 for 24 h. Eotaxin-3 and TARC were measured by ELISA. PCLS containing airways were pre-incubated with IL-13. Bronchoconstriction was induced by addition of methacholine and visualized by videomicroscopy.
Results: Eotaxin-3 and TARC as biomarkers for eosinophil and T-cell recruitment were significantly elevated by human IL-13 in dose-dependent manner. Both cytokines were significantly reduced by addition of specific inhibitors acting either on the IL-13 ligand itself or the IL-4Rα chain of the IL-13/IL-4 receptor complex. Human IL-13 induced hyperreagibility resulted in decreased EC_{50} values of 47 nM compared to 180 nM of control and a 15% stronger bronchoconstriction in the presence of IL-13.
Conclusion: This study shows that PCLS can be used to mimic allergic asthma by IL-13 induced inflammation and airway hyperreagibility in human lungs. The effect of different inhibitors developed as asthma therapeutics could be compared on reduction of eotaxin-3 and TARC in human lung tissue.

Poster Session Group III – Green

TPS 69 – Novel immunological biomarkers and therapies

1479
Lipopolysaccharide induces neovascularization and immunosuppression, and may be considered as therapeutic target for anti tumor therapy

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Background: Previous studies showed that endotoxin – lipopolysaccharide (LPS) is both angiogenic and immunosuppressing, thus promoting metastatic growth (MG). However, the role of LPS as a therapeutic target is unclear. We hypothesized that anti-LPS therapy may decrease MG.
Method: Murine model including 3 groups (25 each) of adolescent mice was used. Metastatic process was modeled by i/v injection of 200 μl spontaneously metastasizing mammary adenocarcinoma cell culture suspension. Control group (CG) animals received 200 μl sterile saline intraperitoneal (i.p.), experimental group 1 (EG1) – 200 μl suspension of 10 μg LPS per mouse, experimental group 2 (EG2) – same plus 20 μg at 0.5 ml anti-LPS monoclonal antibodies. MG evaluated hystochemically within lung metastases.
Results: EG1 showed significantly higher ($P < 0.001$) MG compared with the control. MG was characterised by 61.2% higher mitotic index (MI) in the EG1 and 42.3% lower apoptotic index (AI). MI/AI ratio in the EG1 was 3.2 times higher ($P < 0.001$) than control. LPS injection resulted in reliably ($P = 0.002$) higher levels of serum VEGF than in control with strong positive correlation ($r = 0.971$) between circulating VEGF and LPS levels. Addition of anti-LPS monoclonal antibodies significantly decreased MG, MI and increased AI with respective change of MI/AI ratio. VEGF becomes insignificantly higher than in control whilst LPS concentration decreased reliably ($P = 0.014$).
Conclusion: Despite the well-established role of LPS as pro-inflammatory, pro-proliferator and pro-neovascularization factor, its role in carcinogenesis remains under evaluated. Our findings show that targeted anti-LPS therapy may impact tumor growth due to prevention of neovascularization and inflammation as well as inducing apoptosis.

1480
Clinical and immunologic efficacy of dendritic cell based immunotherapy in stage II breast cancer

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Background: Clinical and immunologic efficacy of dendritic cell (DC) based adjuvant immunotherapy was assessed in patients with Ki-67, p53 and HLA-A2 positive stage II breast cancer.
Methods: The protocol of clinical trials was approved by the Ministry of Health of the Republic of Belarus. There were 22 patients included in the trials who were treated with DC. DC were obtained from peripheral blood monocytes, primed with four p53 peptides and given by subcutaneous injection five times. Standard clinical examination of patients was done to exclude metastases. T-reg cells and antigen-specific T-cell (ASC) counts were assessed before and 6–30 months after the therapy.
Results: Safety and excellent tolerability of DC treatment was shown. In the current investigation there was an increase of ASC in 81.8 ± 8.2% of patients after the course of immunotherapy (before: 0.29 (0.07–0.5)%; after: 1.14 (0.7–1.67), $P = 0.0001$). The number of T-regs were decreased with treatment in 77.3 ± 8.9% of patients (before: 4.18 (2.67–5.99); after: 2.28 (1.85–2.97), $P = 0.0002$). After 3 years of DC-based therapy relapse-free survival was 95.4 ± 0.3% in patients treated with DC and only 75.4 + 1.5% in patients from a retrospective control group, suggesting DC efficacy in preventing metastatic breast cancer.
Conclusion: Clinical efficacy of DC based treatment of stage II breast cancer patients was shown. DC elicit the activation of anti-tumor immune response in the patients treated with dendritic cell immunotherapy.

1481
Extracellular vesicles modulate host-microbe responses by ligand-dependent inhibition of TLR2 activity

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Background: Lactic-acid-bacteria (LABs), including Bifidobacterium and Lactobacillus genera, have been proven beneficial in the maintenance of intestinal homeostasis. Ligation of Toll-like receptors (TLRs) expressed by resident dendritic cells (DC) to cell wall components expressed by LABs contributes to this mechanism of action. Extracellular vesicles (EV), important in cellular communication, originate from a broad range of cell types (including DCs) and can be found in virtually any body fluid. The reported presence of pattern-recognition receptors (including TLRs) on EVs, triggered the hypothesis that EVs can intervene with TLR activity.
Method: Heat-inactivated serum-derived EVs were collected using ExoQuick®. Intact human serum (HS), depleted serum (HS-D) and vesicle-containing pellets, reconstituted to the original volume with medium, (HS-EV) were collected. Monocyte-derived dendritic cells (moDC), THP-1 or HEK cells stably transfected with TLR2/TLR6, expressing an NFkB reporter construct were seeded in the presence of HS, HS-D or HS-EVs and stimulated with bacteria, TNFα or specific TLR2 ligands. After 16H NFkB activity (HEK-transfectants, THP-1) or cytokine release (moDC) was measured.
Results: *Bifidobacterium*, in contrast to *Lactobacillus* strains, induced TLR2 activity which was inhibited by HS or HS-EVs. EVs depletion rescued TLR2 activity. TLR2-heterodimer specific ligands showed that HS-EVs inhibition was TLR2/6 specific. Incubation of bacteria in the presence of HS and HS-EV, in contrast to medium or EV depleted serum, resulted in bacterial aggregation. Both Bifidobacteria and Lactobacilli induced dendritic cell IL-6 and TNFα release, which was either enhanced (Bifidobacteria) or reduced (Lactobacilli) upon EV depletion.

Conclusion: EVs modulated TLR2 and moDC responses strain and ligand dependently. Attachment of EVs to bacteria induced bacterial aggregation and either enhanced (Lactobacilli) or reduced (Bifidobacterium) cellular responses.

1482
Schisandrin exerts anti-inflammatory activity by inhibiting the HMGB1/TLR4 recruitment to lipid raft in RAW 264.7 macrophages

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Background: Schisandrin, an active ingredient isolated from schisandra fruits, showed anti-inflammatory and anti-asthmatic role in animal models. Molecular mechanisms of High mobility group box 1 (HMGB1) binding and signaling through toll like receptor 4 (TLR4) is critical for the host innate immune responses. The anti-inflammatory mechanism through modulating HMGB1/TLR4 signaling by schisandrin remains poorly understood.
Method: Here, we investigated the anti-inflammatory effect, and molecular mechanism of action of schisandrin in lipopolysaccharide (LPS)-stimulated murine macrophages.
Results: LPS-induced HMGB1 expression, translocation from nucleus to the cytosol and extracellular release in RAW 264.7 macrophages was suppressed by schisandrin. Schisandrin inhibited HMGB1-TLR4 binding and HBGB1-TLR4 recruitment into lipid rafts in LPS-induced macrophages. In addition, schisandrin suppressed LPS-induced NF-κB p65 nuclear expression and translocation.
Conclusion: Schisandrin attenuated inflammatory response by LPS through suppression of LPS-induced HMGB1 expression, HMGB1-TLR4 recruitment into lipid raft and HMGB1-TLR4 down signaling.

1483
Immunological follow-up patients with chronic myeloid leukemia treated by imatinib

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Background: The hallmark of CML is the t(9;22) translocation which leads to the formation of the BCR-ABL oncogene and production of a fusion protein which has a dysregulated tyrosine kinase activity. I-matinib mesylate (IM), which is an inhibitor of BCRABL-coded tyrosine kinase is the current standard therapy for patients with CML.
Method: We enrolled 71 patients in chronic phase of CML before starting any therapy and followed them for 3 years. We monitored a wide spectrum of immunological parameters including immunoglobulin levels, presence of autoantibodies, complement components, C-reactive protein, parameters of cellular immunity including Treg and intracellular cytokines induced in stimulated $CD3^+$ cells.
Results: In the course of therapy we observed a decrease of both IgG and IgM in 23/32 patients (72%). The level of C3 complement component was decreased in 17 patients (25%) and C4 in 35%. We also found ANCAb in three patients. Two of them had positive antibodies against proteinase-3 which belongs to tumor-associated antigens in CML. In one patient who was treated by nilotinib these antibodies disappeared. Subpopulations of lymphocytes were investigated in 66 patients. The most important changes concerned NK cells (CD3-CD16, 56+). Therapy led to their increase in 26% patients. We also studied the presence of Treg lymphocytes. We observed an increase of percentage of $CD25^+$ cells among the $CD4^+$ cell population from 3.82% to 6.43%. Thus far the production of intracellular cytokines in stimulated $CD3^+$ lymphocytes was investigated in 27 patients in the course of therapy. Production of IFN- gamma and IL-2 was increased in 93% (25/27) patients, TNF-alpha in all patients and IL-4 in 11% (3/27) patients.
Conclusion: It is the conviction of the authors that increasing the present knowledge of the immunological profiles of CML patients and their changes in the course of treatment is a necessary precondition for developing such a vaccine and for monitoring its efficacy.

1484
Engineering anti-allergen antibodies as candidate therapeutics for allergic disease

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Background: Allergies affect a significant proportion of the global population and allergen-specific immunotherapy (SIT) is the only non-symptomatic, disease-specific therapy available. SIT is associated with the induction of protective IgG_4 antibodies that are proposed to ameliorate the effects of allergen-specific IgE but is limited in its efficacy and safety.
Method: Advanced protein engineering approaches such as phage display, hybridoma and molecular cloning will be utilised in developing human and/or humanized allergen-specific antibodies as new treatment modalities to antagonize allergen-specific IgE.
Results: As part of our initial findings, we report the generation of murine monoclonal antibodies (mAbs) against Blo t 5 and phospholipase A_2 (PLA_2), the major allergens from the common house dust mite *Blomia tropicalis* and honeybee respectively. We define the binding epitope of the anti-Blo t 5 mAb and show that it overlaps with a previously reported conformational IgE epitope. The anti-PLA_2 mAb binds to a region of PLA_2 that constitutes part of its catalytic site. Preliminary results reveal that the anti-Blo t 5 mAb is able to antagonize the binding of allergen-specific IgE from a Singaporean cohort of Blo t 5-sensitised patients, suggesting that it is a good candidate for further engineering as a potential antagonist for Blo t 5/IgE associated allergy.
Conclusion: Future work encompasses the construction of a human immune library from which fully human anti-allergen antibodies will be obtained. Molecular cloning techniques will also be utilised to modify the Fc regions of the murine mAbs to specific human IgG subclasses (including IgG4) to address the clinical utility of employing antagonistic IgGs as therapy for IgE-linked hypersensitivity in both murine models and human patients (based on non-invasive allergen skin tests). These data will help to resolve the role of IgG subclasses in the regulation of IgE-mediated allergy and may lead to the production of candidate therapeutics for a common human disease where there remains an urgent unmet clinical need.

1485
Can225IgG, the first 'caninised' antibody against EGFR is highly effective in mediating tumor cell growth inhibition and phagocytosis *in vitro*

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Background: Dogs *(Canis lupus familiaris)* have become frequently studied in oncology and immunology, because of the remarkable similar immune system to humans. Epidermal growth factor receptor (EGFR)-overexpression is frequently observed in solid tumors in both species, e.g. in mammary carcinoma. Moreover, recent studies of our group revealed high amino acid identity of the receptors along with shared biological functions. Although targeting of EGFR with the monoclonal antibody Cetuximab (225) is exceptionally successful in human medicine, passive immunotherapy has not been established in veterinary oncology yet; we thus aimed to generate a recombinant canine anti-EGFR IgG (can225IgG) antibody.
Method: CHO-DUKX-B11 cells were employed for expression of can225IgG, which was purified using Protein G affinity chromatography. The antibody was produced under serum-free conditions to facilitate future *in vivo* studies.
Results: Biochemical integrity and correct folding of the newly generated antibody was assessed by circular dichroism (CD) analysis and immunoblot. Specificity of can225IgG towards canine EGFR was tested on canine mammary carcinoma cell lines. Subsequently, its growth inhibitory function was investigated, showing very promising, highly significant results. Moreover, immune-mediated tumor cell killing by peripheral blood mononuclear cells in presence of the can225IgG was assessed by a 3-color flow cytometric assay, resulting in significant mediation of phagocytosis of tumor cells.
Conclusion: We report the successful generation of the first recombinant canine anti-cancer antibody with the perspective of a follow-up study in patients with spontaneous malignancies. Furthermore, this study highlights the importance of comparative medicine in order to promote better-suited model organisms for therapeutic drug studies, speeding up clinical trials for the benefit of both human and veterinary patients.

1486
Successful rapid desensitisation to imiglucerase in an adult patient with Gaucher disease and documented IgE-mediated hypersensitivity

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Background: Gaucher disease (GD) is a lysosomal disease. Type I GD is the most common with world-wide prevalence 1/50 000–100 000. We report the case of a 22-yr-old ♀ diagnosed with type I GD at the age of 3, who was referred to our Allergy Unit due to adverse reactions during the infusion of imiglucerase (IMG), the standard of care enzyme replacement therapy for this disease. Anaphylactic/anaphylactoid reactions to IMG have only been reported in three patients. Our patient, pretreated with intravenous (iv) dimetindene, developed pruritus, periorbital angioedema and flushing 10 min after the beginning of IMG infusion (70 ml/h). She had experienced four similar acute infusion reactions to IMG in the past after receiving 30 U/kg/2 weeks for 2.5 years (since the age of 16). Therapy was changed to miglustat for 3 years, but resulted in deterioration of disease parameters. Therefore, the haematologists decided to reinitiate IMG (30 U/kg, 70 ml/h) and the above-described reaction took place.
Methods: Following the drug allergy history record, skin prick test with the reconstituted IMG 200 U/5 ml was negative. Intradermal tests using 1:1000, 1:100 and 1:10 dilutions resulted in erythema, positive 8 mm wheal and positive 16 mm wheal respectively. A rapid desensitisation (RD) protocol for the administration of 1500 U (30 U/kg) IMG was prepared based on a standardised RD protocol already used for other biologicals and chemotherapeutics. Three solutions (each 250 ml in normal saline) were delivered in 12 consecutive steps, each step increasing the rate of administration by 2- to 2.5-fold. Solution 1 was a 100-fold dilution of the final target concentration (steps 1–4), solution 2 a 10-fold dilution of the final target concentration (steps 5–8) and the concentration of solution 3 was calculated by subtracting the cumulative dose administered in steps 1–8 from the total target dose (steps 9–12). Steps 1–11 each took 15 min and step 12 was prolonged to complete the target dose. The patient was premedicated with dimetidine before RD initiation.
Results: The full therapeutic dose was successfully administered in <6 h. Using the same protocol, the patient has been receiving IMG, 1500 U/2 weeks, for the last 2 months.
Conclusion: To our knowledge, this is the first report of successful RD to IMG in an adult patient with GD type I and documented IgE-mediated hypersensitivity to IMG. We additionally demonstrated the safety and efficacy of a well standardised RD protocol in IMG administration.

1487
Active desensitisation of allergic effector cells by disruptive IgE inhibitors

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Background: Immunoglobulin E (IgE) binds with remarkably high affinity to its primary receptor FcεRI on allergic effector cells such as basophils and mast cells. This interaction is critical for the induction of allergic hypersensitivity reactions since it primes the cells to immediately respond to allergen challenge. Due to the exceptionally slow dissociation rate of IgE:FcεRI complexes mast cells and basophils permanently display allergen-specific IgE on their surface. We have previously described a novel molecular mechanism to actively induce the dissociation of IgE from FcεRI. Here we assessed whether this mechanism may be used to remove IgE from allergic effector cells and determined the disruptive potential of different IgE inhibitors.
Method: IgE:FcεRI complex dissociation was investigated on a molecular level using recombinant proteins *in vitro*, on a cellular level using primary human basophils *ex vivo* and on a systemic level performing a passive cutaneous anaphylaxis assay *in vivo* using human FcεRI transgenic mice.
Results: We show that the non-immunoglobulin based macromolecular IgE inhibitor DARPin E2_79 induces removal of IgE from primary human basophils and thus

fully prevents IgE-dependent cell activation as well as release of pro-inflammatory mediators *ex vivo*. Furthermore, we report that the therapeutic anti-IgE antibody Omalizumab also accelerates the dissociation of IgE from FcεRI albeit much less efficiently than E2_79. Using a novel biparatopic IgE targeting approach we further improved the disruptive potency of E2_79 by ~100 fold and show that disruptive IgE inhibitors efficiently prevent passive cutaneous anaphylaxis in mice.

Conclusion: Our data not only sets the stage for the development of a novel class of allergy therapeutics but also provides unanticipated insights in the mechanism of action for the therapeutic antibody Omalizumab. Moreover, the possibility to strip and resensitise primary basophils under physiologic conditions allows the establishment of new cellular diagnostic allergy tests. In summary, these findings highlight the potential of such novel IgE inhibitors as important diagnostic and therapeutic tools to managing allergic diseases.

1488
Discovering the effects of omega-6 fatty acids on allergy using a HEK-Blue cell line

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Background: In recent times, allergy has become a financial, physical and psychological burden to the society as a whole. Allergic reactions can result in life-threatening situations causing morbidity and high economic cost. Therefore, more effective reagents are needed for allergy treatment. Omega-6 fatty acids have gained attention in allergic studies mainly due to their inflammatory properties. Literature suggests that a causal relationship exists between the intake of omega-6 fatty acids such as DPA and AA and atopic individuals suffering from allergies. In an allergic cascade, cytokines IL-4 and IL-13 bind to IL-4 receptor (IL-4R), which activates the STAT6 phosphorylation pathway leading to gene activation of allergen-specific IgE production by B cells. Consequently, IgE production leads to clinical symptoms of allergy. The overall aim of this study is to characterise DPA and AA and their effects on IgE production.

Method: DPA and AA were tested *in vitro* with a HEK-Blue IL-4/IL-13 reporter cell line model, transfected with a reporter gene that produces an enzyme, secreted embryonic alkaline phosphatase (SEAP). SEAP acts as a substitute to IgE when cells are stimulated with bioactive cytokines IL-4 and IL-13. Qunati-Blue, a substrate, breaks down in the presence of SEAP, producing blue coloration. The blue color is detected using a spectrophotometer.

Results: We have successfully used DPA and AA in our studies that demonstrated a decrease of SEAP secretion by HEK-Blue cells when treated with DPA as opposed to an increase in SEAP secretion with AA treatment. The SEAP reaction with Quanti-Blue was read using a colorimetric analysis. A statistical Student's *t*-test revealed the significance of the results, confirming our initial hypothesis.

Conclusion: We have successfully identified and characterised DPA and AA in our allergy model with varying potentials. While AA was a potent stimulator, DPA revealed to be a promising candidate as a potential inhibitor of IL-4R signalling, which regulates the STAT6 induced pathway in allergic cascades *in vitro*. Since IL-4 and IL-13 signalling is a common pathway for many allergies, a prophylactic treatment can be devised based on these findings.

Poster Session Group III – Green

TPS 70 – Pediatric allergy II

1489
Is fraction of exhaled nitric oxide (FeNO) able to predict severity of allergic reaction at an open cooked egg challenge?

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Background: A recent study published by our group(1) has demonstrated the ability of fraction of exhaled nitric oxide (FeNO) to predict severity of clinical reaction at an open peanut food challenge. FeNO is a non-invasive tool correlating to allergic airways inflammation and has been independently associated with increased food specific IgE. Our objective was to explore the utility of FeNO as a predictor of severity of clinical reaction at an open cooked egg food challenge in egg allergic children.
Method: We recruited 47 participants from a cohort of consecutive children aged more than 5 years scheduled for an open labeled cooked egg food challenge (OFC) by their Paediatric Allergist. Participants underwent skin prick test (SPT) measurement for sensitisation to egg white and egg yolk and serum was collected for specific IgE to egg white, egg yolk and ovomucoid. FeNO was also measured in all cooperative children before the challenge. OFC and assessment of reaction was undertaken by clinicians blinded to the test. All patients at time of the open challenge were able to consume baked egg products.
Results: Eighty five percentage of children passed the cooked egg challenge. Out of seven participants that reacted during OFC, only 1 had high FeNO (>45 ppb). There was no significant difference in FeNO levels between the children with clinical allergy vs tolerant children. Two patients had a positive challenge at serum egg white level < 0.6 kU/l. Anaphylaxis was reported in 2 patients at serum ovomucoid level as low as 0.14 and 0.17 kU/l. There was no relation between the skin prick test results and the outcome of OFC.
Conclusion: The majority of children outgrow their egg allergy, especially those who are able to consume baked egg products. FeNO has no role in predicting type of reaction to oral cooked egg challenge in patients with egg allergy. Specific IgE to egg white may not always be predictive of tolerance to cooked egg.
Reference: (1) K. Preece *et al*., J. Clin Exp Allergy. 2013 December 17

1490
Pediatric anaphylaxis cases between 2009–2013 in Estonia: a single-centre experience

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Background: Anaphylaxis is a life-threatening allergic reaction that usually occurs after a contact with an allergen and in children food is the most common trigger. The diagnosis is based on clinical criteria and laboratory tests play a minimal supportive role. Epinephrine is the inital treatment of choice for controlling symptoms and decreasing fatalities.

Our aim was to examine the diagnosing and management of anaphylaxis among pediatric patients receiving care in tertiary pediatric hospital in Estonia.
Method: We retrospectively reviewed all consulted and admitted cases of anaphylaxis (ICD 10 code T78.0-T78.2) in Children′ s Clinic of Tartu University Hospital in 2009–2013. Data extracted included demographic data, symptoms, potential triggers, concomitant atopic disease, laboratory and skin prick tests, medications administered and further management.
Results: We identified 63 patients consulted/admitted for anaphylaxis [mean (SD) age, 7.7 (5.8) years; 60% male] 0.17% of patients were hospitalised, one patient was treated in ICU.

A total of 89% reported symptoms of the skin/mucosa, 83% had respiratory and 24% gastrointestinal symptoms, 6% had documented hypotension. Sixty-eight percent of the patients had anaphylaxis to food, 22% to stings, 5% to medications and 8% to unknown allergens. Most common triggers were fish and seafood, nuts, milk and fruits (kiwi, apple).

The 71% of patients had concomitant atopic disease and 91% were sensitised to some allergens. Serum total tryptase level was measured in 10 and it was elevated in two cases. 16% of patients had epinephrine administered during anaphylaxis episode. Other medications used were systemic antihistamines 89%, corticosteroids 71% and nebulized bronchodilatators 11%.

Altogether 98% of patients were consulted with an allergologist for anaphylaxis education, two patients were assigned immunotherapy and 60% were prescribed an epinephrine auto-injector.
Conclusion: Initial signs in children with anaphylaxis are mostly mucocutaneous and respiratory symptoms. Food is the main trigger of anaphylaxis. Although almoust all patients were consulted by allergologist, the use and prescriptions of epinephrine was unexpectedly low.

1491
Bronchiolitis in early infancy: intrinsic determinants for recurrent episodes

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Background: Bronchiolitis in early life caused by respiratory virus is a very frequent diagnosis, mostly due to respiratory syncytial virus but also other respiratory tract viruses like rhinovirus or adenovirus. Most of the children with bronchiolitis are treated in outpatient care, but some develop severe respiratory symptoms requiring hospitalisation. The intrinsic or extrinsic factors that determine a severe bronchiolitis as well as the determinants that contribute to an augmented risk for subsequent episodes of bronchiolitis remain not completely understood. The aim of this study was to analyze the relationship of intrinsic factors like gender, age, race, weight at birth, prematurity and parental atopy with recurrence of bronchiolitis in children under 6 months old after a first episode of bronchiolitis with hospitalisation.
Method: We selected the clinical processes of 79 children (F = 45; M = 34) hospitalised

with the first episode of bronchiolitis during winter seasons of 2011 and 2012 and followed these children for 12 months. The children were retrospectively monitored for respiratory symptoms through the analysis of the follow-up medical appointments, visits to the emergency service, and by interviews to the parents. We used a Multiple Regression Model to analyze the association between variables in study.

Results: There were no significant correlations between gender, age, race, weight at birth and prematurity with recurrence of bronchiolitis during the following 12 months after the first episode of bronchiolitis. Children with parental atopy had more recurrent episodes of bronchiolitis (63%) than children without parental atopy (33%).

Conclusion: Parental atopy was the only factor associated with recurrent episodes of bronchiolitis ($P < 0.01$).

1492
Allergic diseases and impact of ecological-climatic changes on children's population

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Background: It is well known that allergy and allergic diseases comprise a global problem caused by climatic changes. Ongoing climate changes are not only environmental but also significant social and economic issue.

Goal: Goal of our research is study of prevalence of allergic diseases among children's population against the background of climatic changes.

Materials and methods: Study of allergic diseases was conducted by stages: first stage was screening via questionnaire, common diagnostic criteria of the nosologies subject to study and map of research of prevalence of allergic diseases. Study included 2069 children from 3 to 15 years old (1256 girls and 813 boys) from Tbilisi, Kuraisi and Batumi Region (2012–2013). Study population was categorized into III age groups. Program processing was provided randomly, by means of SPSS/v12 techniques.

Research results: Retrospective analysis of visits due to allergic diseases revealed the trend of growth of allergic diseases conditioned by seasonality and climatic changes. Allergic rhinitis was indicated in 16.9% ($P < 0.05$) population, bronchial asthma 5.8% ($P < 0.05$), atopic dermatitis – 2.5% ($P < 0.05$), among them, number of boys was greater than number of girls ($P < 0.05$). It was established that atmosphere pollution ($P < 0.01$) significantly impacts formation of the allergy.

Conclusion: Population study revealed the risk factors of allergic diseases' development, frequent respiratory infections, drug-induced sensibilization, heritage load, food allergens, sex ($P < 0.001$). Difference factor identified through comparison of the research findings and statistical data will improve accuracy of diagnostics of the allergic diseases ($P < 0.01$).

1493
Soy allergy associated to IgE mediated cow's milk proteins allergy

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Background: Allergy to cow's milk protein (CMPA) is the best-known food allergy in young children. We distinguish IgE-mediated forms with immediate reactions and no IgE-mediated forms also called cell mediated forms with delayed manifestations. CMPA incidence varies from 0.3 to 7.5. Soy allergy association is found in 10–47% of children with IgE-mediated CMPA in literature the aim of this study is to determine the frequency of soy allergy in infants with CMPA.

Method: This study included 66 children with IgE-mediated, CMPA; Determination of both specific IgE anti-soy (soy allergy) and IgE anti- cow′s milk proteins was done by Immunoblot technique measurement, a semi-quantitative method (Germany).

Results: Our results show that 21% (14/66) of children had specific IgE anti-soy and soy's milk prick tests positive. Soy allergy was confirmed in 18% (12/66) after a positive oral challenge test. It is significantly more common in the first trimester of life. The clinical manifestations were similar in allergic and non-allergic to soy group, dominated by the skin and gastrointestinal symptoms. Eosinophilic esophagitis are the most frequently events observed in children with CMPA and soy allergy in children with CMPA and not allergic to soy (33% vs 2% $P = 0.003$) as well as atopic dermatitis (42% vs 2%, $P < 0.0001$).

Conclusion: Soy-allergy in children with CMPA is not uncommon, hence the importance of the determination of serum IgE anti-soy in patients with IgE-mediated CMPA, because of the frequent use of soy's preparations in the care of children with CMPA.

1494
Patterns and prevalence of sensitisation in a pediatric patients sample (age 0–10 years) with a positive medical history of atopy

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Background: It is commonly accepted that sensitisation to food and inhalant allergens is relatively high in infancy and early childhood and is the main cause of respiratory, skin and gastrointestinal symptoms over that life period. That and the recently rejected concept of age limitation to *in vivo* and *in vitro* testing are the two principle arguments for the assumption of sensitisation presence in infants and children just on the ground of positive medical history and objective findings. Antihistamine treatment is started and patients are put on protein elimination diet without any further allergy diagnostics. The objective of that study is to assess prevalence and patterns of sensitisation to environmental and food allergens in pediatric patients with positive medical history for atopy.

Method: Seventy patients age 0–10 years who were referred to the outpatient allergy department of a major private hospital in Sofia were included. All participants had a positive medical history with/without objective findings for at least one of the following: stuffed nose, post nasal drip, cough, wheezing, frequent upper respiratory infections, skin rash at typical places and gastrointestinal symptom with/without food consumption. The patients were tested for sensitisation by detecting specific IgE to 28 inhalant and food allergens (Atopy pediatric panel, Euroline system, EUROIMMUN AG, Luebeck, Germany).

Results: In 32.9% of the patients specific IgE levels were not elevated, using cut-off point of < 0.35 kU/l. 20.0% were sensitised to two allergens, 18.6% – to one and 14.3% – to three allergens. In 27.1% of the patients specific IgE levels were < 0.70 kU/l – class 1 (EAST classes scale) and in 40% – ≥70 kU/l (≥2 EAST class).

Conclusion: Sensitisation prevalence in the sample pediatric group is not different from that in general population. If IgE

levels ≥2 class are considered significantly elevated, clinical symptoms of atopy are probable only in 40% of the sample.

1495
Results of tretament of XOLAIR® (omalizumab) associated with oral immunotherapy of cow's milk in anfilactic patient

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Background: To establish the oral immunotherapy (OIT) associated with omalizumab as an effective alternative in persistent allergic to cow's milk protein (CMP) mediated by immunoglobulin E (IgE) in anaphylactic patients
Method: We conducted a pilot study with five patients (5–16 years) allergic to CMP administering omalizumab 2 months before the start of ITO and 6 months later. They were premedicated with cetirizine.
Results: Table 1 SPT_1: skin prick tets before ITO, SPT_2: skin prick tets after de ITO, CM: cow's milk, SM: sheep's milk, GM: goat's milk, ALA: alfa-lactoalbumin, BLG: beta-lactoglobulin, BA: bronchial asthma, AD: atopic dermatitis, RC: rhinoconjunctivitis, DS: digestive symptoms, EA: egg allergy, NA: nut allergy, LA: legumes allergy, A: anaphylaxis, AE: Angioedema.
Conclusion: Omalizumab in combination with ITO turned out to be an effective and safe therapy in order to obtain a cow's milk protein tolerance in five patients suffering severe milk anaphylaxis. This therapy improve the tolerance to CMP and decrease the risk of anaphylaxis during desensitation. Omalizumab was suspended without relapses in patients who continue to make a diet free of cow's milk. Further studies are necessary to achieve the future role of anti-IgE monoclonal antibodies in the treatment of severe persistent milk allergy.

1496
Prevalence of allergic symptoms in infants hospitalised for bronchiolitis in Reunion Island

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Background: Allergic phenotype is poorly defined in early life as it is thought to constitute the later phases of the atopic march. We aimed to study the allergic symptoms in infants admitted to Paediatric Emergency Department for bronchiolitis.
Method: We review clinical history of 82 infants (median age 12 m, range 3–15 m) hospitalised for bronchiolitis during the period January 2005–December 2010.

Demographic and clinical data were obtained from patient's medical files. Parents answered a structured questionnaire. Skin prick test (SPT) to a panel of relevant aeroallergens and food allergens was performed. We also examined total Eosinophil count and serum IgE levels.
Results: The main allergic symptoms were rhinitis 64%, bronchial asthma 43%, dermatitis 17%, and food allergy 6%. SPT for one or more allergens was positive in 84% infants. The percentage of infants with eosinophil > 400 cells/μl and IgE levels > 30 IU/ml was significantly higher in infants presented more than three episodes of wheezing after hospitalisation.
Conclusion: Preliminary questionnaire based results may indicate higher prevalence of allergic diseases in infants hospitalised for bronchiolitis. Eosinophil and IgE levels are a marker for atopy related phenotype in this age group.

1497
Epidemiological study in child population of the central area of Spain

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Background: The increased prevalence of allergic diseases in children has led us to initiate an investigation on the influence of perinatal, environmental and genetic factors that may predispose to respiratory and food allergy in children.
Method: We have done a prospective clinical study of all pediatric age children (0–14 years) with a history of atopy who visited our clinic for a period of 3 months.

Risk data such as personal (perinatal, breastfeeding, bronchiolitis) and family history (parents and siblings with atopy) were assessed, as well as environmental exposure (pets at home, smoker parents) and personal history of atopy (sensitisations, diagnosis, disease onset).
Results: Two hundred and forty children were recruited with a mean age of 8.3 years; 142 (59.2%) were male.

Skin prick test were performed in all patients according to their clinical history.

One hundred and ninty-five (81.3%) suffered from respiratory tract pathology, 67 (27.9%) had food allergy, 32 (13.3%) atopic dermatitis and 4 (1.7%) a history of drug allergy.

Sensitisation to egg and milk were asociated with asthma (*P*: 0.007 and *P*: 0.003).

The occurrence of bronchiolitis in the first year of life is associated with later development of asthma and atopic dermatitis with the development of rhinoconjunctivitis and food allergy (*P*:0.001).

Food allergy is associated with asthma and rhinconjunctivitis (*P*: 0.001).

There seems to be a higher incidence of rhinoconjunctivitis, asthma and food allergy in the first child as compared with the next siblings (*P*: 0.006).
Conclusion: We conclude that pollens are the predominant allergen in respiratory disease in our pediatric population, according to the climatic conditions of our region, but sensitisation to pet danders and Alternaria were not infrequent. Bronquiolitis, atopic dermatitis and egg or milk allergy were associated with respiratory allergy. These data with the fact that the first sibling showed more allergic diseases would be in agreement with the atopic march and the hygiene theory.

Table 1

Pacients	1	2	3	4	5
Background	BA	NONE	BA, AD, EA, NA, LA	RC, BA	AD, EA
SPT 1/SPT2/Symptoms (Transgressions)	A	A	AE, BA	RC, BA	D, BA
SPT 1/SPT2/Specific IG e(U/ml) (Casein)	6/0/35.1	9/0/67.7	5/0/>100	7/1/40.6	0/0/28.6
SPT 1/SPT2/Specific IG e(U/ml) (ALA)	11/3/35.5	15/0/2.96	9/0/21.9	0/0/0	8/0/12.7
SPT 1/SPT2/Specific IG e(U/ml) (BLG)	9/0/41.5	10/0/3.44	9/0/29.5	0/0/0	103/19.2
SPT 1/SPT2/Specific IG e(U/ml) (CM)	5/0/>100	10/0/55.6	5/0/74.8	7/0/34.8	9/0/67.8
SPT 1/SPT2/Specific IG e(U/ml) (GM)	3/4/>100	5/0/>100	5/2/>100	3/0/72	7/0/55.1
SPT 1/SPT2/Specific IG e(U/ml) (SM)	3/0/>100	5/0/>100	4/2/>100	5/0/65	9/0/5.9
Total IG E (UI/ml)	275.1	339.4	685.5	407	135

	Grasses and olive pollen	Other pollens	Animal dander	Alternaria	Mites	Milk proteins	Egg proteins	LTP	Profilin
Patients	156	110	46	41	12	28	27	23	9

[Sensitizations (prick test)].

1498
The prevalence of aeroallergen-sensitisation in habitual snoring children with adenoidal or adenotonsillar hypertrophy in HRH Princess Maha Chakri Sirindhorn Medical Center, Thailand: a prospective study

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Background: Habitual snoring (HS) is known as an important manifestation of sleep-disordered breathing in children. There have been many risk factors of HS reported, including adenoidal hypertrophy (AH) or adenotonsillar hypertrophy (ATH), obesity, allergy, and exposure to tobacco smoke. Chronic inflammation of adenoid glands and/or tonsils can cause hypertrophy of these lymphoid organs, and little evidences also showed the relationship between allergy and AH or ATH causes HS in pediatric patients. The aim of this study was to investigate the correlation between aeroallergen-sensitisation in HS children with AH or ATH.
Method: Thai children 1–15 years of age who had the symptom of HS with AH or ATH were performed lateral nasopharynx radiograph and investigated for skin prick test (SPT) with common 12 aeroallergens during 6 months of study.
Results: Twenty-six children (69.2% Male) with HS and AH or ATH were prospectively recruited and the median age was 7 years (ranged 1.5–11.0). There was 57.7% of HS children with AH or ATH had both family history of parental atopy and allergic rhinitis (AR). Positive SPT was found in 50% of patients, in which 69.2% of them had multiple aeroallergen-sensitisations and 30.8% of them had no AR. House dust mites was found to be the most common aeroallergen sensitisation, 30.8%, whereas the others, American and German cockroach, Bermuda, Alternaria and Aspergillus, were found positive 23.1%, 19.2%, 11.5%, 7.7% and 3.8%, respectively. There was no significant different in aeroallergen-sensitisation among children who had HS and AH or ATH with or without AR.
Conclusion: Allergy and aeroallergen-sensitisation to common aeroallergens can be found in HS children with AH or ATH and might be the important risk factor related to the symptom of HS and AH. Control of aeroallergen exposure may have a role in the prevention or reducing the symptom of HS according to AH and ATH.

1499
Role of total serum IgE in paediatric allergy

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Background: IgE elevation, in spite of some well-known limitations, is frequently included as a diagnostic criterion for allergic diseases.
Aim of the study: Set up the best possible total Ige values to discriminate between non allergic or allergic patients (pz), monosensitised (MS) and polysensitised (PS) pz.
Methods: The 760 pz of which 122 with respiratory diseases, 127 with food sensibility and 229 with both, stratified into MS (186 pz) and PS (304 pz). Descriptive statistics were calculated and reported as medians (md) and interquartile range. Comparison of total IgE was performed by the non-parametric Mann–Whitney *U*-test. A $P \leq 0.05$ was considered as statistically significant. Receiving operating curve (ROC) was built in order to find the optimal thresholds for total IgE that discriminate between positive and negative ImmunoCap (IC) and between MS and PS pz.
Results: Discrimination between positive and negative IC results, the ROC analysis provided a value of total IgE equal to 73.4 as the optimal threshold, with a sensitivity of 84.02 and a specificity of 73.9. The AUC was 0.846 and the curve significance was $P < 0.0001$. Between MS and PS pz the ROC analysis provided a value of total IgE equal to 166 as the optimal threshold, the AUC was 0.653 and the curve significance was $P < 0.000$. Median values (interquantile range) for total IgE were: 236 (102.5, 614.5) for positive IC, 34.6 (12.05, 81.35) for negative IC; 149.5 (64.6, 372) for MS pz and 320 (132.25, 728.75) for PS pz. The Mann–Whitney test showed significant difference between positive and negative IC results ($P < 0.0001$) and between MS and PS pz ($P < 0.0001$).
Conclusions: Our results show that it is possible to get a discrimination between atopic and non atopic pz devoid of age but also between MS and PS. May be the current cut-off by age has to be correted: this results requires further confirmation in larger cohorts to study the correlation between IgE levels, clinical severity and ethnic differences.

1500
Prospective study of the incidence of anaphylaxis in Irish children

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Background: Anaphylaxis in the community is most frequent in children but it is often under-recognised and undertreated.
Aim: To determine if the diagnosis and treatment of anaphylaxis in Ireland are satisfactory.
Method: A IPSU monthly multi-study report card is sent to every paediatrician. Anaphylaxis is included in this card from September 2013 to March 2015. Data are gathered using EAACI's Anaphylaxis Registry Form.
Results: Twenty-seven cases to date, with data available for 24. There were 18 (75%) boys and 17 (70.8%) new patients in this group. Most reports (70%) came from Cork University Hospital, the National Referral Centre. One fatal anaphylaxis occurred, due to peanut. Food was the implicated allergen in 16/24 cases (66%), with peanut and cashew being the most frequent foods involved, followed by unidentified trigger (21%). FDEIA, insect sting and inhalant allergens caused 1 case each. Skin and airway symptoms predominated (92%), with cardio-vascular (54%) and gastro-intestinal symptoms (54%) also frequent. Only 75% (18/24) of cases presented to hospital either directly (58%) or referred by a General Practitioner (17%). Adrenaline i.m. was given in 14/24 cases (58.33%). Adrenaline was self/parent-injected in 3 cases (21%), by a GP in 5 (36%), after arrival in hospital in 5 (36%) and by Paramedics in 1 case. Only 2/5 known patients (40%), having prescribed Adrenaline Auto injectors, used them.
Conclusion: These data show reasonable awareness of anaphylaxis among paediatricians, emergency physicians and GPs in Cork, but not yet in other regions. A quarter of cases were not referred directly to

hospital. The rate of Adrenaline use reflects other studies and like other countries have found, Adrenaline usage clearly needs to improve in Ireland.

1501
Is there a relationship between inhalant allergies and nocturnal enuresis (NE)?

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Background: Nocturnal enuresis (nighttime urinary incontinency) and allergy are the commonest chronic disorders of the childhood. Previous studies have linked NE to upper air obstruction.

The aim of this study was to investigate whether there is a relationship between NE and aeroallergen sensitisation.

Method: Eighty one children with monosymptomatic enuresis and 25 healthy children, aged between 7–14, were included in the study. In addition to clinical examination, skin prick tests with common inhalant allergens were performed.

Results: There was a statistically significant difference between the enuretic group and the control group in terms of house dust mite sensitisation ($P < 0.05$). *D. pteronyssinus* yielded the highest prevalence (40.7%), followed by *D. farina* (34.6%), and grass pollen (25.9%). There was no statistically significant difference for upper airway obstruction between the two groups.

Conclusion: We suggest that inhalant allergy might play a role in the pathogenesis of NE and it should be considered in the clinical assessment of enuretic children. Further studies are needed and an in depth look into the immunological changes associated with these conditions is warranted.

1502
The distribution pattern of total/specific IgE levels for children and adolescents in Korea

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Background: Childhood allergies are serious problems because they may lead life time chronic disease. Determination of total and specific IgE is known as a diagnostic tool for allergic sensitisation; however, it is affected not only by allergic diseases but also by various factors such as age, gender, ethnicity. Thus, we studied the distribution of total IgE and specific serum IgE levels to 7 inhalant allergens in children/adolescents aged 2–18 by various factors in Seoul, Korea

Method: Total/specific serum IgE determination for seven common allergens were performed on 1352 children aged 2–18 in Seoul Korea. Demographic characteristics were surveyed from parents or participants by modified International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire. Diagnosis of allergic diseases was based on questionnaire.

Results: The geometric mean of total IgE was 86.02 ± 3.83 kU/l in age 2–18. It was higher in boys (boys, 99.14 ± 3.65 kU/l; girls, 76.91 ± 3.93 kU/l, $P < 0.001$) and in atopic subjects (atopic, 170.49 ± 3.11 kU/l; non-atopic, 39.85 ± 3.08 kU/l, $P < 0.001$). High monthly household income and high BMI level bore the increment of both atopy prevalence and total IgE level. The most prevalent allergic diseases was allergic rhinitis (30.8%) followed by atopic dermatitis (28.8%) and asthma (6.3%) respectively.

Conclusion: Total and specific IgE levels showed various range with age in children. It was also shown that gender, household income, BMI and atopic sensitisation may affect total IgE levels. The relationship between total/specific IgE and allergic diseases was positive. This study might help to establish reference values for age 2–18 to diagnose atopy and allergic diseases.

1504
Clinical relevance of inhalant and food allergens sensitisation in a pediatric patient sample(age 0–10 years) with medical history suggestive of atopy

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Background: Elevated IgE levels do not always correlate with clinical symptoms. Combined with symptoms and medical history they are a powerful instrument for defining allergic diseases in pediatric patients considered atopic without any allergy diagnostics. The objective of the study is to assess clinical relevance of allergens sensitisation in a pediatric patients sample.

Method: Seventy patients age 0–10 years, referred to the outpatient allergy department of a major private hospital in Sofia were included. All participants had a positive medical history for skin, respiratory and gastrointestinal complaints. Specific IgE levels to inhalant and food allergens were assessed(Euroline system, EUROIMMUN AG, Luebeck, Germany). The clinical relevance of each of the positively tested allergens was assessed according to patient history and two distinct categories – no clinical relevance and clinical relevance were defined. Relevant is a sensitisation causal to the symptoms. No relevance was stated in the opposite case.

Results: Clinically relevant sensitisation is present in 35.7% of the patients and in 27.1% the detected sensitisation is not clinically relevant. If patients with IgE levels ≥2 EAST class are considered then the proportion of clinically relevant sensitisation is 28.6%. In the subgroup of patients with respiratory symptoms clinically significant sensitisation is found in 44.4%. In 51.9% of the patients with skin itchy rash at typical places clinically significant sensitisation is found. IgE levels in both subgroups are ≥2 EAST class. In patients with gastrointestinal problems no clinically significant sensitisation is detected.

Conclusion: Our data confirm the importance of IgE level assessment in infants and children with respiratory, skin and gastrointestinal problems suggestive of atopy before the final diagnosis, treatment and dietary regime are settled.Nearly half of the patients with skin and respiratory symptoms show clinically relevant sensitisation.

Poster Session Group III – Green

TPS 71 – Pediatric cutaneous and drug allergy/epidemiology

1505
Basophil activation test is useful in diagnosing allergy to beta-lactams in children

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Background: Testing allergy to beta-lactams (BL) in children might be difficult also because of unwillingness of small children to compy with *in vivo* testing protocols. We examined a role of additional *in vitro* diagnostic tool – basophil activation testing (BAT) in diagnosing suspected BL allergy in children.
Method: We investigated 51 children (31 girls and 20 boys, aged 1–17 years) with allergy to BL [23 fenoximethilpenicilin (PENV), 23 amoxicillin (AX) or amoxicillin with clavulanic acid (AX-cl), three both PENV and AX-cl and two ceftriaxon (CEF)]. In 29 children clinical history was suggesting immediate reactions to BL. Diagnostic procedure included detailed history, skin testing, specific IgE antibodies to BL, basophil activation tests (BAT) with culprit BL and provocation testing. BAT was considered positive when stimulation index was >2. BAT with BL was made also in controls with proved clinical tolerance.
Results: Allergy to BL was confirmed in 8 children with drug provocation testing (immediate 5, non-immediate 3), in 31 children with skin testing (immediate 27, non-immediate 4), in 8 children skin test to BL was suspected immediately positive and 4 children had strong clinical history of immediate reaction. Specific IgEs to BL were positive in two children who also had positive skin tests. During skin testing four children developed systemic allergic reactions.4 (50%) children with positive BL provocation testing results, 15 children (48%) with BL allergy proved by skin testing, 4 (100%) children with strong clinical history of reaction and 7 (88%) children with suspected positive skin tests had positive BAT to culprit BL. All controls with clinical tolerance to BL had negative BAT results.
Conclusion: BAT to BL such as PENV, AX, AX-cl and CEF showed a high positive predictive value, therefore it seems a valuable additional *in vitro* tool in diagnosing drug allergy in children.

1506
Umbilical cord blood erythrocyte membrane fatty acid composition and maternal atopic dermatitis history: the mass spectrometry study

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Background: Some studies have been hypothesized the presence of congenital polyunsaturated fatty acids metabolism disturbance, which plays its role in the pathogenesis of atopic dermatitis (AD). The deficit of delta-6-desaturase enzyme function is postulated, which leads to insufficient content of linoleic acid derivatives (gamma-linolenic (C18:3ω6), dihomo-gamma-linolenic and arachidonic acids). Cord blood erythrocyte membrane fatty acid status has not been studied well in this relation.
Method: Erythrocyte membrane fatty acid compositions were studied in two newborns groups: the 1-st one is newborns from mothers without AD history ($n = 40$) and 2-nd one is newborns from mothers with AD history ($n = 17$). Absolute (mg/l) and percentage content of erythrocyte membrane fatty acids using a gas chromatograph-mass spectrometer (6890/5975C, 'Agilent Technologies', USA) were evaluated. Statistical analysis was performed using the Mann–Whitney *U*-test. Data are shown as median (25–75 quartiles).
Results: Twenty-six fatty acids were detected (from 12:0 to 24:0) in cord blood erythrocyte membrane. In neonates from mothers with presence AD history we have only found the decreasing percentage of iso-pentadecanoic (i-C15:0, $P = 0.025$) acid and almost total absent of gamma-linolenic acid (C18:3ω6, negative AD history newborn group – 0.025 (0–0.048) %, positive AD history newborn group – 0 (0–0.028) %, $P = 0.1$) in cord blood erythrocyte membranes. No differences have been found between absolute contents of erythrocyte membrane fatty acids in assigned newborn groups.
Conclusion: Thus, maternal history of AD is associated with low level of gamma-linolenic acid in cell membranes already on the moment of infant's birth. These findings can suggest the genetic background of the gamma-linolenic acid lowering and/or influence of maternal fatty acids metabolism and placental transference level.

1507
Allergy to betalactamics in peadiatrics

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Background: The betalactamic antibiotics are frequently used in Peadiatrics. Some infectious acute diseases in childhood can be accompanied by cutaneous symptoms that can be mistaken by hypersensitivity to drugs originating inadequate diagnosis of drug allergy.
Method: The authors characterise a peadiatric population (patients < 18 years of age) that had oral provocation tests (PT) to antibiotics on a Day Care Unit at the Immunoallergology Department over 1 year (2011). The following data was analized: gender, age, presence of atopy, suspected drug, symptoms, number and purpose of the test, cutaneous tests and *in vitro* dosage of specific IgE.
Results: We evaluated 60 children, 41 male (67%) with an average age of 6 years (1–14). Atopy was found in 19 children (32%). The suspected drugs were amoxicilin and clavulanic acid (60%), amoxicilin (27%), cephalosporins (8%), penicilin (3%), flucloxacilin and ampicilin (2%). 95% of the patients presented with cutaneous symptoms (maculopapular exanthema in half of the cases) and 5% had gastrointestinal symptoms. Late reactions occurred in 78% of the cases. Cutaneous tests with betalactamics were done in 15 children

(25%) and *in vitro* tests in 30 (50%), all negative. The PT were performed with amoxicilin and clavulanic acid in 34 children, amoxicilin in 20, cephalosporins in 7 and flucloxacilin in 1. All the PT were negative. In 58 of the PT the goal was exclusion of the diagnosis (97%) and 2 PT (3%) were done with alternative drugs. Two children had 2 PT due to presumptive allergy to two antibiotics.

Conclusion: The diagnosis of drug allergy was excluded in the majority of our patients, despite presence of atopy. The PT had an important role in the management of these patients. There is an overdiagnosis of betalactamic allergy in the peadiatric population. Their reference to Immunoallergology in order to rule out the diagnosis it's essential, allowing the use of first line antibiotics in a population prone to infectious diseases.

1508
Trimethoprim-sulfamethoxazole (cotrimoxazole) desensitisation in a 5-years-old girl HIV-infected

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Background: Trimethoprim-sulfamethoxazole (cotrimoxazole) has been used extensively in the treatment and prevention of opportunistic infections in HIV-infected patients. In these patients, cotrimoxazole use causes a higher rate of adverse drug reactions than in the general population.

Method: A 5-year-old girl native of Nigeria and HIV infected through vertical transmission was referred to our department because she had developed a generalised pruritic erythematous maculopapular rash after treatment during 2 weeks with cotrimoxazole 7 ml/day, 3 times/week (Septrim Pediatric oral suspension®: 8 mg trimethoprim/40 mg sulfamethoxazole/1 ml). As CD4 cell count was < 200 cell/mm^3, prophylaxis with cotrimoxazole was mandatory, and an oral desensitisation was performed.

Results: Prick test with trimethoprim (10 mg/ml), and prick (10 mg/ml) and intradermal (10 mg/ml) tests with sulfamethoxazole were negative. On the 1st day, gradually increasing doses of cotrimoxazole (Septrim Pediatric oral suspension®) at 15-min intervals (1–5 ml of dilution 1/200 and 1–2 ml of dilution 1/20) were tolerated. The 2ndday she received 3 and 4 ml of 1/20 dilution (every 15 min) and the 3rd day 2 undiluted doses of 0.5–1 ml at 45-min intervals. On the 4th day, 30 min after the undiluted dose of 4 ml (cumulative dose 6 ml), she developed a generalised pruritic erythematous maculopapular rash. We backtracked to a dose of 0.5 ml following 0.5 ml increments and similar reaction occurred with a dose of 3 ml. Both reactions were stopped by dexchlorpheniramine and corticosteroids. A new slowing of the protocol (increments every 72 h) resulted to be successful reaching a maintenance daily dose of 5 ml.

Conclusion: Although several cotrimoxazole desensitisation protocols have been performed in HIV patients, there is a lack of such protocols in pediatric population.

Here we describe ours, emphasizing that although 2 allergy reactions occurred, these were not serious, and responded well to conventional medication.

1509
Drug reaction with eosinophilia and systemic symptoms syndrome and Epstein-Barr virus infection in a child with cat scratch disease

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Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a rare, potentially life-threatening adverse drug reaction. Although aromatic anticonvulsants are the most common causes of DRESS syndrome, a number of drugs including antimicrobials have been implicated in its etiology.

We present here a child patient with cat scratch disease diagnosed with DRESS syndrome and Epstein-Barr virus (EBV) infection.

A 6 year-old girl was admitted to our hospital because of cervical lymphadenopathy and lymphadenitis after 1 month history. She had been taking ampicillin-sulbactam for 5 days. The antimicrobial treatment was continued. After 6 weeks of ampicillin-sulbactam and 4 days of clindamycin she developed an itchy morbilliform rash on her trunk, hands and feet. The patient's indirect fluoresence assay of *Bartonella hansela* was found to be 1/128. One month earlier she had been in contact with cats. As well as the rash she had fever, facial edema, hepatomegaly, leukopenia, peripheral eosinophilia, atypical lymphocytosis, pyuria and hematuria. During the admission EBV VCA IG M/G and after 10 days nuclear antigen were found to be positive. As a result of these findings late primary EBV infection and DRESS syndrome possibly caused by ampicillin were considered. The antimicrobials were immediately stopped. Intravenous immunoglobuline (IVIG) (1 g/kg) was given. The third day of IVIG she developed oral mucosal lesions. The corticosteroid treatment was added. During follow-up the patient's eruption and eosinophilia regressed within 1 week. The steroid treatment was gradually tapered over 2 weeks.

The reactivation of herpes viruses including EBV virus is commonly seen in DRESS syndrome. However in our case according to the evidence of serological findings of EBV, we considered EBV infection was primary not reactivated. Underlying factors like certain infections might trigger DRESS syndrome in susceptible patients.

1510
Pleurisy and mody in DRESS syndrome

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Introduction: Pulmonary involvement but hematological, hepatic, renal, cardiac, neurological, gastrointestinal and endocrinological abnormalities in DRESS syndrome is extremely rare.

Case: A female patient aged 14 was admitted to hospital with symptoms of a week-lasting rash and fever. It was known that 15 days ago she had been given carbamazepin treatment for epilepsy. She was presented with intense maculopapular rashes and 38.5°C fever together with crackles of lungs. With prediction of DRESS syndrome carbamazepin treatment was withdrawn and antihistaminics and systemic steroids were implemented. Chest X-ray demonstrated only closed costaphrenic sinuses. Thoracal ultrasound revealed 6 mm thick pleural effusions bilaterally. Thorax CT was performed which demonstrated a consolidation at medial segment of right lung middle lobe, athelectasies at lower lobes of both lungs. At the second day of steroid treatment hyperglycemia occured so the steroid dose was reduced by half and insulin treatment was started. Formerly, the patient was found hyperglycemic. The 33-year-old mother was diagnosed with type 2 diabetes at the age of 26 years at the time of diagnosis. Islet cells cytoplasmic autoantibodies (ICA) were negative as tested by indirect immunofluorescence and her glutamic acid decarboxylase autoantibodies (GADA), which was measured by RIA, were also negative and fasting levels of C-peptide

and insulin remained detectable throughout the observation period (C-peptide 2.1–6.23 ng/ml). The combination of long-standing non-ketotic hyperglycemia, glycosuria, at a relatively high fasting and postprandial blood glucose, and negative pancreatic auto-antibodies in a child with a diabetic mother raised the possibility of MODY. Direct DNA sequencing of all exons and intron-exon bounders of the MODY genes are planned to analyze in our patient.

Conclusion: This case is noteworthy, differently presenting as pleurisy and MODY.

1511
Dress syndrome induced by anti-tuberculosis drugs. A case report

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Background: DRESS syndrome (Drug Rash with Eosinophilia and/or atypical lymphocytosis and Systemic Symptoms) reflects a serious hypersensitivity reaction to drugs. The drugs most frequently involved are antiepileptics and allopurinol.

The pathophysiology remains unclear but a defect in detoxification of the causative drug, immunological imbalance and infections such as human herpes virus 6 have been suggested. The mortality is about 10% in patients with severe multiorgan involvement.

Methods: A 15 year old boy was treated with pyrazinamide, ethambutol, rifampicin and levofloxacin under the suspicion of pulmonary tuberculosis. One month later he was hospitalised due to fever, a confluent morbilliform rash and lymphadenophathy. Blood tests showed leukocytosis (17 900/μl) with atypical lymphocytosis (13%) without eosinophilia and liver parameters alterations (AST 267 UI/l, ALT 488 UI/l). DRESS syndrome was suspected and all anti-tuberculosis drugs were stopped.

Results: On day 7 of admission the levels of transaminases were increased (AST 468 UI/l, ALT 1078 UI/l) and protrombin time was afected (39%). The thorax ultrasound showed pleural effusion. Parvovirus B19 IgG was negative but IgM was positive. The PCR search for viral DNA was negative. Serological tests for other viral infections were negative. The skin test biopsy showed intraepidermal esinophil and lymphocyte infiltration and spongiosis supporting drug reaction.

Systemic corticosteroid treatment was iniciated with clinical improvement.

Three months later patch tests were performed with pyrazinamide, ethambutol, rifampicin and levofloxacin. The result was strongly positive with ethambutol.

Conclusion: Ethambutol is not usually associated with DRESS syndrome but we report a case attributable to this drug.

Patch tests may be a useful method for detecting the culprit drug when multiple drugs are involves.

Further investigations might be required to investigate the relevance of other viral infections like Parvovirus B19 in the development of DRESS.

1512
Is premedication necessary before desensitisation in an infant with Pompe disease having α glucosidase anaphylaxis?

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Pompe disease is an autosomal-recessive disorder resulting from a lysosomal acid α-glucosidase deficiency. Enzyme replacement therapy has improved cardiac and motor functions in patients with Pompe disease. Infusion- associated reactions occur in 50% of those patients. These reactions may disable patients to get specific therapy. Desensitisation is indicated in patients who had life threatening hypersensitivity reactions.

We present 1 year old boy with Pompe disease who had previously anaphylaxis during recombinant human acid alpha-glucosidase (rhGAA) medication. Epidermal tests with rhGAA at concentration of 1:1000 and 1:100 were negative 4 weeks later the anaphylaxis. Intradermal test with rhGAA at concentration of 1:1000 was positive with 7 × 8 mm induration and surrounding hyperemia. Premedication used for radiocontrast media allergies was applied prior to desensitisation protocol. We performed desensitisation protocol started by administering dose of 10 mg/kg weekly rhGAA with serial dilutions that individually prepared and delivered based on patient's clinical manifestations and tolerance. During the first week in the 10th and 12th steps of desensitisation patient developed urticaria on his ears, eyes, face and rarely on his trunk. After repeating premedication no interruption of drug infusion was necessary. No reaction was observed in the second week of desensitisation.

In this case we emphasize that premedication prior and during the desentization enables us to give the enzyme replacement therapy to the patient successfully who had rhGAA anaphylaxis.

1513
Eyedrops life-threatening adverse drug reaction in a 7-year-oldchild with congenital glaucoma and asthma

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Background: Elevated intra-ocular pressure (IOP) is the main feature of Congenital glaucoma Treatmentstrategies seek lowering IOP and topical therapy with beta-blockers is the first-line therapy. Timolol, a non-selective beta-blocker, is the most commonly prescribed drug.

Method: We present a 7 year-old child diagnosed of occasional episodic asthma and congenital glaucoma. He had been receiving treatment with Timolol in daily basis since he was a newborn, due to non allergic occasional asthma, he had also received concomitant treatment with salbutamol with good tolerance. Two months before his visit to our department, the parents decided to discontinue Timolol because he had also been prescribed antibiotics to treat an acute sinusitis. After 7 days without Timolol, he started treatment with salbutamol due to an asthma attack. After 24 h on salbutamol regularly, and after 8 days without Timolol, he restarted Timolol treatment (correct dosage). Ten minutes after administering Timolol, he had two puffs of salbutamol and suffered an immediate and severe asthma attack along with lost of consciousness requiring emergency treatment and cardiopulmonary resuscitation as well as admission in the intensive care unit for 2 days.

Results: We performed Skin Prick-tests with Salbutamol 0.5 mg/ml and Timolol 5 mg/ml with negative results. Intradermal tests (ID) with Salbutamol at 0.005 mg/ml and 0.05 mg/ml as well as IDwith Timolol at 0.05 mg/ml were also negative. Challenge test with salbutamol showed negative results. Timolol was not challenged due to ethical reasons. The patient was diagnosed of Adverse Pharmacologic Reaction due to Timolol and was advised to avoid Timolol as well as other non selective beta-blockers.

Conclusion: We present a case of life-threatening drug reaction to topical Timolol in a patient with anacute asthma attack, due to its beta-blocker non-selective action.

Non-selective betablockers, regardless of the route, should be extrictly avoided in every asthmatic patient.

1514
Increase of complicated pneumonia and pneumococcal associated hemolytic uremic syndrome post PCV-7 vaccination

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Background: Studies in the US, Canada and UK suggested that the incidence of complicated pneumonia may increase after widespread use of the 7 valent pneumococcal conjugated vaccine (PCV7) in childhood.
Method: We performed a retrospective population-based study from the central computerized database for children 18 years or younger to determine rates of hospitalisation pre and post PCV7 vaccination by retrieving all cases with a discharge diagnosis of complicated pneumonia or parapneumonic effusion from January 2007 to November 2013. PCV7 was included in the public immunisation schedule provided by the government free of charge starting in Sept 2009. It was subsequently changed to PCV13 in December 2011 but without booster PCV13 to those at risk chiuldren aged between 2–5 years. Detailed assessment of all children admitted to a tertiary university hospital was used to validate the computerized territory wide data.
Results: From January 2007 to 2013, there was statistically significant increase in the incidence of complicated pneumonia, the adjusted incidence of complicated pneumonia has increased from 3.8 (2007 to 2009) to 11.0/100 000/yr (2011 to 2013) for children aged 5 and below ($P < 0.01$). In the Prince of Wales Hospital, there were a total of 41 children admitted with complicated pneumonia. Twenty-one of them had a confirmed microbiological diagnosis. Eighteen of them (86%) were due to *Streptococcus pnenmoniae*. Four deaths occurred in the post PCV7 period. All died from complicated pneumonia and associated hemolytic uremic syndrome (two cases each of serotype 3 and 19).
Conclusion: This territory wide study documented a significant increase of complicated pneumonia and related HUS shortly after PCV7 vaccination was started in Hong Kong. Serotype replacement may be a significant contributor to the increase. The severe and death cases are caused by serotypes not covered by PCV7 or 10. Further analyses are needed to determine the exact causes of such increase of complicated pneumonia.

1515
Evaluation of biomarkers associated to local inflammation and vascular remodeling in Takayasu arteritis

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Background: Takayasu Arteritis (TA) is an idiopathic large vessel vasculitis resulting in arterial stenosis and aneurysms. The identification of a hierarchy among events in TA pathogenesis, of reliable activity markers and more effective therapies is a crucial need. Inflammatory pathways associated with IL-6 and TNFα are involved in TA: they represent the target of molecular therapies and cause ESR and CRP elevation, which are used to assess TA activity. Various data suggest that systemic inflammation *per se* does not account for all the complexity of TA manifestations. Local inflammation and vascular remodeling might have a role in TA.
Method: We cross-sectionally analyzed serum levels of CRP, pentraxin 3 (PTX3, a marker of local inflammation) and chromogranin A (CgA) and CgA-derived peptides in a well-characterised cohort of 44 TA patients. Biomarkers performance was evaluated in relation to disease activity, defined by two sets of criteria, and progression and vascular enhancement at imaging.
Results: CRP levels correlated with activity status but not with the presence of vascular progression or enhancement. PTX3 levels correlated with the presence of activity and vascular enhancement but failed to identify patients with vascular progression. PTX3 showed higher performance in patients without TNFα-blockers, possibly because TNFα directly regulates molecule's production. PTX3 and CRP levels did not correlate. Levels of CgA and derived peptides were influenced by therapy with proton pump-inhibitors (PPIs). In the more homogenous subgroup of TA patients on PPIs, levels of the native CgA (endowed with anti-angiogenic activity) were lower in patients with vascular progression, suggesting deficiency of protective mechanism.
Conclusion: Our data suggest that systemic inflammation, local inflammation and tissue remodeling might concur in TA pathogenesis and that they should be all taken into consideration when searching for novel activity markers and therapeutic targets.

1516
High prevalence of self-reported allergies in adults: second interim analysis on 4088 subjects of Leipzig Interdisciplinary Research Cluster (LIFE)

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Background: We aimed to assess prevalence of allergies, type 1 sensitisations, and any association thereof with age, gender, socioeconomic status (SES) and/or history of clinical allergy in adults from the city of Leipzig (East-Germany).
Method: Second Interim Analysis of LIFE, including $n = 4088$ subjects (49.0% ♂, 51.0% ♀, 40–79 years). SES was divided into three categories. We performed allergy interview, skin prick test (SPT; 6 aeroallergens/ALK-Abello), and CAP-FEIA for IgE (positive: tIgE ≥100 kU/l, sx1/fx5 ≥ 0.35 kU/l).
Results: SES class 1 $n = 266$ (6.5%), 2–2473 (60.5%), 3–1349 (33.0%). Self report of any allergy positive in 62.5% (♀ 70.0%–♂ 54.6%). Physician diagnosed asthma 327 (8.0%), atopic dermatitis 99 (2.4%), allergic rhinitis 1215 (29.7%), urticaria 218 (5.3%), allergic shock 115 (2.8%), food allergy 461 (11.3%), insect allergy 343 (8.4%), drug allergy 916 (22.4%). SPT (available data $n = 1972$) ≥1 allergen positive 542 (27.5%, ♂ 30.2%, ♀ 24.7%). Most frequently positive was birch. tIgE increased (available data 2906/71.1%) 672 (23.1%); sx1 (1657/40.5%)/fx5 (1658/40.5%): sx1 526/1657 (31.7%), fx5 98/1658 (5.9%). tIgE and sx1 were increased in men compared to women ($P < 0.01$) in all age-groups.
Conclusion: Our data show high prevalence of self reported allergies, especially to drugs and food. Allergy reports were more common in females, SPT and IgE values were more often positive in men. In comparison with data from the German Health Interview and Examination Survey for Adults (DEGS, $n = 7988$), only slight differences were shown for asthma (8.6% vs. 8% LIFE) and atopic dermatitis (3.5% vs. 2.4%). In contrast, in LIFE, allergic rhinitis showed higher prevalence (14.8% vs. 29.7%). Currently, our data cannot be regarded as being representative for the population in Leipzig as sampling shows deviation from known population structure, requiring adjustment. Investigations of LIFE study group are to be continued and aim at including 10 000 subjects.

1517

Prevalence of skin sensitisation to mulberry pollen in the Southeast of Spain

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Introduction: Mulberry (*Morus alba*) trees are common in the region of Murcia where, for a longtime, raising of silkworms was a popular tradition.

The aim of this work was to study the prevalence of sensitisation to mulberry pollen in the area of Cartagena, on the coast of the region of Murcia, and to investigate the relationship between sensitisation to mulberry pollen and pan-allergens.

Material and methods: Consecutive patients reporting respiratory symptoms (rhinitis, conjunctivitis and/or bronchial asthma) were included. All individuals were skin prick-tested with common pneumoallergens (dust house mites, pollens, fungi and dander), pan-allergens (lipid transfer protein-LTP-, profilin and polcalcin) and *Morus alba* pollen extract (Leti laboratories S.L. Madrid, Spain). Finally, all patients enrolled in the study were asked about symptoms after contact or ingestion of plant-derived foods.

Results: One hundred and seventy-one patients (105 females, 66 males, mean age 31.8 years, range 4–70) were included. Skin prick testing with pollens were positive in 61 (35.7%) patients, and 12 (19.7%) of them were sensitised to mulberry pollen. 18 (10.5%) patients were sensitised to LTP, 8 (4.7%) to polcalcin and 6 (3.5%) to profilin. 11 (6.4%) individuals referred food allergy.

The prevalence of sensitisation to mulberry pollen was 19.7% in patients with pollinosis and 7% in the population studied. All patients sensitised to mulberry pollen were sensitised to four or more pollens and 8 (66.7%) of them were sensitised to some pan-allergens: 6 (50%) to polcalcin and 2 (16.7%) to LTP. No patient was sensitised to profilin. Six (75%) of the patients sensitised to polcalcin were sensitised to mulberry pollen. Only two patients sensitised to mulberry pollen referred symptoms with plant-derived food (peach) and both patients were also sensitised to LTP.

Conclusions:

- In the population studied, prevalence of sensitisation to mulberry pollen was high in the patients with pollinosis.
- Correlation between sensitisation to polcalcin and mulberry pollen was found, but not with other pan-allergens studied.

Poster Session Group III – Green

TPS 72 – Pediatric epidemiology

1518

Children from rural areas of the forest-steppe zone of central Ukraine are more sensitive to grass and weed pollens than to tree pollens

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Background: Allergy symptoms may vary in different populations depending on age and gender. Grass and tree pollen are important allergens for the Ukrainian adults (18–50 years old) in the Vinnitsa region. This study assesses the allergens of primary importance for infants and children in this same region of Ukraine.
Method: Symptoms of seasonal allergy were analyzed by reviewing medical records from an allergy specialty clinic at Vinnitsa Regional *Clinical* Children's *Hospital*, Vinnitsa, Ukraine. Thirty-eight patients aged from 3 to 16 years were reviewed with 20 selected for further analysis among children admitted from 2004 to 2013. Prick tests for inhalant pollens using extracts made in Ukraine were done.
Results: Seventeen or 85% of patients were males. Only three were from urban Vinnitsa, others being from rural areas. Children aged 6–10 years old typically had the first appearance of allergy symptoms. 13 or 65% of children were tested at this age for the first time. Sensitisation to pollens prevailed over other sensitisations in children aged 6–16. Ragweed and sunflower allergens were leading causal agents for allergy symptoms for children aged from 3 to 5 years, often with very high sensitivity, while sensitisation to Poaceae allergens was mild. Children age 6–10 were sensitised to grasses usually *Festuca, Trigonella, Phléum,* and *Poa*. Sensitivity to ragweed and sunflower pollen varied from mild to very high. Sensitivity to tree pollen was low with some cases of moderate reactions to alder and hazelnut allergens. Birch and hornbeam allergy were low. Reactions to grass or weed were absent or very low. Reaction to trees became prominent in patients from rural areas aged over 11 when children became moderately to very sensitive to birch, alder and hazelnut pollen but sensitivity to grass and weed pollen still prevailed over sensitivity to tree pollen. Children showed moderate sensitivity to mugwort and sunflower and moderate to very high sensitivity to dandelion and ragweed allergens.
Conclusion: Children from rural areas of central region of Ukraine are much more sensitive to grass and weed allergens than tree pollens from early childhood. Severity of sensitisation to tree pollens increases with age but grass and weed sensitivity remains high corresponding with high sensitivity of Vinnitsa adults to tree and grass pollens.

1519

Prevalence of atopic eczema, asthma and allergic rhinitis in the first 6 years of life: trends in the T-CHILD birth cohort study

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Background: The allergic march, which refers to the natural history of atopic diseases, is characterised by a typical sequence of sensitisation and manifestation of symptoms which appear during a certain age period, persist over years, and often show a tendency for spontaneous remission with age. Despite many epidemiologic studies in the world, few studies in Japan showed how allergic march develops by ages. We investigated the 12-month prevalence of allergic diseases at age 1–6 in the same children in a hospital based birth cohort study, named as the T-CHILD (Tokyo Children's Health, Illness and Development) study.
Method: In the T-CHILD study, questionnaires about atopic eczema and asthma were collected annually from age 1 to 6 and from 3 to 6 about allergic rhinitis. The assessment of allergic diseases is based on a modified Japanese version of the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire.
Result: Of the 1550 participants included, 710 (48%) were female. The prevalence of atopic eczema at 1, 2, 3, 4, 5, 6 years old was 40, 34, 31, 32, 21, 22 and 16%, respectively. The prevalence of asthma was 21, 22, 7.5, 15, 16, 17 and 14% respectively. The prevalence of allergic rhinitis at age 3, 4, 5, 6 was 5, 7, 11 and 17%, respectively. Thirty four % of eczema at age 2 disappeared before age 6. Children with eczema at age 2 developed asthma in the following 4 years more than those without eczema at age 2. On the other hand, there was no difference in development of allergic rhinitis between children with and without eczema at age 2.
Conclusion: The onset of atopic eczema emerged in earlier ages than that of the other allergic diseases. Eczema at the age of 2 could be an important factor for the transition to asthma in later life. This study indicates that the allergic march starts from atopic eczema as the initial manifestation of allergic diseases followed by the development of asthma and allergic rhinitis.

1520

Risk factors of wheezing in Ukrainian infants

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Background: Wheezing in infants is one of the common problems during common cold.
Method: It was cross-sectional study. We used a validated questionnaire from International Study of Wheezing in Infants for parents of children aged from 12 to 15 months treated in 6 primary health care units in Vinnitsa in Ukraine during 2012–2013. We defined occasional wheezing as up to two episodes of wheezing and recurrent as three or more episodes of wheezing. The independent variables were shown using frequency distribution to compare the groups. Measures of association were based on odds ratio (OR) with a confidence interval of 95% (95% CI).
Results: Six hundred and thirty-five infants had wheezing episodes in the first

12 months of their life; of these, 95 (14.9%) had recurrent wheezing. Risk factors for occasional wheezing were family history of asthma (OR = 2.07; 95% CI: 1.83–2.56) and six or more episodes of common cold (OR = 2.06; 95% CI: 1.84–2.93). For recurrent wheezing, risk factors were male gender (OR = 1.58; 95% CI 1.21–2.49); a wheezing onset during first 3 months of life (OR = 1.73; 95% CI: 1.73–3.24); signs at night (OR = 2.46; 95% CI: 1.65–3.58) and more than six or more episodes of common cold (OR = 2.09; 95% CI 1.45- 3.00).

Conclusion: The main risk factors associated with occassional and reccurent wheezing in Ukrainian children were frequent respiratory infections and family history of asthma.

1522
Is childhood asthma a risk factor for enuresis?

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Background: There are some studies proposing that there could be an association between enuresis and food allergy and asthma. Purpose of the study is to investigate the prevalence of enuresis in children with asthma and to determine possible risk factors

Method: The study group consisted of 240 asthmatic patients followed up by Bezmialem Vakıf University Department of Pediatric Allergy between April 2011-February 2012. Two hundred and two patients without any atopic disease between the age of 5–17 years who were examined at the outpatient pediatric section were chosen as control group. Asthma diagnosis was made according to the GINA 2008 criteria. Enuresis nocturna (EN) was defined as 2 or more bed wetting per week for at least 3 months at the age of 5 and over.

Results: About 44.6% of the patients ($n = 107$) were female, and the mean age was 8.64 ± 2.77 years in the asthmatic group. Of the control group 52% ($n = 105$) was female, and the mean age was 9.01 ± 3. Prevalence of enuresis was 20% ($n = 48$) in asthmatic group, and 15.8% ($n = 32$) in control group, respectively. Although there was a high prevalence of enuresis in children with asthma, statistically significant difference was not found between in children with asthma and control group ($P > 0.05$). There was no significant difference between asthmatic patients with and without enuresis according to allergen sensitisation ($P > 0.05$).

Conclusion: Although prevalence of enuresis was higher in children with asthma than controls, the difference was not statistically significant. Childhood asthma is not a distinct risk factor for enuresis.

1523
The prevalence and correlates of allergic rhinitis in a Gulf Arab population

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Background: Allergic rhinitis has become a public health problem. Little firsthand information is known about its prevalence and associated risk factors in the United Arab Emirates (UAE). This study estimated the prevalence of allergic rhinitis (AR) and independent risk factors among UAE nationals in Al-Ain City, UAE.

Method: Overall, 7550 children and their parents filled out a self-administered questionnaire. Data pertaining history of rhinitis (sneezing, rhinorrhea, irritation, nasal blockage) in the past 12 months was recorded.

Results: Due to incomplete data, 6543 subjects (median age 30 years) were included in the analysis. Crude prevalence of AR was 36% while direct standardisation to age/sex distribution of UAE yielded a prevalence of 32%. Linear regression analysis revealed that AR was independently associated with younger age [$r = -0.006$; 95% CI: 0–0.009–0.002], female gender [$r = 0.374$; 95% CI: 0.262 −0.486] higher education [$r = 0.100$; 95% CI: 0.039 −0.162], and Arab origin [$r = 0.261$; 95% CI: 0.176–0.346].

Conclusion: The prevalence of AR in the UAE is higher than found in other Gulf countries, and is associated with age, gender, nationality, and education level. Specialised treatment should be considered particularly among young children with family history of allergy.

1524
Allergic rhinitis prevalence and impact on asthma control therapy in children

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Background: Over the past 50 years the relationship between allergic rhinitis (AR) and asthma was clarified, and most of the clinical, epidemiological and biological data recommend integrated management. Data from several sources indicate worldwide increases in prevalence of asthma and AR.

Method: Medical data of 690 children (260 girls and 430 boys, mean age 7 year 6 months) admitted for asthma attack in the ward for chronic pulmonary diseases for children aged 2–18 years for a period of 3 years (January 2010-December 2012) was analyzed according gender, age, AR, controller therapy for asthma in total and for each year separately.

Results: For the three consecutive years the total number of patients was not significantly different and there were no significant difference in gender and age distribution. AR was documented in 385 children (average 55.79%) with increasing prevalence from 51.52% in 2010 to 58.76% in 2012. Boys had higher AR prevalence 60–61% vs.51–56% in girls. All patients regardless their AR status received antihistamines as additional therapy and 15 didn't have controller therapy (14 in 2010 and 1 in 2011). While in 2010 the children had as a controller therapy Inhaled corticosteroids (ICS) more often (>60%), in 2011 and 2012 leukotriene receptor antagonist (LTRA) alone or in combination with ICS prevailed(>60%). Combined therapy (ICS + LTRA ± long acting beta2 agonist) was mainly prescribed for children older than 10 years. Some of the patients were re-admitted in the studied period – all of them with poor asthma control and AR. There were no re-admissions of children without AR.

Conclusion: Antihistamines are not part of the controller therapy in asthma, and in later years less children with asthma are left only on these medication. As all guidelines and research papers state the role of LTRA – there is increasing use of them in children with asthma even in cases without AR. Better understanding and control of AR is related with better asthma control and less emergency department visits and hospitalisations.

1525
Childhood asthma hospital admissions and readmissions in Denmark 1977–2012

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Background: Childhood asthma has consistently reported to have increased in recent decades in most westernized

countries, but it is unknown if this represent increase across severities. We aimed to study the time-trend of acute hospital admission and readmission for asthma of school-aged children in the recent 35 years in Denmark.

Methods: We analyzed time-trends in the national incidence of hospitalisation for acute severe asthma in children aged 5–15 in Denmark during the 35-year period 1977–2012 in the Danish national registry. Only in-patient admissions with a principal diagnosis of asthma (ICD-8: 493** and ICD-10: J45** and J46**) were included. Among children with asthma hospitalisations we investigated the risk of readmissions separated by 1 month from first admission. Admissions were summarized as rates per thousand children per year.

Results: The overall time-trend through 35 years of observation is stable with a rate of 1 admission per year per thousand children at risk and a per-year incidence rate ratio 1.01 [95% CI: 1.01–1.01]. The rate of any readmission decreased from almost 20 per 1000 children in the eighties to below 10 in the early nineties before stabilizing at around 10 per thousand children from mid-nineties onwards.

Conclusion: We find a highly stable incidence rate ratio of first hospital admissions during the recent 35 years, which we interpret as a surrogate marker of the incidence of moderate to severe asthma disease.

Rates of readmission have gone down and stabilized, which we interpret being closer related to disease control.

Overall our data are suggesting that the reported increase in childhood asthma is mainly due to milder disease.

1527
Change of asthma prevalence after pandemic 2009 influenza in Korea; using big data of 48.1 million South Korean health-care records

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Background: Asthma was one of the most common underlying medical conditions among patients hospitalised with influenza infection, in 2009 worldwide reported that children with asthma had increased susceptibility to influenza infection. The prevalence of asthma has increased worldwide for past few decades. However, in some countries, it remains stable or even decreased. The aim of this study was to estimate the prevalence of asthma and the effect of influenza infection in Korea.

Method: To investigate the prevalence of asthma, we did analyze the nationwide database (National Health Insurance Corporation) which included the health-care records of 48.1 million individuals between January 1, 2007, and December 31, 2012.

Results: Prevalence of asthma in Korea showing a decreased tendency; 4.75% (2007), 4.74% (2009), 4.56% (2010), 4.41% (2011) and 4.32% (2012). Also, all age groups decreased between 2007 and 2012; under 6 years old age group had decreased 23.87% to 21.67%, 7–12 years group 8.10% to 7.98%, 13–18 years group 2.11% to 2.01%, 19–29 years group 1.54% to 1.45%, 30–39 years group 2.34% to 2.16%, 41–49 years group 2.52% to 2.18%, 50–59 years group 3.53% to 3.11%, 60–69 years group 5.64% to 5.12%, 70–79 years group 7.72% to 7.24%, and over 80 years group 7.83% to 7.38%. But slightly increased after pandemic influenza 2009; 7–12 years old age group had increased 8.13%, and 13–18 years group 2.41%.

Conclusion: Prevalence of asthma in Korea showing a decreased tendency, however increased after pandemic influenza 2009 in child and adolescent group.

1528
Vitamin D and the progression of early wheeze to childhood asthma and asthma severity

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Background: Vitamin D has been associated with childhood asthma, but in predisposed children this relation is unclear. The present study aims to investigate whether, in preschool wheezing children, vitamin D is associated with progression to asthma. Additionally, we investigated the relationship between vitamin D and asthma severity in school-aged children.

Method: This study was conducted in the KOALA Birth Cohort Study. Children with wheeze at age 0–2 years were followed-up until age 8–10 years. Presence of wheeze and asthma was evaluated regularly during childhood using ISAAC questionnaires, and severity of asthma (mild; severe) was assessed at ages 8 and 9, using a definition based on the Method of Canadian Consensus. Plasma level of 25-hydroxyvitamin D (25(OH)D) was measured at age 2 years. Vitamin D supplement use was assessed by parental questionnaires, repeatedly in the first 2 years of life and at ages 8 and 9 years. Multivariable logistic regression analysis and GEE models were used.

Results: In the highest quintile of 25(OH) D, the adjusted odds ratio for progression from wheeze to asthma was 6.56 (95%CI 1.02–42.19) compared to the lowest quintile. No association was found between vitamin D supplementation in the first 2 years of life and progression to asthma, nor between supplementation and asthma severity.

Conclusion: Our results show that high vitamin D plasma levels are associated with a higher risk for asthma in wheezing children, although no association was found with vitamin D supplementation. This could have resulted from asthma-associated genetic variation in vitamin D metabolism. Therefore, we cannot recommend or advise against vitamin D supplementation as a preventive measure for asthma development in wheezing children.

1529
Is adenovirus an important risk factor for childhood asthma?

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Background: Virus-induced wheezing episodes in early infancy often precede the development of asthma in children. Respiratory syncytial virus and rhinovirus have been implicated as important pathogens in early childhood wheezing. The aim of this study was to evaluate the relationship between virus-induced wheezing and asthma development in Slovene children at high risk.

Method: Between for at least 6 months exclusively breast fed children with a positive family history for an allergic disease, we selected 118 children with clinical manifestation of atopic dermatitis and/or food allergy in the first year of life. Allergic aetiology was confirmed (elevated spec. IgE, positive skin prick testes). None of them had symptoms of respiratory illness in the first year of life. They were followed prospectively for 5 years by the same paediatrician. At the first episode of wheezing respiratory illness viral aetiology was assessed using throat swab samples and multiplex reverse transcriptase-polymerase chain reaction. Depending on the results of the throat swab children were divided in two groups: Group A: 55 children with confirmed viral aetiology and group B: 63 children without viral aetiology of wheez-

ing. Current asthma was diagnosed at the end of the sixth year of life.
Results: In the study group 24.6% of children had asthma. The prevalence of asthma was significantly higher in children with confirmed viral aetiology of wheezing (group A: 38.2% vs group B: 12.6%); ($P < 0.001$). Adenovirus (AdV) was most frequently identified virus as the cause of first wheezing illnesses (61.8%) and it tended to be more strongly associated with asthma at age 6 years in comparison with other viruses (subgroup A_1); ($P = 0.01$).
Conclusion: We demonstrated that apart from heredity, virus-induced wheezing is an important risk factor for childhood asthma. Our data show clearly link AdV wheezing illnesses during early life with progression to the subsequent development of childhood asthma.

1531
Allergic disorder and its risk factors in pre-school children in Guangzhou: an epidemiological survey

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Background: In recent decades, the prevalence of allergic disorders in many countries has increased, particularly among children. According to previous study, we know the influential factors included individual characteristics (allergic constitution), genetic factor, environmental factor and so on. Allergy epidemiology shows that the incidences of allergic disease in different countries and regions vary widely. The risk factor of allergic disease in different regions is different. The number of studies on allergic disorder in pre-school children is limited. So it's necessary to investigate allergic disease and its risk factor in our area.
Method: The questionnaire was designed based on the internationally accepted International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire with combination of the epidemiological characteristics of local allergic disorder in Guangzhou city. Kindergartens were selected by a random, cluster-sampling method. Parents of kindergarten children completed the questionnaire after taught by teacher. Relevant investigators confirmed the effectiveness of the questionnaire by phone call. The results were analyzed by SPSS 17.0.
Results:
1) Applied logistic regression analysis of children allergic factors in children food allergies: the first degree relatives suffered from food allergy and allergy rhinitis, the risk of children with food allergies increased ($P < 0.05$).
2) Analysis of the relevance of various types of allergy revealed by spearman correlation analysis, food allergy and drug allergy, atopic dermatitis, bronchial asthma, eye allergy, allergic rhinitis, the correlation coefficient were statistically differences ($P < 0.035$).
3) Applied logistic regression analysis of related risk factors in children with allergic rhinitis: Ocular allergies; Bronchial asthma; Food allergies; allergic rhinitis suffered from siblings; Father and (or) mother suffering from allergic rhinitis; Home or school near the road; Family has lots of toys which was make of plush or foam; pet ownership; parental smoking were some risks factors for allergic rhinitis ($P < 0.05$).

Conclusion: Allergic factors; Family history; Allergic disease; Children.

1532
House dust mites allergens are critical for allergic young children in central Ukraine

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Background: Allergy symptoms may be differently expressed in various populations. This study determines the allergens of primary importance for infants and children in the central region of Ukraine.
Method: Pediatric allergy symptoms were analyzed from the medical records at Vinnitsa National Pirogov Memorial Medical University, Vinnitsa Regional *Clinical* Children's *Hospital*, Vinnitsa, Ukraine. Thirty-eight patients aged from 3 to 16 years were reviewed with 20 cases selected for further analysis among patients admitted from 2004 to 2013. Prick tests were done for inhalant allergens and foods using extracts made in Ukraine.
Results: 17 or 85% of patients were males. Seventeen patients are from rural areas, just three being from Vinnitsa city. Two of three infants admitted to allergy who were 1–5 years old were tested initially and again at age 6 to10. The most severe non-seasonal allergy symptoms were seen in children aged from 6 to 10 years who reacted to allergens containing house dust mites. Very high sensitivity was shown for both patients from Vinnitsa city and rural areas. Children were frequently sensitive to feathers from pillows and mildly sensitive to domestic crude dust. Non-seasonal allergy symptoms were less prominent in children aged 11–16 years. Mild sensitivity to household allergens was noted in this group with seasonal allergy appearing to be a greater factor for these older children.
Conclusion: Ukrainian boys are much more likely tend to be sensitised to environmental allergens than girls. Children aged 6–10 years old are the most susceptible to non-seasonal allergy in the central region of Ukraine due largely to house mite allergen.

1533
Prevalence of eczema in children 6/7 years and adolescents 13/14 years living in San Francisco city, Argentina

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Background: ISAAC Phase III in Argentina collected data from four cities (Córdoba, Rosario, Salta, Neuquén), but there was not data from smaller cities. San Francisco is a town of 61 260 inhabitants located in Córdoba province in the central area of Argentina.
Objectives: To determine the prevalence of current flexural atopic eczema (AE) in children (6–7 years) and adolescents (13–14 years) living in San Francisco city, Argentina.
Method: This cross-sectional study included children (6–7 years) and adolescents (13–14 years) living in San Francisco city. ISAAC questionnaire was used to determine the prevalence of current flexural eczema.
Results: A total of 1315 children aged 6–7 years and 1576 adolescents aged 13–14 years were studied. The prevalence of current flexural eczema was 6.69% in children and 9.96% in adolescents.
Conclusion: In this study, eczema was more prevalent in San Francisco city than the Argentinean average in children (6.4%). In adolescents, the prevalence was the highest registered in Argentina (Córdoba: 6.3%; Rosario: 6.4%; Salta: 8%; Neuquén: 8.4%) and higher than the Latin American (8.3%) and Global (7.3%) averages. The prevalence of AE founded is higher than expected; more studies are needed in order to explain this unexpected result.

Poster Session Group III – Green

TPS 73 – Plant food allergies

1534
Banana allergy

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Introduction: The prevalence of allergy to banana has increased in the last decade, but is often associated with Latex-fruit syndrome. Banana allergy isolated is a rare entity and can therefore be devalued.
Case report: We report the case of a child with 3 years old, male, caucasian, referenced to the Food Allergy consultation per episode of dyspnea and hypotension 20 min after ingestion of a banana in the nursery school. The child was transported to the Emergency Service and did therapeutic IV (not itemized) with clinical improvement. Until the reaction, he had regular intake of bananas and yogurt with banana flavor without adverse reactions. The child regulary eat all fruits, including tropical fruits and vegetables without adverse reactions. He has complaints of serous rhinorrhea all the year and, in the past, had four bronchiolitis in the 1st year of life (the first at 2 months of age requiring hospitalisation). No previous surgeries or invasive medical maneuvers were reported. Usual contact with latex products (e.g balloons) without clinical reaction.

Skin prick tests were preformed with standardised extracts (BIAL Aristegui®) for aeroallergens, including latex and artemisia, as well as for banana, peach, whole squash, avocado, chestnut, prup3 (LTP), prup4 (profilin) and they were all negative with exception of banana that had a positive result (wheal 10 × 5 mm). The laboratory tests showed: Total IgE 521 kU/l and specific IgE for banana (Musa paridisiaca) 33.60 kU/l.

The diagnosis of food allergy to bananas was established and the patient keeps eviction ingestion of bananas without occurrence of new reactions.
Conclusion: Food allergy to banana, although rare, can be potentially serious. The authors draw the attention to the possibility of severe allergy to bananas in small children witch is of extremely importance because this fruit is one of the firsts to be present in food diversification from 4 to 6 months of age.

1536
Solanum tuberosum, a rare cause of food allergy

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Introduction: Food allergy might present as a diagnostic challenge to the allergist when its cause is an unusual food.
Case report: The authors describe the case of a 2-year-old boy who developed lip oedema and erythema few minutes after ingestion of the first soup, by the age of 4 months. Similar episodes occurred several times after eating soup and the mother realised it only happened when potato was used. Later, an identical reaction occurred when egg was introduced in the diet. During the 5 months prior to our first evaluation, the child developed a daily serous rhinorrhea and regular episodes of cough and wheezing. At the initial visit, there were no relevant findings on physical examination. The skin prick tests were negative to aeroallergens and to latex and prick-to-prick tests revealed positivity to raw egg yolk and white, to cooked egg white and raw potato, with negative results to cooked egg yolk and potato. An increased specific IgE (sIgE) to potato (23.60 kU/l), egg white (3.07 kU/l) and yolk (0.38 kU/l) was determined. Nasal topical and inhaled corticosteroid and oral antileukotriene were prescribed and potato and egg eviction diet was maintained. One year later, there was further increase in sIgE to potato (>100 kU/l). Immunoblotting analysis identified a putative Kunitz-type proteinase inhibitor, homologous to a kiwi protein. Two years after our first evaluation, blood analysis was repeated, revealing a decrease in sIgE to potato (63.9 kU/l). After initial parental refusal, oral food challenges with cooked egg yolk and with potato were then performed, with negative results.
Comments: Potato (*Solanum tuberosum*) has been rarely associated with hypersensitivity reactions. Allergens belonging to the family of Kunitz-type soybean trypsin inhibitor might be found in various plant foods and cross-reactivity can be expected among those molecules and with pollen allergens. Tolerance to cooked potato is achieved in up to 80% of children by the age of 4 years.

1537
Mugwort (Artemisia vulgaris) pollen-related food allergy to cabbage

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Background: IgE-mediated allergy to foods of the Brassicaceae family has been increasingly reported and most of them showed associated sensitisation to mugwort (Artemisia vulgaris) pollen. We sought to study the clinical manifestations of mugwort hypersensitivity in patients with cabbage allergy, identify the common allergens, and evaluate their IgE crossreactivity.
Method: Three Patients with lethal anaphylaxis to raw cabbage and specific IgE antibodies to mugwort were investigated. Total and specific immunoglobulin E (sIgE) levels were measured by ImmunoCAP 250™ System (Thermo Fisher Scientific, Uppsala, Sweden). The existence of mugwort-cabbage cross-reactivity was verified by ELISA and immunoblotting inhibitory experiments. A major cross-reactive allergen was identified and characterised by Western-blot and Mass spectrometry (MS) analysis respectively.
Results: All patients had sIgE to mugwort and cabbage > 3.5 kUA/l (Level 3). ELISA inhibitory experiments showed significant cross-reactive phenomena in all three patients. In IgE immunoblotting the three patients reacted to a 25 kDa allergen of both mugwort and cabbage and can be cross inhibited. Pre-incubation of sera with mugwort crude extract can totally inhibit IgE binding to the cabbage 25 kDa band, but only partial inhibition was observed vice versa. Mass spectrometry (MS) analysis of the peptides generated from the 25 kDa of both mugwort and cabbage indicated that these spots shared a commom peptide containing 15 amino acid residues with Glutathione S-transferase contained in Arabidopsis thaliana which also belongs to the Brassicaceae family as cabbage.

Conclusion: Sensitisation to mugwort maybe initial factors of the lethal anaphylaxis to cabbage, suggesting a new cabbage-mugwort allergy syndrome. The common peptide stands a good chance to be a new B cell epitope both in mugwort and cabbage, and might participate in inducing severe allergic reactions in patients sensitised to cabbage.

1538
Cross-sensitisation profiles of edible nuts and seeds in a birch-endemic region

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Background: Cross-reactivity is well recognised for nuts and seeds but it exists also between nuts and pollen. In birch-endemic regions birch pollen acts as a primary sensitising agent and induces cross-reactivity for edible nuts and seeds.

Aim of this study was to elucidate the strongest cross-sensitisations to nuts, seeds and birch pollen among a population of nut-sensitised patients living in a birch-endemic region.

Method: Patients referred to Skin and Allergy Hospital in Helsinki, Finland for food allergy testing during 1997–2013 were included in the study. Skin prick tests were performed to walnut, pecan nut, brazil nut, cashew, pistachio, macadamia nut, coconut, hazelnut, almond and peanut. In patients with suspected seed allergy, SPT were carried out to sesame seed, sunflower seed, poppy seed, pine nut and linseed. A wheal diameter of 3 mm or more was considered positive. Data was analysed with correlations and hierarchical cluster analysis.

Results: Skin prick test results of 1066 patients were analyzed. Strongest associations were found among tree nuts between pecan nut and walnut which belong to the botanical family of Juglandaceae, and pistachio and cashew belonging to Anacardiaceae. Correlation with Spearman's rho between pecan nut and walnut was 0.623* and between pistachio and cashew 0.586*. Of the 1066 patients, 850 were tested for birch sensitisation and 59.7% (636/850) of them were positive. Partial correlations between pecan nut and walnut, and cashew and pistachio were stronger (0.723* and 0.700*) when controlled for birch. Birch pollen sensitisation was most strongly associated with hazelnut (0.533*) and almond (0.526*). Seeds associated mainly with other seeds except sesame seed which correlated moderately also with almond (0.566*) and peanut (0.555*). Peanut, hazelnut, almond and birch formed a cluster in the hierarchical cluster analysis $*P = 0.000$.

Conclusion: Although birch is a major driving factor for sensitisation patterns for nuts, there are clear associations between individual nuts such as cashew and pistachio, possibly indicating primary sensitisation and clinical allergy.

1539
Level of sIgE to PRU p3: is there any clinical significance in Sicilian peach allergic patients compare to north-east Italian peach allergic patients?

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Background: In Italy, LTP is the more frequent cause of food allergy and anaphylaxis. The clinical expression range from asymptoms, OAS, gastrointestinal, urticaria/angioedema and anaphylactic shock. An increase level of tryptase is considered the best marker of anaphylaxis but it's still unknown its role in food allergy. We've investigated the levels of sIgE to Pru p3, basal serum tryptase and the severity of the clinical reaction in two different peach allergic patients from two different Italian areas.

Methods: 133 patients Pru $p3^+$ were recruited, 71 (41 F/30 M) from Allergy Unit Buccheri La Ferla and IBIM-CNR (Palermo, South Italy) and 62 (34 F/28 M) from S.M. degli Angeli Pordenone (North-east Italy). All have a positive history with peach confirmed by SPT and *in vitro* test. Patients were divided into groups: asymptomatic, OAS, mild reactions grade I–II and severe reactions grade III–IV. sIgE levels of Pru p1, 3, and 4 were measured by ImmunoCAP system. After 3–4 months of the allergic reaction, tryptase was measured in 55 Sicilian patients by immunofluorescence.

Results: Sicilian ROC curve has identified a value of 2.87 kUA/l that discriminate asymptomatic from allergic patients(sensibility: 91.04% (95% CI: 81.5–96.6), specificity: 75% (95%CI: 19.4–99.4) LR + 3.64 (95% CI:2.1–6.4). A value of 10.2 kUA/l discriminate severe reactions from other reactions (sensibility: 70.0% (95% CI:45.7–88.1), specificity: 88.9% (95%: CI:65.3–98.6); LR + 6.30 (95% CI:4.5–8.8). Pordenone ROC curve has identified a value of 2.68 kUA/l that discriminate asymptomatic from allergic (sensibility: 36.0%; 95% CI: 22.9–50.8), specificity (69.2%; 95% CI:38.6–90.9), LR + 1.17 (95% CI:0.7–2.0). AUC that assessed symptomatic vs asymptomatic from Palermo and Pordenone were 0.873 and 0.631. AUC that assessed severe reaction vs all other reactions were 0.819 e 0.755. Significant difference in the levels of sIgE to Pru p3 was found in Sicilian allergic vs asymptomatic patients (Mann–Whitney; $P = 0.0126$), in reactions grade I–II vs reactions grade III–IV (Mann–Whitney: $P = 0.0008$). There was a correlation between the grade of the clinical reaction and the levels of sIgE to Pru p3 (Spearman's rho = 0.366; $P = 0.0017$). Non significant difference was found in the levels of sIgE to Pru p3 in none of the northeast patients. Significant correlation was found between the grade of the clinical reaction and tryptase levels (Spearman's rho = 0.344; $P = 0.0102$).

Conclusion: Our results suggest that the levels of sIgE to Pru p3 could be used to assess the clinical risk of an allergic reaction.

1540
Sensitisation to lipid transfer proteins and profilin – the Portuguese reality

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Background: Lipid transfer proteins (LTPs) and profilins are the most important panallergens in pollen and plant food allergic patients. LTPs are food allergens that usually induce systemic symptoms; profilins are responsible for the pollen-fruit syndrome, in which fruit-allergic patients cosensitised to pollens experience oral symptoms.

Methods: A study was conducted in order to find the frequence of symptomatic/asymptomatic sensitisation to LTP (Pru p3) and profilin (Pho d2) in patients with positive skin prick tests (SPT) to pollens/fruits/vegetables (PFV). During 4 months, all the patients who had positive SPT to PFV performed SPT to LTP and profilin and filled a questionnaire to evaluate food allergy (FA).

Results: We evaluated 227 patients, mean age 21.7 years (50.7% female). We found that 32 had sensitisation to LTP (FA in 19), 19 to profilin (1 with FA) and 3 were sensitised both to LTP and profilin (none with FA). Of the 218 patients with positive SPT to pollens, 27 were positive to LTP (12.4%) and 18 (8.3%) to profilin. Of the 27 patients with positive SPT to pollens and LTP, 14 had FA. Among the 18 patients with positive SPT to pollens and profilin, 1 had FA. Of the patients who

presented positive fruit SPT (29), 18 (62.1%) were positive to LTP and 2 to profilin (6.9%). All patients with positive SPT to fruits and LTP had FA.

Conclusion: In this sample, there is a high prevalence of sensitisation to pollens but the number of patients sensitised to profilin is lower than expected and this sensitisation is not associated with the presence of allergy to fruits/vegetables (FV). The data shows that sensitisation to LTP is frequent in patients sensitised to FV and in these cases clinical manifestations are frequent. On the contrary, when there is only pollen sensitisation, the percentage of LTP sensitisation is lower. The cosensitisation to pollens and FV does not seem to be associated with the severity of clinical manifestations of FA in patients where food allergy exists.

1541
Food-specific IgE show a predictable hierarchical order in patients with LTP syndrome

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Background: Lipid transfer protein (LTP) is a widely cross-reacting allergen in plant foods. This study aimed to assess whether IgE to vegetable foods show predictable trends in LTP allergic patients.

Method: Clinical allergy to plant foods other than peach was sought in 15 consecutive peach-allergic adults monosensitised to LTP. IgE specific for peach, apple, hazelnut, walnut, peanut, lentil, maize, soybean, tomato, sesame, mustard melon, kiwi, and celery as well as to mugwort pollen was measured.

Results: Peach-specific IgE levels exceeded IgE to all other study foods. The higher were peach-specific IgE levels, the higher was the probability that other plant-derived foods scored positive. Mean IgE levels specific for all study foods were strongly correlated to peach specific IgE. Food-specific IgE followed a rather precise hierarchy both in terms of number of positive *in vitro* tests and of IgE levels, with apple at the second place after peach, followed by walnut, hazelnut, peanut, lentil, maize, soybean, tomato, kiwi, sesame, mustard, melon, and celery. Such hierarchy was not necessarily paralleled by clinical allergy as lentil, maize, and soybean scored positive in the majority of patients but induced allergy in 0, 1, and 0 patients, respectively. IgE levels were not necessarily correlated with the severity of clinical allergy. Little or no IgE reactivity to mugwort pollen was found.

Conclusion: In LTP syndrome IgE reactivity to foods other than peach is in most cases predictable and follows a regular sequence that probably depends on the degree of homology with Pru p 3. The reasons why some foods are tolerated by most patients despite elevated IgE reactivity remains to be elucidated.

1542
Analysis of molecular profiles and search for biomarkers to optimise management of patients with allergy to nuts

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Nut allergy is a common and severe cause of food allergy which decreases the quality of life and can elicit life threatening reactions. The aim of the project is to investigate and describe profiles of sensitisation to purified allergens at molecular level, the cross-reactivity among homologous proteins in order to establish clinical syndromes of nut allergy based on allergy to purified allergens. These findings along with clinical patterns of allergy to different nuts led us to describe biomarkers to diagnosis of nut allergic patients.

Patients with nut allergy were selected following the diagnostic algorithm from SEAIC (anamnesis, skin tests and/or IgE and/or challenge tests) with the methodology recommended in the guidelines for the study of food allergy. The major allergens described in tree nuts [7S vicilins, 11S legumins, 2S albumins, lipid transfer proteins (LTPs) and thaumatin-like proteins (TLPs)] were purified from chestnut, hazelnut, peanut and walnut. The allergenic molecular basis of these proteins was studied in order to try to understand the possible mechanisms that are mediating sensitisation and cross-reactivity and the prevalence of these proteins in a Spanish population, with the use of protein microarrays.

1543
Diagnostic accuracy of specific IgE to components in diagnosing peanut allergy: a systematic review

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Background: In the diagnostics of peanut allergy the predictive value of skin prick test (SPT) and specific IgE (sIgE) to peanut extract in diagnosing peanut allergy is suboptimal. Recent studies have evaluated sIgE to peanut components as a possible new diagnostic tool. Our aim was to systematically search the literature to assess the diagnostic value of sIgE to peanut components in diagnosing peanut allergy.

Methods: A literature search was performed in PubMed, Embase and the Cochrane Library and results were subsequently screened for in- and exclusion criteria. The quality of eligible studies was assessed using a standardised quality assessment tool (QUADAS-2). Data on sensitivity, specificity, positive and negative predictive values and positive and negative likelihood ratios was extracted or calculated for a descriptive analysis.

Results: Twenty-two studies were eligible for analysis, of which 21 studies in pediatric populations. Most studies reported on sIgE to peanut extract (15) and sIgE to Ara h 2 (12), followed by SPT (9), sIgE to Ara h 1 (7), Ara h 3 (6), Ara h 8 (5), Ara h 9 (4) and Ara h 5 (2). All studies were at risk of bias or caused applicability concerns on at least one item of the QUADAS-2 quality assessment tool. The best combination of diagnostic accuracy measures of all diagnostic tests was found for sIgE to Ara h 2. This finding was independent of geographic location. Compared to SPT and sIgE to peanut extract, sIgE to Ara h 2 was mainly superior in diagnosing peanut allergy in case of a positive test result. Worst diagnostic accuracy measures were found for sIgE to Ara h 8 and sIgE to Ara h 9.

Conclusion: sIgE to Ara h 2 showed the best diagnostic accuracy of all diagnostic tests to diagnose peanut allergy. Compared to the currently used SPT and sIgE to peanut extract, sIgE to Ara h 2 was superior in diagnosing peanut allergy and should therefore replace these tests in daily clinical practice, especially in children.

1544
Investigation to the sensitisation profile against PR10, profiling, non-specific lipid transfer proteins (nsLTP) and storage proteins (SP) in pollen positive serum

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Introduction: Although structural similarity and related cross reactivity (e.g. pollen vs. food) among PR10, profilin, nsLTP and SP allergen groups is well known, the cause of sensitisation is often unknown. PR10 and profilin may cause oral allergy syndrome and nsLTP and SP systemic reaction. We investigated the sensitisation pattern of recombinant allergen components of PR10, profilin, nsLTP and SP groups in IgE pollen positive serum samples.
Materials and methods: In 117 pollen positive (birch, timothy or mugwort) serum samples (43 f., 4–70 years, 74 m., 2–76 years) we determined sIgE against allergens PR10: Bet v1, Gly m4, Api g1, Pru p1, Ara h8, Cor a1; profilin: Bet v2, Phl p 12, Pru p4; nsLTP: Pru p3, Ara h9, Cor a8; SP: Ara h1, Ara h2, Ara h3, Cor a9, Cor a 14, peanut (f13), hazelnut (f17) using CAP. Results were considered positive at sIgE >0.10 kU/l.
Results: Correlations and fractions of double-positive samples are marked in PR10 and profiline groups (structural similarity), while they are weak in nsLTP and SP groups (structural differences).

Pairwise correlations within recombinant allergen groups yielded (R^2):

(a)PR10: Bet v1/Gly m4 0.77, Bet v1/Api g1 0.55, Bet v1/Pru p1 0.84, Bet v1/Ara h8 0.83, Bet v1/Cor a1 0.93, Gly m4/Api g1 0.66, Gly m4/Pru p1 0.90, Gly m4/Ara h8 0.91, Gly m4/Cor a1 0.74, Api p1/Pru p1 0.62, Api g1/Ara h8 0.69, Api g1/Cor a1 0.54, Pru p1/Ara h8 0.88, Pru p1/Cor a1 0.82, Ara h8/Cor a1 0.81;
(b)profilin: Bet v2/Phl p12 0.90, Bet v2/Pru p4 0.85, Phl p12/Pru p4 0.96;
(c)nsLTP: Pru p3/Ara h9 0.60, Pru p3/Cor a8 0.71, Ara h9/Cor a8 0.61;
(d)SP: Ara h1/Ara h2 0.79, Ara h1/Ara h3 0.76, Ara h1/Cor a9 0.57, Ara h1/Cor a14 0.27, Ara h2/Ara h3 0.60, Ara h2/Cor a9 0.54, Ara h2/Cor a14 0.27, Ara h3/Cor a9 0.67, Ara h3/Cor a14 0.32, Cor a9/Cor a14 0.64.

Fractions of double-positives are 85–100% (PR10), 82–100% (profilin), 62–100% (nsLTP) and 63–93% (SP).

Fractions of double-positive samples for native and recombinant allergen components were 78–89% (PR10), 27–31% (profilin), 22–35% (nsLTP) and 27–32% (SP) for f13 and 78–92% (PR10), 26–31% (profilin), 22–34% (nsLTP) and 26–35% (SP) for f17, respectively.
Conclusion: Our results indicate the need to determine the complete sensitisation pattern of PR10/profilin and nsLTP/SP groups, esp. in food allergy, to better estimate clinical relevance of sensitisation. *In vitro* sensitisation pattern may not replace clinical challenge test, but will help to identify patients at risks for systemic reaction.

1545
Patterns of sensitisation and clinical reactivity to wheat and grass pollen in children

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Background: Adverse reactions to wheat are often reported by children and adults. Interpretation of sensitisation to wheat pollen and wheat flour with or without sensitisation to grass pollen can be a clinical problem in these patients. We set out to look at the patterns of wheat and grass pollen sensitisation and clinical reactivity in a group of 11 year old children in the United Kingdom.
Method: The FAIR birth cohort included all babies born on the Isle of Wight (UK) between September 2001 and August 2002 (n = 969). Children were followed up at 1, 3 and 10/11 years; the 10/11 year follow up was completed in 2011–12. 584 children were skin prick tested during the 11 year old follow-up.
Results: At 11 years of age, 145 (24.8%) children were sensitised to any of the predefined allergens; 85 (17.1%) to any of the predefined food allergens (milk, egg, wheat, cod, peanut, sesame and lupin) and 141 (24.1%) to any of the predefined aeroallergens (house dust mite, cat and grass). 96 (16.4%) were sensitised to grass pollen, 79 (13.5%) were sensitised to wheat pollen and 75 (12.8%) was sensitised to both wheat and grass pollen. Out of 79 children sensitised to wheat pollen, 75 were also sensitised to grass. Sixty-six of the children sensitised to wheat pollen had a repeat SPT to wheat flour. Only one child was sensitised to wheat flour. This child was not sensitised to grass pollen but clinically allergic to wheat proven by food challenge. Of the remaining 78 children sensitised to wheat pollen only one child was clinically allergic to wheat proven by double blind placebo controlled food challenge. No child showed sensitisation to wheat flour but not to wheat pollen. Specific IgE levels to grass and wheat is currently being analysed.
Conclusion: Care should be taken with choice of SPT solution and interpretation of results when dealing with sensitisation to wheat allergens.

1547
Relevance of soy allergens: Gly m 4, Gly m 5 and Gly m 6 in soy allergy diagnosis

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Background: Soy is one of the major food allergens and tools to diagnose soy allergy are currently not accurate enough. Our objective was to improve diagnosis of soy allergy by characterization of 27 patients with a clinical history of soy allergy. Eventually, dietary advice and treatment strategy can be adapted to the specific diagnostic profile of the patient.
Method: Adults with diagnosed soy allergy were selected from an outpatient clinic (n = 27). Patients completed a questionnaire to report their symptoms upon soy consumption. sIgE to soybean, Gly m 4, 5 and 6 was determined by ImmunoCAP. sIgE levels were used to make a distinction between different soybean allergy types as well as to evaluate their diagnostic value.
Results: Of 27 patients, 16 patients (59.3%) reported allergy towards soy milk only, five patients (18.5%) reported allergy towards both soy milk and processed soy, five patients (18.5%) reported allergy to processed soy only and one patient did not report symptoms. Based on ImmunoCAP outcomes, patients were divided into three groups, (i) Gly m 4 positive (81.5%), (ii) Gly m 5 and 6 positive (7.4%) and (iii) Gly m 4, 5 and 6 positive (11.1%). Twenty-five patients (92.6%), including all patients with symptoms towards soy milk only and being part of group 1 and 3, showed positive IgE values for both Gly m 4 and homologous Bet v 1. A positive correlation was found between Gly m 4 and Bet v 1 sIgE (R^2 = 0.668) and a negative correlation was found between Gly m 4 and soybean (R^2 = 0.028). Patients with positive levels for Gly m 5 and 6 (group 2),

and Gly m 4, 5 and 6 (group 3) had significant higher IgE for soybean ($P < 0.05$) compared to those with only Gly m 4 positive IgE (group 1). Positive correlations were found between Gly m 5 and soybean ($R^2 = 0.747$) and Gly m 6 and soybean ($R^2 = 0.918$).

Conclusion: Total soybean IgE is not an accurate tool in diagnosing soy allergy. By measuring soybean only, 59.3% of patients were misdiagnosed.

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Table 1. Correlations (r) among IgE levels to corresponding allergen sources (P < 0.0001 for all correlations)

	All children		Children exclusively sensitized to seed storage proteins	
	Lemon seed	Orange seed	Lemon seed	Orange seed
Cashew nut	0.90	0.85	0.97	0.94
Pistachio	0.90	0.85	0.94	0.91
Ana o 3	0.79	0.75	0.84	0.84

1548
Cross-reactivity between Anacardiaceae (cashew/pistachio) and Rutaceae (orange/lemon) seeds

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Background: Allergy to Rutaceae (orange, lemon, mandarin) seeds, although rather rare, has been exclusively reported in patients with IgE-sensitisation and/or clinical allergy to cashew nut. The aim of this study was to delineate potential cross-reactivity between proteins of Rutaceae seeds and closely related Anacardiaceae family members (cashew, pistachio).

Method: Sera from children allergic to cashew ($n = 63$), pistachio ($n = 63$) and children with a positive challenge ($n = 5$) or history suggestive of orange/lemon seed allergy ($n = 11$) were analyzed for IgE against cashew, pistachio, orange and lemon seed extracts and Ana o 3 by ImmunoCAP. Additionally, molecular sensitisation profiles of all patients were analyzed by using the ISAC chip. Correlation tables were drawn and Pearson correlation coefficients (r) were calculated.

Results: Lemon and orange seed-specific IgE levels were found to be highly correlated with IgE levels to cashew and pistachio, with an r ranging from 0.85 to 0.90. After exclusion of sera from children sensitised to panallergens (LTP, PR-10, profilin & CCD/ $n = 51$), the observed correlations were exceedingly high, with an r of 0.97 between cashew- and lemon seed-IgE levels. IgE levels to lemon/orange seeds were also found to correlate well with IgE levels to the cashew 2S albumin,

Ana o 3.

Conclusion: Our results indicate high level of cross-reactivity between cashew/pistachio and orange/lemon seed storage proteins. Cross-inhibition experiments are underway to confirm the findings and reveal the primary sensitiser in subjects displaying this cross-reactivity pattern.

1549
Safe food for LTP syndrome

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Background: Lipid Transfer Protein (LTP) allergy constitutes the first cause of food allergy to vegetables in Southern Europe. LTPs are highly stable proteins, resistant to both gastric digestion and high temperatures. Allergic reactions to multiple vegetables not phylogenetically related are produced based on the cross-reactivity among these proteins. This phenomenon has been named LTP syndrome.

In previous studies we reported about four patients with wheat allergy that tolerated a whole-grain wheat cereal biscuit without suffering from any symptoms. The high pressures and temperature used in the manufacturing process seemed sufficient to inhibit the allergenic capacity of the LTPs, so that this process could be applied for other plant foods to obtain the proteolysis of these allergens.

Method: In this work, we have extended the study and tested the resistance of the LTPs from walnut, hazelnut, peach, wheat and pasta in a similar treatment. For this, we cooked the different foods in a pressure cooker trying to mimic the industrial manufacturing process. Molecular characterisation of the extract was determined by SDS-PAGE and we tested the presence of different relevant allergens by specific antibodies.

Results: The treated extracts showed the decay of the LTP and other storage allergens such as globulins and vicilins. Finally, we checked the decrease of IgE recognition with a pool of sera from allergic patients. In clinical trials, oral food challenge was performed in three patients with LTP syndrome; although 2 of them suffered from mild reactions, one of them tolerated this prepared foodstuff.

Conclusion: In conclusion, more research would be necessary to find a safe alternative for patients with LTP syndrome.

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1551
The burden of chronic urticaria from the patients' perspective

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Background: Chronic spontaneous/idiopathic urticaria (CSU) is a skin disorder characterised by itchy hives for ≥6 weeks, without an identified trigger. It can impact patients' lives but data quantifying the burden are scarce. This study was conducted to assess the burden of disease of patients with CSU using patients currently treated for chronic hives (CH) as a proxy.
Method: Data came from the 5EU National Health and Wellness Survey collected in 2010, 2011, 2013, representative of the adult population of France, Germany, Italy, Spain, and the UK in terms of age and sex. PRO measures included SF-12v2 (2010 & 2011) or SF-36v2 (2013), the Work Productivity and Activity Impairment questionnaire, and self-reported healthcare use in the prior 6 months. Respondents who indicated current use of a prescription for CH (cases) were matched 1:4 to those who reported never experiencing CH (controls) according to year of survey, country, gender, age (±2 years), and Charlson comorbidity index (CCI) category (0, 1–2, 3–4, or 5+), and compared using *t*-test and chi-square.
Results: Cases ($n = 343$) and controls ($n = 1372$) did not significantly differ in terms of country of residence, sex, age, body mass index, marital status, educational attainment, or mean CCI (all $P > 0.05$). Cases had worse mental (39.9 vs. 44.8, $P < 0.001$) and physical component scores (44.1 vs. 48.5, $P < 0.001$), SF-6D health utility scores (0.63 vs. 0.70, $P < 0.001$), more activity impairment (44.8% vs. 28.0%, $P < 0.001$), and more healthcare provider visits (10.8 vs. 5.8, $P < 0.001$) than controls. Employed cases reported greater absenteeism (11.6% vs. 5.8%, $P < 0.01$), presenteeism (31.0% vs. 18.0%, $P < 0.001$) and overall work impairment (37.1% vs. 21.7%, $P < 0.001$) than employed controls.
Conclusion: CSU may have a substantial impact on patients' well-being, healthcare use, work productivity, and activities of daily living. Further research confirming the burden of disease in diagnosed CSU patients should be considered.

1552
Diagnostic procedures in chronic urticaria: a national survey of existing protocols

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Background: Chronic urticaria (CU) is frequently evaluated by Allergists. In recent published guidelines on diagnostic procedures when assessing CU there is a clear tendency to restrict routine diagnostic procedures, ordering tests only if suggested by a thoroughly history. We aimed to analyse existing diagnostic protocols in CU in Spanish allergy clinics and to compare them with existing guidelines.
Methods: In 2012, on behalf of the Skin Allergy Committee of the Spanish Society of Allergy and Clinical Immunology (SEAIC) an online questionnaire was sent to all members of the SEAIC asking to fill out one per allergy clinic. It queried in detail the main diagnostic procedures ordered to a given patient suffering from chronic urticaria and if they were performed following local protocols. We then compared data with available guidelines from EAACI, WAO and BAD.
Results: We obtained 71 responses of different allergy clinics. 45% of them follow a local study protocol while the rest agreed with published guidelines. Differential blood count, biochemistry, thyroid hormones and skin prick tests (SPT) are performed in more than 75% of centers. ESR, complement parameters, autoimmune status as well as total IgE are ordered in more than 50% of centers. Other diagnostic procedures were mainly performed if specific underlying disease was suspected.

Allergens tested by SPT, were in 59% a battery of food allergens, in 42% a battery of inhalant allergens and in 72% *Anisakis simplex*. *Helicobacter pylori* infection is rarely assessed and autologous skin test is not considered a protocol method in any center. Skin biopsy is only performed on specific suspicion.
Conclusions: There are large differences among diagnostic protocols when assessing CU, not only when comparing to other existing guidelines but also within one country. International guidelines are helpful but they should be adapted to local characteristics. This study shows as well the need to develop simpler real life guidelines.

1553
Chronic urticaria as a possible manifestation of primary biliary cirrhosis

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Background: Chronic spontaneous urticaria (CSU) is a quite common disease defined as presence and spontaneous recurrence of wheals for at least 6 weeks. The cause of CSU remains unknown in 70–90% of cases, but in some patients it can be associated with various underlying autoimmune diseases. We present one of the first cases of combination CSU with primary biliary cirrhosis (PBC) – a rare autoimmune liver disease.
Method: 30 year old female suffered with CSU and angioedema for 3 years with no other complaints and with a good response from antihistamines. The quality of life was not significantly reduced.
Results: The laboratory studies revealed high blood level of eosinophils (9%) and ESR 40 mm/h, high serum levels of ALT (48 IU/l), AST (41 IU/l), GGT (91 IU/l), total protein (87.9 g/l), tumor necrosis factor (9.7 pg/ml), IgG (21.5 g/l), IgA (5.5 g/l), low serum level of vitamin D (10.4 pg/ml). We found positive anti-mitochondrial antibodies (AMA) 52.9 U/ml, antinuclear antibodies (ANA) at a titer of 1:640, smooth muscle antibodies (ASMA) at titer 1:20. The histological analysis of a liver

biopsy showed nonsuppurative portal inflammation and was diagnostic of PBC.
Conclusion: We are aware of four case reports describing CSU as a presenting symptom of PBC. In our case, we showed that the PBC may last for a long time without clinical symptoms but with concomitant urticaria, increased levels of liver enzymes and the presence of specific autoantibodies. Therefore, our data indicate that broader laboratory assessment should still be considered in individual cases even in patients with mild CSU, good quality of life, the efficacy of treatment and without other signs or symptoms of PBC.

1554
Chronic spontaneous urticaria – the Saskatchewan experience and questionnaire survey

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Background: In this questionnaire study, we examined duration of the urticaria, perceived response to treatment, frequency of hospital visits, disruption to work and school, beliefs and suppositions, current disease activity, and satisfaction with treatment.
Methods: The patients were ascertained from the patients seen in the Division of Dermatology. One-hundred and seventy three 173 patients with CSU had been seen over the 10 year period between 2003 and 2013 (F:130, M:43). One-hundred and one participants responded to several mailings and follow up phone calls.
Results: Of the 101 respondents, 80 were women and 21 men. The mean age was 36 years. The average duration of symptoms was 9.3 years. Half the respondents no longer had hives. One fifth of the patients had experienced episodes of angioedema, 12% had difficulty breathing at some time, but only 4% had to be seen in the emergency room. Many (71.2%) had missed work or school because of the urticaria. Common symptoms associated with attacks of hives were pruritus, anxiety, disturbed sleep, and concerns regarding their appearance. About one in ten was concerned about dying during an episode. While more than 30% could not attribute an identifiable cause for their urticaria suggested triggers included stress (22%), environmental factor (18%) and foods (15%).

Half the patients were frustrated by the lack of effective treatment but about one-third felt antihistamines alone gave adequate relief of urticaria. Patients also reported use of prednisone and intravenous steroids and antihistamines as treatments for acute episodes. An Epi-pen was used by only two patients.
Conclusion: In this follow-up questionnaire study the average duration of urticaria was over 9 years but half the patients reported no episodes of hives for at least the past 3 months. CSU has significant effects on quality of life and there is frustration at the lack of effective treatment.

1555
Prevalence of physical, cholinergic and spontaneous urticaria between patients with chronic urticaria in a tropical environment

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Background: The epidemiologic profiles of chronic urticaria (CU) vary considerably among regions, and few such data are available in Latin America. We evaluated the prevalence of physical (PU), cholinergic and spontaneous urticaria (CSU) between patients with CU in two different Latin American cities, using clinical history and physical provocation test.
Method: We performed a prospective multicenter study in two tropical cities from Colombia, including patients over 12 years with chronic urticaria defined as recurrent wheals with/without angioedema lasting for ≥6 weeks. We asked to each patients about physical triggers and with physical provocation test, we evaluated in all patients if wheals are evoked by a cholinergic or physical stimulus such as water, pressure, friction or cold contact.
Results: Two-hundred and thirteen patients with chronic urticaria agreed to participate in the study. One hundred and thirty four were female, the mean age at diagnosis was 26 years (14–61) and the mean disease duration was 2 years (range 3–156 months). 70.4% had CSU, 1.4% had cholinergic urticaria, 5.6% had PU, and 23% had CSU and PU. 67% patients associated symptoms with one or more physical triggers (friction 43%, Heat 32%, cold 23%, pressure 19% and exercise 8%). The most common type of PU demonstrated with physical provocation test, was symptomatic dermographism (33%) followed by cold urticaria (14.9%), pressure urticaria (7.9%) and delayed pressure urticaria (1.8%), respectively. Self-report had a good and statistically significant association with dermatographic and pressure provocation test, but had not association with others physical provocation test. None of the cases had multiple types of PU.
Conclusion: The frequency of PU is high in tropical cities between patients with chronic spontaneous urticaria. Self-report is useful to identify friction and pressure as precipitating factors, but for other physical triggers, provocation test with different stimulus is necessary, to clarify clinical relevance.

1556
Epidemiological and clinical profile of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers-induced angioedema at the emergency department

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Background: Angiotensin converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARBs) may cause angioedema (AE) by interference with the bradykinin metabolism. This side-effect is so unpredictable, that often goes unnoticed at the Emergency Room (ER).
Methods: All cases of AE caused by ACEi/ARBs attended at the ER of a 3th level hospital in Madrid, from the 1st of January to the 30th of November 2013, were later studied at the Allergy Department.
Results: 102 576 patients had received attention for medical emergencies at the ER. 247 (0.24%) of them referred AE without urticaria. Twenty eight cases of AE (11%) were caused by ACEi (7.7%), ARBs (2.8%) or both (0.8%). The patients mean age was 65.28 years (±14 SD), 67.9% males. Seven patients (25%) had had previous outbreaks of AE, none had a familiar history of AE, and 11 (39%) were atopic. The antihypertensive treatment mean duration was 34.61 months (±30.9 SD; median 24; range 1–120). The AE localised exclusively in face and/or neck, with upper airway involvement in seven patients (25%). Tracheal intubation was needed in one patient. All patients had been treated with corticosteroid and/or antihistamine drugs, except from 2, who didn't received treatment. The mean time to the onset of symptoms relief was 4.48 h after treatment (±2.96 SD; median 4; range 1–24), with complete resolution in 46.93 h (±47.58 SD, median 24, range 8–168). The ACEi/ARBs drugs had been suspected as the causal agents at ER only in five patients (18%).
Conclusion: The ACEi/ARBs are, rarely suspected, but not uncommon causes of the AEs attended at the Emergency Departments. It is mainly a not peripheral

AE, which very often affects the upper airways. Commonly, the first outbreak starts after a prolonged treatment and it is not related to a familiar history of AE. The response to conventional treatment is very poor, so new drugs should be more often tried.

1557
The biomarkers of underlying systemic diseases in patients with chronic urticaria

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Background: Chronic urticaria (CU) is a quite common disease defined as a presence and recurrence of wheals for at least 6 weeks. According to recent studies in 10–50% cases CU can be a symptom of an underlying systemic disease such as autoinflammatory, autoimmunity or infection. The aim of our study was to evaluate the importance of the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and D-dimer as biomarkers of underlying disorders in patients with CU.
Method: We followed up 120 patients with CU of different severity and divided them into two groups: idiopathic/spontaneous ($n = 57$, 47.5%) and CU associated with underlying diseases and autoimmune disorders ($n = 63$, 52.5%). The latter group included patients with Schnitzler syndrome (SS, $n = 2$), Churg-Strauss syndrome (CSS, $n = 2$), Sjögren's syndrome (SjS, $n = 1$), systemic lupus erythematosus (SLE, $n = 1$), other autoimmune diseases ($n = 47$) and infections ($n = 10$). Autologous serum skin test (ASST) was performed for revealing autoimmune processes and serum levels of ESR, CRP and D-dimer were measured.
Results: Serum levels of ESR, CRP and D-dimer were significantly higher in patients with CU and underlying systemic diseases in comparison with the idiopathic urticaria group (mean ± SD: 16.3 ± 11.7 vs 8.9 ± 7.9 mm/h, $P < 0.005$; 14.6 ± 15.5 vs 3.6 ± 6.2 mg/l, $P < 0.005$; 643.6 ± 866.0 vs 250.8 ± 384.8 ng/ml, $P < 0.005$, respectively). Moreover, high serum levels of ESR, CRP, D-dimer and positive ASST were more frequently observed in patients with severe autoimmune urticaria than in those with idiopathic disease.
Conclusion: Chronic urticaria may be a manifestation of an underlying disease, and we recommend measuring the serum levels of ESR, CRP and D-dimer as well as performing ASST in all CU patients. It may help in CU severity assessment and in early diagnosis of autoimmune and autoinflammatory disorders such as SLE, CSS, SjS, SS and others. In these cases, treatment of the underlying condition may be warranted.

1558
'Chronic idiopathic urticaria' – the gap between state-of-the-art medical knowledge and drug licenses in force

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Background: 'Chronic idiopathic urticaria' (CIU) is a term difficult to accept in view of current state of knowledge, mainly due to its vague definition and contradictory uses in literature. Therefore, the EAACI experts recommended in 2009 to cease using this term in allergy practice. This has been reinforced at the 4th International Consensus Meeting on Urticaria (2012). Although the present urticaria classification does not acknowledge the existence of such entity, the term 'chronic idiopathic urticaria' remains preserved in ICD-10 and numerous Summaries of Product Characteristics (SmPC) defining the allowable uses of drugs. The aim of the study was to analyse this discrepancy.
Method: Medicines authorized exclusively for the treatment of 'chronic idiopathic urticaria' were identified in three EU countries: Germany, Poland and United Kingdom.
Results: Among 210 drugs registered in Germany for the treatment of urticaria of any kind, SmPC of 86 medicinal products (40.9%) contained the official indication 'chronic idiopathic urticaria' as the only type of urticaria mentioned. In Poland, the respective numbers were 213 and 61 (28.6%), out of 158 drugs registered in UK for urticaria treatment, 78 (49.4%) medicinal products were licensed for 'chronic idiopathic urticaria' only.
Conclusion: A considerable proportion of drugs available in the EU for urticaria treatment are licensed exclusively for 'chronic idiopathic urticaria' – a diagnosis inconsistent with current medical knowledge. Adhering to the state-of-the-art urticaria classification makes any prescription of such drugs into 'off-label use'. Lawyers might interpret this as 'medical experiment' requiring bioethics clearance and 'clinical trial insurance' for each such patient. As in most cases law wins over knowledge and reason, the use of such drugs seems risky for doctors required to act according to both state-of-the-art medical knowledge and legal regulations.

1559
Acute urticaria caused by infections in China: a hospital-based study

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Background: Urticaria is the most common cutaneous allergic disease. Infections, food and drugs are common causes of acute urticaria. To date, few reports have been published on the clinical features, treatment, and prognosis of acute urticaria caused by infections in Chinese patients.
Method: This retrospective study included 69 inpatients diagnosed acute urticaria caused by infections from 2008 to 2013 at the First Hospital of China Medical University.
Results: Of 245 inpatients with acute urticaria, 69 cases were caused by infections (28.2%). The infections included 28 upper respiratory infection (40.6%), 12 gastroenteritis (17.4%), 7 mycoplasma pneumonia (10.2%), seven urinary tract infection (10.2%), etc. The peripheral blood white blood cell and neutrophil counts, erythrocyte sedimentation rate, serum C-reactive protein and procalcitonin were significantly higher in the patients with acute urticaria caused by infections than those patients caused by other factors. Systemic corticosteroids combined with systemic antibiotics were administered in 48 cases (69.6%). The mean regression time of skin lesions were 7.2 days (SD, 7.1). The treatment duration of systemic corticosteroids, antibiotics and antivirals were 6.3 days (SD, 3.1), 5.5 days (SD, 2.2) and 6.7 days (SD, 1.8), respectively. Of the 69 patients, 65% of the patients healed in 1 week, 88.4% cured in 2 weeks, 95.7% cleared in 3 weeks, and 100% resolved in 6 weeks.
Conclusion: Infections, especially viral and bacterial upper respiratory tract infection, accounted for a major cause of inpatients with acute urticaria. Infection-related laboratory parameters including white blood count and differential count, erythrocyte sedimentation rate, C-reaction protein, and procalcitonin were useful for monitoring the disease activity. After effective treatment with systemic corticosteroids, antihistamine, antibiotics or antivirals, the overall prognosis was good in all the patients.

1560
Coagulation defects in chronic urticaria

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Background: Patients with chronic urticaria (CU) show some alterations of the coagulation components, with thrombin generation and activation of the tissue factor pathway. The role of these findings is still unknown, being the expression of a pro-inflammatory effect or representing a defect in the coagulation cascade. The thrombin generation test (TGT) is a global assay that measures the overall tendency of a plasma sample to form thrombin after the initiation of coagulation.
Objective: To perform TGT in plasma of patients actively suffering from CU and to find out if the results have a relation with the type or severity of urticaria, the presence of comorbidities or with other analytical parameters.
Method: We performed an observational, descriptive study in 22 adult patients diagnosed with CU and eight healthy controls. All patients were informed about the aims of the study and accepted to participate. A broad spectrum of blood tests and the autologous serum skin tests (ASSTs) helped to classify the urticaria as autoimmune, and rule out other conditions. The severity of the disease was evaluated by the questionnaire Urticaria Severity Score (USS). Plasma was collected to analyze the generation of thrombin.
Results: There were not statistically significant differences between the severity index and the results of the TGT. However, we observed a tendency to a hypercoagulable pattern in patients with severe CU (10/22). Patients with a history of oedema (50%), showed a higher thrombin peak-height and an increased area under the curve (73%). Patients who presented previous symptoms of oedema, showed higher levels of thrombine than patient without oedema. The difference was more pronounced when compared with healthy controls. We couldn't find differences between TGT and other analytical or clinical parameters.
Conclusion: Patients with a history of swelling showed increased levels of thrombin compared with patients without it. These findings show an increase in the coagulation potential of patients with oedema, but the clinical relevance of these findings is still under evaluation.

1561
Recurrent angioedema induced by a pacemaker

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Background: Angioedema (AE) is a self-limited, localised swelling that involves subcutaneous tissues or mucosa. Its causes are diverse: allergic reactions to drugs, foods or insect bites; related to treatment with drugs such as angiotensin-converting enzyme inhibitors; associated with C1 inhibitor deficiency or with an autoimmune disease or infection; or idiopathic.
Case report: A 78 year-old man was referred to our Service in January 2011. He had been suffering from AE attacks involving the face (mainly the lips and cheeks) the last 2 months. He had no familial history of AE and no relation between the episodes and any food or drug administration. An allergic study (including *in vivo* and *in vitro* test) was negative. Subsequent investigations including complete laboratory tests, dental examination and thorax X-ray were all normal. During the next weeks new AE attacks appeared. In March 2011 the patient was admitted to the hospital due to the rejection of the pacemaker (PM) implanted in July 2010. There was an atypical inflammatory reaction around the generator, with a positive culture to *Staphylococcus epidermidis*. The PM was removed, but the electrode remained in. The patient continued suffering new AE attacks and in November 2011 a transesophageal echocardiogram revealed the presence of vegetations in the remaining electrode, which was then finally removed. Antibiotic treatment was prescribed during a few weeks. Only one AE attack appeared since then (January 2012). Suspecting the PM was the origin of AE and in order to rule out an allergic mechanim, we realised patch-test with the materials used in its manufacture (information provided by the manufacturer), with negative results. However, 2 years after removing the generator and the leads, the patient remains asymptomatic with no more AE episodes.
Observations: In our patient, the clinical history and temporary evolution reinforces the hypothesis of a connection between the PM and the episodes of AE. Although we couldn't establish an allergic mechanism, the infection and subsequent inflammation could have been responsible of the induction of the AE attacks.

1562
Successful treatment of Hypocomplementemic Urticarial Vasculitis syndrome with recombinant human C1-inhibitor, methotrexate and prednisolone

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A 62 year old healthy man had an acute episode of fever, widespread rash, diarrhea and articular pain in 2006. The symptoms gradually disappeared but similar attacks were experienced thereafter. In 2008, plasma C3, C4 and C1-inhibitor (inh) levels were shown to be low during the attacks, but normal during the asymptomatic phase. Hypocomplementemic Urticarial Vasculitis Syndrome (HUVS) was confirmed by the presence of C1q antibodies. Antinuclear antibodies have never been detected. Despite treatment with hydroxychlorochine and corticosteroid the patient continued to have HUVS attacks. Methotrexate (MTX) was started with no obvious effect. In 2010 the patient was hospitalised for 1 month due to a severe attack (CRP 220 mg/l). MTX was substituted by mycophenolate mofetil (MMF). Later in 2010 he experienced another severe attack with a peak CRP of 240 mg/ml. An experimental therapy with 2000 U of plasma derived C1-inh seemed to resolve the symptoms. Prophylactic treatment with C1-inh was initiated (1000 U twice a week). The HUVS attacks were not totally prevented, but were milder without a need to hospitalisation. Due to these milder attacks the prophylactic dose was increased in June 2011 to 1000 U three times a week and in September 2011 to 1500 + 1000 + 1500 U/week. The highest CRP in 2011 was 48 mg/l. The MMF was substituted by MTX in 2011 due to intolerance.

In April 2012 the patient had a severe attack lasting longer than those in 2011 and C1-inh therapy was changed to recombinant C1-inh, first by 2100 U three times a week and soon the dose was reduced to 2100 U twice a week. Additionally he is at present receiving MTX 25 mg/week and prednisolone 10 mg/day. With lower prednisolone dose minor HUVS symptoms appear. The highest CRP level during current treatment has been 25 mg/l in 2012 and 4 mg/l during 2013. Based on this case it is suggested that C1-inhibitor therapy should be considered in severe cases of HUVS.

1563
Quality of life in patients with chronic urticaria

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Background and purpose: Chronic urticaria (more than 6 weeks) is defined as a relative common and very distressing disease for patients, their families, and even physicians. The aim of this study was to evaluate the effects of chronic urticaria on quality of life in patients referred to Tooba allergic clinic and Bou Ali Sina Hospital in sari.
Material and method: This cross sectional study was performed on 155 Patients with chronic urticaria referred to Tooba allergic clinic and Bou Ali Sina Hospital in sari during 2013. A standard questionnaire based on the Dermatology Life Quality Index (DLQI) included demographic characteristics, criteria of the disease and various questions related to chronic urticaria was selected. Each question had five items included: always, often, sometimes, just a little and not at all. Then each item was scored between 0–4 respectively. The total score was calculated from 0 to 100. The worst score of quality of life was considered 100 and the best quality of life have been scored zero.
Results: Out of total 155 cases, 132 were enrolled in which 99 (75%) were female subjects and 33 patients (25%) were male (female to male ratio; 3–1). Seventy nine (60%) were in grade of diploma to a bachelor science. Most of the patients were married (87 people) and 58 of the patients were housekeepers. The numbers of lesions were often between 1 and 10 in 55 cases (42%). Daily living activities have been the worst among patients under the age of 20 years, and the best daily activities were belonged to the patients older than 40 years.
Conclusion: Data analysis has shown no significant relationship between quality of life and sex, duration of the disease, educational level, marital status and occupation. While more severe disease is associated with worse quality of life.

1564
Iatrogenic adrenal suppression following steroid treatment in a patient with chronic urticaria and in a patient with atopic eczema

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Background: We report iatrogenic adrenal suppression after long term steroid treatment in a case with refractory chronic urticaria and in a case with atopic eczema.
Case 1: A 27-year-old lady presented to our department with a 3 year history of therapy-resistant chronic spontaneous urticaria. She made little or no response to multiple H1 antihistamines, ciclosporin, methotrexate, dapsone, sulphasalazine, colchicine, azathioprine, narrow-band ultraviolet B phototherapy or intravenous immunoglobulins and consequently relied on oral corticosteroids for partial control of her disease. She made an excellent response to omalizumab but was unable to stop taking steroids despite complete control of her urticarial symptoms because a synacthen test showed that she had developed iatrogenic Addison′s disease.
Case 2: An 18 year-old lady with a lifelong history of atopic eczema and asthma presented to our department with extensive striae and skin atrophy. She was found to be hypoadrenal on a short synacthen test with no evidence of autoimmune Addison′s disease. Her previously recorded skin treatment included 2.5% hydrocortisone and 0.05% clobetasone butyrate creams. Her eczema has been treated with topical calcineurin inhibitors and emollients with steroid replacement therapy since her adrenal suppression was diagnosed.
Conclusion: Adrenal suppression is a potential complication of oral and topical corticosteroid treatment. These cases are a reminder of the potential long term risks of using steroids to control inflammatory skin disease.

1565
Efficacy and safety of Omalizumab treatment in a patient with anaphylaxis and cold urticaria

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Background: Omalizumab (anti-IgE) is currently marketed for the treatment of severe allergic asthma. Many case reports show the efficacy of this therapy in physical urticaria. We report a patient with anaphylaxis and cold-induced urticaria refractory to standard therapy. Omalizumab treatment was a helpful option in this patient.
Method: A 60-year-old woman presented with severe cold intolerance with generalised urticaria for 2.5 years. Onset occurred while swimming in cold water. The patient experienced anaphylactic symptoms during a bath in the sea. At a later date she developed itching, redness, asthenia, dyspnea and generalised urticaria few minutes after exposure to cold. She did not tolerate ingestion of cold drinks, immersing hands in cold water or staying near air conditioning. Her quality of life was very poor. Personal and family history was negative. Laboratory studies included complete blood cell count, chemistry profile, serum protein electrophoresis, immunoglobulin and cryoglobulin levels, C3, C4, C 1 inh, screening for virus, auto-antibodies, ice-cube test, skin pricks tests and serum specific IgE to food and pneumallergens.
Results: Only the ice-cube test was positive. Patient was diagnosed anaphylaxis and acquired cold-induced urticaria, by clinical history and positive ice-cube test. We prescribed avoidance of cold exposure and antihistamines, antileukotrienes and corticosteroids treatment. The patient did not respond to the therapy, therefore after 2 years, we started off- label treatment with omalizumab with good control of symptoms within 3 weeks after the first injection and no side effects were observed. She shows a long-lasting improvement with omalizumab 300 mg/6 weeks.
Conclusion: Omalizumab is a safe and effective treatment for this patient. In spite of numerous therapies before anti-IgE use, the patient suffered from her cold urticaria for years. Omalizumab resulted in complete symptom control and improved the patient's quality of life.

1567
Efficacy of rituximab, pefloxacin and elimination diet in Schnitzler syndrome

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Background: Schnitzler syndrome (SS) is a rare condition characterised by chronic urticaria, monoclonal IgM gammopathy, bone pain and other symptoms. We present the cases of three patients with SS: two males aged 42 and 50 years respectively and a female aged 49 years. The first patient showed a good response to the treatment with pefloxacin (a fluoroquinolone antibiotic) and rituximab (an anti-CD20 monoclonal antibody), while in the other two the improvement was achieved by following elimination diet.
Method: All patients had chronic urticaria, IgM gammopathy and the elevation of the serum levels of inflammation markers.

The second and the third patient demonstrated high total IgE level (2000 U/ml and 540 U/ml respectively) without any underlying cause (e.g. allergy). The first and the second patient did not respond to the treatment with antihistamines, while the third one partially responded only to high doses. The response to corticosteroids was good, but incomplete.

Results: The treatment with rituximab (2 g followed by a 1 g dose given every 6 months) and pefloxacin (1200 mg/d, then 800 mg/day) in the first patient resulted in rapid and sustained improvement in symptoms and allowed to discontinue prednisolone. In two other patients, following strict elimination diet led to resolution of rash, but systemic symptoms persisted and improved only after adding prednisolone to the treatment.

Conclusion: On the basis of this experience and the review of the literature, we can conclude that the combination of rituximab and pefloxacin may be a promising treatment option for SS. Such combination therapy can be considered for individuals with SS if other treatments are unavailable or show no effect. Hyperimmunoglobulinaemia E revealed in other two patients and the efficacy of elimination diet indicate the need to search for other mechanisms involved in the disease pathogenesis and thus to explain the reasons behind excessive IgE synthesis in individual cases.

Poster Session Group III – Green

TPS 75 – Vaccines

1568
Hiding allergens into polymeric matrix: safe vaccines for allergen specific immunotherapy

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Background: Type I allergy is manifested by the release of vasoactive factors induced by IgE contact with full-length allergen. Specific immunotherapy (SIT) is the only curative option to stop allergy progression. During SIT low doses of allergen extracts are injected to prevent side effects. SIT therapy can last for several years due to low doses used, and requires visits to the physician. Development of quick, effective and safe therapy for allergy can significantly increase the number of patients undergoing SIT and improve their quality of life.
Methods: We have developed a new type of vaccines which we called 'caged' vaccines (CV), in which full length house dust mite allergens (HDMs) Der f 1 and Der f 2 were packed inside chitosan nanosized core particles shelled by alginate conjugated to hydrophilic Der f 1 and Der f 2 peptides. The structure of CV was developed basing on two fundamental facts:

i)IgE usually does not recognise linear epitopes of allergens;
ii)full-length allergen contains many T-cell epitopes required for IgG induction.

To produce CV, recombinant Der f 1 and Der f 2 expressed in *E. coli* were conjugated to carbodiimide activated lauryl-succinoyl-chitosan and core particles were formed by water-organic phase exchange.
Results: Core particles were 220–300 nm in diameter and had −25 mV zeta-potential. Alginate was activated by carbodiimide, mixed with synthetic HDM peptides and added drop-wise to the solution of core particles at shaking. CV was 250–400 nm in size and had −35 mV zeta potential. CV and its components were used to analyze IgE binding in sera from HDM allergy patients.
Conclusions: We demonstrated that IgE in HDM positive sera bound pure Der proteins and did not bind:

i) Pooled Der peptides;
ii) Core-Der particles;
iii) Core-Der-Alginate particles,
iv) CV showing that neither Der peptides (free or immobilized) nor caged Der proteins were recognised by IgE specific to HDM.

1569
Maturation of a mite allergy vaccine

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Background: Ageing or maturation is a well-known phenomenon in protein adsorption onto aluminium hydroxide (AlO(OH)). Mite allergy vaccines used in this study contain mite extracts bound to AlO(OH). For safety and efficacy the vaccines are required to be stable. Both the protein and AlO(OH) can undergo physical and structural changes which in turn can affect the nature and binding strength of the partners. This study is aimed at revealing possible changes of these aspects in time. Fresh and old mite allergy vaccine preparations were monitored for a period of 7 months using various physicochemical assays. Investigation was done on binding strength, protein structure, AlO(OH) structure and the appearance.
Method: Protein desorption behaviour: The amount of protein desorbed from the AlO(OH) treated with 0.5 M phosphate buffer was determined. Circular Dichroism (CD): Spectra were recorded from 190 to 260 nm. The CD ratio 207/222 nm was monitored.

Analytical centrifugation: The percentage of sediment after analytical centrifugation at 400 rpm was monitored.

Light-scattering: The 90° light-scattering intensity at 400 nm was monitored.
Results: The binding of the mite extracts to the AlO(OH) in freshly prepared vaccines changed considerably in the first 3 months. The desorption of protein with phosphate buffer gets more difficult in time indicating increase of the binding strength of the extracts. No changes were recorded with respect to (i) appearance of the suspension (ii) protein structure of the mite extracts as observed with CD or (iii) AlO(OH) structure as observed with analytical ultracentrifugation and light scattering for a period of 7 months.
Conclusion: This study demonstrates that the binding strength of mite extracts to AlO(OH) in a mite allergy vaccine becomes stronger in time, especially the first 3 months after adsorption. The results obtained in this study reflect the effect of ageing or maturation.

1570
Stress stability study on a birch pollen extract

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Background: Stressed and non-stressed birch pollen extracts were investigated with several analytical assays to monitor identity (SDS-PAGE, immunoblot), content (protein, major allergen Bet v 1), potency (IgE potency) and structure (CD, Fluorescence, HP-SEC).
Method: Stressed conditions: Incubation at 45°C (12 days), 60°C (3 days) or 90°C (1 h), freeze-thawing(5 times) or shaking (15 min at 2600 rpm).

SDS-PAGE: Reduced samples on 4–12% Bis-tris gels and stained with silver.

Immunoblot: After SDS-PAGE, proteins were transferred to PVDF membrane and stained using pooled sera from birch allergic patients, HRP-conjugated antibody and TMB substrate.

Protein: Bradford assay using BSA as a standard.

Major allergen content: An ELISA was used to quantify Bet v 1 content.

Potency: the allergenic activity was measured using an IgE-inhibition assay.

CD: Spectra were recorded from 260 to 190 nm.

Fluorescence: Emission spectra were recorded from 290 to 400 nm, excitation at 280 nm.

HP-SEC: A Bio-Sec 3 size exclusion chromatography column was used with UV-detection.
Results: SDS-PAGE showed disappearance of bands and appearance of higher molecular weight bands for the birch extract upon thermal stressing. Immunoblot showed

reduced intensity of major allergen bands for the 90°C stressed sample. The protein content was not affected by stressing the birch extract. The Bet v 1 content and IgE potency decreased by temperature stressing. Temperature stressing induced unfolding of proteins according to CD and fluorescence spectroscopy. HP-SEC showed aggregation of birch proteins after thermal treatment. Freeze-thawing and shaking did not affect any of the investigated properties of the birch extract.

Conclusion: Temperature stressing of a birch allergen extract affected the protein profile, Bet v 1 content and IgE potency. In parallel, protein unfolding and protein aggregation occurred.

1571
Structural characterisation of a recombinant Bet v 1 allergen established as a safe and efficacious treatment for birch pollen allergy

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Background: A vast majority of birch pollen-allergic patients exhibit IgE against Bet v 1, and most of those patients react exclusively to this relevant allergen. In this context, we developed a recombinant Bet v 1.0101 isoallergen (rBet v 1) intended for the treatment of birch pollinosis by allergen immunotherapy (AIT). This pharmaceutical-grade rBet v 1 was thoroughly characterised and clinically evaluated.

Method: Recombinant Bet v 1.0101 was expressed in *Escherichia coli* and purified to homogeneity by chromatography, following the current good manufacturing practices (cGMP). Primary, secondary, tertiary and quaternary structures were assessed based on several methods, including mass spectrometry (MS) and X-ray crystallography.

Results: The primary structure of rBet v 1 was fully covered using tandem MS (MS/MS), with a perfect fit with the known Bet v 1.0101 amino acid sequence. Secondary and tertiary structures of rBet v 1 were confirmed to be highly similar to the ones determined for natural Bet v 1 and reported in the literature. These structural studies confirmed that a highly pure pharmaceutical grade rBet v 1 molecule has a similar 3D structure (resolved at 1.2 Å) when compared to a form complexed with a hydrophobic exogenous ligand, representative of the natural form involved in patient sensitisation. This highly pure rBet v 1 was tested in birch pollen-allergic patients, either via the subcutaneous route or as sublingual tablets. These clinical studies confirmed the efficacy and safety of rBet v 1 when used in both routes.

Conclusion: We developed a cGMP-grade rBet v 1 demonstrated to be highly homogeneous and structurally similar to natural Bet v 1. This rBet v 1 was shown to be a safe and efficacious active principle for AIT.

1572
L-tyrosine: benefits as a depot adjuvant

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Background: Sub-cutaneous immunotherapy is an effective treatment for allergy. It works by helping to re-balance an individual's immune response to allergens and the ability to drive an antibody titre response is greatly improved by the use of adjuvants, the most common being aluminium hydroxide. There is a natural, safe and biodegradable alternative to aluminium – L-tyrosine.

Method: A series of preclinical safety investigations comprised single-dose parenteral studies in the mouse and rat, repeat-dose parenteral toxicity studies over 28 days in the rat and dog plus genotoxicity and local tolerance studies. A literature review was conducted to assess whether individuals receiving aluminium-adjuvanted allergy immunotherapy may be more susceptible to long-term health problems associated with aluminium.

Results: *In vitro* and *in vivo* studies have shown that L-tyrosine has ideal adjuvant properties, comprising a high adsorptive power for proteins, enhancement of IgG antibody induction with no stimulatory effect on IgE antibody level; highlighting its effectiveness of action as an effective and biodegradable depot adjuvant in immunotherapy. In addition, no signs of toxicity or genotoxicity were seen. There are few reliable data purporting to neither the safety nor the toxicity of aluminium adjuvants used in allergy immunotherapy.

Conclusion: L-tyrosine has ideal adjuvant properties; results have highlighted its effectiveness of action as a safe, effective and biodegradable depot adjuvant in immunotherapy. There are few reliable data purporting to neither the safety nor the toxicity of aluminium adjuvants used in allergy immunotherapy. These gaps in knowledge should be remedied in future clinical trials of new immunotherapies and in records of clinical practice of therapies currently in use.

1573
Acarovac Plus development and clinical report of a novel tyrosine-adsorbed, modified house dust-mite allergen product

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Background: Allergy to house dust mite is one of the most common causes of allergic rhinitis. A novel tyrosine-adsorbed, modified allergen product, Acarovac Plus, developed for the treatment of perennial mite allergy seeks to address the underlying cause of allergic rhinitis in this instance. One of two dosing regimens may be used, either the Conventional Regimen or the Cluster Regimen. We sought to compare the efficacy and safety of a specific immunotherapy, developed for the treatment of perennial mite allergy, administered under a Conventional and Clustered dosing schedule in patients with persistent allergic rhinitis.

Method: 60 adult patients, between 18 and 65 years old, with allergic rhinitis and/or asthma secondary to hypersensitivity to *Dermatophagoides pteronyssinus* were selected for treatment. A Nasal Challenge Test, monitoring clinical symptoms (including peak inspiratory flow) and serum-specific IgG4 to *Dermatophagoides pteronyssinus* (including total and specific IgE and relevant cytokines), was measured. A TSQM survey was completed after each patient's final visit.

Results: The Nasal Challenge Test led to a decrease in positive symptoms and symptom scores for both dosing regimen groups. A significant decrease in mean peak inspiratory flow was recorded in both groups, with a significant increase in IgG4-specific antibody titres. No significant changes were observed in concentrations of total IgE, specific IgE or cytokines (IFN-g, IL-4, IL – 5, IL-10 and IL-13). Patients declared themselves most satisfied in relation to 'Secondary effects', with high overall satisfaction.

Conclusion: Cluster and conventional specific immunotherapy resulted in no adverse reaction(s) and led to similar decreases in clinical symptoms and improvements in immunological parameters and quality of life.

1574
Biological standardisation and comparability of IHRP for use in the assessment of allergen immunotherapy products

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Background: Biological standardisation of an In-house Reference Preparation (IHRP) is required according to current European Pharmacopeia 8.0 guidelines. Differences in the manufacturing processes of drug substance and IHRP, or in the range of quality testing performed on each, create a need to assess the comparability of IHRP and drug substance. Biological standardisation and comparability to drug substance are therefore essential factors for assessing the suitability of IHRP for qualitative and quantitative evaluation of allergen immunotherapy products.
Method: In the preliminary study for biological standardisation, 5 tenfold dilutions of the IHRP (reconstituted) were prepared including controls and applied on the forearm on each of the 50 patients. The concentration that gave a wheal the same size as the positive control was used as the lowest dose in the final test.

In the final test, three concentrations of the IHRP and controls were applied on the forearm. The area of the wheal was determined and the histamine equivalent concentration was calculated for each patient. This represents the protein concentration corresponding to the potency of the IHRP.

For comparability, the IHRP was reconstituted to the mid-specification of the relevant drug substance and subjected to the full range of chemical and immunochemical tests carried out at the drug substance stage, e.g. total protein content, carbohydrate content, potency, and protein and allergen profiling.
Results: Preliminary results suggest direct comparability between IHRP and drug substance in both *in vitro* characterisations and biological activity.
Conclusion: The IHRP is suitable for use as a standard in the both *in vivo* and *in vitro* assays used in the assessment of immunotherapy products for batch to batch consistency.

1575
The nature and extent of adsorption of adjuvant MPL to a MATA complex in candidate therapeutic formulations for use in immunotherapy

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Background: The nature and extent of adsorption between adjuvant and antigen in vaccines, has been shown to affect efficacy. The World Health Organisation (WHO) recommends adsorption of 80% or more of tetanus and diphtheria toxoid antigens by aluminium containing adjuvants, though no such recommendation exists for adjuvants used in allergy immunotherapy. Therefore the nature and extent of adjuvant antigen adsorption should be considered during immunotherapy formulation development. The adsorption of Monophosphoryl Lipid A (MPL) to the modified allergen tyrosine adsorbate (MATA) complex in formulations for use in immunotherapy has been shown to produce a better immune response than the individual components alone. However the extent and nature of adsorption in MATA-MPL formulations has not been adequately described.
Method: The adsorption profile of MPL to the MATA complex and individually L-tyrosine was investigated via MPL content by gas chromatography on the MATA-MPL complex supernatant and subnatant. The nature of adsorption of MPL to the MATA complex was investigated via MPL content by gas chromatography on the MATA-MPL complex supernatants, after changes to the formulation.
Results: The adsorption profile of MPL to the MATA complex and individually L-tyrosine demonstrated ≥80% adsorption within 24 h of formulation. The nature of adsorption of MPL to the MATA complex was indicated.
Conclusion: The extent of adsorption of MPL to the MATA complex has been described and exceeds the WHO recommendations in place for antigen adjuvant adsorption. The nature of adsorption of MPL to the MATA complex was indicated as being pi – CH attraction between the aromatic ring on the L-tyrosine and exposed C-H on the di-glucose core of the MPL.

1576
Optimal dose for SCIT immunotherapy with House Dust Mite (HDM) native allergenic extract determined by a dose-range finding study according to EMA guidelines

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Background: A dose-response trial was performed with SCIT from DPT extracts according to EMA guideline.
Method: A phase II, multicenter, randomized, double blind, placebo-controlled trial in parallel groups (5 active treatments with different doses plus a placebo) was performed in 11 Spanish sites in order to obtain the optimal dose for a confirmatory efficacy phase III trial. One-hundred and thirty patients between 18 and 60 years with rhinoconjunctivitis ± asthma sensitised to DPT were randomized. Selection criteria were defined according to ARIA and EMA guidelines. The principle endpoint was the difference of the DPT extract concentration needed to produce a positive nasal provocation test (NPT) from baseline (V0) to final visit (FV). Secondary endpoint included Immunoglobulin determination (specific IgE, IgG and IgG_4), dose response prick-test and safety. Doses ranged from 0.0625 to 0.75 Skin Prick test (SPT) units. Placebo was exactly as the active groups without allergen. Treatment duration was 17 weeks, five for the induction phase (1 weekly injection) and 12 for the maintenance phase (1 monthly injection).
Results: There was an increase in the concentration needed to induce a positive response on NPT in all groups, without significance due to sample size. The difference was greater with higher doses but 0.125 SPT presented better safety profile showing 7 (3.8%) systemic adverse reactions over the total 82 (7.2%) observed with the 1 147 injections administered. Specific IgG and IgG4 levels increased and specific IgE levels and skin reactivity to HDM extract decreased significantly in all active groups.
Conclusion: A dose-dependence in the effect of SCIT with *Dermatophagoides pteronyssinus* native extract has been demonstrated by *in vivo* and *in vitro* determinations. Taking into account also the safety constraints a concentration of 0.125 SPT was estimated as the optimal dose.

1577
Biochemical and immunological characterisation of depigmented-polymerised allergen extract of *Betula alba* pollen

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Background: In 2009 the EMA document: Guideline on allergen products: Production and Quality Issues (EMEA/CHMP/BWP/304831/2007) came into force providing principles and guidance for the manufacturing and quality control of allergen extracts produced by a method involving an industrial process. In this context depigmented-polymerised allergenic extracts have been purified (depigmentation) and chemically modified to reduce IgE-binding activity while maintaining their immunogenicity. The objective was to characterise the depigmented-polymerised birch pollen extract according to the regulatory requirements.
Method: The presence of the relevant allergens in the modified molecule was determined by mass spectrometry. Quantification method of major allergen using monoclonal antibodies and EDQM standard was validated. The reduction of IgE-binding activity compared with the native extract was tested by ELISA-competition. An additional *in vitro* biological potency assay was developed using ELISA inhibition with rabbit polyclonal IgG antibodies. The profile of polymerization of the allergoids was determined by HPLC.
Results: Peptide sequencing confirmed the presence of five isoforms of Bet v 1, as well as other allergens such us Bet v 2, Bet v 6 and Bet v 7. Quantification of allergens in the extracts showed that the content of Bet v 1 in the final product was 14 μg/ml. The degree of polymerization was high with no proteins lower than 200 kDa and IgE-binding reduction in more than 95%. The HPLC profiles showed high consistency between batches. The biological potency using a validated ELISA-Inhibition based on IgG antibodies was established.
Conclusion: The depigmented-polymerised allergen extract of birch pollen has been characterised according to the specifications included in the regulation of allergen products.

1578
Quantification of grass pollen and house dust mite relevant allergens in allergenic extracts by using mass spectrometry

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Background: The quantification of relevant allergens within allergenic extracts intended for allergen immunotherapy (AIT) should be as comprehensive and accurate as possible. Commonly used immunological methods, such as monoclonal antibody-based sandwich ELISA, may underestimate the amount of allergens because the used antibodies are often specific for a limited spectrum of isoallergens. To tackle this issue, we developed and validated mass spectrometry (MS)-based assays for the comprehensive quantification of grass pollen group 1 and house dust mite (HDM) group 2 relevant allergens.
Method: Allergens were purified by liquid chromatography (LC) and characterised by LC coupled to tandem MS (LC-MS/MS). Allergen quantification was performed by LC-MS/MS after digestion of allergenic extracts with trypsin.
Results: Characterisation of the isoallergens of purified grass pollen group 1 and HDM group 2 relevant allergens allowed the selection of proteotypic (or consensus) peptides. Based on those consensus peptides, MS quantification assays were developed and validated. The two assays were selective, linear ($R^2 > 0.98$), accurate (recovery close to 100%) and sensitive (level of detection below 0.5 ng/ml). For both assays, intra- and inter-run precisions as well as repeatability were below 20%. Allergen concentrations thus obtained by LC-MS/MS were up to ~100-fold higher than the concentrations measured with the corresponding ELISAs.
Conclusions: MS-based assays allow the quantification of grass pollen and HDM relevant allergens in a sensitive, accurate, repeatable and comprehensive manner. Thus, for important allergens, MS-based assays can favourably substitute to immunological assays, especially when the latter do not allow a comprehensive quantification of all allergen variants and isoforms due to restricted antibody specificities.

1579
Fractionation of source materials facilitates high reproducibility of SQ-HDM SLIT-tablets

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Background: The drug substance for house dust mite vaccines for allergy immunotherapy has traditionally been based on purified mite bodies or whole mite culture, which are quite variable raw materials due to their biological origin. The objective of the present study is to establish a highly reproducible drug substance for the ALK SQ-HDM SLIT-tablet, which offers independent control of the major allergens.
Method: *Dermatophagoides farinae (Der f)* and *Dermatophagoides pteronyssinus (Der p)* grown separately under controlled conditions were harvested and separated into fractions by sieving. Two fractions were isolated from each mite species containing primarily mite bodies and mite fecal particles, respectively. Extracted fractions were subsequently mixed into two drug substances to reflect a constant ratio between the 4 major allergens, Der f 1/2 and Der p 1/2. The quality and reproducibility of the drug substance was verified by assessment of 20 and 23 independent batches, respectively. Analyses comprised composition by crossed immune-electrophoresis, dry matter content, protein content by BCA, total IgE binding potency by Centaur assay and major allergen determination by radial immune-diffusion. Identification of relevant house dust mite allergens was performed by mass spectrometry.
Results: The normalised mean and standard deviation of the content of dry matter and protein was 100.0% ± 7.2% and 100.0% ± 12.0%, respectively. The total IgE-binding potency relative to the in house reference preparation (IHRP) was 1.06 ± 0.17, while the contents of major allergens relative to the IHRP were 1.15 ± 0.13 (Der f 1), 0.98 ± 0.09 (Der p 1) and 1.12 ± 0.18 (Der f 2 + Der p 2), respectively, demonstrating high consistency in the ratio between major allergens.
Conclusion: The production process for the ALK SQ-HDM SLIT-tablet is based on fractionating of the HDM source material enabling independent control of the major allergens and high reproducibility of the drug substance.

1580
Formulation and evaluation of custom made sublingual films of house dustmite extract

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Background: House Dust mite (HDM) is one of the common causes of asthma and allergic symptoms. It thrives in the indoor environment like bedrooms and living rooms. Sublingual Immunotherapy (SLIT) Films emerged as an alternative to the traditional drops and sprays. SLIT Films containing HDM extract are prepared using hydrophilic polymers that dissolves under the tongue delivering the allergens to the systemic circulation via dissolution when in contact with saliva. The objective is to

formulate the Sublingual Films with purified extract of HDM for SLIT.

Method: Sublingual Films containing HDM extract (*D. farinae*) are prepared by solvent casting method using Film Forming Polymers (Hydroxy Propyl Methyl Cellulose), Plasticizers (Propylene Glycol), Sweetening Agent (Sucralose), Flavoring Agent (Peppermint), Preservatives (Methyl Paraben and Propyl Paraben) and Thickening Agent (Carrageenan). Parabens are dissolved by heating and stirring in purified water. Polymers are added one by one followed by sucralose and peppermint. After stirring for 2 h, the standardised HDM extract (34 μg/film) is added as per prescription and dissolved by stirring for 5 mins. The casted viscous solution is then dried between 32 and 350°C for 6 h in a controlled chamber blowing air below the casting glass plate. The casted Films are removed and cut into 2 × 1 cm dimensions.

Results: The SLIT Films are evaluated for Thickness (0.08–0.1 mm), Weight Variation (24–26 mg), Folding Endurance (more than 200 times), Surface PH (6.5–6.6), Disintegration time (not more than 1 min.), Biologically active content (90–110% of the stated label claim). *In vitro* dissolution test is performed as per USP type II apparatus using distilled water as the medium at a speed of 50 rpm, maintaining at 370°C. More than 95% of allergens are released in 5 min.

Conclusion: An optimised formulation of custom made SLIT Films of House Dust Mite with all desirable characteristics and parameters are developed and evaluated.

1581
Pilot trial to downregulate allergy by IntraLymphatic allergen immunotherapy

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Background: Allergen immunotherapy (AIT) is the only treatment of allergic rhinoconjunctivitis (ARC) that leads to tolerance. The dominating administration form of AIT is subcutaneous, which takes several years and imposes a substantial economic burden. Emerging evidence shows that allergen immunotherapy with intralymphatic injections (ILIT) yields a faster result with a 1000-fold lower dose. To evaluate if this method could be used in our settings we did a pilot-study with patients allergic to birch or grass.

Method: Ten patients with ARC and sensitivity to birch (4) or grass (6) participated in the study. Symptom score (RTSS), quality of life (RQLQ) and medication score for the last pollen season were collected. Immunological blood tests and skin prick test was done. Three inguinal intralymphatic injections with 1000 SQ-E of ALK-Abello Alutard Birch or 5-grass allergen extracts were given 4 weeks apart, controlled and documented by means of ultrasonography with a needle guide.

After the following pollen season RTSS, RQLQ and medication use were collected as well as new immunological blood analyses and skin prick test.

Results: One patient had a systemic allergic reaction after the first injection and was excluded from the study. No other severe reaction was seen. RTSS and RQLQ for one grass pollen allergic patient were missing. Seven of the remaining eight patients had fewer symptoms with lower RTSS. All eight scored better in RQLQ and used less medication compared to the season before treatment. No clear changes were seen in skin prick tests nor in immunological blood tests.

Conclusion: This pilot study shows beneficial results of ILIT therapy with fewer symptoms, lower medical use and better quality of life during the first pollen season after the treatment compared to the preceding season. We judge that the benefits for the patients outweigh the risks. We will now implement this treatment in a larger study to evaluate the significance of these results.

1582
Rush up-dosing regimen with an Artemisia vulgaris depot allergoid preparation

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Background: Subcutaneous specific immunotherapy is up-dosed in a stepwise fashion. An accelerated up-dosing regimen with a grass depot allergoid preparation has been found as safe as the conventional up-dosing and is already approved. Data regarding the tolerability of a accelerated up-dosing regimen with Artemisia vulgaris (mugwort) were not available until now.

Method: 7 practitioners who had already treated patients allergic to Artemisia in autumn/winter 2012 with the rush up-dosing regimen (weekly injection (inj.) of 0.1–0.3–0.5 ml of depot allergoid preparation Artemisia vulgaris; HAL Allergy, Leiden, the Netherlands) were asked to retrospectively document their experiences based on data in the patient charts. The documentation with a standardised questionnaire included the up-dosing and the maintenance treatment.

Results: In total 31 patients (Mean age 42 years; 17 females) were included in the analysis. 196 inj. could be evaluated (100 in the up-dosing and 96 in the maintenance). Thirty patients (96.7%) reached the maintenance dose of 0.5 ml. During up-dosing 2 patients (6.4%) required a dose adjustment due to a local reaction. During maintenance phase 1 patient (3.2%) required a dose adjustment due to a local reaction. Most often local reactions like swelling and redness were observed. These were reported following 56 inj. (28.6%) in 16 patients (51.6%). The mean swelling size was small: 2.1 cm (0.2–5.0 cm) during up-dosing and 1.8 cm (0.2–3.0 cm) during maintenance phase. Mild systemic reactions were observed following 10 inj. (5.1%) in four patients (12.9%). Very rarely cooling or an antihistamine (1.5% of inj.) was necessary for the treatment of an adverse reaction. Eighteen patients were very satisfied, 12 patients were satisfied and one patient was rather dissatisfied with the up-dosing regimen. Judgement of the physicians corresponded to this.

Conclusion: The rush up-dosing regimen was proven to be well tolerated and might be used to up-dose patients within 2 weeks.

1583
Safety comparison of two different ultra-rush cluster non-conventional protocols with subcutaneous depot (IR/ml) allergen immunotherapy

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Background: Analyze the safety of two unconventional ultra-rush cluster schedules of depot allergen immunotherapy administration (AIT), by subcutaneous route (SCIT) in hospital settings.

Method: Retrospective analysis of patients' clinical records who received depot AIT (IR/ml) by subcutaneous route. Patients who received AIT starting with a concentration vial of 10 IR/ml and reaching maintenance doses in 2 weeks (2 × 2 schedule) were compared to those patients who reach the maintenance dose in 3 weeks using 1 IR/ml and 10 IR/ml concentration vials (3 × 2 schedule). The data collected

was from patients treated with grass, grass + olive and *D. pteronyssinus* extracts.
Results: Information has been gathered from 703 patients, whose mean age was 23.5 ± 11. 5 years (52% females): 221 were treated with 2 × 2 schedule and 482 with 3 × 2. In group 2 × 2, 47.5% of the patients were diagnosed rhinoconjuctivitis (RC) while the remaining 52.5% were diagnosed RC + asthma. In group 3 × 2, 37.5% were diagnosed RC, 2.2% asthma and 60.4% RC + asthma. The systemic reactions rate for the 2 × 2 group was 4.1% of the patients and 1.0% for the 3 × 2 group. No systemic reactions higher than grade 2 were recorded in any of the groups (EAACI grade system 2006).

In this study, the possibility of having an adverse reaction using the 2 × 2 schedule is 3.82 times higher than for 3 × 2 schedule (IC 95%, [1.386–10.577]), whereas, in patients without asthma, both schedules are equally safe (P = NS). Neither patient's age or immunotherapy composition were factors that influence the safety of these schedules.
Conclusion: Ultra-rush initiation with cluster protocols in two or 3 weeks is safe using IR/ml depot extracts. In asthmatic patients, a 3 visits schedule (3 × 2) seems to be more convenient.

1584
Minor allergens in products for diagnosis and immunotherapy of birch pollen allergy

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Background: As allergy to birch pollen is elicited predominantly by the major allergen Bet v 1, the potency of birch pollen allergen products is adjusted nearly exclusively to this allergen. Nevertheless, many patients have also specific IgE-antibodies against minor birch pollen allergens. However, as long as no test methods for the determination of minor birch allergens are commercially available, their content and variability in birch pollen allergen products and thus their importance for safety and efficacy remain unclear.
Methods: On the basis of in-house produced allergen-specific monoclonal antibodies and antisera, three sandwich ELISA systems were developed to enable the quantification of the minor allergens Bet v 4, Bet v 6 and Bet v 7, respectively. After successful assay validation, the concentration of these three minor allergens was determined in a diverse set of birch pollen allergen products from different manufacturers. The results were subsequently analyzed in relation to allergenic activity, major allergen and total protein content.
Results and conclusion: Validation of the newly developed sandwich ELISAs confirmed high specificity as well as sensitivity, allowing for the quantification of Bet v 4, Bet v 6 and Bet v 7 even in matrices containing these minor allergens only in the nanogram range. In general, a large variability in minor allergen contents was observed in birch pollen allergen products. Only for one of the examined minor allergens a potential correlation with the amount of Bet v 1, total allergenic activity and total protein content could be identified, limiting the chances to adjust the composition of birch pollen products to more than one allergen in the future. Nonetheless, the new ELISA systems will enable efficient monitoring of Bet v 4, Bet v 6 and Bet v 7 in birch pollen products and hence provide tools to generate insights into the relevance of minor allergens for diagnosis and immunotherapy of birch pollen allergy.

Poster Session Group III – Green

TPS 76 – Various faces of drug reactions

1585
Desensitisation to acyclovir in a patient with multiple myeloma

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Background: Desensitisation is the administration of a drug to which the patient is allergic increasingly in order to temporarily inhibit their response to it.
Method: Seventy-four year old female with a history of osteoporosis, ulcerative colitis and infection HZV. Go to hematology consultation for asthenia, bone pain and loss 4–5 kg in 2 months. Important nocturnal pain and paresthesias in extremities that prevents night rest.

It is diagnosed with IgG-lambda multiple myeloma stage IIIA and grade II–III neuropathy. Being treated with Zometa, Melphalan, Velcade and Acyclovir. At 2 days begins with rash on abdomen and extremities, with intense itching. Suspecting the antiviral acyclovir allergy is removed: improving the rash. Since hematology we report the need for treatment with acyclovir to prevent recurrence of HZV. Aciclovir desensitisation arises. Since hematology we report the need for treatment with acyclovir to prevent recurrence of HZV. We propose acyclovir desensitisation.
Results: Desensitisation was started in fifteen steps up to a cumulative dose of 1600 mgr. Running time: 4 h and 50 min.

Was performed in day hospital under medical supervision and after signing informed consent. No reactions during desensitisation. The patient continued treatment at home (400 mgr/12 h) with good tolerance.
Conclusion: The temporal relation between the initiation and/or cessation of the drugs and the development of the rash suggested a hypersensitivity reaction to the antiviral drugs. The timing of the reaction and clinical appearance were suggestive of a cellular rather than IgE mediated reaction. The history and examination findings were central to this diagnosis. There is no commercial serological assay for aciclovir specific IgE.

This report is an example of acyclovir hypersensitivity and successful oral desensitisation.

1586
Fixed drug eruption due to atorvastatin

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Introduction: Atorvastatin is a synthetic 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor which has been commonly used to treat hypercholesterolemia. HMG-CoA reductase inhibitors are considered safe and adverse reactions secondary to statins are infrequent.
Case report: An 84-year-old man was referred to our department for a 7-month history of multiple erythematous macules extending from the trunk to arms. Previous hystological examination of lesions revealed chronic superficial dermatitis with infiltration of leucocytes, polymorphonuclear cells and eosinophils in perivascular areas. The results were compatible with fixed drug eruption and caused the derivation of the patient to the department of allergy.

The patient had a history of hypercholesterolemia, diabetes mellitus and arterial hypertension. He was under treatment with atorvastatin, metformin, trimetazidin, ramipril, clopidogrel and omeprazole.

Consecutive discontinuation of metformin and trimetazidin treatment with an interval of 6 weeks was done. No changes in the skin lesions morphology were observed. Two months following atorvastatin withdrawal, a reduction of the erythema was observed, and the next month the lesions disappeared.

Closed patch test was performed with atorvastatin 1/1000 in ethanol, as it had been done with simvastatin in previous reports. Patch test was positive (++) at 96 h on residual lesions and negative on healthy skin at 48 and 96 h. We tested six controls, and all of them were negative. These results and the absence of lesions after atorvastin withdrawal confirmed the diagnosis of fixed drug eruption.
Conclusion:

1 We report a fixed drug eruption due to atorvastatin.
2 To our knowledge, fixed drug eruption to atorvastatin or other statins has not been previously reported.

1587
Acute eosinophilic pneumonia: a case report

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Introduction: Acute eosinophilic pneumonia (AEP) is a rare and severe entity.

We present a case of AEP probably due to piperacillin/tazobactam (P/T).
Case report: A 61 year-old man received prophylactic treatment with P/T for a programmed biliary surgery. Six days after the start of this therapy he developed fever (up to 38.3 °C), cough, expectoration, dyspnea and hypoxemic respiratory failure that required non-invasive mechanical ventilation support. Leukocytosis (16 500/mm3) with moderate peripheral eosinophilia (800/mm3 at entry but up to 1400) was observed. Thoracic CT scan and x-Ray showed interstitial infiltrates. Abdominal ecography showed the absence of complication by biliary surgery. Blood, sputum, urine, dregs and drainage samples were taken with negative results for pathological bacteria, virus, fungi and parasites cultures and autoinmunity diseases. Bronchoalveolar lavage (BAL) showed a 70% of eosinophils.

As we considered the reaction could be related to P/T due to the temporal relationship between the onset of the treatment with P/T and symptoms, this drug was removed and corticosteroid therapy was administered (2 mg/kg/day) with a favourable response (Peripheral blood eosinophilia and fever disappeared, radiographic findings improved and ventilation support was removed within 24 h).
Allergologic study: We performed skin prick and intradermal tests with PPL, MDM, penicillin and piperacillin-tazobactam, patch-test with penicillin and piperacillin-tazobactam and specific IgE to penicillin G, penicillin V, ampicillin, amoxicillin with negative results.
Conclusions: We report a case of an AEP based on laboratory, radiograhic, BAL findings and clinical manifestations. Due to clinical manifestations during treatment with P/T, the prompt and complete response to corticoids after removing P/T,

suggest that P/T could probably be the drug involved. According to our knowledge this would be the second case reported in database and the first in literature of AEP related to P/T.

1588
A case with fixed drug erupsion with clarithromycin but not with azithromycin

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Hypersensitivity reactions with macrolide antibiotics are rare. As well as immediate type hypersensitivity reactions, cases of delayed type hypersensitivity reactions were reported in the literature. We will report a case who developed fixed drug eruption after clarithromycin oral provocation test but tolerated azithromycin. Fifty three years old female was first evaluated in our clinic in 2008 because of Steven Johnson Syndrome history due to beta-lactam antibiotic use. In this period placebo controlled oral provocation tests (OPT) with clarithromycin and levofloxacin were negative. She admitted to our clinic in April 2013 for the second time. She was able to use claritromycin between 2008 and 2010. However in 2010, 8 h after the first dose of clarithromycin she had itch, erythema and mild upper lip swelling. She also gave hypersensitivity reaction history with moxifloxacin and levofloxacin. In 2009 immediately after the use of moxifloxacin lip swelling was occurred. And also, 2 months ago, immediately after the use of levofloxacin she had erythematous plaque on her leg. We performed skin prick and intradermal tests with levofloxacin and moxifloxacin. They were both positive. Since the drug options were limited, OPT with claritromycin was done. Three hour later she had fixed drug eruptions on her left wrist internal side, right and left forearm. One months after this reaction patch tests were done with 1/1 and 1/10 concentrations. Tests were negative both on the affected areas and the back. OPT with azithromycin was negative and the patient used azithromycin for 3 days without a reaction. Cross reaction data between macrolide antibiotics is limited. Cross reaction is not detected for this patient in terms of late type hypersensitivity.

1589
Lichen planus associated with enalapril and valsartan

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Background: Lichen Planus (LP) is a chronic inflamatory T-lymphocyte-mediated disease. It is characterised by pruritic, violaceous, poligonal papules and plaques involving skin and mucous membranes. Etiology is idiopathic, although drugs may be involved in it. Patients using Angiotensin-Converting Enzyme Inhibitors (ACEI) or Angiotensin II Receptor Antagonist (ARA II) experience skin Adverse Drug Reaction (ADR); although there are few references in the literature about LP. This ADR is included in Summary of Product Characteristics (SPC) of captopril, but not in SPC of the other ACEI or ARA II.
Method and design: Case series, five patients with LP associated with enalapril and valsartan.

Scope: Allergy service, Hospital Central de la Defensa, Madrid.

Period: 03/01/09-12/31/13.

Main Variables assessed: demographic and clinical variables, diagnostic criteria, treatment, evolution, causal relationship between drugs and LP.
Results: Two men (63 and 71 years), three women (72, 73 and 80 years).

Drugs: enalapril ($n = 3$); valsartan ($n = 2$).

The average time of treatment: 13 years (10–20).

Patients were treated at the emergencies department showing an extreme pruritus rash with lacy and violaceous papules in limbs, back and oral mucous. Additionally to cutaneous lesions, three of them showed angioedema and hoarseness.

Allergologic study: immediate and delayed prick test was negative. Epicutaneous test for standard, enalapril and valsartan was negative. Skin punch biopsy specimen: findings consistent with LP. Blood count, biochemistry, total IgE, ECP, complement and inmunoglobulins were normal.

Treatment: Drug withdrawal, achieving complete remission in all cases.

Causal realtionship between drugs and LP were probable in all patients.
Conclusion: ACE/ARA II are widely used for a long time, they should be taken into account in patients with skin disorders, as drug withdrawal achieves complete remission.

1590
Myalgias induced by desloratadine

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Background: Desloratadine is a histamine antagonist long-acting, non-sedating, selective antagonist with activity in peripheral H1 receptor, indicated for relief of symptoms of allergic rhinitis and urticaria from 12 years of age. It is a drug with a good safety profile. In clinical trials the most common adverse drug reactions (ADRs) were fatigue, dry mouth and headache. The myalgias are (ADR) reported like a very rare post-marketing.
Method: 26 years old male presenting perennial rhino conjunctivitis tracking dog dander sensitisation with seasonal exacerbations by sensitisation to grass pollen. Current treatment with desloratadine 5 mg daily intermittently for 5 months. For 2 months has referred myalgias associated with antihistamine, temporarily suspends disappearing in about 5 days, to reintroduce the drug reappear myalgias, reducing the dose to 2.5 mg a day with good tolerance. Has been treated previously with ebastine 20 mg daily and bilastin respectively, which are suspended by intense fatigue and drowsiness.
Results: In order to evaluate a possible causal relationship between desloratadine and myalgias karch-Lasagna modified algorithm was used, resulting the adverse drug reaction as defined.
Conclusion: Myalgia is a (ADR) described in post-marketing as very rare reports, which greatly affects the quality of life of patients with the disease, and because of its low incidence of occurrence the patient delay to relate it to their antihistaminic sometimes overlook by your allergist.

1591
Hiccup induced by enalapril

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Background: Hiccup is an involuntary contraction of the diaphragm, may repeat several times per minute. It may be triggered by a number of common human conditions and drugs. Enalapril, an angiotensin-converting enzyme inhibitor, widely used, may cause this rare Adverse Drug Reaction

(ADR), that is not described in the summary of product characteristics.

Method: Design: Case series, three patients with hiccup induced by enalapril. Two females (66 and 86 years), one male (38 years).

Scope: Allergy service, Hospital Central de la Defensa, Madrid

Period: 03/01/09-12/31/13

Main Variables assessed: demographic and clinical variables, diagnostic criteria, treatment, evolution, causal relationship between enalapril and hiccup according to the modified Karch lasagna algorthm.

Results: The patients presented prolonged hiccup episodes as well as other associated symptoms: hoarseness, coughing and choking. Average time taking enalapril 12 months. Previously, in the oldest patient, valsartan was withdrawn due to ADR such as diarrea, cough, angioedema and rhinitis. All three patients were being studied in Gastroenterology service for hiccup; imaging scans and endoscopies showed negative results. In all patients hiccup disappeared after withdrwing enalapril. Re-exposure to enalapril was positive in a case. Causal relationship between enalapril and hiccup were defined in a case and probable in the other two cases.

Conclusion: Enalapril is widely used and it should be taken into account in patients with persistent hiccups, the physicians should include this drug in the differential diagnosis of hiccup. ARD caused by this drug is resource-consuming and has a direct effect in the patient's quality of life. Postmarketing Surveillance Systems should inform health professionals of this ARD.

1592
Enalapril-related purpura

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Background: Purpura is the outcome of extravasation of blood into the skin or the mucous membrane, which is caused by a defect in primary hemostasis. The primary hemostatic mechanism involves multiple steps of platelets interacting with each other and vessel walls. Enalapril, an angiotensin-converting enzyme inhibitor, is used in diabetics, heart disease and high blood presure. It can cause Adverse Drug Reactions (ADR) as it reduces platelet aggregation in patients with moderate hypertension that correlated with lowering of blood pressure. This effect was only observed at therapeutic concentrations of enalapril. Thrombocytopenia has been reported during Postmarketing Surveillance of enalapril in 0.5–1% of patients.

Aim: To describe, diagnose and treat purpura induced by enalapril.

Method: Design: A case series of seven (three males, four females) patients with purpura associated with enalapril, average age 74 years (61–83)

Scope: Allergy service, Hospital Central de la Defensa, Madrid

Period: 03/01/09–12/31/13

Main Variables assessed: demographic and clinical variables, diagnostic criteria, blood cell count and bleeding time, treatment, evolution, causal relationship between drug and purpura using the modified Karch Lasagna algorithm.

Results: The patients showed ecchymosses flat and notable extravasation in limbs, trunk and face was observed. Ecchymoses initially form an irregular purple patch, which eventually turns yellow and fades. Also enalapril caused pruritus and dysesthesia without an obvious eruption. Enalapril treatment time average of 60 months (2–240). The platelet count was in the reference range and a prolonged bleeding time was found in all patients. Enalapril withdrawal, achieved complete remission in all cases. Causal relationship between enalapril and purpura was defined in two cases, and probable in the rest.

Conclusion: Enalapril is widely used and ADR should be taken into account in patients with purpura and pruritus. Health authorities should inform health professionals of this ADR.

1593
Acute generalised exanthematous pustulosis related to ciprofloxacin

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Background: Acute generalised exanthematous pustulosis (AGEP) is a rare entity usually caused by drugs although it can be associated to infections or exposure to mercury. A case of AGEP probably related to ciprofloxacin is reported.

Method: A 70 year-old man with psoriasis, suffered from generalised pruriginous erythema with pustules in trunk and extremities, fever (up to 38°C) and malaise. Mucous membranes weren't involved. He had exclusively started treatment with ciprofloxacin 48 h for an urine infection. Due to clinical manifestations ciprofloxacin was removed and corticoids treatment was administered with resolution within 10 days but with laminar generalised desquamation of the skin.

Results: Leukocytosis (25 400/mm3) with peripheral neutrophilia (21 500/mm3) and eosinophilia (1400/mm3) was observed. Skin biopsy showed discrete acanthosis, subcorneal pustules, intraepidermal polymorphonuclear leukocites, edema in papillary dermis and inflammatory infiltrate with neutrophlis, lymphocites and some eosinophils.

Conclusion: We report a case of AGEP based on clinical manifestations and histologic findings.

Based on the temporal relationship between the onset of the therapy and clinical manifestations ciprofloxacin could be the responsible drug.

1594
Steven–Johnson syndrome or toxic epidermal necrolysis induced by erythropoetin

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Background: Steven- Johnson Syndrome and Toxic Epidermal Necrolysis (SJS/TEN) is a rare condition induced by drugs. Anyone can develop SJS/TEN unpredictably, usually develops within a few days up to 1 month. The diagnosis is suspected clinically and classified based on the skin surface area detached. Human erythropoietin is a glycoprotein that is synthesised mainly in the kidney and that stimulates erythropoiesis through actions on erythroid progenitor cells. Millions of patients have received EPO for correction of renal and nonrenal anemias.

Method: We present a 39 year-old female with renal failure due to chronic bilateral pielonephritis, with secondary arterial hypertension and secondary anemia. I consulted the patient only one time at the intensive care unit (ICU) of Infection Diseases on 30 November. She was hospitalised on 27 September in department of nephrology; she had headache and nausea. She had familiar history for chronic renal failure. She had anemia with Haemogloblin 6.7 g/dl, HTC 19.3%, Urea 249.0 mg/dl, Creatinine 11.53 mg/dl and albumin 2.9 g/dl. The 24 h diuresis resulted 1.5 l/24 h. Symptomatic treatment for the anemia, hypertension, and nausea was started. The patient was supporting it very well. On 8

Oct. was started therapy with Mircera (Methoxy polyethylene glycol-epoetin beta). Four days later, she had isolated vomits. The next day she had hypertension, itching, generalised urticarial vasculitis, diarrhea, fever 39°C, oral mucosal erosions, and normal diuresis. Therapy with prednisolone, furosemid, atenolol were started. The patient was stabilised on 19 Oct. According to the protocol of nephrology for CRF the patient must have a second dose of Mircera 2 weeks after the first one. She took the second dose and 3 days after she complained vomiting with fever 39°C. The patient experienced new skin eruption; bullous, itching, mucosal erosions, diarrhea, desquamation all body, mucosal ulcerations, the diuresis begun to fall to 100 ml/24 h. She started hemodialysis and at that time she was transferred to the intensive care unit for the persistent diarrea. Although all the therapies in the ICU the patient died.

Result: Since the diagnosis of SJS/TEN is mostly clinical examining carefully the case we concluded that the patient had suffered a SJS/TEN syndrome to erythropoietin.

Conclusion: This is one of the few reports on EPO adverse reaction. Physicians should be aware of this syndrome because it is sometimes self-limited but sometimes it is fatal.

1595
Dercum's disease associated with omalizumab

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Background: Dercum's Disease (DD) or adiposis dolorosa is chracterized by generalised overweigh, pronounced pain in the adipose tissue and a number of associated symptoms. The aetiology of DD is unknown but there have been reported cases of drug induced DD. Omalizumab, a recombinat humanized monoclonal antibody to IgE, is an option for the treatment of severe persistent asthma. Reported adverse drug reactions (ADR) of omalizumab include anaphylaxis, rash, diarrea, nausea, vomiting, epistaxis and increase of weight. DD due to omalizumab has not been previously reported.

We present a case of DD related to omalizumab.

Method: A 68 years old woman, diagnosed of severe persistent asthma, treated for 5 years with omalizumab 150 mg/month. She refers after starting treatment weight increase of 7 kg and since 2 years ago painful nodules on the trunk and proximal limbs. One year later she was diagnosed of depression. Omalizumab was withdrawn. The diagnosis, based on clinical criteria, was made by systematic physical examination, thorough exclusión of differential diagnoses, ultrasonography and Doppler. The case has been reported to the Spanish Postmarketing Surveillance System.

Results: The diagnosis was confirmed by the Services of Dermatology and Endocrinology. Other diagnoses were excluded. Ultrasonography reported 14 subcutaneous lesions well-defined, homogeneous and hyperecogenic relative to the adyacent fat tissue, without flow in color Doppler. This was suggestive of superficial lipomas. Ninety days after use of omalizumab was discontinued physical examination showed that the patient had lost 3 kg, had no pain and the nodules were drastically reduced.

Conclusion: The allergist should keep in mind this possible and rare ADR in patients treated with omalizumab showing weight gain, as discontinuing omalizumab, when it is possible, leads to rapid and large clinical improvement.

1596
Slow desensitisation of imatinib-induced non-immediate reactions and dynamic changes of peripheral blood $CD4^+$ $CD25^+$ and $CD8^+$ $CD25^+$ T lymphocytes

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Background: Imatinib is a tyrosine kinase inhibitor indicated for the treatment of chronic myelogenous leukemia, gastrointestinal stromal tumors (GISTs), and some other neoplastic diseases. Non-immediate adverse reactions are very common and drug avoidance is recommended for the management of serious non-immediate reactions to imatinib. We describe the process of imatinib slow desensitisation and the alteration of peripheral blood $CD25^+$ T lymphocyte percentages.

Method: Three patients diagnosed with GISTs and had a recent history of imatinib-induced non-immediate reactions (two cases of exfoliative dermatitis, one case of palmoplantar erythrodysesthesia) were desensitised as the following protocol. The reintroduced imatinib dosage was stepped up every week starting from 10 mg/d to 25, 50, 75, 100, 150, 200, 300, until achieving the target dose of 400 mg/d. Prednisolone up to 20 mg/d was allowed along with oral antihistamine and topical corticosteroid if allergic reactions revisited. The percentages of $CD4^+$ $CD25^+$ and $CD8^+$ $CD25^+$ T cells after incubating peripheral blood mononuclear cells with 1 μM imatinib at baseline and after successful desensitisation were analyzed by using flow cytometry technique.

Results: All patients were able to maintain 400 mg/d of imatinib within 9 weeks after starting desensitisation, and prednisolone was completely tapered off within 1 year. The percentages of $CD4^+$ $CD25^+$ and $CD8^+$ $CD25^+$ T lymphocytes significantly increased from $3.1 \pm 1.0\%$ and $11.4 \pm 5.9\%$ at baseline to $6.2 \pm 0.4\%$ and $29.4 \pm 4.4\%$ after desensitised, respectively.

Conclusion: Slow oral desensitisation is a helpful procedure to manage imatinib-induced non-immediate reactions such as exfoliative dermatitis and palmoplantar erythrodysesthesia. The increase of imatinib-induced regulatory T cells in these patients may be responsible for the induction of immune tolerance.

Poster Session Group III – Green

TPS 77 – Veterinary allergology

1597
Nanoparticulate immunotherapy in asthmatic horses

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Introduction: Equine asthma (Recurrent airway obstruction, heaves) shares many similarities with human allergic asthma and is the most common allergic airway disease in horses. Causes are potential allergens in dusty hay and moulds in straw, its high exposure in conventional stabling conditions in industrialized countries in combination with harmful gases and a genetic predisposition. In affected equine lungs increased pro-inflammatory (IFN-γ) and pro-allergic (IL-4) cytokine profiles have been detected.

Cytosine-Phosphate-Guanosine-Oligodeoxynucleotides (CpG-ODN) are known to stimulate mammalian immune system via TLR9 towards cell mediated Th1-line away from Th2 (Th2/Th1-shift). Gelatin nanoparticles are a biocompatible and biodegradable immunological inert drug delivery system which protect CpG-ODN against nuclease degeneration and enhances intracellular targeting.

The aim of this explorative study was to evaluate theses effects in a clinical trial under double blinded, randomized and placebo-controlled conditions.

Methods: Twenty-four asthma-affected horses received inhalations every second day for a total of five times. Horses were examined with respect to clinical, endoscopic, cytological and immunological parameters before, direct after inhalation regimen and after 4 weeks without any treatment or changes in environmental conditions.

Results: In contrast to placebo (nanoparticles and water), inhalation of verum (nanoparticle-bound CpG-ODN) showed statistical significant decrease as well as of breathing rate and type, nasal discharge, tracheal secretion, viscosity of tracheal mucus, neutrophil percentage and increase of partial oxygen pressure of arterial blood gas.

Conclusion: Administration of nanoparticle-bound CpG-formulation demonstrated a potent effect on allergic and inflammatory clinical parameters in asthmatic horses. It therefore offers an innovative, promising and well-tolerated therapeutic strategy beyond conventional symptomatic therapy.

1598
Increased frequencies of FoxP3$^+$CD4$^+$CD25^{high} cells with increased suppressive capability in foals compared to adult horses

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Background: A recent study in Icelandic horses has shown that first exposure to allergens in adult horses results in a higher incidence of insect bite hypersensitivity (IBH), an IgE-mediated dermatitis, than when first exposure to these allergens occurs before the age of 1 year. Our hypothesis is that exposure of horses to IBH allergens during maturation of the immune system is required for establishment of Treg tolerance. Our aim was to characterise FoxP3$^+$CD4$^+$CD25^{high} cells in foals, evaluated their suppressive capacity and their *in vitro* induction compared to adult horses.

Method: Freshly isolated PBMC from foals, their mothers and from 1-year old horses were examined for the presence of FoxP3$^+$CD4$^+$CD25^{high} cells using flow cytometry. Their suppressive capability was examined in an MLR. Furthermore, CD4$^+$ CD25^{high} cells were expanded, or induced from CD4$^+$CD25$^-$ cells *in vitro* with a combination of ConA, rIL-2 and rTGF-b1 (cocktail). Proliferation and cytokine production were measured by flow cytometry.

Results: The proportion of FoxP3+ cells within circulating CD4$^+$CD25^{high} cells was significantly higher in foals compared to their mother and to 1-year old horses. CD4$^+$CD25^{high} cells from foals displayed a significantly higher suppressive capability then those from mares and contained a higher proportion of IL10$^+$FoxP3$^+$ cells. Expansion of sorted CD4$^+$CD25^{high} cells with cocktail resulted in significantly higher proportions of FoxP3$^+$IL10$^-$, IL10$^+$FoxP3$^-$ and FoxP3$^+$IL10$^+$ cells in foals compared to mares. CD4$^+$CD25^{high} cells induced from CD4$^+$CD25$^-$ cells from foals displayed a significantly higher suppressive capability then those from mares and contained significantly more FoxP3$^+$IL10$^+$ cells.

Conclusion: These results demonstrate that CD4$^+$CD25^{high} Tregs with a strong inhibitory capacity can be induced more steadily in young horses compared to adult animals. These findings suggest that exposure of horses to allergens during maturation of the immune system is required for establishment of Treg tolerance.

1599
In vitro evaluation of equine dendritic cell targeting with DC-specific peptides

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Background: Horses can be affected by various allergic diseases such as insect bite hypersensitivity, urticaria or recurrent airway obstruction. Currently, allergen-specific immunotherapy (ASIT) is the only causative treatment, but it needs improvement, due to low success rate and occurrence of side effects. In order to reduce the amount of allergen necessary for injection, antigen presentation can be improved by targeting the allergens directly to DCs by using DC-targeting peptides. The aim of the study was to evaluate the *in vitro* effects of FYPSYHSTPQRP (pep3) fused to ovalbumin (OVA) as a prototype antigen on uptake by equine DC and to analyze the antigen-pulsed DCs for their capacity to activate T-cells.

Method: Monocyte derived dendritic cells (MoDC) from healthy horses were incubated with fluorescence labelled pep3 fused to OVA (pep3-OVA) or fluorescence labelled OVA as a control. Uptake of labelled pep3-OVA or OVA alone was

visualized by flow cytometry and fluorescence microscopy. MoDC were matured and functionally analyzed by co-incubation with CFSE-labelled homologous $CD4^+$ T-cells. Proliferation of $CD4^+$ T-cells was quantified by flow cytometry.
Results: First results have shown a markedly higher antigen-uptake of pep3-OVA than of OVA (mean fluorescence intensity (MFI) of pep3-OVA = 1506; MFI of OVA = 473). This was confirmed by visualization of labelled pep3-OVA inside the DC by fluorescence microscopy. Additionally, an increased proliferation of $CD4^+$ T-cells stimulated by pep3-OVA compared to OVA pulsed DC was found.
Conclusion: The DC targeting peptide pep3 appears to be a promising tool to enhance antigen-uptake by equine dendritic cells. Recombinant fusion proteins of pep3 with allergens have the potential to increase the overall efficacy of ASIT by improving the antigen presentation and lowering the side effects.

1600
Oral administration of Staphylococcus aureus superantigen to new-born Beagle puppies is well tolerated and promotes immune stimulation

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Background: The hygiene hypothesis suggests that a decreased exposure to microbes during infancy results in a decreased stimulation of the immune system and as a consequence immunoregulatory disorders such as allergy or inflammatory bowel disease may arise (1). We observed, in a Swedish infant birth-cohort, that children that were colonised by Staphylococcus aureus (S. aureus) during their first 2 weeks of life had a reduced risk of developing food allergy (2). S. aureus produce enterotoxins, Staphylococcal enterotoxins (SEs) that are superantigens with a unique ability to stimulate the immune system. New-born mice that are fed SEs increase their number of lymphocytes and in particular there is an increment of naive T cells expressing CD45RA (unpublished data). Moreover, neonatally SEA-treated mice become less allergic as adult. This was demonstrated in a model of airway allergy (3) and food allergy (4). The ojective of the study was to find a non-toxogenic dose of SE that will stimulate the immune system of new-born dogs. In order to, in further studies, investigate if such treatment reduce the risk of allergy development in dogs.
Method: Thirteen puppies were given a specific SE during their first weeks of life. The SE was given as a per oral dose (0.5, 2.5, 5, 165, 25, 50 or 100 μg/dose) at three occations, every other day. Five puppies were given Placebo (PBS). Blood samples were collected before treatment and once a week the following 4 weeks. The blood samples was analyzed by flow cytometri and plasma was analyzed for cytokines by luminex.
Results: None of the puppies that were given SE showed signs of adverse reactions such as vomiting, diarrhoea, fever or influence of the general condition.

One weak after start of treatment, puppies given SE had a larger proportion of naive $CD45RA^+$ T cells among their $CD4^+$ T cells as compared to placebo treated puppies. A larger proportion of their $CD4^+$ T cells expressed CD25 and FoxP3 which demonstrates either signs of activation or induction of regulatory T cells. There was no dramatic shift in general white blood cell populations in SE-treated puppies compared to placebo puppies.
Conclusion: New-born puppies given a specific SE perorally show no signs of adverse events. They show signs of immune stimulation. Further studies will evaluate if such early immune stimulation can reduce the risk for later allergy development.

1601
Do atopic dogs with allergic conjunctivitis have tear film osmolarity abnormalities?

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Background: It is known that anything that causes ocular surface inflammation, whether an infectious agent or an allergy, can lead to alteration of the tear film. Elevated tear osmolarity, a hallmark of dry eye, is also frequently encountered by allergy specialists as a clinical finding in Man. Dogs are a specie very prone to cutaneous and ocular allergies. Striking similarities between the disease in Man and in dogs have been highlighted in recent years. It is likely that dogs with allergic conjunctivitis also present elevated tear osmolarity. Therefore, we aimed to evaluate for the first time tear film osmolarity in atopic dogs with allergic conjunctivitis and to compare our findings with those described for man.
Method: A group of atopic dogs with allergic conjunctivitis ($n = 20$) and a healthy control group ($n = 20$) were included in the study. All animals underwent dermatological (CADESI classification, which evaluates the severity of the atopic dermatitis) and ophthalmic examinations to assess clinical signs of allergic conjunctivitis (chemosis, pruritus, epiphora, conjunctival hyperemia, ocular discharge, corneal disease) rated from 0 to 3. Tear film osmolarity was evaluated using TearLab system ® (Produlab, Lisbon, Portugal). Statistics was performed with GraphPad Instat (Mann–Whitney test and linear regression).
Results: Tear film osmolarity was 320.8 ± 9.6 mOSms/l in the control group and 340.3 ± 21.6 mOSms/l in the atopic group, this difference being statistically significant ($P < 0.0001$). Tear film osmolarity in atopic dogs exhibited a positive correlation with atopic dermatitis severity [CADESI values ($P < 0.0001$)] but no correlation was found with allergic conjunctivitis score ($P = 0.8385$). No significant differences were found between osmolarities of both eyes from the same animal in the control ($P = 0.5244$) or atopic groups ($P = 0.123$). In atopic patients CADESI values were 180.1 ± 66.50 and allergic conjunctivitis score was 8.2 ± 2.36.
Conclusion: Tear film osmolarity is altered in atopic dogs with allergic conjunctivitis showing that, as in Man, allergy and dry eye symptoms are frequently present as comorbidities. Higher alterations can be expected in dogs with more severe cases of atopic dermatitis. This test is easy to perform in dogs and may prove useful for diagnosis and to assess response to therapy.

1602
Generation and characterisation of recombinant species-specific FcεRIα for diagnosis of allergic diseases in veterinary patients

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Background: Similarly to humans also pet animals may suffer from IgE-mediated diseases. Atopic dermatitis, food allergy or insect hypersensitivity are just few clinical examples that can affect dogs, cats or horses and cause symptoms like chronic pruritus, papules, erythema, eosinophilic

granuloma (in cats and horses), sometimes urticaria or in severe cases asthma or COPD (in cats and horses). This also points out that pets and horses represent interesting model patients for human disease.

To diagnose hypersensitivities, a reliable, fast and non-invasive serological IgE-detecting assay would open up further possibilities to treat allergic diseases at an early stage.

The alpha chain of FcεRI (FcεRIα) is responsible for mast cell and basophil activation and has extremely high binding affinity to IgE. Hence we propose its usage as a powerful IgE detection tool.

The aim of this project was the construction of soluble feline, canine and equine FcεRIα, for the establishment of veterinary allergy diagnosis by a custom-designed allergen microchip in order to detect specific IgE in serum.

Method: The FLAG-tagged fusion protein of the extracellular domain of canine, feline and equine FcεRIα was expressed by a SV40 mammalian expression vector in CHO-DUKX B11 cells. Upon evaluation of the productivity and product quality of 384 clones for each species, the supernatants of selected candidates were purified by anti-FLAG M2 affinity gel.

Results: Structure information, obtained by CD-spectroscopy, confirmed correct folding of the protein. Specific binding to the respective IgEs was assessed by Western Blot. Subsequently the recombinant soluble FcεRIαs are intended to identify allergen-specific IgE in veterinary patient serum on the ISAC ImmunoCAP microchip.

Conclusion: Our study describes the production and characterisation of species-specific soluble FcεRIα to establish molecular and allergen-specific diagnosis of atopic diseases in veterinary patients.

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1603
Skin prick tests in dogs-should we do them instead of the intradermal tests?

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Background: Atopic dermatitis is a common disease in dogs with a suspected prevalence of about 10%. Allergen specific immunotherapy is advised for the management of these patients in addition to symptomatic treatment. Therefore, allergy testing is commonly performed either by serological or intradermal testing (IDT). In human immune-allergology those have been largely replaced by skin prick tests (SPT) as they show numerous advantages, such as being more specific, safer, quicker, less expensive, easier to perform and less uncomfortable to the human patient. To our knowledge there is only one anecdotal report of the use of this technique in dogs, made several years ago when extracts were very different from those available today. In this study we wanted to perform SPT in dogs and evaluate if the advantages reported for Man also apply.

Method: In a first phase 10 non-atopic dogs were divided in two groups (five sedated and five non-sedated). They all performed SPT with 21 extracts for use in human allergology (ALK-Abelló®, Madrid, Spain). An adapted form of the Glasgow pain scale was applied to non-sedated-group. Serum cortisol concentrations were evaluated before and after the procedure.

In a second phase, IDT for 28 allergens (Greer Laboratories®, Lenoir, North Carolina, USA) and SPT (with the same ALK-Abelló® extracts) were performed in 13 sedated atopic dogs.

Results: First phase showed the technique to be well tolerated as no pain was expressed by the animals; also it was easy to perform even in non-sedated dogs. Additionally, after SPT, both groups revealed physiological serum cortisol concentrations. Thus, the validity of the technique doesn't appear to be challenged by activation of the hypothalamic-pituitary-adrenal axis. The allergen concentrations used did not cause irritant reactions.

Results from the second phase show higher specificity of SPT vs IDT. Nevertheless, SPT positive reactions were much more feeble than those from IDT making interpretation sometimes difficult.

Conclusion: SPT are well tolerated and able to elicit positive reactions in atopic dogs. The allergens used for SPT may be too diluted for a clear-cut and easy interpretation of positive reactions in the dog. Further studies are needed to adequately evaluate the potential of this technique in canine dermatology and most importantly ideal allergen concentration for testing.