

Bibliographic updates in Allergology 2016

By: Claude Molina and Jacques Gayraud



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1. Obesity and Asthma in Children

A.Charles et B.Heude : Bulletin de l'Académie de Médecine 2015 (sous presse)
H Graseman .Mol.Cell.Pediatr 2015 Dec 2(1)6 doi

According to WHO, 42 million children under age of 5 were obese or overweight in 2013 and the prevalence has dramatically increased in the second half of the 20th century. Many factors interfere with early development, from the prenatal period, where the main factor is the maternal BMI before pregnancy, to the post-natal period: e.g. the first 2 years of life, where maternal and infant weight gain, smoking during pregnancy, caesarean delivery, are important risk markers. Moreover, advances in genetics and in intestinal microbiota should help to understand the mechanisms of this obesity and the susceptibility to association with Asthma, Eczema and other non- communicable diseases such diabetes.

As for Asthma, the relationship remains controversial. The clinical presentation is distinct from other Asthma phenotypes and depending on age of onset of symptoms. More frequent in girls, it tends to be more severe, not typically associated with allergy, and less responsive to standard anti-inflammatory therapy, including inhaled corticosteroids and β_2 agonists. Obesity may lead to Asthma via a number of mechanisms including changes in lung mechanics, the nitric oxide metabolism, and by causing inflammation. Conversely poorly controlled Asthma may precede Obesity which is favored by sedentarity and intensified treatment with systemic corticoids. Anyway, all supportive interventions should include weight loss.

2. Blood eosinophil count as therapeutic guide in Asthma (A)

D.B.Price et al Lancet Respiratory Med 2015 3 849-858

The authors investigated, in a large UK cohort of asthmatics, aged 12-80 years, with 2 years of continuous records, the relation between a blood eosinophil definite count of 400cells/ μ L and prospective annual A. outcomes.

- 20 929(16%) of 130 248 patients had a count greater, during the outcome year, and they, significantly, experienced more severe exacerbations and acute events than those with a count less. They had also lower odds of achieving A. control, defined as limited reliever use and no asthma-related hospital admission or course of oral corticosteroids.

- Moreover, exacerbation rates increased progressively with 9 ascending categories of blood eosinophil count as compared with a reference of 200 cells / μ L or less.

In conclusion, blood eosinophil count, greater than 400cells / μ L, easier to practice in primary care, than sputum count, is a good predictor of Asthma exacerbations. In these patients who have poorer asthma control the eosinophil count which is in relation with outcomes may act as a guide for an efficient therapy.

3. Th2 immunity in atopic children: dissociation between sensitization and symptomatic allergic symptoms

P.Holt et al JACI décembre 2015 In press

Among children with asthma and rhinitis, sensitized to aero-allergens, mainly HDM and grass, only a minority are symptomatic, implying a mechanism of anti-inflammatory control, attenuating expression of IgE responsiveness to allergens.

The authors analyzed in 3 independent populations (Australia, UK, Sweden) relationships between allergen specific IgE and corresponding specific IgG, and associated immunophenotypes.

Depending on age/allergen specificity 20% to 40% of children with sIgE of 35kU/L or greater in the serum, had negative skin tests and a high ratio of IgG/IgE. IgG1 (not IgG4) from these children inhibited basophil activation in a dose –dependent fashion and are associated to a strong IL 10-dependent gene signature. Among non symptomatic there was also a significant higher IL 10/Th2 cytokine (protein) ratio.

Conclusion, IL 10 might have a dual function of attenuating effector activation of late phase allergic response and promoting IgG 1, which modulates the acute phase reaction. This sIgG 1/ sIgE balance represents an accessible therapeutic target for asthma and rhinitis control.

4. Management of chronic refractory cough (CRC)

P.G Gibson et al BMJ 2015 Décembre 14 and Chest 2015 1496

Defined as a cough that persists despite guideline base treatment, more than 8 weeks, CRC also described as unexplained cough or cough hypersensitivity syndrome, has a substantial impact on quality of life. Seen in adults, the symptoms include dry irritation around the laryngeal region, sometimes globus, dyspnea or dysphonia. 11 Randomized control clinical trial and 5 systematic review edited guidelines.

- Its pathophysiology is complex including reflex sensitivity, central and peripheral sensitization.
- Several treatments have been developed over the past decade such speech pathology interventions, use of neuro-modulators such as gabapentine and pregabalin.
- Potential novel treatment with AF 219 an oral purinergic receptor antagonist (in airways afferent vagal nerves) was associated with a significant 75% reduction in cough frequency (Lancet 2015 385 1198-2005).

5. Primary prevention of Atopy

Randomized controlled trial with house-dust-mite allergen oral immunotherapy in early childhood: Z.Zolkipli et al JACI Dec.2015 136 6 1541-1547

In 111 infants 5 to 9 months of age at high risk of atopy, with negative prick-tests, drops of high doses HDM active extracts (57 patients) and appropriate placebo solution (54 healthy) were administered orally twice daily for 12 months.

Co-primary outcomes were cumulative sensitization to HDM and to any common allergen during treatment whereas development of eczema, wheeze and food-allergy were secondary outcomes.

The results met the trial's pre-specified criteria to proof of concept, in reducing sensitization to any allergen. However, no significant preventive effect was observed on allergy related symptoms or HDM sensitization. Further follow-up will determine whether this effect will translate into a reduction in childhood asthma or allergic rhinitis.

6. Environmental Microbial exposure and Protection against Asthma

P.G Holt and P.D.Sly : NEJM 2015 373 26 2576-78

In a review on the prevention of Asthma, the Australian authors recall the basic research on the atopic component of the disease, the role of microbe-rich animal barn-dust in the natural resistance, the contribution of lipopolysaccharides in this protective effect due to increase in the synthesis of the enzyme A 20, the production of which by airways epithelial cells may implicate it as a potential therapeutic target. Other molecular mechanisms are able to suppress asthma but environmental microbial or viral stimuli are also causal pathways which deserve more investigations.

7. Dog allergen Immunotherapy

C.A.Coop et al Annals of A.A.IJan2016 in press

The author performed the published medical literature on the use of dog extracts immunotherapy in patients with hypersensitivity to dogs, taking in account that dogs part of familiar environments of atopic and dog allergens are present in 49% of homes in USA and in Europe. 215 articles, 17 clinical trials were investigated and showed poor and conflicting results of clinical efficacy which has been attributed to poor quality extracts (Canis familiaris f 1 to f 6) and the complex allergenic profile that remains without a clearly dominant allergen.

8. Immunologic profile of Food-Allergy in children (egg and peanut)

T.D.Dang¹ et al PAI 2016 27 1 Feb 35-43

S.Mayumi et al PAI 2016 16 Jan Accepted article

The 1st Australian article examines changes in peripheral blood of regulatory T cells (Tregs) in 37 infants allergic to egg or peanut, 35 only sensitized and 15 placebo, before and after Oral Food Challenge (OFC).

One hour, then 2 days and 6 days after OFC, non-allergic infants showed stable total Treg frequencies. Food-sensitized a transient fall in Treg percentage with recovery to baseline by day 6. Food-allergic infants showed persistent reduction in Treg with impaired capacity to regenerate the Treg pool, which may be the more important factor that determines clinical allergy versus simple sensitization.

The 2nd Japanese article is a pilot study investigating in 26 children, 5 years of age, with egg allergy the changes in serum the levels of Immunoglobulins (sIgE, subclasses of IgG, IgA) before and after Oral Immunotherapy (OIT) with egg-powder, beginning by a rush phase and during 1 year.

The response to OIT was associated with significant increases of IgG 1 after rush phase and high IgA levels whereas there were small changes in low-responders. This may be useful biomarkers for the prediction of positive clinical response to OIT.

9. Upper airway remodeling and Chronic Allergic Rhino-Sinusitis

AO. Eifan et al: AJRCCM 2015 192 1431-1439

Testing the hypothesis that upper airway remodeling may account for the chronicity of Rhinosinusitis, like in Asthma, the British authors performed a careful examination of 46 patients suffering from severe CARS (19 control subjects) and nasal biopsies using state of art immune-histology with measurement of classical mediators (e.g; matrix metalloproteinase 9). They showed that tissue remodeling is not a feature of persistent allergic rhinitis. Then, targeting the upper airway remodeling is not an appropriate therapeutic approach. Dietary modifications may offer a non-pharmacologic alternative (Nayan J.et al Journal of Rhinology &Allergy 2015 Nov – Dec 170-174).

10. Aspirin-Exacerbated Respiratory Disease: The Pathogenic Puzzle

T.M.Laidlaw :NEJM 2016 Feb 4 484-488

The Samter's triad: Asthma, Chronic Rhinosinusitis with nasal polyposis and pathognomonic respiratory reactions to aspirin, is characterized by eosinophilic inflammation and mastocytes activation in the respiratory mucosa. All nonsteroidal anti-inflammatory drugs that inhibit both cyclooxygenase COX 1 and COX 2 may provoke the same reactions. In

contrast the patients may tolerate the COX2-selective drugs such Celcoxib and high doses of aspirin induce a refractory state which has therapeutic benefits.

The hallmark of the syndrome is dysfunction of 5-lipoxygenase LTC₄ synthase pathway which converts arachidonic acid to the cysteinyl leukotrienes responsible for bronchoconstriction, eosinophilic inflammation and platelets activation. Both Zileuton and Montelukast which block these mediators can improve or attenuate the symptoms of AERD.

But an ubiquitous product of cyclooxygenases, mainly COX 2 dependent: Prostaglandin E₂ (PGE₂), inhibits 5-lipoxygenase function, prevents cells activation and changes in lung function induced by aspirin. Moreover mast-cell activation reflects release of another mediator PGD₂, potent chemotactic factor which elicits bronchoconstriction through T prostanoid receptors on the smooth muscle bronchial cells. The role of type 2 immune system, involvement of many cytokines, mediators and mucosal cells create a puzzle not yet solved. However clinical trials study possible efficacy of an antiplatelet drug: Prasugrel and an antagonist of T prostanoid receptors: Ifetroban.

11. Effective treatment of HDM-induced Rhinitis with 2 doses of SLIT tablets. Results from a randomized DBPC phase III trial

P.Demoly et al JACI Feb 2016;137:2 444-451

This trial conducted in 12 European countries including 992 adults with moderate to severe HDM induced Allergic Rhinitis (AR) demonstrated absolute reduction of symptoms and medication scores compared with placebo. The significant effect was evident from 14 weeks of treatment on ward and confirmed with the two doses: 6 SQ HDM or 12 SQ HDM. The treatment was well tolerated and the QOL was improved.

SLIT is from now on, a worldwide new option for HDM or Pollen-induced allergic rhinitis.

12. SLIT in HIV-positive patients

I.E Lemoly et al Allergy March 2016 71:3 412-415

If HIV infection is a relative contra-indication of Immunotherapy, in the last decade highly active anti-retroviral therapy has improved the immune function and life-expectancy in HIV-infected patients. The Italian authors evaluated the safety and clinical effectiveness of SLIT tablet (Oralair[®]) in a group of 13 grass pollen allergic patients submitted to antiretroviral and symptomatic therapy, compared with 9 patients receiving symptomatic therapy alone. Clinical efficacy data showed a significant improvement in SLIT group compared to controls, without significant alteration of TCD 4 counts and viral load in any group. These preliminary studies show that SLIT therapy in viro-immunological controlled HIV positive patients, was efficacious safe and well tolerate.

13. Short-term subcutaneous grass pollen immunotherapy under the umbrella of anti-IL4: a randomized controlled trial

A.M.Chaker et al JACI Feb 2016 137 2 452-461

To evaluate the induction of sustained tolerance to allergen when anti-IL4 was combined with a suboptimal course of grass pollen subcutaneous immunotherapy, (SCIT) the British authors enrolled 37 patients with seasonal allergic rhinitis. In a randomized double blind trial 3 parallel group were designed:

- one received suboptimal SCIT in combination with antiIL4(VAK694),
- the 2nd SCIT + placebo antibody,
- the 3rd double placebo,

all 13 weeks before the pollen season. The 1st primary end point was the size of late phase response (LPR) of the skin-test at 12 months, as surrogate of clinical efficacy. Exploratory end-points include the immunomodulatory activity of treatment. Both active arms led to a substantial and sustained reduction of LPR without additional suppression with association of anti-IL4. Addition IL4 to SCIT, compared to SCIT alone led to a reduction in allergen-specific IL4 producing cells counts. Both active arms led to induction of dual IL4/IL10 producing cells during the pollen season.

14. Allergy to hen's egg in infancy: Incidence and natural history

P.Xepapadaki : Allergy march 2016 71 3 50-357

A large multinational cohort study (12 049 newborns, followed up to 2 years of age) on food allergy with gold-standard allergic methods showed that the mean incidence of egg allergy, usually perceived as a common food was considerably lower than previously documented: 1,23% (95% CI 0,98-1,51) with center-specific incidence ranged from 2,18% (UK) to 0,07% (Greece). Moreover, half of the children gained tolerance within 1-year post diagnosis.

On another point of view, it was shown that a technological process using a combination of enzymatic hydrolysis and heat treatment led to a strong decrease of hen's egg allergenicity. Hydrolysed egg products may be beneficial for suspected allergic patients to extent their diet. (B.K Ballmer-Weber Allergy 2 Feb 2016 Accepted article).

15. Occupational Asthma: (OA) Predictive value of methacholine bronchial challenge

J.A.Pralong JACI 2016 137 2 412-416

The Canadian authors sought to evaluate the sensitivity, specificity, positive and negative predictive value of methacholine challenge at baseline of the specific inhalation test: "gold standard" of the diagnosis. A database was used to review 1012 cases suspected of

OA between 1983 and 2011 and submitted to specific and nonspecific challenges at the work place and outside work.

When considering all subjects tested at work (479 cases) it appears that the sensitivity value is 98,1% and the negative predictive value 97,7%.

So even in doubtful cases, a negative methacholine challenge in patients still exposed to causative agent, makes the diagnosis very unlikely.

16. Lidocaine and Severe Atopic Dermatitis

H.Li et al JACI 2016 Feb 137 2 613-617

Lidocaine (L) is a widely used short-acting local anesthetic which, in previous studies has demonstrated, by aerosols in patients with severe asthma, attenuation of bronchoconstriction. Because of the similarity of allergic diseases, L was used by Chinese authors in the treatment of severe AD in young patients and in murine models sensitized by ovalbumin. 20 patients were administered 3mg/kg day L. via a slow intravenous drip, with a good tolerance, improvement of skin inflammation and clinical remission. Skin biopsies and immune studies uncovered the molecular mechanism of L. in T.reg regulation, with promotion of Fox P3 transcription by activating TGF β -induced Smad3 phosphorylation. Moreover L. improved the TH1/TH2 cell et 17A/17 E cytokine imbalance, in both patients with AD and murine models, exerting its regulatory effects on immune cells.

17. Avoidance on peanut allergy in infants after early consumption

G.Du Toit et al : NEJM 2016 March 4 On line first

In a previous randomized trial in more than 600 infants at high risk for allergy, the early introduction of peanuts was shown to prevent peanut allergy. At the end of the primary trial, the authors instructed participants to avoid peanuts for 12 months; then 2 groups are followed until 5 years of age; the first group with exclusive avoidance and the 2nd group who carry on peanut consumption. At 72 months, peanut allergy was most prevalent in the peanut avoidance group than among those in the peanut consumption group. So it appears that a 12 months period of peanut avoidance was not associated with an increase of peanut allergy. Moreover, the participants of this group have a higher level of IgG4, high level of Ara2 and higher IgG4/IgE ratio.

So the tolerance went on for a few years after early consumption.

18. Introduction of Allergenic Foods in breast-fed infants and Prevalence of Allergy

M.R.Perkin et al : NEJM 4 March 2016

§The British authors sought to evaluate whether early introduction of allergenic foods in the diet of breast-fed infants would protect them against food allergy. They recruited from the general population 1303 infants, exclusively breast-fed, who were 3 months of age, and randomly assigned them to: either early introduction of six allergenic foods: peanut, cooked egg, cow's milk, sesame, white fish, wheat, or carry on exclusive breast-feeding to 6 months of age. The primary outcome being food allergy to one or more of the six foods between 1 and 3 years of age. The results were disappointing: 7.2% of Food allergy in the standard group, 5.6% in the early introduction group. However, a per-protocol analysis showed a lower prevalence of peanut and egg allergy, maybe dose-dependent.

In conclusion, this trial, which was totally safe, did not show the efficacy of early introduction of multiple allergenic foods.

19. Prevention of food allergy in Infancy

G.W.K.Wang NEJM 2016 Editorial On line first

The age at which allergenic foods should be introduced into the diet of breast-fed infants is uncertain. Classical recommendation for decades urged parents to avoid early exposure which risk allergic sensitization.

The first compelling trial of British pediatricians: Learning Early about Peanut Allergy (LEAP) showing that the early consumption in infants, on the contrary, decreased the risk of peanut allergy, turned this idea on its head and provided new guidance as primary preventive strategy. But what about other common foods such milk, egg and fish? The second important trial (Enquiry about Tolerance - EAT) attempted to answer these questions in designing a protocol with early introduction of six foods in exclusively breast-fed infants from the general population and starting at 3 months until 3 years of age. The first analysis (intention to treat) and a such demanding protocol in real life, makes the early feeding approach ineffective. However, we know that administering these foods is safe and at a population level, evidence is building that early rather delayed consumption is likely to be more beneficial as prevention strategy.

So, in conclusion, the author gives with humor this advice: " Feed your children and hope that they will EAT".

20. Chronic RhinoSinusitis (CRS) Cluster analysis and Prediction of treatment outcomes An American survey

Z.M.Soler JACI April 2016 137 4 1054-1062

Simplified discriminant analysis based on unsupervised clustering has identified novel phenotypic subgroups of CRS. A prospective study of 690 patients with data on demographics co-morbidities, questionnaire-test with 22 items, age, objective disease measures with

olfactory testing, computed tomography, and endoscopy scoring, allowed to separate patients in five clusters and set-up a prognosis in patients choosing surgery versus continued medical management.

At 18 months of follow-up 3 common variables: age, sino-nasal outcome test-22 and missed productivity were able to provide information regarding prognostication of the disease, according to surgery (3 clusters) or medical treatment (2 clusters).

21. CRS dissected: Inflammatory endotypes based on cluster analysis of biomarkers

P.Tomassen et al JACI May 2016 137 5 1449-1456

Current phenotyping of CRS into CRS with and without Polyposis, do not adequately reflect the pathophysiology and diversity of clinical cases. So, the European authors using cluster method with biological markers compared to clinical phenotypes, identified inflammatory endotypes.

In a survey of 173 patients recruited in 10 specialty centers, they discerned 10 clusters with 3 major endotypes based on Th2 markers according to the high or moderate severity of the RSC and associated with low to high co-morbid prevalence of Asthma; whereas Th1 and Th 17 related inflammation has little effect on disease severity . In conclusion distinct CRS clusters with inflammatory markers provide an accurate description of mechanisms involved in diverse phenotypes.

22. Epicutaneous Immunotherapy (EPIT) for the treatment of Peanut Allergy (PA) using the Viaskin-patch: Safety: Phase1.

SM.Jones et al JACI 2016 137 4 1258-1261.e10

EPIT has shown promise in animal studies and in single pilot study about efficacy (H.A.Sampson et al JACI February 2016 137 2 supplement AB 408). The purpose of this research is to evaluate the safety and tolerability when the new patch is applied on intact skin.

100 subjects (80 receiving active treatment and 20 Placebo, age 6 to 50, including 70 adults and children with non-severe PA and 30 adults severe PA) were enrolled in a DBPC phase 1 study at 5 clinical sites in USA. Viaskin patches with low doses: 20, 100µg progressing on to the next escalation in non-severe adult cohorts (children did not receive the 500µ dose) by using an interactive web-based response system. The safety and tolerability were assessed by the presence of adverse events. The findings revealed that the novel Viaskin delivery system is safe and well tolerated with high adherence by study participants.

23. Anaphylaxis (A) in Children and adolescents: The European registry

L.BGrabenenrich et al JACI 2016 April 137 4 1128-1137

Between 2007 and 2015, 1970 patients, younger than 18 years, and coming from 90 allergy centers in 10 European countries were recorded and identified as severe allergic reactions. Most incidents occurred in private homes (46%) and outdoors (19%). One-third of patients have experienced A. previously.

Food items were the most frequent elicitors (cow's milk and hen's egg in the first 2 years, hazelnut and cashew in pre-school age children, peanut at all ages) followed by insect venom (19%) then drug induced up to age 10 years.

The symptoms are well known: vomiting and cough in the first decade, throat tightness dizziness later in life, skin diseases at all ages (urticaria, angioedema, erythema). 30% of cases were lay treated (often by a teacher) of which 10% with epinephrine auto-injector. Emergency treatment with epinephrine increased between 2011 and 2014 (12 to 25 %).

26 patients (1,3%) were admitted in intensive care unit. 5 deaths were to deplore. Still in children, measurement of Tryptase levels may be useful in cases of mild or late reactions as in the Canadian clinical report (S.De Shryver et al JACI 2016 401138-1142).

24. Mycoplasma Pneumoniae (MP) and Asthma (A)

JJ. Yeh & al JACI April 137 4 1017-1023 & P.Giavina-Bianchi & J.Kalil 1024-1025

Identifying 1591 cases of MP during the 2000-2008 period, matched with 6364 patients without MP infection from the general population, according to age, sex, and index year, the Taiwan authors found in the cohort MP an higher risk of incident A. than those without it. The adjusted hazard ratio for Asthma was of 3,35. The risk was higher in male patients, in those with co-morbidities including atopic disorders, or late-onset A., those treated by corticoids, and within the less than 2 years follow-up after MP infection. In conclusion, this study showed that incident cases of early-onset and late-onset Asthma are closely related to MP infection, even in non-atopic patients.

As underlined by Italian authors, in their comment, MP infection and A. present a 2-way interaction, MP may induce bronchial inflammation and exacerbation, conversely if Asthma comes first it may favor infection, but in this study MP appears as an independent risk factor for incident Asthma.

25. Patterns of Growth and Decline in Lung Function in persistent Childhood Asthma

M.J.McGeechie et al NEJM 2016 12 May 3741842-1852

Looking for links between childhood asthma and subsequent chronic airflow obstruction in the 3th decade of life, the authors classified asthmatic children in 4 patterns of lung function growth and decline on the basis of graphs showing values of FEV₁. Of the 684 study participants 514 (75%) had abnormal patterns:

- 176 had reduced growth and early decline,
- 160 (23%) had reduced growth only
- and 178 (26%) normal growth and a early decline.

Lower baseline values for FEV₁ and airways responsiveness with smaller bronchodilator response and male sex are associated with reduced growth. At the last spirometric measurement 73 participants 11% met criteria for COPD.

In conclusion children with persistent asthma and reduced lung function are at increased risk for fixed airways obstruction and possibly COPD in early adulthood.

26. Serious events with Fluticasone (F) + Salmeterol (S) versus Fluticasone alone

D.A.Stempel NEJM 2016 374 1822-30

A multicenter randomized trial was designed to evaluate the risk of administering LABA S in a fixed dose combination with F in a single inhaler, compared with F alone.

11,679 patients, 12 to 64 years of age, with persistent Asthma were treated during 26 weeks. The primary safety end-point was the 1st serious asthma event; the efficacy end point was the 1st severe exacerbation. At the end of this study:

- 34 patients had serious asthma related events in S+F group,
- 38 in the F group.

There were no asthma-related death. 2 patients in the F group underwent hospitalization and intubation. The risk of severe exacerbation was 21% lower in the S+F group than in the F group with at least 1 severe exacerbation in 480 of 5834 S+F as compared with 597 of 5845 patients in the F group.

In conclusion the treatment of persistent asthma by a fixed dose combination of S+F in a single inhaler did not have a significantly higher risk of serious asthma-related events that did those who received F alone. There were fewer exacerbations in the 1st group.

27. Clinical relevance of molecular diagnosis of pet allergy:

A.Uriarte et J.Sastre: Allergy 20164 may Accepted Articles

Sensitization to pets are present in up to 60% of European households. The Spanish authors describe the patterns of specific pet IgE to whole extracts and recombinant allergens and their association with clinical symptoms.

159 patients with Rhinitis/ Asthma (R/A) sensitized to dog cat and horse were recruited.

- Specific IgE to Can f1 was significantly associated with persistent R, Can f2 with A, Can f3 with moderate/severe R, Can f 5 with R.
- Positive IgE to Fel d2 was associated with R and A.
- Equ c1 with moderate R, Equi c3 with persistent R and severe A.

Sensitization to more than 2 molecules or to pet albumins was associated with severe respiratory symptoms.

In conclusion, molecular diagnosis in patients with pet allergy may help clinicians to predict clinical symptoms and their severity.

28. Higher omega-3 Fatty-acid levels contribute to the asthma-protective effect of farm milk

T.Brick et al JACI June 20161699-1706

In a study of 934 children living in rural areas in 5 European countries from birth to age 6 years the authors showed that the risk of asthma was reduced by previous consumption of unprocessed farm milk compared with shop-milk. This effect was explained by higher fat content of farm milk, particularly higher content of omega-3 poly-unsaturated fatty acids.

However, consumption of raw milk is no solution because it bears a risk of potentially life-threatening infections. Hence there is a need to identify those components of native cow's milk that carry this asthma-and allergy-protective, as well as anti-infectious, effect. A candidate molecule class with relation to immune functions are the microRNAs (miRNAs), which have been described in both cow's milk and human breast milk (B.Kirchner et al :JACI même n° 1893-95) and interfere with genes implied in allergy and asthma development.

29. Asthma risk in Amish and Hutterite Farm Children

M.M Stein et al NEJM 2016 375 411-421

US agricultural populations whose lifestyles as well as genetic ancestry, are remarkably similar but whose farming are distinct, the former follow traditional practices, the latter use industrialized farming practices.

The authors knowing striking disparities in prevalence of asthma in the two populations tried to explain these disparities in studying and comparing, in 30 Amish and 30 Hutterite children, environmental exposures and immune profile (levels of allergens, serum

IgE levels and endotoxins, gene expression, cytokine responses, blood peripheral leucocytes phenotyping) and microbiome composition of indoor dust samples. Moreover the effects of dust extracts were assessed in a murine model of experimental allergic asthma. The results of this important study showed that the prevalence of asthma and allergic sensitization is 4 to 6 times as low in the Amish, whereas levels of endotoxins in Amish house dust is 6,8 times as high. Profound differences are observed in innate immune cells between the 2 groups of children. Intra-nasal instillation of dust extracts in mouse model from Amish, but not Hutterite homes inhibited airways hyper reactivity and eosinophilia. This protective effect was abrogated in mice deficient in MyD88 and Trif, molecules critical in innate immune signaling;

In conclusion, in humans and mice the Amish environment provides protection against asthma by engaging and shaping the innate immune response.

30. News in venom Hypersensitivity

G.Sturm :EAACI Newsletter 2016 43 2 27

Hymenoptera Venom Allergy (HVA) is responsible for more than 10% of all cases of Anaphylaxis and accounts for more than 40% in the 13-17 years age group and 20- 50% in mastocytosis rising to 60- 80% in indolent systemic mastocytosis without skin lesions. Current available tests are not able to distinguish between asymptomatic sensitization, large local reactions and severe systemic reactions. However recent developments had improved diagnostic precision in HVA in particular sIgE in Honey bee marker allergens such rApi m3 et rApi m10 which allows the detection of genuine sensitization in 46-65% of Api m1negative sera and useful in case of double sensitization or cross reactivity. But until the end of 2016, 5 bee venom components are available for routine diagnosis: Api m 1 2, 3, 5, 10. A recent study showed that high levels of sIgE to rApi m1 and rApi m2 could be predictors of severity of a sting reaction. Another development is focused on biomarkers of HVA: So the serum concentration of CCL5/RANTES is reduced after 6 days of Venom Immunotherapy (VIT) independantly of sIgE.

There is also in venom allergic patients an up-regulation of CD 26, CXCR4, CXCR3 CD 150 and ICOS and conversely a down regulation of CD 30 CD 154 and 152 a decrease of basophil degranulation and increase of INF gamma in T cells after 4 month of VIT. Moreover precision medicine is also reached by means of analysis of gene expression : a predictive model could be used in clinical practice to assess the efficacy of VIT. As for adherence to subcutaneous VIT, a recent five years follow-up study indicates excellent results. Moreover, we must recall the physicians and patients concerns about excessive price of EpiPen in USA.

31. Corticosteroid response in pediatric patients with severe asthma

C.J.Bossley et al JACI 2016 138 2413-420

Severe therapy-resistant asthma (STRA) is heterogeneous thus response to steroids is not uniform in all patients. The English authors thought to evaluate the utility of multidomain approach incorporating symptoms, lung function and inflammation (eosinophilia). 82 children, median age 12 years with STRA received a dose of intramuscular steroid (triamcinolone) Changes in 4 separate domains were assessed 4 weeks later: symptoms score, spirometric results (FEV₁), fraction of exhaled NO₂ levels, sputum eosinophils counts.

- 54 had complete data in all 4 domains.
- A similar proportion of children responded in each domain (43-54%).
- Only 7 (13%) were complete responders in all domains 8 were no-responders.

These results confirm that STRA is heterogeneous. However individual response patterns might be useful in guiding the choice of add-on therapies (mainly monoclonal antibodies) in each child as a step toward achieving personalized medicine.

32. Safe drugs for young asthmatic patients

a) Acetaminophen as Ibuprofen are commonly used in USA for the alleviation of pain or fever and studies have suggested that they are responsible for complications among asthmatic children. In a multicenter prospective randomized parallel group trial , W.J Shehan and al NEJM 2016 August 18 375 619-630 300 children were enrolled age range 12 to 59 months and assigned to receive A or I during 48 weeks. The results showed that A as needed use, was not associated with a higher incidence of asthma exacerbations or worse control than was as-needed I.

In conclusion the two drugs are harmless in young children with moderate asthma.

b) Safety of adding Salmeterol to Fluticasone in children with asthma LABAs (Long acting-beta agonists) has been shown to increase the risk of asthma-related hospitalization among children (and even death in adults) D.A Stempel et al NEJM 2016 375 840-849 1 september: in a trial among children 4 to 11 years of age showed that salmeterol in a fixed dose combination with fluticasone, during 28 weeks was associated with the risk of a serious asthma –related event similar to the risk of fluticasone alone.

33. Early polysensitisation is associated to allergic multimorbidity

S.Gabet et al Ped All Immunol 2016 8 august

A population-based prospective birth cohort in Paris (France) studied allergic sensitization to 12 foods and 4 inhalant allergens assessed at 18 months and health data collected at 2 and 6 years. In a cluster analysis 3 profiles of increasing severity were identified and compared with regard to allergic morbidity and multimorbidity.

It appears that early sensitization can predict multimorbidity (asthma, rhinitis, eczema, food allergy) in childhood and in case of early multisensitisation, multimorbidity is more frequent as soon as in infancy.

34. Airways smooth muscle (ASM) enlargement and Severe Asthma (SA)

M.Aubier et al JACI 2016 138 3 729-739

The increase in ASM is a component of airways remodeling in SA. The French authors sought to compare, by bronchial biopsies in 12 controls, 24 patients with moderate and 105 SA, ASM area (enlargement = more than 15% of total mass) with clinical and pathobiological characteristics (cellular and mitogenic factors in Broncho-alveolar lavages).

Analyses across ASM quartiles demonstrated that patients with the highest quartile, were younger, rather male, and has lower asthma control after one year of optimal management of. ASM enlargement occurs independently of features of airways inflammation or remodeling, whereas it was associated with Protease active receptor 2 (PAR 2) over expression, higher alveolar Tryptase and KLK levels. Targeting PAR 2 seems to be a novel therapeutic option in SA.

35. Drug allergies documented in electronic health records

L.Zhou et al Allergy 2016 Sept 71 9 1305-1313

The authors aimed to describe the prevalence of common drug allergies and patient characteristics documented in a large healthcare network from 1990 to 2013 in Boston large tertiary care hospitals. Among 1 766 328 patients 35% had at least one reported drug allergy with an average of 1,95 per patient. The most commonly reactions were due to penicillin (12%), sulfonamide antibiotics (7,4%), opiates (6,8%), NSAID (3,5%). Drug allergies were most prevalent among females and white patients except for NSAID, ACE inhibitors, and thiazide diuretics more prevalent in black patients.

The relative proportion to ACE inhibitors and Statins have more doubled since early 2000, while allergies to antibiotics decrease emphasizing the role of increased exposure, usage overtime, and modern-day therapy, as well as geographical and environmental factors which must be taken into account.

As for Pharmacogenomics or Pharmacogenetics (D.A.Kahn JACI October 2016 943-955) their clinical utility has not been established.

36. Omalizumab (O) facilitates Rapid Oral Desensitization (ROD) for Peanut Allergy (PA)

A.J.Mac Ginnitie et al 2016 August in press

In a double-blind placebo control trial 37 subjects, median age 10years, IgE = median 90mg, who failed a food challenge to ≤ 100 mg of peanut protein (pp) were randomized to O =29 or placebo = 8. After 12 weeks of treatment, the children underwent a DOR of 250mg of pp. over 6 hours followed by weekly dose increases up to 2000mg. O or Placebo were discontinued and subjects continued on 2000mg of pp daily. 12 weeks later, the children underwent a challenge to 4000mg. If tolerated, they continued on this dose daily. The results are as follow: Of 29 O (27 of whom received DOR) 23 tolerated 2000 mg pp 6 weeks after stopping study versus 22,5mg for placebo (P= 0,0011). 12weeks later 22 tolerated 4000mg after discontinuing study drug.

Conclusion: O allows patients with peanut allergy to be rapidly desensitized. Additional studies are needed to confirm these observations.

37. Symptomatic treatment of pollen-related allergic Rhino-conjunctivitis (AR)

J.B.Wartna et al Allergy October 2016 Accepted article

In a randomized trial, 150 children, aged 6-18 years with pollen related AR were treated in 3 parallel groups: intra-nasal corticosteroids (INCS) either daily, or on demand (fluticasone propionate) or oral anti-histamine (levocetirizine) on demand for 3 months during grass pollen season. The trial shows that INCS daily was not superior to INCS on demand (22% versus 30% of symptom free-days: not significant) or anti-histamine (15%) not significant.

On-demand strategy has the advantage of lower corticosteroid exposure and less costs.

38. Sublingual Immunotherapy tablets (SLIT) or Pharmacotherapy for Allergic Rhinitis (AR)

S.R.Durham et al :JACI October 2016 1081-1088

In spite of heterogeneity of the study design, (randomized and placebo-controlled) and use of rescue medications in SLIT tablet's trials, effects of nasal symptoms with grass (3094 adults) and ragweed tablets (658 patients) during the pollen season, and HDM-tablets during 8 weeks of perennial rhinitis (1768 patients) were nearly as great as with corticoids (mometasone furoate 200mg) and greater than with montelukast (10mg) or desloratadine (5mg). House-dust-mite tablets offer the additional benefit of long term efficacy.

39. New Monoclonal Antibodies (MA)

A. Ligelizumab (L) (QGEO 31) and Mild Asthma:

G.M.Gaudreau et al JACI October 2016 138 4 1051-1059

The Canadian and American researchers have tested in a randomized multicenter study, this fully humanized IgG 1 antibody, which binds with higher affinity to IgE than Omalizumab (O) and provides greater suppression of free IgE and IgE bound to mast cells and basophils.

3 doses were administered every 2 weeks in 37 patients with mild asthma: 24, 72 or 240mg, during 10 weeks and compared with parallel groups of O. and Placebo. The results confirm the efficacy and safety of this MA, with a greater efficacy than O on inhaled and skin allergen response. Whether these results translate into clinical benefits in severe asthma and chronic spontaneous urticarial need to be evaluated in larger clinical investigations.

B. Reslizumab® in poorly controlled and eosinophilic Asthma:

L.Biermer et al CHEST October 2016 150 4 789-798- and J. Corren et al same review 799-810

Anti-IL 5 MA, humanized, (CINQ air) R was studied by a Canadian group in a randomized phase 3 trial in 179 patients aged 12 to 75 years with non-controlled asthma with inhaled corticosteroids + short-acting β agonists and a blood eosinophil count ≥ 400 cell/ μ L. They receive every 4 weeks for 16 weeks a dose of 0.3 or 3.0 mg/kg. R improved lung function, asthma control, (symptoms) and quality of life. It was well tolerated, in spite of small number and moderate adverse effects: headache, naso-pharyngitis or worsening of asthma. Over all the 3.0 mg/kg dose provided the greatest improvements with comparable safety that the lower dose.

A similar study by an American team, in 492 patients treated at a dose of 3.mg/kg every 4 weeks for 16 weeks confirmed the efficacy and safety of R. in inadequately controlled asthma, and across a broad range of eosinophil counts.

C. Benralizumab: Add-on treatment for severe eosinophilic Asthma:

3 articles devoted to: in Lancet 2016 29 October-4November Vol 388 Issue 10056
M.Castro 2059-2060; E.R.Bleeker et al 2115-2127; JM.Fitzgerald et al 2128-2141

Anti-interleukin 5 receptor α MA that induces direct, rapid, depletion of eosinophils, B. has been tested in randomized parallel groups placebo-controlled phase3 at 303 sites in 11 countries (CALIMA) and respectively at 374 sites in 17 countries (SIROCCO) for patients aged 12-75 years with severe asthma uncontrolled by ICS+LABA, as add-on therapy, at the dose of subcutaneous injection of 30mg every 4 weeks or every 8 weeks, the baseline blood eosinophils being 300cells per μ L or greater.

Whatever the regimen (every 4 or 8 weeks) the results confirm that B. significantly reduced annual exacerbation rates and was generally well tolerated in this type of patients as additional option.

40. New therapeutic options for already known MA

A. Dupilumab (D) for Atopic Dermatitis in Adults

E.L.Simpson et al NEJM 2016 October 11 1-13

Human MA against IL 4 receptor α , D. inhibits signaling of IL4 and IL13 type 2 cytokines and has been assessed in 2 randomized placebo-controlled phase 3 trial of moderate to severe atopic dermatitis in adults, inadequately controlled by topical treatment. The design was identical in the two trials of 671 and 708 enrolled patients: subcutaneous injection of D.300mg or placebo weekly or the same dose every other week alternating with placebo, for 16 weeks. Improvement (symptoms of the disease: pruritus, anxiety, depression and quality of life) occurred in 38% patients who receive D every other week, 37% those who received D weekly, compared with 23% placebo. D was well tolerated except some rare cases of conjunctivitis and injection-site reactions. The 2 trial confirm the efficacy and safety of D. but long term effectiveness must be assessed by trials of longer duration.

B. Anti-IL5 MA, a possible option for the phenotype Asthma-Obesity: role of Innate Lymphoid Cells (ILC)

L.Everaere et al JACI 2016 November 138 5 1309-1318

Obesity is a risk factor for asthma but the mechanism is unclear.

French authors sought to determine the potential involvement of ILC type 2 and 3 in allergic airways disease exacerbation caused by high fat diet-induced obesity.

In experimental studies they show, that compared with a low fat diet, obesity decreased the number of ILC in mouse adipose tissue while increasing it in the lung with parallel to strong eosinophil infiltration. Moreover, in house dust mite allergic airways inflammation by intra-nasal administration, lung ILC, eosinophils, airways hyperresponsiveness and lung Th2 and Th17 profiles were aggravated in obese mice. To confirm the role of ILC, they depleted this population with an anti- CD 90 2 antibody: this ILC

depletion led to a profound reduction in all parameters of the allergic reaction. So, ILC type 2 and 3 participate in the aggravation of this house dust mite induced airways inflammation in obesity. The authors suggest that therapies targeting eosinophils such as anti-IL5 antibodies might be of interest in the obese asthma phenotype.

41. Unexpected role of Pneumocystis (PC) in the pathogenesis of Asthma

T.Eddens et al Am.J;Resp.Crit.Care.Med 2016 194 7 779-793

In the 1980, PC jirovecii emerged as the classic lethal opportunistic pathogen in the AIDS epidemic. And now it appears as an aero-allergen which has the ability to induce in mouse and man an adaptative immune response in the lung, highly dependent of CD4+ T cells and eosinophilic perivascular inflammation (without cross-sensitization with other aero-allergens such house-dust-mite and independent of Innate Lymphoid Cells 2).

Moreover, comparing a cohort of patients with severe asthma with healthy control patients, the authors found significant elevation of PC IgE and IgG, correlated with worsened lung function on spirometry. Of particular interest, the possibility arises that therapeutic intervention could be envisaged in such patients appropriately sensitized and symptomatic with PC-active agents (trimethoprim-sulfamethoxazole) or as prophylactic use, in patients receiving, long term, high doses of inhaled or oral corticosteroids.

42. Identification of fungal candidates for asthma protection

S.Mueller-Rompa et al Ped All.Immunol 2016 Nov Accepted article

Exposure to molds has been related to asthma risk both positively and negatively. The aim of the present analysis was to assess in environmental dust samples, asthma-protective fungal candidates with a comprehensive molecular technique.

Mattress dust samples of 844 children from the GABRIELA study were analyzed by PCR single-strand-SSCP of the fungus-specific (ITS) region. Known asthma candidate species were tested for their association with asthma, and further gel positions were sought to explain the above. As a second, data-driven, analysis, was tested the association of each individual gel position with asthma.

The results reveal that *Penicillium chrysogenum* emerged significantly as inversely associated with asthma. The effect size was changed by 39% toward the null when adjusting for the two bands 683 and 978. The data-driven approach yielded an additional band (containing DNA of *Pseudotaeniolina globosa*) with significant reduced risk of asthma.

So large population-based study revealed several fungal taxa with inverse associations with childhood asthma. Molds produce a variety of bioactive compounds with detrimental but also beneficial immunoregulatory capacities, which renders them promising targets for further asthma research.

43. Non Coeliac Gluten Sensitivity (NCGS)

P.Molkhou : Rev. Française d'Allergie Nov 2016 56 7-8

NCGS is a new entity that has been distinguished from other enteropathies associated with Gluten consumption. It differs from Coeliac disease (CD) in terms of absence of mucosal lesions, atrophied villousities, of anti-transglutaminases or extra-digestive symptoms. More frequent than CD, NCGS is characterized by non-specific gastro-intestinal signs; its diagnosis is based on clinical history, elimination of CD or other enteropathy such Food-Allergy to wheat, IgE-mediated, and gluten elimination-reintroduction challenge tests. However in individuals with NCGS a group of researchers found signs of systemic immune activation to microbial products (M.Uhde et al Gut 2016 ahead of print). At last there appears to be some overlap between NCGS and "irritable bowel syndrome".

44. Specific Risk factors for childhood Wheeze

Sze Man Tse et al JACI 2016 138 5 1561-1568

This Canadian study aims to identify sex-risk factors for wheeze from birth to mid childhood and identify distinct phenotypes using a large cohort of 1623 children. The authors found that paternal asthma is a stronger predictor of ever wheezing in boys whereas being black or Hispanic was a stronger risk factor in girls. When looking at the trajectories of wheeze over the first 9 years of life, they identify 3 patterns: never or infrequent, early transient and persistent wheeze. Similarly, paternal asthma was associated with persistent wheeze in boys only whereas being black or Hispanic was associated with persistent wheeze in girls only. These observations might have prognostic value in the care of children with asthma.

45. Field-testing the new Anaphylaxis classification

L.Kase-Tanno et al Allergy 2016 November Accepted article

In order to consolidate the new classification model addressed to the allergic and hypersensitivity conditions according to the International Classification of Diseases (ICD)-11 revision timeline, the French authors propose a real-life application of quality assurance methodology to evaluate sensitivity and accuracy of the "Anaphylaxis" subsection.

They applied field-testing methodology by analyzing all the consecutive inpatients' files documented as allergies from the University Hospital of Montpellier electronic database for the period of one year. The files clinically validated as being anaphylaxis were manually blind-coded under ICD-10 and current ICD-11 beta draft. The correspondence of coding and the impressions regarding sensibility were evaluated.

From all 2,318 files related to allergic or hypersensitivity conditions, 673 had some of the anaphylaxis ICD-10 codes; 309 files (46%) from 209 patients had anaphylaxis and allergic or hypersensitivity comorbidities description. The correspondence between the two coders

was perfect for 162 codes from all 309 entities (52.4%) with the ICD-10 and for 221 codes (71.5%) with the ICD-11. There was a high agreement regarding sensibility of the ICD-11 usability.

The same authors (Allergy 2017 72 1 120-125) using ICD revision in 2016 state that there is a decrease in the under-notification of cases of deaths due to Anaphylaxis in Brazil between 2008 and 2010.

In conclusion, there are attempts of real-life application to validate the new ICD11 “Anaphylaxis” subsection. By allowing all the relevant diagnostic terms for anaphylaxis to be included into the ICD-11 framework, WHO has recognized their importance. Thus the memory of Charles Richet this great scientist, ancestor of our discipline and Nobel prize in medicine, whose the name has been removed from an hospital of Paris region by a political and dishonorable decision, has been rehabilitated according to a scientific decision of the Ethic Committee of EAACI.

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Claude Molina
claude.nelly.molina@orange.fr

Jacques Gayraud
Jacquesgm.gayraud@gmail.com

Ana Antunes
ana.antunes@eaaci.org
Scientific Content Officer at EAACI