

# Bibliographic updates in Allergology

2014

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**EAACI**  
EUROPEAN ACADEMY OF ALLERGY  
AND CLINICAL IMMUNOLOGY

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## 1. New life for an old drug: Theophylline... against cough

**Theme:** Asthma

**Key words:** Theophylline – Cough – Capsaicin – C Fibre – Vagus nerve

Theophylline has been used in the treatment of respiratory disorders for 80 years, particularly for chronic lung diseases and occasionally for asthma, but its side effects, mostly digestive, have restricted its prescription and it has become a backup treatment.

In fact, cough is one of the most frequent causes of consultation and also of self-medication. In the USA over-the-counter sales amount to billions of dollars.

The work presented by Eric Dupuis et al. (JACI 2014 7 Janvier in press) of the London Pharmacological Laboratory is original in that it demonstrates, via a series of ingenious experimental and electro-physiological investigations, that apart from its bronchodilatory effects, Theophylline inhibits the cough reflex through a hitherto unknown mechanism.

In the conscious guinea pig model, inhaling citric acid and capsaicin (a chilli pepper derivative) is inhibited by Theophylline; similarly, in vivo activation of airway afferent C-Fibres and in vitro depolarisation of human and guinea pig vagus are considerably reduced.

Then, through a sequence of pharmaco-dynamic experiments, the authors show that Theophylline lessens the sensorial excitability of airways through greater opening of calcium activated potassium canals. Finally, there is a demonstration of the antitussive activity of Theophylline in a cigarette smoke exposure model.

From a clinical point of view the product efficacy is well known in the treating of cough induced by some anti-hypertensive drugs such as angiotensin converting enzyme inhibitors like Captopril. But these interesting experiments offer undeniable arguments in favour of a hitherto unknown beneficial property of Theophylline.

This will encourage the development of new antitussive derivatives, which in limiting secondary effects will mean that the use of opioids can be avoided. Finally, we should remember that Theophylline is a harmless and low-cost medicine, the use of which is already justified in all forms of cough, acute and above all chronic, often a problem for pneumo-allergists.

## 2. Vernal keratoconjunctivitis (VKC) and tear peptide profile

**Theme:** Ocular allergy

**Key words:** Vernal keratoconjunctivitis – Tear peptide profile – Serum albumin – Transferrin – Hemopexin – Mammaglobin B – Secretoglobulin ID

It is known that VKC is a severe form of conjunctivitis affecting -young patients (aged 5-20) which reappears regularly in the spring and is characterized by the sensation of a foreign body in the eye with itching, photophobia, secretion, and corneal ulcers. An allergic origin is usually discovered, although often disputed, all the more since antiallergic therapy is generally unsuccessful.

The aim of the study presented (A. Leonardi et coll. Allergy décembre 2013 early view) was to analyse the peptide profiles in the tears of VKC subjects by means of sophisticated

isotopic technology, in conjunction with mass spectrometry in order to elucidate compositional differences between healthy subjects and patients affected.

Tears were collected from 10 VKC patients and 10 healthy subjects (plus 8 others suffering from VKC which was more or less controlled by anti-inflammatory medication).

The peptidic separation of these samples was carried out by qualitative and quantitative isobaric analyses together with high performance liquid chromatography.

A significant number of peptides were examined and 78 proteins were identified.

The findings were as follows:

- In all VKC samples, serum albumin, Transferrin, and Hemopexin levels were 100 times higher than in control tears, and the presence of these proteins correlated significantly with the severity of the disorder and the degradation of the corneal surface.

- These bio-markers, as well as mammaglobin B and secretoglobulin ID, were over expressed in VKC tears compared to controls.

- Lastly, tear samples from VKC patients treated with corticosteroids or topical cyclosporine showed a dramatic reduction in these protein levels.

All these peptides are therefore serum proteins like albumin, transferrin and apolipoprotein, but other proteins were revealed like certain metabolic enzymes, immunoglobins, lipophilin, complement proteins, cytokins, growth factors, most of these having anti-inflammatory properties.

Finally, these techniques have defined a particular VKC tear peptide profile, both qualitative and quantitative, and although they are not available to all laboratories they could be useful in diagnosing and treating the disorder, and possibly for other ocular inflammatory lesions.

PS : a general review of VKC has been published in Pediatric Allergy et Immunol January 2014 early view P.Vichyanond et al.

### 3. Molecular phenotyping in sputum of allergic asthma

**Theme:** Asthma

**Key words:** Molecular phenotyping of sputum – Allergic asthma – Th2 expression – Periostin Chloral channel accessory – Serpin – Interleukin 4, IL 5, IL 13 – Hyper eosinophilia

The San Francisco team of pneumologists and geneticists has recently published a pilot study on this subject (MC Peters et al: JACI 2013 in press).

It is known that allergic asthma is the translation of a Th2 inflammation for which the authors have identified 2 phenotypes: one high and one low Th2 expression, these two subtypes having different symptomatology, sensitivity to treatment, and evolution.

The same team had already demonstrated a high genetic expression of IL5, IL4 and IL13 cytokins in airway epithelial cell samples examined by bronchial biopsy; they also showed that the IL13-activated gene signature of periostin (P), chloride channel accessory (CLCA 1) and Serpin (S) could be revealed by brushings and led to a clearer classification of allergic asthma.

In fact, little is known about gene profiling in sputum. The authors therefore sought to use this non-invasive method in order to measure gene expression of these allergic asthmas.

37 asthmatics averaging 35 years of age and 15 controls were enrolled for the study: provoked sputum was analysed by PCR, with RNA extraction and examination of 14 genes indicating airway inflammation, in order to measure the gene expression in epithelial cells of IL13 activation (P, CLCA 1, S) at the same time as Th2 cytokine genes (IL4, 5, 13).

The findings were as follows:

- gene expression levels are significantly higher than normal for CLCA1 and P, but not for S, in asthmatic sufferers' sputum cells.

- IL 4, 5 and 13 expression levels are also significantly higher among asthmatics but with individual variations.

- 26 of them, i.e. 70%, correspond to a high Th2 gene expression asthma and present increased blood and sputum eosinophilia, bronchial obstruction with decreased FEV1 and FENO, and lesser sensitivity to corticosteroids, that is to say a more severe form of asthma.

In conclusion, gene transcripts for IL4, IL5, and IL13 cytokines are easily detected in sputum cells from asthmatic patients and offer a non-invasive and reliable means of identifying the different aspects of asthma. They lead to the differentiation of high and low Th2 gene expression asthmas, the first corresponding to a severe form, the second more reactive to corticosteroids.

#### 4. Link between atopic (AD) and contact (CD) dermatitis

**Theme:** Skin allergy

**Key words:** Atopic dermatitis – Contact dermatitis – Interleukins 13, 17 – Interferon  $\gamma$

D.Simon's Swiss team in Bern (Allergy 2014 69 1 125-131) point out in an original paper that AD, and CD whether allergic (ACD, due to Nickel for instance) or irritant (ICD), are characterized by the same clinical signs, although due to different causes.

From a pathologic point of view, Th17 cells are known to be present in the 3 types, albeit with different immune mechanism.

The authors were seeking to investigate IL17 expression in acute forms of the three types of D, its significance, and its correlation with lesion remodeling markers.

To this end, 9 patients underwent patch-tests followed by biopsies, concerning aero-allergens (house dust and pollen), contact allergens and irritants (lauryl-sulfate), on days 2, 3 and 4. Inflammatory cells, as well as the expression of different cytokines and extra-cellular matrix proteins, were evaluated by immunofluorescence with the help of corresponding antibodies. 27 specimens were examined and statistically analysed.

- Findings showed that IL17, but also IL21 and IL22, were expressed in the three D types, something new for ICD.

- As expected, ACD and ICD were characterized by IFN  $\gamma$  expression, whereas in AD IL13 expression and high numbers of eosinophils were prominent.

- The number of IL22 + T cells correlated with the number of eosinophils.

- Markers of remodelling such as pro-collagen 3, MMP-9 and tenascin C, were observed in the three acute lesion types, and the last 2 mediators correlated with Th17 cells.

In all, the expression of IL17 and related cytokines such as IL22 was found in all acute eczematous lesions whatever their origin, allergic or irritant. IL17 is therefore the common denominator, in relation to host defence mechanism and also intervene in skin remodeling.

On the same subject and in the same journal J. Thyssen et al. (2014 69 1 29-38), based on clinical investigations, mention the risks for AD sufferers treated by anti-inflammatory or emollient drugs of becoming sensitive to “metal” allergens or irritants. For other authors, the AD Th2-response may reduce this risk. Whatever the case, according to the state of the skin barrier (low hydration, high pH, presence of bacteria) and to environmental exposure (emollient ingredients, occupational exposure to chemicals such as DNCB, piercing), several factors are likely to complicate AD into contact eczema. It is therefore up to the clinician to adapt AD treatment to skin fragility.

## 5. In utero sensitisation to tobacco smoke and development of childhood asthma

**Theme:** Asthma – Pediatric allergy – Prevention

**Key words:** Tobacco smoke – In utero sensitization – Childhood asthma – PArkin CoRegulated Gene

An extensive European and Canadian survey, involving 57 researchers and 45 pneumo-allergy and genetics centres (including three French teams), is focused on the interaction between genetic and environmental factors in the development of early onset childhood asthma.

It is well known that the Genomewide study has identified multiple asthma development genes, yet they only explain a limited proportion of asthma heritability. The assumption of interaction between genetic predisposition and in utero or early life exposure to a well known environmental factor, tobacco smoke, is a possible explanation (S .Scholtens et al JACI décembre 2013 in press).

To test this, a first meta-analysis of this interaction was carried out using 9 studies participating in the GABRIEL consortium, including 6000 subjects of European descent. The findings were replicated in 4 independent studies enrolling 13000 subjects. Childhood asthma was defined as diagnosed by a doctor before the age of 16, tobacco smoke exposure as in utero if during pregnancy (2654 cases and 3073 controls in 7 studies) and as childhood exposure if from birth to age 16 (3048 cases and 3509 controls in 9 studies). The results of each of these investigations were analysed separately and then subjected to logistic regression statistics.

It appears that, overall, in utero tobacco smoke exposure increases the risk of childhood asthma. 536 705 SNPs (Single Nucleotide Polymorphism) were included in the analysis: 27 were identified, but only 4 on chromosome 10 were significant (linkage disequilibrium) and the most important marker was located on chromosome 18 close to gene EPB41L3.

This gene belongs to the membrane protein family and is an essential part of biological processes such as intercellular junction and apoptosis; it influences lung development in

children in general. This in utero tobacco smoke exposure effect, which affects gene expression, could be explained by a series of mechanisms involving this marker.

As for childhood exposure to tobacco smoke, the Genome meta-analysis reveals that it also increases the risk of asthma development. 7 SNP on chromosome 5 had a certain significance (linkage disequilibrium). The chief marker was located on chromosome 6 in the PACRG (Parkin CoRegulated Gene), a gene associated with leprosy and Parkinson's disease and playing an important role in the ciliary function in general and in airway mucus clearance.

In conclusion, this is the first discovery of SNP interaction between tobacco smoke exposure and asthma development, different from those reported so far and which could explain the absence of asthma heritability in general.

## 6. Fatal Asthma: recent findings

H.Oda et al Annals of Allergy, Asthma & Immunology Volume 112, Issue 1, Pages 23-28.1, January 2014

Lung tissues were obtained at autopsy examination from 12 nonsmokers who had died of asthma disease (slow or sudden onset), then from 5 nonsmokers with well-controlled mild asthma and 10 nonsmokers who had undergone surgical resection.

The numbers of eosinophils, neutrophils and lymphocytes, but not basophils or macrophages, as well as CD8+ T cells, (but not CD4+ T), were significantly increased in the lungs of patients with fatal asthma compared with the other 2 groups. IL-18 protein and IL-18 receptor were also strongly expressed. Possible blockade of IL 18 by immuno-biologic drugs may be of clinical benefit in these severe forms of asthma to prevent fatal issue.

## 7. Psoriasis: Immunopathology

JF.Nicolas: Bulletin de l'Académie Nle de Medecine: (France - in press)

Psoriasis is an autoinflammatory skin disease mediated by the chronic interaction between keratinocytes, dendritic cells and T lymphocyte inducing a vicious circle of cell activation leading to the development and persistence of the skin lesions. Inflammatory cytokines produced by the 3 cell types, especially TNF $\alpha$ , IL-23 and IL-17, are central to the disease and are the target of the very effective immunobiological therapies that have been developed (such ustekimumab with outstanding improvement).

Advances in the pathophysiology and treatment of psoriasis have applications far beyond the skin disease. Indeed, psoriasis serves as model for studies of mechanisms of chronic inflammation such as rheumatoid arthritis, Crohn's disease, atherosclerosis and type 2 diabetes and for developing new targeted therapies for autoinflammatory diseases.

## 8. Allergy to furry animals: Jon R. Konradsen

Pediatric Allergy and Immunology 2014 January - Early View



Children with severe allergic asthma had higher specific IgE levels to cat, dog and horse than those with well-controlled asthma:

Refined assessment using molecular-based allergy diagnostics revealed a more complex molecular spreading of allergen components in children with the most severe disease.

## 9. A link between Obesity and Asthma

Juan C Celedón & Jay K Kolls NATURE Medicine January 2014- pp19 – 20

The concordant epidemics of asthma and obesity are both associated with inflammation, and obesity has been shown to be an independent risk factor for asthma. A new study in mice indicates that part of the immunological connection between obesity and asthma involves inflammasome activation and production of the cytokine interleukin-17 by innate lymphoid cells in the lung (H.Y. Kim et al pages 54–61). Inhibition of this pathway by a monoclonal antibody “anakinra” is promising.

## 10. Aspirin allergy in patients with myocardial infarction: the allergist's role

Kathryn L. McMullan, MDNext » Annals of Allergy, Asthma & Immunology Volume 112, Issue 2, Pages 90-93, February 2014

Patients with coronary artery disease and aspirin hypersensitivity may be safely and effectively desensitized by a 7 step protocol.

## 11. Nasal filters for the treatment of Allergic Rhinitis

**Theme:** ENT Allergy

**Key words:** Seasonal rhinitis – Nasal filter

In a randomized, short clinical trial, P. Kenney et al (Aarhus Denmark JACI March 2014 in press) demonstrates that Rhinix<sup>®</sup>, a new nasal filter, was significantly more effective than placebo in alleviating nasal symptoms in 24 adults with seasonal allergic rhinitis (SAR), primarily through its effect on nasal itching, sneezing, and nasal discharge. It is well tolerated and safe to use.

## 12. New data on Occupational Asthma

**Theme:** Occupational asthma

**Key words:** Asthma – Irritant products

S.M Tarlo and C.Lemierre (NEJM 2014 370 Feb 640-649) review the classical sensitizer agents (High Molecular Weight such animals and Low MW such di-isocyanates) and focus on new agents (manufacture of cytotoxic drugs for example) but draw mainly attention to irritant induced asthma such airways dysfunction to persons exposed to very high levels of alkaline dust from the dramatic collapse of World Trade Center in New-York (Only 36% of subjects recovered after 9 years of follow-up). Work exposure may cause or exacerbate asthma. Primary and secondary prevention in most cases minimize the risk of long term impairment. However, symptoms and airway hyper responsiveness persist in 70% of patients, even several years after exposure avoidance.

## 13. A new life for Tiotropium

M.A.Birrell et al JACI 2014 3 133 679-687 London

**Theme:** Respiratory Allergy

**Key words:** Tiotropium – Cough – Capsaicine

Recent studies have suggested that the Long Acting Muscarinic receptor Antagonist: Tiotropium, a drug widely prescribed for its bronchodilator activity in patients with COPD and asthma, improves symptoms and attenuates capsaicine induced cough in pre clinical and clinical challenge studies. The authors demonstrate for the first time, that Tiotropium inhibits TRPV1-mediated effects on sensory afferents through a mechanism unrelated to its anticholinergic activity, and account for possible other clinical benefits associated with taking Tiotropium.

## 14. Reduction of inhaled corticosteroids (ICS) and risk of asthma exacerbations.

J.B Hagan Mayo Clinic Rochester Allergy 2014 69 4 510-516

**Theme:** Asthma

**Key words:** Controlled asthma - Inhaled Corticosteroids

Systematic review and meta-analysis of 206 randomized controlled trials confirm that decreasing by 50% the dose of ICS among stable asthmatics after a period of 4 weeks or more

(according to international guidelines) and comparing statistically to those who maintain a stable dose, do not affect the risk of asthma exacerbations after a mean follow-up of 22 weeks. This work supports the current European and American guidelines.

## 15. Common variable Immunodeficiency: Clinical Picture and treatment of 2212 European patients

B.Gathman JACI Feb 2014 in press

**Theme:** Clinical Immunology

**Key words:** Common variable Immunodeficiency - Hypogamma globulinemia

Data from 28 medical centers analyze retrospectively the clinical presentation, diagnostic and treatment of this entity, (also called hypogamma globulinemia) the common denominator of which, being a profound antibody deficiency caused by intrinsic defect of B cells and lack of T cell co-stimulation. The main features include respiratory tract infections (this infection- only type results in better quality of life), an early onset disease ( $\leq 10$  years) male subjects (39,8%); splenomegaly enteropathy, auto-immunity, granulomas (not bronchiectasis) form a set of interrelated symptoms. Immunoglobulin replacement, very different between centers, include doses ranging from 130 to 750mg/Kg/month, (patients with levels of less than 4g/L have poor clinical outcome), whereas higher levels reduce frequency of serious bacterial infections. A common electronic European registry of such patients, to synthesize diagnostic and treatment protocols, is strongly recommended.

## 16. Biologic targeted therapy in allergic asthma

**Theme:** Therapy

**Key words:** Biologic targeted therapy – Allergic asthma

In a comprehensive review of the recent literature, illustrated by a suggestive table, J.B. Bice & al (Annals of Allergy, Asthma Immunology 2014 112 108-115), draw up a list of the therapies targeted at major immunologic pathways (approximately 30 drugs and dozens in development, predominantly monoclonal antibodies) through IgE, IL4, IL5, IL 13, TNF $\alpha$ , Toll-like receptors 7 and 9, Prostaglandin D2 Chemo-attractant Receptor: CR Th2 and D Prostanoid Receptor DP 1. Efficacy and costs of these agents are discussed.

## 17. Home indoor Moisture and Allergy

M.Choi et al. Indoor Air 14 March 2014 on-line

**Theme:** Allergen

**Key words:** Indoor moisture, Allergy

A study of relationship between residential cultivable fungi, (1-3, 1-6)- $\beta$ -d-glucan and ergosterol concentrations, in dust samples of child's bedroom in the home of 198 multiple allergy case children and 202 controls, completed by parent or inspector-reported home dampness, did not show any significant differences. The association between asthma, rhinitis or eczema and home indoor fungi remains controversial.

## 18. Beneficial role for supplemental Vit D3 treatment in chronic urticaria

A.Rorie et al: Annals of Allergy Asthma Immunol.2014 March in press

**Theme:** Skin allergy – Urticaria

**Key words:** Vit D3 – Chronic urticaria

In a randomized study, high doses of Vit D3 (4000UI/d) for 12 weeks in 42 patients provided by standardized triple drug therapy, demonstrate a significant decrease in a severity score and could be considered as a safe and beneficial immune modulator.

## 19. Traffic-related air pollution and airways hyper responsiveness

Byoung - Ju-Kim et al JACI 15 March 2014 in press

**Theme:** Respiratory allergy

**Key words:** Traffic roads – Air pollution – Airways Hyper Responsiveness – TH17 – IL17

In a prospective epidemiologic study which concerns 1340 Korean children, the authors found that the rates of new airways hyper reactivity and increased airways response are higher in children residing closer to traffic roads. In the same issue (Ichiro Inoue JACI in press) a Japanese team evokes the key role of IL 17 A and TH 17 cells in diesel exhaust particle mediated severe allergic asthma, already mentioned by Brandt et al (JACI Nov 2013 132 1 194-204).

We must however recall that all new cars are now equipped with filters of great efficacy.

## 20. Perinatal safety of Long Acting $\beta$ 2Agonists and Inhaled Corticosteroids use during pregnancy

B. Cossette et al Annals of Allergy Asthma Immunology 2014 April in press

**Theme:** Therapy

**Key words:** Pregnancy – Long Acting  $\beta$ 2 Agonists – Inhaled Corticosteroids

There is no statistical differences for low birth weight, preterm birth or gestational age newborns, between asthmatic women exposed to LABA or ICS whatever the choice for one over the other preferred medication within each class.

## 21. Omalizumab (O) in Asthma and risk of malignancy

A.Long et al : JACI in press 2014 27 March

**Theme:** Treatment in Allergy

**Key words:** Omalizumab, Asthma, Malignancy

A long term (O) safety and clinical effectiveness in moderate to severe asthma in 2 prospective observational cohorts (with and without O) suggest that O therapy, after 5 years, is not associated with an increased risk of malignancy.

## 22. Prognostic value of Component-resolved diagnosis in infants with peanut-allergy

Philippe Bégin et al, Ped. Allergy, Immunol 2014 early view, 18 March

**Theme:** Food allergy – Allergens

**Key words:** Prognostic in Allergy – Component-resolved diagnosis – Peanut allergy

Using a longitudinal cohort of peanut allergic infants and toddlers (110; mean age 14 months), the authors show that Ara h1, Ara h2 and Ara h3 are the dominant allergens, confirm the diagnostic value of component-resolved diagnosis. However, the results are redundant with specific IgE and do not provide additional independent predictive value at 13 years.

## 23. Oral Immunotherapy for peanut allergy

K.Anagnostou et al: The Lancet 2014 383 9925 1297-1304

**Theme:** Treatment in Allergy – Immunotherapy – Allergens

**Key words:** Peanut allergy – Oral Immunotherapy

In a randomized controlled crossover trial of Oral Immunotherapy (OIT) in 99 children, age 7-16 years, the team of Cambridge (UK) demonstrates that OIT successfully induced desensitization in most children (62% in active group and none of the control group) with a clinically meaningful threshold (800mg: approximately five peanuts), improvement of quality of life, a good safety profile and corresponding immunological features. Wider studies in specialist's settings are recommended.

## 24. Asthma and Depression

T.D Trojan et al: Annals of Allergy Asthma Immunol 2014 April in press

**Theme:** Asthma

**Key words:** Asthma – Depression

A cross-sectional study of 12.944 adults conducted from 2000 and 2012 at the Cooper Clinic (Dallas Texas) has shown that Asthma was significantly associated with an increase of current depressive symptoms. A lifetime depression was observed in a large sample of adults, predominantly white and well educated. Likelihood of depression is not exclusively related to poorly controlled or severe asthma. Asthmatics may benefit from depression screening in clinical settings.

## 25. Clinical problems: Angioedema Anaphylaxis Isolated Uvular

### Angioedema

A.V.Tejedor NEJM 2014 April 10 e24

**Theme:** Anaphylaxis

**Key words:** Angioedema – Angiotensin converting enzyme inhibitor.

A 59 years old man is admitted to the coronary care unit for myocardial infarction. A bare-metal stent was successfully implanted in the circumflex coronary artery, followed 6 hours later, by injection of 6.25 mg of Captopril: an Angiotensin converting enzyme inhibitor (ACE). After 30 minutes the patient reported throat pain and difficulty swallowing. On examination, only the uvula was markedly edematous: Improvement was obtained within 24 hours by antihistamines and glucocorticoids. The clinician must be aware of this uncommon response to ACE.

In this connection: an excellent review: Anaphylaxis to bee sting: a common problem for allergists: (T.B Casale and W.Burks :NEJM 2014 370 1432-9).

## 26. History of Allergic diseases and Lung Cancer risk

M.El-Zein et al: Annals of Allergy Asthma Immunol 2014 112 230-236

**Theme:** Physiopathology of Allergy

**Key words:** Allergy – Lung cancer

Using data from a population (based case-control), in this study conducted in the Montreal metropolitan area (1996-2002) from 1169 incident lung cancer cases (1486 controls) and their possible association with a history of allergy, the authors found that the 3 main allergic diseases are inversely associated with lung cancer, although the protective effect after consideration of potential confounders, including life-time smoking history, is weaker for asthma, of moderate strength for eczema and strongest for hay fever.

## 27. Competitive swimming and airways inflammation: a 3 years longitudinal study

M.Couto et al: Ped Allergy Immunol 2014 25 193-195

**Theme:** Physiopathology of Asthma

**Key words:** Airways inflammation – Competitive swimming

In 120 non-elite young swimmers from two main Portuguese teams, a prospective study at 3 years follow-up, showed that those who remained active (high level of competitive swimming) significantly increased their levels of airway inflammation measured by exhaled NO, independently of their gender, age, atopy or asthma status. Nevertheless, asthma incidence did not increase in this group and physical training is still recommended in asthmatic children as long as the disease is controlled.

## 28. Best response to step-up asthma therapy

J.Malka et al JACI 2014 May in press Letter to the editor

**Theme:** Asthma, Paediatrics allergy

**Key words:** Asthma – Inhaled corticosteroids – Long acting  $\beta$ 2 agonists – Anti Leukotrienes

In 163 children inadequately controlled to low-dose of inhaled corticosteroids (ICS) the addition of a Long-Acting- $\beta$ 2-agonist is compared to increasing the ICS dose or adding a leukotriene receptor antagonist (LTRA) in a randomized triple cross over trial of 16 weeks. The

best response for the entire study was LABA step-up. A post-hoc analysis showed that eczema and race are determinants for differential response: a best response to LABA in asthmatics without history of eczema; in asthmatics with history of eczema: black children are more likely to respond to ICS step-up; white Hispanic to LTRA and white non-Hispanic to LABA or LTRA.

## 29. Stress ad Atopy

I.RV Hartwig and all: JACI 2014 in press 23/04

**Theme:** Psychology allergy

**Key words:** Stress – Atopy – Pregnancy

In a study of 1587 Australian children, the authors found a significant association between prenatal maternal stress (adverse life events) during the second half of gestation and increased likelihood of asthma and eczema at age 6 years or 14 years. A stronger increase in the odds to develop asthma was present in children of mothers without asthma compared with mothers with asthma (which is all the more plausible that the pre-existing maternal hereditary component is absent).

## 30. A new target for the treatment of Allergic Asthma

G.M.Gauvreau et al : NEJM 2014 May 29 370 2102-2110

**Theme:** Physiopathology of asthma – Asthma treatment

**Key words:** Thymic Stromal Lymphöpoietin – AMG 157

A monoclonal antibody against Thymic Stromal Lymphöpoietin (TSLP): AMG 157, an epithelial derived cytokine, randomly assigned to 31 patients with mild allergic asthma, significantly reduced allergen-induced bronchoconstriction (early and late response) and airways inflammation (decrease of blood and sputum eosinophils and fraction of exhaled NO). The clinical value of this anti-TSLP therapeutic deserves further and extensive work.

## 31. Acquired Angioedema (A.A.E): short term prophylaxis

H.Farkas JACI April 24 in press Letter to editor

A.Tohani : Annals of Allergy Asthma Immunol 2014 265-266

**Theme:** Physiopathology of Allergy – Immune deficiency

**Key words:** Acquired angioedema – C1. Inhibitor - Angiotensin-Converting-Enzyme Inhibitors



A.A.E resulting from the deficiency of the C1-Inhibitor associated with lympho proliferative or auto-immune disorders is rare and differs from drug-induced AAE due to ACEI (Angiotensin-Converting-Enzyme Inhibitors) cured by corticoids and anti-histamines and elimination of the trigger factor.

Here the diagnosis is established by clinical symptoms: (edematous cutaneous and subcutaneous attacks, onset after 40 years, negative family history, and Complement testing: C1-INH normal or low, C1q level strongly reduced. Plasma derived C1-INH concentrate (Berinert® is used in small observational studies before surgery for short term prophylaxis, but for the first time, in this single case\*, recombinant human rh-C1-INH (Ruconest®) intravenously was successful. However, therapy of underlying disease is essential (chemotherapy, rituximab).

## 32. Fatal Anaphylaxis with Neuromuscular-blocking agents (NMBA)

**Theme:** Drug allergy

**Key words:** Fatal anaphylaxis – Neuromuscular blocking agent

Evaluating mortality rate from Anaphylactic Reactions (AR) to NMBAs in France, between January 2000 and December 2011, M. Reitter et al from the National Pharmacovigilance Center (Allergy July 2014 69 7 954-959) retrieved 2022 cases of NMBA hypersensitivity. Among the 1247 cases of severe AR, 84 were fatal: 4,1%. Multivariate analysis showed that the significant risk factors, independent of the type of NMBA, are: male gender, undergoing surgery in an emergency setting, a history of hypertension or other cardiovascular disease, obesity and ongoing  $\beta$ -blocker treatment. 31 patients with a fatal outcome received epinephrine according to international guidelines. This high mortality rate suggests some epinephrine resistant cases and a need to develop new therapeutic approaches.

P.S. In this connection we must mention the new EAACI guidelines in the treatment of Anaphylaxis edited in Allergy 2014: A. Muraro et al: vol.69 N°8 1026-1045.

## 33. Bitter Taste Receptors in the Lungs: Recent findings

S.Grassin-Delyle et al Rev.Pneumol.Clin2014 70 148-155

**Theme:** Physiology of Asthma

**Key words:** tastes: salty, sweet, bitter, umami – Taste Receptor – Mastocytes

Among the receptors responsible for the 4 basic tastes: salty, sweet, bitter and umami, the bitter taste type 2 ones (TAS2R) are G protein coupled including 25 subtypes. Initially confined to the oral cavity, their expression has been described in the gastro-intestinal tract

but mainly in the lungs at 3 levels: on the cilia of epithelial cells responsible for the increase of cilia vibration, in bronchial smooth muscle cells which leads to bronchial relaxation and on immune cells involved in the modulation of inflammatory cytokines and particularly in mastocytes, leading to inhibition of release of histamine and PGD<sub>2</sub> from IgE activated receptor. M. Ekoff et al: JACI 2014 June Letter to editor 02.029 and JACI 134 2 August 2014 285-286).

### 34. Dupilumab (D) treatment in adult Atopic Dermatitis (AD)

L.A.Beck et al NEJM 2014 10July 130-138

**Theme:** Skin Allergy

**Key words:** Atopic dermatitis – Dupimumab – IgE - Thymus & Activation Regulated Chemokine – Transcriptome – Kératin 16

D. human monoclonal antibody that blocks IL 4 and IL 13, performed in randomized trials involving adults who had AD not controlled with topical medications (glucocorticoids and calcineurin inhibitors) was evaluated as monotherapy in two 4 weeks trials and one 12 weeks trial; end points included Eczema area and severity index Score, investigator's global assessment, pruritus score, serum biomarker levels and disease transcriptome (TARC, IgE , RNA expression and Keratin 16 levels). In the 4 weeks monotherapy studies, D resulted in rapid, significant and dose-dependent improvement in clinical indexes, biomarker levels and the transcriptome. These results were confirmed and extended in the 12 weeks study. The side effects were mild and not dose-limiting.

In conclusion D has shown rapid and marked efficiency in AD in adults and may benefit to all atopic diseases which share Th2 mediated inflammation.

### 35. Clinical features of Food-protein-induced Enterocolitis syndrome (ES)

J.C Caubet et al : JACI 2014 134 2 382-389

**Theme:** Food allergy – Pediatrics allergy

**Key words:** Enterocolitis – Food Protein

It is a non IgE-mediated food allergy frequently observed in USA. 160 subjects, median age of diagnosis being 15 months, were recruited, medical features recorded and oral food challenge performed. The symptoms are vomiting and lethargy 2 to 4 hours after ingestion of the suspected food followed 10h later by diarrhea. The diagnosis is often delayed in absence of classic allergic symptoms and lack of biomarkers. The most common foods were cow's milk (44%), soy (41%), rice (22,5%), oat (16%). Spontaneous resolution is usual. Median age for

tolerance is 4 to 6 years except for cow's milk if specific IgE occurs over time (41% of subjects changed from a milk Es to an IgE mediated phenotype).

A recent British pediatricians experience (S.Ludman et al Annals of Allergy, Asthma, Immunol September 2014 113 3 290-294) confirms, among 54 children, median age 8 months, these clinical features, and relates a frequent delay in the diagnosis of this syndrome (more than 12 months).

### 36. Depression and Risk of Incident Asthma in Adults

W.M.Brunner et al : AJRCCM2014 May 189 9 1044-1051

**Theme:** Respiratory allergy – Asthma

**Key words:** Depression – Asthma – CARDIA Cohort

The temporality of the association between Asthma and depression has not been established. So American epidemiologists (Minnesota and New Mexico) examined bidirectionally this association in the CARDIA cohort including 3614 participants free of Asthma in search of elevated depressive symptoms and 3016 participants, free of depressive symptoms in search of self reported current asthma, prevalent or not. After adjustment for covariates, the relative hazard of incident Asthma was 1,26. Therefore Depression appears as a marker for incident adult Asthma.

Health care providers must be aware of the potential for new-onset asthma in their patients with depression.

On the other hand, prevalent Asthma is not associated with incident depression in middle age.

### 37. Mepolizumab (MP) revisited in the treatment of Severe Eosinophilic Asthma (SEA)

NEJM Alert 7-8 September 2014 On-line first

**Theme:** Respiratory allergy – Asthma

**Key words:** Mepolizumab – Severe Eosinophilic Asthma

Unlike previous studies, two recent randomized trials report successful results in SEA treated with MP, this monoclonal antibody directed against interleukin 5.

- One published by H.G Ortega et al, involves patients whose asthma is uncontrolled despite high doses of glucocorticoids and long acting bronchodilators. MP was administered either as 75mg intravenously dose or 100mg subcutaneous dose, every 4 weeks, during 32 weeks, in patients selected by the characterization of their eosinophilic phenotype based not on IgE levels or sputum eosinophils but on the basis of blood eosinophilic count of at least 150 to 300 cells per microliter. On the other

hand, considering the balance between this expensive drug and the clinical benefit expected, adherence to the prescribed therapy recommended by international guidelines must be effective. The result was a clear decrease of A. exacerbations (47 to 53% according to the dose).

- In the other study E.H Bel & al, the sparing effect by MP of glucocorticoids was impressive, the mean percentage reduction in the dose being 50%.

In these two studies MP was safe and had an acceptable side-effects.

In conclusion, Mepolizumab significantly reduced asthma exacerbations, was associated with improvements in markers of asthma control and had a sparing effect on the high doses of glucocorticoids used in SEA.

### 38. Application of moisturizer to neonates prevents development of Atopic Dermatitis (AD) The Japanese trial

K.Horimukai et al JACI 134 4 824-830

In a randomized study of 118 neonates, the authors demonstrate that daily application of moisturizer during the first 32 weeks of life, significantly reduces the risk of AD/eczema in infants, but not allergic sensitization (IgE antibody against egg-white). Moreover, the intervention group has higher level of stratum corneum hydration than the control group. However, during this time period, allergic sensitization was associated with the presence of eczematous skin.

### 39. Prevention of Atopic Dermatitis by enhancement of the skin barrier with emollients: The Anglo-American trial: Portland Nottingham, Dundee

E.L.Simpson JACI 2014 134 4 818-823

In a randomized controlled and joint trial, performed in the USA and UK, emollient therapy from birth, on 124 neonates at high risk for AD ,significantly reduced of 50% at 6 months, the relative risk of incidence of the disease and represents a simple, feasible, safe, low-cost and effective intervention which may prevent AD and maybe allergic sensitization and the global burden of allergic diseases . Recent advances in cutaneous biology suggest skin barrier defects as key initiators of AD.

### 40. Relationship between Pollen exposure and drug treated Seasonal Allergic Rhinoconjunctivitis (SAR) over 10 years

D.Caillaud et al Allergy Octobre 2014 accepted articles

In an urban area in central France the prevalence of SAR rose by about 55% in 10 years. Comparative study of Pollen concentrations and daily anti-allergic drug prescriptions (oral and local) demonstrate that the relative risk of SAR significantly increases with pollen concentration of Fraxinus, Betula Poaceae, for the whole pollen season and Urticaceae in the 1st semester, but also for Carpinus, Platanus in spite of their low pollen counts. A robust correlation with Parietaria suggests a potential role of this species in this non –Mediterranean area.

#### 41. Pathophysiological features of Asthma in the Elderly

Hideki Inoue et al: Annals of Allergy Asthma, Immunol 2014 October in press

Comprehensive studies are scarce in this field, in spite of their clinical importance. Study of 45 asthmatic older than 65 years and 67 non-elderly asthmatics, retrospectively analyzed by spirometry, computed tomography, impulse oscillation analysis, showed that elderly patients with asthma have greater involvement of small and larger airways than non-elderly asthmatics. Moreover, total and specific IgE levels against several allergens are significantly lower in elderly.

#### 42. Usefulness of FE NO in Asthma

Evidence is given by 3 articles

Impact of FENO measurement on treatment decision in Asthma (Craig La Force et al: Annals of Allergy, Asthma Immunol Sept 2014 in press): Based on observation of fifty asthmatics 7 to 60 years old, knowledge of FENO measurement, affects medication treatment decision to augment or decrease pharmacotherapy, which has important long-term asthma management and has the potential to lower the costs and morbidity associated with asthma exacerbations

Responsiveness to metacholine correlates with FENO in Asthma (Wei-je Guan et al Clin.Resp.Journal sept 2014 ahead of print): In 62 asthmatic patients enrolled, the Chinese group of Canton University demonstrates a significant correlation between FENO performed by a portable instrument and airways responsiveness to inhaled metacholine, particularly in non smokers and without rhinitis but not to LTD4.

Occupational Asthma (OA) phenotypes identified by increased FENO after exposure to causal agents (C.Lemière et al JACI August 2014 in press): Increase in FENO after exposure to agents causing OA, occurs more consistently in subjects with OA caused by high molecular weight agents (ex: cereals, flour) than in those with OA due to low-molecular weight (ex: isocyanates).

### 43. Chronic Asthma associated with shorter Leucocyte Telomere

D.W.Belsky et al Amer.J.of Resp. Crit.Care Med 2014 190 4 384-391

**Theme:** Asthma – Respiratory allergy

**Key words:** Telomere – Asthma

Asthma is increasingly recognized as a disease of aging. In the Dunedin New-Zealand cohort of 1037 asthmatics, at nine in-person assessments spanning 9-38 years, Leucocyte Telomere Length (LTL) was measured at ages 26 and 38 years. This epidemiologic study reveals that only Childhood Asthma that persists through midlife, is related to shorter LTL, possibly via systemic eosinophilic inflammation. So LTL is proposed as biomarker of persistent Asthma and accelerated aging.

### 44. Respiratory virus and Asthma

N.Voraphani et al AJRCCM 2014 190 4 392-398

**Theme:** Asthma – Respiratory allergy

**Key words:** Asthma – Virus – Wheezing

It is well known that Lower Respiratory Illnesses (LRI), especially when induced by Respiratory Syncytial Virus (RSV) can be followed by asthma-like symptoms and later on by a physician diagnosis of Asthma. Wheezing episodes after RSV- LRI have been shown to reduce by adolescence, suggesting that this is a childhood risk, during the lung development, in the first decade of life. The authors showed, in children of the Tucson birth cohort, that this is the case and not at all an asthma risk. However, when young adults had RSV-LRI in early life and are smokers, the risk of having asthma is significantly increased. Treatments of RSV or other rhinovirus (Palivizumab, Inhalation of IFN $\beta$ ) have been tested more or less successfully.

### 45. Eosinophilic esophagitis (EeO)

J.Molina-Infante et al JACI2014 134 Novembre 1093-1099

**Theme:** Food allergy

**Key words:** Eosinophilic esophagitis – 4 Food elimination diet

This Esophageal disorder is predominantly induced by food antigens. EeO was treated in a multicenter (4 hospitals) Spanish prospective study by an empirical strategy eliminating 4 food group in diet of adult patients (dairy products, wheat, egg, legumes). Remission was defined by clinical and histological features (15 eosino/hpf). Four-Food elimination diet accomplished complete remission in 54% of patients and almost a third of non-responders

could be rescued by six food elimination coming to an overall effectiveness of 72%. Therefore, this Four Food elimination diet benefit from less restrictive intervention and fewer endoscopies all the more that food reintroduction allows to identify just one or two food triggers. So this strategy is simple, practical transferable to pediatric population and represents advantages for patients and health care system.

#### 46. Occupational contact Dermatitis (OCD)

JF.Nicolas in press Bull.Acad.Nat Med 2014), (UF Fries et al Contact Dermatitis 2014 6 364-70

**Theme:** Skin allergy – Occupational allergy

**Key words:** Occupational contact dermatitis – Eczema – Irritant contact dermatitis

Occupational Contact dermatitis is a common inflammatory skin disease that occurs at the site of contact with non-protein chemical molecules (xenobiotics). There are two major types of OCD: irritant (ICD) and allergic (ACD) which are very similar in terms of clinical, histological and molecular features. However, it is necessary to differentiate these 2 types, according to the higher severity of ACD and its serious professional consequences: Mechanisms underlying the skin inflammation are also different.

- The ICD are non-specific inflammatory lesions mainly due to chemicals toxicity on skin cells that induce inflammation by activating innate immunity.

- The ACD, are an adaptive, delayed type hypersensitivity response due to activation of specific T Lymphocytes (TL).

Psychological stress, frequently present in the occupational world, worsens contact dermatitis. Experimental models of ACD showed that stress acts as an adjuvant to cutaneous inflammatory responses through noradrenaline released in the skin by fibers of the sympathetic nervous system. Dendritic cells migrate quickly and in greater numbers at the lymph nodes where they activate numerous effector T cells inducing a greater and prolonged ACD response. These studies identify a number of immunological and environmental factors at the origin of contact dermatitis that can be targets for preventive action and tools facilitating the diagnosis of ACD.

#### 47. Common variable Immunodeficiency (ID)

B.Guthman et al JACI 2014134 1 116-126

**Theme:** Clinical Immunology

**Key words:** Common variable Immunodeficiency – Immunoglobulins – Bacterial infections

This is the most frequent primary ID. In a retrospective data 2212 European patient coming from 28 Centers, one third presented with the first symptoms very early (before 10 years of age) Male subjects are prone to pneumonia, less to other complications such enteropathy autoimmunity and lympho-proliferative disorders. The delay between onset and

diagnosis, usually more than 5 years is high in early onset patients whose prognosis is poor. Patients with high dosing levels of immunoglobulins show reduced frequency of bacterial infections whereas low levels less than 4g/L are associated with poor clinical outcomes. There were different strategies in European countries with a great difference in Immunoglobulin dosing, ranging from 130 up to 750mg /kg/month.

## 48. Early-onset Atopic Dermatitis (AD) and sensitization to inhaled allergens

J. Just et al. Ped. All. Immun (PAI) 2014 October early view

**Theme:** Atopy – Allergy in childhood

**Key word:** Early onset atopic dermatitis – Multiple sensitization – Inhaled Allergens – Food Allergens

This often-severe phenotype of AD conveys the risk of developing multiple sensitizations to allergens but little is known about the pathway of this sensitization. In following a cohort of 229 infants, in Paris (France) every year during 6 years, in order to identify the most predictive, clinical or biological marker to inhaled allergens, the authors demonstrates that a multiple sensitization to food allergens (which decreased over time) conveys a significant higher risk of sensitization to inhaled allergens than single sensitization.

## 49. Anti-infective proteins of breast-milk and asthma associated phenotypes

G.Zhang et al Ped.All. Immun. Octob 2014 25 6 544-551

**Theme:** Asthma – Allergy in childhood

**Key word:** Anti-infective proteins – Breast milk - Asthma

As part of a prospective cohort study on the role of respiratory infections in asthma development in high risk children, the authors measured the concentration of a panel of proteins in maternal milk samples (s IgA, lactoferrin, Lysozyme, total proteins) and analyzed associations between these subsequent atopy-infections and asthma related outcomes to age 10 years.

They observed significant but transient inverse association between these concentrations and susceptibility to upper respiratory infections in year 1 only and parallel but positive transient associations with early lower infections and atopy.

No association were seen with asthma-related outcomes.

The role of breast milk feeding in the prevention of these diseases is discussed. However, in the UK financial incentives for breastfeeding, regarded as intervention of great importance to public health, are now planned (The Lancet 19 Nov 2014 384 Suppl 2).



## 50. Hypersensitivity reactions(HR) to antineoplastic agents (ANA)

A.Urena-Tavera et al : JACI 2014 Nov in press

**Theme:** Atopy – Drug allergy

**Key word:** Colorectal cancer - Leucovorine – FOLFOX protocol – FOLFIRI protocol

This is an increasingly important problem for some patients doomed to therapy discontinuation by fear of inducing severe reactions. HR to Oxaliplatin (O) have been reported with the incidence of 12% to 17% whereas there are very few cases of HR to Folinic Acid (FA). Colorectal cancer treatments use 2 types of protocol FOLFOX including Folinic acid (AF) - 5 Fluorouracile (5 FU) O. or FOLFIRI: Folinic acid, 5 FU and Irinotecan (IRI).

The authors report 5 cases of HR among 44 patients, 52 to 73 years of age, hospitalized between 2013 and 2014 for colon adenocarcinoma. The diagnosis of HR due to Leucovorine (L) (Calcium racemic Folate) may be more frequent than it seems. If Skin-tests were all negative, Provocation tests performed with L-isomer calcium folinate were positive in the 3 cases tested (negative with O and IRI); on therapeutic point of view, 4 patients decided with their oncologist to avoid L. For the 5th patient, a protocol of rapid Desensitization (D) was programmed and performed with success: It is the first intravenous rapid D to L in a reactive patient.

## 51. Antibiotics in fetal and early life and subsequent childhood asthma: nationwide population-based study with sibling analysis

Anne. K Örtqvist et al BMJ 201428/11

**Theme:** Atopy – Asthma

**Key word:** Antibiotics – Fetal life – Early life – Asthma

A cohort study of 493 785 children born 2006-2010, including sibling control design, and 180 894 eligible, was investigated with Cox proportional hazard regression model adjusted for shared factors within families and confounding by respiratory infections and specific groups of antibiotics. Antibiotic exposure in fetal life was associated with an increase risk of asthma in cohort analyses but not in the sibling analyses where this association disappeared indicating that this association is affected by factors shared by siblings. The risk for asthma was stronger after exposure to antibiotics used for respiratory infections than those used for urinary tract or skin infections implying confounding by indication or reverse causation.

In conclusion the association between antibiotics use in fetal and early life and subsequent childhood asthma is questioned, if all confounding factors are taken into account.

## 52. Immunologic features in patients with Down syndrome

**Theme:** Clinical Immunology

**Key word:** B cells – Down syndrome

Patients with Down syndrome carry immunologic defects as evidenced by risks for autoimmune diseases, hematologic malignancies, and respiratory tract infections. Moreover, the low number of circulating B cells suggest impaired humoral immunity. The study of 17 children has shown that these patients seem capable of normal germinal centers and plasma cell formation. Blood memory B cells were reduced and showed impaired molecular maturation of IgA and IgM important for mucosal immunity. These defects contribute to increased susceptibility of these children to respiratory tract infections.

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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