

Bibliographic updates in Allergology 2015

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EAACI
EUROPEAN ACADEMY OF ALLERGY
AND CLINICAL IMMUNOLOGY

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1. The Gut Microbiota

P. Debré et J.Y Le Gall : Rapport à l'Académie Nationale de Médecine 2014 (sous presse)

C.E.West et coll. The gut microbiota and inflammatory non communicable diseases J.A.C.I 2015 January 135 1 3-13

Theme: Immunology

Key words: Microbiota – Microbiome.

Accelerating development of molecular biology methods and next generation sequencing associated with bioinformatics gave a detailed description of both the microbiota, without requiring growth or isolation and its genome: the microbiome. It appears that an adult harbor as many 100 trillion resident microbes and the microbiome contains 150-fold more genes than the host genome. All the methods for investigation on the role of this gut microbiota in immune development are well documented. The changes in microbial composition and diversity are implicated in large series of non-communicable diseases including allergic diseases and asthma. Studies in animal models, establishment of gut microbiota in infants, environmental factors (mode of delivery, nutritional patterns, antibiotics, climate) account for dramatic increase in allergic manifestations. Modulation of this microbiota for the treatment and prevention of these diseases is well exposed in these two articles.

2. The human microbiome in immune cell development

N.H.Salzman 18 September 2014 Annals of Allergy Asthma Immun. 1-5

Theme: Immunology

Key words: Microbiome – Immunity – dysbiosis – Hygiene hypothesis

The author analyzes the post natal immune development in animals (germ-free) and in neonates, with impact on innate then adaptive immunity and the respective role of B cells and IgA, Regulatory T cells (Treg) TH 17. Immune response is carried out at local and distant sites. Disruption of homeostasis (dysbiosis) results in inflammatory processes such allergy and asthma. The hygiene hypothesis which is now discussed, suggests that the lack of environmental microbial exposure causes immune dysregulation and increases Th2 response. Gut Microbiota is an essential force in immune development.

3. The microbiome in Asthma

Y.J.Huang and Homer.A.Boushey JACI 2015 135 25-30

Theme: Immunology – Asthma

Key words: Microbiome – Asthma

Although most work were initially focused on gut microbiota, interest has expanded to include study of relationships between the airway microbiome and asthma with its phenotypes. The authors provide their perspective on differences in the airway microbiome between asthmatic and healthy subjects as well as relationships between environmental, gut microbiota, immune function and asthma development. They underline approaches involving directed manipulation of the gut and airway microbiomes for the treatment and prevention of allergic asthma.

4. Skin Microbiome and Atopic diseases

A.Salava et A.Lauerma : Role of the skin microbiome in atopic dermatitis Clin.and Translat. Allergy 2014 4 33doi10

L.Nylund : The severity of atopic disease inversely correlates with intestinal microbiota diversity Allergy 2014 Nov 21 ahead of print

N.Fyrhrquist et al Acinetobacter species in the skin microbiota protects again allergic sensitization and inflammation JACI 2014 134 1301-9

Theme: Immunology – Skin allergy

Key words: Skin Microbiome – Atopy – Dysbiosis

Molecular genetics have dramatically changed our vision of the skin microbiome and its role in atopic dermatitis (AD). Additionally, to the known dysfunction in barrier of the skin (filaggrin mutations) evidence is rising that AD is connected with dysbiosis of the microbial community. In severe forms of AD, an active treatment has been associated with recolonisation and higher cutaneous and gut microbial diversity.

Furthermore, in the skin microbiota of 118 atopic subjects analyzed by 16S RNA sequencing and in vitro assays on skin cells, it was shown that incubation with *Acinetobacter* species (Proteobacteria), induced a strong TH1 and anti-inflammatory responses by immune cells and skin cells and protected against allergic sensitization and lung inflammation through the skin. The same results were obtained in a mouse model. So the skin commensals play a key role in tuning the balance of TH1/TH2 response to environmental allergens.

On practical point of view, we must remember that abundances of Proteobacteria are associated with much forest and agricultural lands which enrich the microbiota, with far reaching consequences for public health.

5. Modulation of Gut Microbiota in Prevention and Treatment of Allergy

Theme: Immunology – Allergy treatment

Key words: Gut Microbiota – Probiotics – Prebiotics – Fecal Transplantation

Probiotics, Prebiotics and dietary fibers, are approaches widely used to favorably modulate the disruption of host-microorganism homeostasis, but, apart from experimental models, the results are generally modest in humans.

As for Antibiotics, there is evidence, in animal models, of their role in increased lung inflammation: vancomycin treated mice revealed an increase of Lactobacillaceae family members and reduction in Bacteroides, directing the immune response towards an allergic phenotype and in neonates towards asthma. But other antibiotics, such as streptomycin do not show this effect.

Fecal Transplantation is rather used for the treatment of Intestinal Bowel diseases.

Manipulation of the microbiota with specific microbial groups to favour the growth of particular bacteria, begin to be tested as strategies to prevent allergic diseases.

6. Basophil Activation Test (BAT) in Peanut Allergy (PA)

A.F.Santos et al : JACI 2015 135 179-86

Theme: Immunology – Food Allergy – Peanut

Key words: Basophil Activation Test – Oral Food Challenge – Peanut

In order to assess the utility of the BAT to predict the severity and threshold of reactivity to peanut, during Oral Food Challenge, the British authors submitted 124 children, on the same day, to clinical evaluation, skin prick-tests, specific IgE dosage and BAT before and after the Challenge. 52 (median age 5 years) reacted with clinical symptoms ranged from mild oral symptoms to anaphylaxis; 57% reacted to 0,1g or less of peanut protein. The percentage of activated basophils (CD63+) measures basophil reactivity at different allergen concentrations whereas the concentration of allergen at which basophils become activated measures basophil sensitivity. This study demonstrates that reactivity is independently associated with severity of allergic reactions to peanut, whereas the threshold sensitivity is significantly associated with the threshold of allergic reactions during the Challenge. These two distinct parameters of BAT may be used to predict severity of PA and the threshold of allergic reactions during Oral Food Challenge.

7. Biomarkers of corticosteroid response to Asthma

D.C.Cowan et al : JACI 2015 January in press

Theme: Asthma – Allergy treatment

Key words: Asthma – Corticosteroid response – Bromotyrosin

Using a panel of 3 biomarkers in steroid-naïve asthmatic patients in order to predict clinical responsiveness to inhaled corticosteroids, (FENO, sputum eosinophil count, urinary bromotyrosin) the authors demonstrated on 46 patients (between 18 and 75 years old, with stable persistent asthma, 80.4% are atopic and 65.2% eosinophilic), that each of the biomarkers had utility for predicting steroid responsiveness but the combination of high FeNO values and high urinary Bromotyrosin levels (BrTyr) had the best power to predict a favorable response. BrTyr is a noninvasive marker of oxidant stress and eosinophil activation and its association with FENO measurement avoid the need for sputum induction, processing and analysis which are time-consuming, and uncomfortable for the patient.

8. Icatibant in ACE- inhibitor induced Angioedema

M.Bas et al. New England J.Med.2015 January 25 132 418-25

Theme: Drug Allergology

Key words: Bradykinin angioedema – ACE inhibitor – Icatibant

In a, multicenter, double blind, double dummy, randomized phase 2 trial, 27 patients, 18-95 years old, were assigned to treatment with 30mg of subcutaneous Icatibant (selective bradykinin β_2 receptor antagonist (13 cases) or to the current off-label, standard therapy (Prednisolone 500mg IV + Clemastine (anti-histamine - 14 cases).

All 27 patients had complete resolution of edema (one patient required tracheotomy) but the time to complete resolution of edema was significantly shorter with Icatibant than with combination therapy glucocorticoid- antihistamine.

9. Eosinophilic Chronic Rhinosinusitis with Nasal Polyposis treated by budesonide transnasal nebulization

C.Wang et al JACI January 2014 in press

Theme: ENT Allergology

Key words: Eosinophilic chronic rhinoinusitis – Nasal Polyposis – Budesonide

Short term treatment (14 days) in a randomized trial on sixty patients (19-76 years old) significantly reduced polyp size and improved symptoms. Polyp IL5 and eotaxin expression decreased significantly whereas TGF β and IL 10 expression increased. Budesonide reduced polyp eosinophil infiltration and Th2 cell frequencies. Indices of remodeling were

decreased whereas collagen deposition increased. This treatment did not suppress the hypothalamic-pituitary-adrenal axis or cause any serious side-effects. It is an effective and safe option of corticosteroid therapy for this type of Rhinosinusitis.

10. Misuse of medical devices: a persistent problem in self-management of asthma and allergic disease

R.S.Bonds et al Ann.All.Asthma.Immunol 2015 114 63-76

Theme: Allergy treatment

Key words: Self management – Asthma

This study sought to identify factors associated to misuse of epinephrine auto-injectors (102 patients) and Metered-dose inhalers (MDI) and/or spacers (44 children or adult asthmatics). Only 16% of patients used epinephrine auto-injector properly, missing 3 or more steps of the technique. Only 7% of MDI users demonstrated perfect technique despite allergist/ immunologist care. So, the rate of correct use of these devices since earlier reports did not show any improvement. Novel methods of providing repetitive training for patients are highly recommended.

11. Prevention of peanut allergy through early consumption

G.Du Toit et al NEJM 2015 26 Feb 372 803-813 & R.S.Gruchalla and H.A Sampson 875-877Edito.

Theme: Food Allergy – Peanut

Key words: Peanut allergy - Early consumption

The early introduction of peanuts significantly decreased the frequency of the development of peanut allergy (approximately 70 to 80%) among children at high risk and modulated immune responses to peanuts: this is the result of a randomized prospective trial conducted in London among 530 infants followed during 60 months. These compelling findings suggest new forthcoming guidelines in the management of Peanut-Allergy, the frequency of which is increasing and alarming.

12. Asthma and exercise-induced-bronchoconstriction (EIB) in Athletes

L.P Boulet et P.M.O'Byrne : NEJM 372 7 12 Fev 2014 641-648

Theme: Asthma

Key words: Asthma – Exercise inuced bronchoconstriction

Intense exercise in athletes impose demands on the cardiorespiratory system and accounts for increase prevalence of various respiratory ailments such as asthma and rhinitis and transient narrowing of the airways that occurs among athletes who may not have a diagnosis of asthma or even have any respiratory symptoms. The complex mechanism of this EIB has not been established with certainty. The diagnosis based on history requires also documentation on variable airway obstruction, by broncho-provocation tests (β_2 agonists, metacholine) or eucapnic voluntary hyperpnea. The treatment must minimize the deleterious effects of exercise, mandatory to allow optimal performance. Non-pharmacologic and pharmacotherapy are detailed, largely based on expert opinion. Adherence to anti-doping regulations regarding asthma drugs are important for competitive athletes.

In a closer approach, Belgian authors (S.F Seys et al Allergy Vol 70 2015 2 187-194) demonstrate increased presence of damage-associated molecular patterns in the sputum of non asthmatic athletes, particularly elite swimmers who presented after exercise-induced bronchostriction, biomarkers of airways epithelial damage, in sputum, predominance of neutrophils in the airways and release of inflammatory cytokines, molecular signature of airways alterations.

13. Eczéma (E) and Environment

T.Tsakok et al / The Lancet 26 Feb 2015 385 special issue 59

Theme: Skin allergy – Eczema

Key words: Eczema – Environment – ISAAC2 study – Damp – Mould – Socio economic factors

In a cross-sectional study of ISAAC phase 2, among 46 051 children aged 8-12 years, from 20 countries, the authors suggest an association between childhood eczema symptoms and damp housing conditions, which may be causal. Modification to home environment to reduced damp and mould could be harnessed to improve or even prevent this debilitating disease.

In a similar approach, J.I.Silverberg (Ped.All.Immun. 2015 26 54-61) analyzing data from 3049 children and adolescents ages 8-19 years from the 2005-2006 National American Survey, observe that children with atopic dermatitis have lower body mass index due to malnutrition with low bone mineral density and belong to Hispanic ethnicity.

So indoor pollution and socio-economic factors play a role in the onset of eczema in children.

14. Phenotypes of wheezing and asthma in children: Lessons from cohort studies

J. Just et al Ped.All.Immun 21 Feb 2015. accepted articles

Theme: Respiratory allergy – Asthma

Key words: Asthma phenotypes – Wheezing

Phenotyping asthma by multivariate and unsupervised analyses allow to describe three wheeze types in children of pre-school age:

- The mild episodic viral wheeze with a good prognosis.
- The multi-trigger atopic wheeze, more prevalent in boys with poor prognosis
- The severe non-atopic wheeze, more prevalent in girls, the prognosis of which depends of the time of onset (early or late) of allergic expression.

Further studies are mandatory to better define wheezing phenotypes, and to find non-invasive biological markers, in order to prevent the risk of developing severe asthma.

15. Occupational Anaphylaxis (OA)

A. Siracusa et al Allergy 2015 70 141-152

Theme: Occupational allergy

Key words: Hymenoptera venom – Latex

Hymenoptera stings and now, more rarely natural rubber latex are the commonest triggers of OA. Other triggers include food, medications, insect/mammal/snake bites and chemicals. Underlying mechanism is usually IgE mediated, less frequently non-allergic. Some aspects of exposure, (route, frequency, type of allergens) may account for the variability of symptoms. After identification of the trigger, prevention is based on removal from further exposure. Immunotherapy is recommended only for OA due to Hymenoptera stings.

16. Gene expression in bronchial epithelium and Clinical Phenotypes of asthmatic disease

BD Modena et al, AJRCCM : 2014 12 1363-1372

TS Hallstrand S. Agharib, AJRCCM 2014 and 1333 to 1335

Theme: Asthma – Genetics & Allergy

Key words: Asthma phenotypes – Bronchial epithelium – Asthma biomarkers.

The molecular basis of Asthma phenotypes remains poorly understood. The authors show

that bronchial epithelial cell gene expression, as related to the asthma biomarker FeNO, can identify distinct asthma phenotypes with gene transcription characteristics (such Th2-high Asthma defined by 3 genes) also suggesting the presence of novel gene pathways relevant to these phenotypes.

17. Filaggrin gene and food allergy

CD Van Gicke Allergy 2015 & al, Allergy: 2015 70 461-464

Theme: Food Allergy – Genetics & Allergy

Key words: Filaggrin – Food allergy

Of 155 children reactive to food allergy, diagnosed by DDBFC, 33 had at least one variant of Filaggrin gene loss of function. Among them, 29 were clinically reactive to at least one food, (odd-ratio 4,9) corresponding to a relative risk of 1,5 , compared to carriers of wild-type allele (it will be needed to refine the model for each specific food).

In another research: GWAS identifies peanut allergy specific loci. (X.Hong et al: Nature communications 2015 6 24 feb. n°6304). A GWAS in 1315 children and 1444 parents in Chicago Food Allergy Study, identifies specific loci in the HLA-DR and DQ region at 6p21.32. These associations were replicated in participants of European ancestry and show evidence of epigenetic mediation. According to the authors, this study suggests that the HLA-DR and DQ region probably poses significant genetic risk for peanut allergy.

18. Exhaled biomarkers and Gene expression at pre-school age improve Asthma prediction at 6 years age.

EM.M. Klaassen et al AJRCCM 2015 191 2 201-207

Theme: Asthma – Genetics & Allergy

Key words: Exhaled biomarkers – VOC - Asthma gene expression – Asthma prediction

Information on exhaled VOCs combined with possibly expression of inflammatory genes, at pre-school age, enhance a correct asthma diagnosis at 6 years, in around 90% of children with wheeze.

19. Probiotics and risks of Eczema and Atopy

G.Marlow et al Ped.All.Imm Mars 2015 accepted article

Theme: Eczema – Genetics & Allergy

Key words: Eczema – Probiotics - Atopy

The aim of this study was to investigate differential effects of 2 probiotics: Lactobacillus rhamnosus HN001 and Bifidobacterium animalis HN019 on the TLR genes, in a high risk infant population (331 children of European ancestry).

26 TLR SNPs interacted with HN001, resulting in significantly reduced risk of eczema, eczema severity and atopy. Only 2 reacted with HN019.

In conclusion: TLR genotypes may be positively affected by probiotic supplementation HN001 had a much stronger effect than HN019.

20. GWAS of short-acting β 2-agonists: A novel significant locus

E. Israël et al, AJRCCM: 2015 March 1 191 5 530-535

Theme: Asthma – Pharmacogenetics

Key words: Short acting β 2 agonists

In a phenotypic and genotypic analysis of 724 subjects, a GWAS of acute bronchodilator response to inhaled β 2 agonists was performed. 444,088 SNP were examined and the top 50 was replicated in a population of 444 asthmatics. 4 SNP reached statistical significance on the genetic region of chromosome 2 near ASB 3 gene region associated with smooth muscle proliferation, suggesting influence of smooth muscle relaxation that occurs in asthma. This is an example of a pharmacogenetic study predictive for an individual responsiveness to β 2 agonists leading towards a personalized medicine.

21. Prediction of Atopic Dermatitis (AD) in infants before leaving maternity ward

M.Kelleher et al JACI 2015 135 930-5

Theme: Paediatrics allergy – Skin allergy

Key words: Atopic dermatitis – Trans-epidermal water loss - Fillagrin

Impairment of the skin barrier function by trans-epidermal water loss measurement at birth and at 2 months predicts the development of AD at 1 year, effect independent of parental atopy of child Filaggrin mutation status. These findings have implications for the optimal timing of interventions for the prevention of AD.

22. Cow's Milk Allergy (CMA) in Children and contact urticaria to Milk

V.Scichter-Confino et al Ped.All.Imm :2015 26 3 218-222

Theme: Paediatrics allergy – Skin allergy

Key words: Milk allergy – Contact urticaria – Finger test

CMA is the most common Food Allergy in infancy, generally triggered through ingestion (and in majority IgE mediated) but also through skin contact. The authors showed that the finger test (applied on the cheek by a physician finger), detects contact urticaria which exists only in patients with IgE mediated CMA. The finger test should be part of the evaluation of CMA patients and its positivity suggests the potential for multiple food allergy, especially to sesame and egg.

23. Dog and cat exposure and respective pet allergy in early childhood

K.Pyrhonen et al Ped.All.Immun 2015 26 3 247-255

Theme: Paediatrics allergy – Pet allergy

Key words: Cat, dog allergy – Early exposure to allergen – Allergy prediction.

In a nationwide population-based study (South Karelia Finland) early exposure to dog and cat at home was associated with a higher incidence of respective pet allergy (more for cats than for dogs) during the first four years of life. These results were independent of parent's allergies. However further evidence with longer follow-up is required to justify any recommendation, concerning early pet contacts with a view to preventing pet allergies later in life.

24. Diagnostic and experimental food challenges in adult patients with non-immediate reactions to food: role of enhancers

K.Brocow et al JACI 2015 135 4 977-9; A.Tripathi et al JACI 2015 135 4 985-987

Theme: Food allergy

Key words: Non-immediate reaction to food – Provocation test – Enhancers: alcohol, exercise, aspirin.

The first article provides evidence that an oral gluten challenge protocol, alone or associated with aspirin or alcohol improve the diagnosis in wheat -dependent exercise induced anaphylaxis. The second paper underlines the role of the co-factors: exercise, aspirin, alcohol as “enhancers” of challenge positivity in non immediate food allergy (for example delayed urticaria or anaphylaxis after eating red meat or pork kidney).

25. Sensitization and Clinical allergy to peanut. Respective part of specific IgE and IgG4

A.F.Santos et al/ JACI 2015 135 1249-56

Theme: Food allergy

Key words: Peanut – Sensitization – Allergy – IgE – IgG4

Most children with detectable peanut specific IgE are not allergic although sensitized (with or not positive prick-test). Differences in IgE levels may partially explain these two phenotypes. In this study, the authors show that levels of IgE are significantly higher in Peanut Allergic patients (PA) than in Peanut-Sensitized patients (PS). Moreover, Specific IgG4 acts as IgE inhibitors in the serum of PS patients and in activation of basophil and mast cell of these patients as well in patients submitted to oral immunotherapy (POIT). Furthermore, depletion of IgG4 from plasma of Children with PS and POIT partially restore mast cell activation. Future studies will explore clinical implications of these findings.

26. A New Target in the treatment of Allergic Asthma

N.Krug et al : NEJM 21 May 2015 1987-1996

Theme: Asthma – Respiratory Allergy – Allergy treatment

Key words: Th2 lymphocyte – GATA 3 – DNAzyme – SB010

Therapeutic targeting of GATA 3, an important transcription factor of the Th2 pathway, with SB010, a novel DNA enzyme (DNAzyme) by means of inhalation once daily for 28 days, in a double-blind placebo-controlled multicenter clinical trial, significantly attenuated both late and early asthmatic responses after allergen provocation, in 21 patients with allergic asthma (20 placebo). Sputum eosinophilia was also attenuated, whereas levels of serum tryptase and plasmatic IL 5 were lower. However, allergen-induced FeNO and airways hyper responsiveness were not affected.

27. Exacerbations in Asthma, predictive factors and Risk Score

E.D.Bateman et al JACI 2015 135 6 1457-1464

S.J.Teach et al:JACI 2015 135 6 1465-147

Theme: Asthma – Respiratory Allergy

Key words: Asthma exacerbation risk factors – Seasonality

Risk of uncontrolled Asthma at 3 months and a severe exacerbation within 12 months can be estimated from simple clinical assessments. Prospective validation from a large data of 3

studies (7446 patients) showed, on multivariate analysis that GINA step, reliever use, post bronchodilator FEV1, 5-item Asthma Control Questionnaire are dominant factors, as well as smoking status and Body Mass Index. Increments in Risk score based on 5 selected predictors increase the risk.

In the second study among 400 inner city children, median age 13 years, exacerbations occurred most commonly in the fall. Multivariate model showed that exacerbation in the previous season was the strongest predictor in fall and Winter whereas a higher requirement for inhaled corticosteroids was the strongest predictor in spring and summer. Anyway, the best predictive power is for fall exacerbations (role of virus).

28. Chronic Rhino-Sinusitis (CRS) with Polyposis (P): IL 25 as therapeutic target

Hyun-WooShin et al JACI 2015 135 6 1476-1485

Theme: Rhinitis – Respiratory Allergy – Allergy treatment

Key words: Nasal Polyposis – IL25

The Korean authors investigated IL 25 expression and its cellular origins in Nasal Polyps (NP) of human subjects using immuno-histo-chemistry, quantitative RT-PCR and ELISA of NP tissue. IL 25 expression was significantly up-regulated in NP mucosa. In NPs, IL 25 nRNA expression positively correlated with the expression of several inflammatory markers.

In a murine model of NP, anti-IL 25 treatment reduced the number of NP, collagen deposition and inhibited expression of local inflammatory cytokines. These results suggest the novel possibility of treating NP with anti-IL 25 therapy.

29. Sinus Microbiota (SM) and Phenotypes of Chronic Rhino- sinusitis (CRS)

V.R Ramakrishnan et al: 2015 JACI in press

Theme: Respiratory Allergy – Rhino-Sinusitis

Key words: Sinus Microbiota – Actinobacteria – Chronic Rhino Sinusitis Phenotypes

Analysis of SM in a large cohort of patients reveals that 2 particular Phenotypes of CRS (association with Asthma or Purulence) are characterized by distinct composition of resident bacterial communities.

Biodiversity and bacterial composition, with the presence of relative higher abundance of Actinobacteria, are predictors of better outcome, particularly after surgery.

PS: We recommend the book edited by the EAACI group in 2015: Global Atlas of Allergic Rhinitis and Chronic Rhinosinusitis

30. Peanut Allergy (P.A): Ara h2 and Ara h6 best predictors of severity

AK.Kukkonen et al Allergy 2015 June Accepted articles

Theme: Food allergy – Peanut allergy.

Key words: Ara h2 – Ara h6 – Peanut allergy.

Component resolved diagnostic (CRD) coupled with double-blind placebo-controlled challenges and allergen activity of products by IgE microarray inhibition, revealed, in 102 patients of birch endemic region, that co-sensitization to Ara h 2 and Ara h 6 are associated with severe reactions. Spe. IgE to Ara h8 added no diagnostic value. Moreover, the products, roasted or not, on the contrary to Ara h 1,2 3 6 and 8, lacked Ara h9 activity. CRD reduces the need for oral challenges in P.A.

31. Cockroach sensitization (C+) as surrogate of microbial exposure and mitigation of Allergic Rhinitis (AR)

W.He et al :JACI sept 2015 136 3 658-666

Theme: Rhinitis – Respiratory allergy

Key words: Cockroach sensitization – Hygiene hypothesis

C+ assayed by skin prick tests in patients with AR, in natural settings or allergen challenges (21 to HDM, 21 to mountain cedar, 34 to oak, 23 to ragweed) revealed mitigation of symptom severity and more rapid resolution of inflammation induced by aero-allergens, which confirms that C+ may serve as proxy for prior microbial exposure and argue the concept of hygiene hypothesis. However, cockroach allergens are not well known.

32. Conversely, Are rigorous personal or home cleanliness a risk for Asthma or Allergy?

J.Weber et al (AJRCCM 2015 191 n°5 522-529)

Theme: Asthma – Respiratory allergy

Key words: Home cleanliness – Allergy risk – Asthma risk – Hygiene hypothesis

In a comprehensive study of a German cohort (399 children), the authors showed that, if bacterial exposure (or microbial biomarkers in house dust) is associated with reduced prevalence of atopic sensitization or childhood asthma, neither personal nor home cleanliness (reflected by dust parameters) was associated with a risk for asthma or allergies. This is a limit to the interpretation of hygiene hypothesis.

33. Early-term birth and respiratory morbidity

M.O.Edwards et al JACI :2015 Sept 136 3 581-587

Huan. E et al: AJRCCM 2015 August 192 520-521

Theme: Asthma – Respiratory allergy

Key words: Early-term birth – Asthma risk

Two epidemiologic studies, the 1st from United Kingdom, the 2nd from USA tried to assess whether early-term born children (ETB) have greater respiratory symptoms (Wheezing or Asthma) compared with full-term born (FTB) ones. EB births are defined as birth at 37 to 38 weeks' gestation compared with 39 to 42 for FTB. In UK, of 2845 children, surveyed 1-to 10 years, EB birth lead to increased admissions to the neo-natal units and hospital in the first year. In children less to 5 years old there was a higher rate of wheeze (49% versus 39%). Similarly, children older than 5 years reported higher rate ever or recent wheezing over the last 12 months, than FTB subjects. these symptoms persisted even when stratified by family atopic history or mode of delivery.

As for Asthma, of 2540 American children surveyed 5 to-7,8 years, an increased prevalence was observed in ET birth subjects, compared with FTB ones, whatever the age range of Asthma or length of follow-up.

ET birth is for the authors an important risk of Asthma and early delivery should be avoided where possible.

34. Mode of delivery and Childhood Asthma

A.C. Van Berkel et al :Ped.All.Immunol 26 330-33

Theme: Asthma – Respiratory allergy

Key words: Mode of delivery – Asthma risk

The authors examine the associations of different modes of delivery with childhood wheezing patterns, asthma, FeNO and airways resistance, up to school age. In a cohort of 6128 children from Netherlands, increased risk of early and persistent wheezing was associated with caesarean section, whether the process is elective or emergency.

Only elective cesarean was associated with a higher Fe NO level.

The other modes of delivery (vaginal, forceps-assisted) were not associated with any asthma or related outcomes.

In conclusion, elective and emergency caesarean section are associated with increased risks of early and persistent wheezing up to school age. This is probably due to airways inflammation reflected by higher FeNO level.

35. Omalizumab is an effective and safe therapy in Chronic Spontaneous and Inducible Urticaria in Adults and Children

Theme: Urticaria – Skin allergy

Key words: Omalizumab – Chronic urticaria

In Adults, recent trials came to the conclusion that O is an effective and rapidly active therapy in randomized and real-life cases of CSU or CindU. when standard of care with H-1-antihistamines, even at-up to 4 times the approved dose, is inefficient. The optimal dose of 300mg by subcutaneous injections at 4 weeks intervals, during 12 to 24 weeks confirms rapid resolution, and good tolerance, (A.Kaplan US, M.Metz : Germany), even longer than 1 year (D.Har US). Periodic attempts at weaning patients should be performed to test a chance of remission. Anyway after retreatment, patients experienced complete response (M.Metz).

In children, due to the low prevalence of CU, O has not be studied in large cohorts (U. Wahn: Germany) except in Thailand (S. Chansakulporn: 92 children) and O has been only used after the age of six in asthma. However recent reports of refractory solar and physical Cind U (S.Arasi: Italia or A.Levi : Israël or I E .Netchiporouk Caanada) have shown beneficial effects and good tolerance of O in children of 6 to 16 years.

36. Gluten-related disorders

M.F.Martinez-Munoz et al : Ped.All.Immunol 2015 Sept. on line

Theme: Food allergy – Wheat

Key words: Gluten – IgE – Celiac disease – Gluten sensitivity

Gluten, the main structural protein complex of wheat, is responsible for 3 different immune responses with various clinical, pathogenic and epidemiologic expression:

1) IgE-mediated Wheat allergy with typical manifestations of Th2 response: dermatologic, respiratory, intestinal anaphylactic reactions.

2) Celiac disease CD, auto-immune, gliadin-specific Th1 cell response, with intestinal (diarrhea) or extra-intestinal (weight loss, anemia) symptomatic or latent form discovered by serological or genetic screening.

3) Gluten sensitivity, possibly immune-mediated, with intestinal symptoms after absorption of gluten or cereals, in non-allergic, non-celiac patients and source of popularity and often excessive gluten-free diet.

(A recent state of art review on CD is published in BMJ 5 october 2015 351; h4347 B.Lebwohl et al)

37. Celiac disease in collision with Asthma: role of Leukotrienes

F.Tang et al Journal of Exp.Medicine 2015 212 10 1487-1495 and J. Groojans et al idem 1485

Theme: Food allergy – Wheat

Key words: Celiac disease – Asthma – Leukotrienes

Inflammatory T cell response to dietary gluten in genetically susceptible host, Celiac disease is characterized by injury to intestinal epithelial cells, atrophy of the villi, caused by infiltrating cytotoxic CD8 cells. Antigen Gluten, elimination of which is a recognized therapy, promotes IL15 which in turn recruits additional toxic cells responsible for up-regulation of cysteinyl-leukotrienes (CystLts), demonstrable in active celiac but not in healthy or on gluten-free patients. These CystLts are metabolites of Arachidonic acid, linked to allergic disorders including Asthma. Moreover, Montelukast, inhibitor of CystLts is beneficial in Asthmatics and pre-treatment of intestinal toxic cells decrease their cytolytic capacity. So, this drug may be a potent therapeutic target for celiac disease.

38. Food Allergy and Celiac Disease (CD)

R.Pillon et al Allergy 2015 701346-1349*

Theme: Food allergy – Wheat

Key words: Celiac disease – IgE

The Spanish authors* report the first case of wheat allergy associated with latent celiac disease in a 19 month – old boy, suffering atopic dermatitis and bronchospasm; the diagnosis of CD was made by family history and genetic results (HLA –DQA1 05 cis DQB 02); wheat allergy occurred at 5 years and grass pollen allergy at 11.

In the second patient, a girl (17 months), CD diagnosed by serum IgA anti-transglutaminase and anti-endomysium and intestinal biopsy. Grass pollen allergy occurred at 6 years and wheat allergy (IgE +) at 12, revealed by inadvertent ingestion of wheat. Italian pediatricians **screening for CD 319 patients with severe food allergy observed a prevalence of 5% (1% among healthy school children) and recommend routine genetic and serological markers in case of severe reactions against food proteins with elevated IgE levels.

39. Allergic multi-organ diseases induced by Wheat–Flour

E.Gomez-Torrijos et al :JACI 2015 October 1114-1116

I.Sanders et al: JACI 2015135 1529-1537

Theme: Food allergy – Wheat

Key words: Rhinitis – Asthma – Anaphylaxis - Eosinophilic Esophagitis – Albumin – Globulins – Gliadins – Glutenins

Clinical profiles of WF allergy and component resolved diagnosis revealed high degree of heterogeneity in the recognized allergens (more than 19 recombinant proteins and 2 carbohydrate determinants). It appears that mainly salt-soluble proteins fractions (albumin, globulins) are associated with baker's Asthma and Rhino-sinusitis, and prolamine (gliadins,glutenins) with wheat-dependant Anaphylaxis induced by exercise. Both fractions, salt soluble and insoluble, are incriminated in Food allergy. In fact, Gliadins may be also causative in baker's Asthma.

And now, it has been recently reported the case of a 31 years old young woman exposed since birth in the bakery of her family, where she subsequently worked, who successively suffered Rhino-sinusitis with Ocular symptoms and Asthma then Eosinophilic Esophagitis induced by inhalable wheat flour, without gastro-intestinal symptoms by ingestion of cereals products. It is the first case of Occupational Allergic Eosinophilic Esophagitis triggered by inhalation. All these disorders went into remission when the patient was removed from the workplace.

40. Emerging therapeutic options for the treatment of Asthma

R.A.McIvor Annals of Allergy, Asthma, Immunol.2015 115 4 265-271

Theme: Respiratory allergy – Asthma – Allergy treatment

Key words: Monoclonal antibodies – Phosphodiesterase – Muscarinic antagonists

Despite treatment according to guidelines, approximately 40% of patients remain symptomatic. A search restricted to the previous ten years was performed by this Canadian author about emerging therapies in phase 2 or 3 development. They include monoclonal antibodies (anti-interleukin 5 or anti-IL 13 agents) a chemoattractant molecule expressed on a Th2–lymphocyte antagonist (OC000459), a phosphodiesterase 4: Roflumilast and Long-Acting Muscarinic–Antagonists. The most advanced drug is inhaled Thiotropium. In 3 randomized trials, including more than 1000 patients, this LAMA appears to be well tolerated, and efficacious as an addition to maintenance treatment with ICS + LABA in adolescents or adults with moderate to severe asthma, once daily at 0,2µg dose.

(G.J.Rodrigo Annals of A.A.I 2015 115 3 211-216)

Nevertheless, the authors remind us that it should be considered that clinical trial efficacy is often distinct from real-life effectiveness.

41. Mite specific extracts suitable for worldwide immunotherapy

T.Batard et al :Allergy :2015 October Accepted articles

To design such products appropriate to treat children and adult Dermatophagoides allergic patients, the authors had explored the patterns of IgE sensitization from cohorts living in various geographical areas (1302 patients).

IgE specific for 12 purified allergens from *D. pteronyssinus* or *D. farinae* were assessed in sera by microarray assay and mass spectrometric. It appears that all patients have IgEs to allergens present in mite bodies and feces. So a mixture of *D. pt* and *D. f* manufactured from these two sources is suitable for Mite specific immunotherapy in Europe, Asia and North America.

42. Sublingual Mite-Specific Immunotherapy in Asthma

P.Devilliers et al Allergy October 2015 Accepted articles

In a clinical, randomized trial, 484 French adults 16 to 50 years of age, suffering from moderate persistent asthma, were submitted to a daily treatment by a sublingual solution of *D. pt* and *D. f* extracts during 12 months. This is one of the largest studies in such cases. Analysis of the efficacy data revealed a significant active versus placebo difference, in both well or totally controlled moderate asthma. No serious adverse events were reported. However, a high incidence of abdominal pain was noted, surprisingly in active as well as in placebo groups, usually rare in sublingual therapy.

In conclusion, in patients allergic asthma to house dust mite (HDM) sublingual immunotherapy is safe, well tolerated and of value for asthma, requiring low to moderate doses of inhaled glucocorticoids.

43. A new faster and safe nasal provocation test for mite allergic rhinitis

F.de Blay et al. Annals of All.Asthma Immun 2015 115 5 385-390

Nasal Provocation Test (NPT) is the gold standard of diagnosis in allergic rhinitis, but it is time-consuming and its use is limited because it requires a skin end-point titration and measurement of nasal patency by rhinomanometry. The French authors suggest a faster and easier alternative (NPT-R) which was evaluated in 88 patients with rhinitis (49 allergic to HDM and 39 controls with and without atopy). The NPT-R was performed 4 weeks after the classic NPT and only the clinical score was measured.

The study population was young (mean 27.7) composed mostly of women (61 vs 27), 24% reported asthma. The sensitivity and specificity of NPT-R were 83,7% and 100% respectively. The correlation with NPT was statistically significant ($P \leq 0.0001$); the two tests were

completely safe. Performing NPT-R was more rapid (22+/-8 minutes vs 97 +/- 20minutes).

This new method appears to be useful in case of uncertain diagnosis or before immunotherapy.

44. Nocturnal Eczema: sleep and circadian rhythms in children

A.B.Fishbein et al : JACI 2015 136 5 1170-1177

Children with atopic dermatitis (AD) experience significant sleep disruption and the disease worsens in a circadian manner, at night with negative consequences and impaired linear growth. Assessing sleep is a crucial parameter of disease control with appropriate treatment. The mechanism of the nocturnal and the role of sleep cycle and circadian rhythms (assessed by Polysomnography and Actigraphy) are discussed, as well as treatment options, future directions for research.

45. Asthma and Pregnancy

S.Kim :JACI 2015 November 136 5 1215-122

Uncontrolled maternal asthma is associated with a range of adverse perinatal outcomes. The effect of pregnancy on health care use and prescriptions patterns had been evaluated in an epidemiologic randomized study of Corean National Health Insurance data, between 2009 and 2013.

3,357 pregnant asthmatic patients (PAP) were compared with 50,355 non-pregnant asthmatics (NPA) and 10,311 pregnant patients (PP). The results are surprising:

- PAP underwent more hospitalizations but significant fewer drug prescriptions and outpatient visits, than NPA.

- The prevalence of asthma exacerbations during pregnancy was 5,3% but the risk of perinatal outcomes afterwards was not increased, except for cases of cesarian section.

That is precisely what Finnish authors studied in a cohort of 60,069 children, followed during 21 years, underlining increased frequency of cesarian section rates worldwide and the risk of "non communicable diseases" (NCD). (R.Miettinen et al JACI 2015 Nov 136 5 1398-1399).

In fact, the prevalence of NCDs was significantly greater in children born by means of cesarian section than in children born by vaginally delivery due to heighthened cases of asthma, obesity and celiac disease. The role of mother's intestinal microbiome is discussed.

EAACI would like to kindly thank Claude and Jacques for their wonderful hard work and commitment to the Bibliographic updates of Allergology. Please do not hesitate to contact us for further questions:

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