Bibliographic updates in Allergology

2018

By: Claude Molina and Jacques Gayraud

Contents

1. IgE sensitization in relation to preschool eczema and filaggrin mutation

E.K.Johansson et al JACI 2017 140 6 1572-1579

Eczema (atopic dermatitis) is associated with an increased risk of having IgE antibodies. IgE sensitization can occur through an impaired skin barrier. Filaggrin gene (FLG) mutation is associated with eczema and possibly also with IgE sensitization. The Swedish authors sought to explore the longitudinal relation between preschool eczema (PSE), FLG mutation, or both and IgE sensitization in childhood.

A total of 3201 children from the Stockholm birth cohort recruited from the general population were included. Regular parental questionnaires identified children with eczema. Blood samples were collected at 4, 8, and 16 years of age for analysis of specific IgE. FLG mutation analysis was performed on 1890 of the children.

Results:

1) PSE was associated with IgE sensitization to both food allergens and aeroallergens up to age 16 years. This association was even stronger among children with persistent PSE.

2) FLG mutation was associated with IgE sensitization to peanut at age 4 years, but not to other allergens up to age 16 years.

3) This association is independent of the existence of PSE.

4) Sensitized children with preceding PSE are more often polysensitized.

2. Persistent cow´s milk anaphylaxis from early childhood

F. Schocker et al Ped.All. Immunol Dec 2017 Accepted Article

The German authors refer to a 29 years old adult patient with persistent cow´s milk allergy who reacted to breast milk during his infancy, often associated with severe reactions. (Some breast-fed babies with cow`s milk allergy still show symptoms despite a strict cow`s milk-free diet of the nursing mother, and they react until the mother discontinues breast feeding). This patient experienced severe anaphylactic reactions, in childhood, despite his life-long training of milk protein avoidance. To get access to this severe case on the molecular level, investigation was undertaken on his serum sample in terms of the IgE reactivity against cow´s milk and human milk proteins in 2D immunoblots. Cross-reactivity has been detected between caseins from cow´s and human milk with bovine caseins inhibiting IgE against human caseins. Due to the severity of these reactions after accidental ingestion of traces of milk proteins, an OIT with cow`s milk was not started unless an adjunctive treatment with Omalizumab (O) had been initiated to reduce the risk of immunotherapy. The biological relevance of IgE reactivity was analyzed by means of the basophil activation (BAT) test before and after 6, 12 and 17 months of O treatment (and before and 2 and 7 months after OIT, respectively. Finally, after 12 months of O.therapy and 2 months of OIT, the basophil activation has further decreased.

In the light of this phenomenon it is important to address the question whether or not the persistent reactions can be explained by a genuine primary sensitization to human breast milk or by a cross-reactivity between human and bovine milk. The evidence seems highly suggestive for the last proposal.

A group of Canadian researchers (R.Jimenez-Saiz et al JACI 2017 140 1604-1615) showed that life-long IgE titers are not sustained by IgE PCs but by memory B cells that replenish the IgE PC compartment on allergen exposure in an IL4 and CD4 T cell dependent manner. Transformative therapies should focus on disabling this machinery that maintain and activates memory responses.

3. Anaphylaxis associated with Omalizumab (O) administration: Risk factors and patient characteristics

P. L. Lieberman et al JACI 2017 dec 140 6 1734-1736

The authors report on a larger sample size of 132 patients with potential anaphylaxis associated with O that was adjudicated by the same independent clinical expert; 96 (73%) were adjudicated as cases of anaphylaxis related to O. Demographic characteristics revealed a preponderance of female subjects (84%), and mean age of 40.5 (range 9-86) years. O was prescribed for asthma in most patients (80%). A prior anaphylactic event unrelated to O was documented in 43% (n = 37) of patients who provided an anaphylaxis history.

The most common symptoms reported during O-associated anaphylaxis involved the respiratory tract (95%, 91 of 96 patients). The majority of patients also reported experiencing cutaneous/angioedema symptoms. The majority of anaphylactic reactions were observed during the first 2 (69%) or first 3 (72%) doses. Time to onset of reaction following administration of O was documented in 81 cases of anaphylaxis: the reaction occurred within 60 minutes of O administration in the majority of cases (64%, 52 of 81); median time to anaphylactic reaction was 60 minutes. Treatment of anaphylaxis included use of antihistamines (69%, 66 of 96 patients), epinephrine (60%, 58 of 96 patients), systemic corticosteroids (57%, 55 of 96 patients), and inhaled beta-agonists (41%, 39 of 96 patients). Hospitalization was reported in 16 cases (17%). No treatment was needed in 2 cases (2%), and there was no information on treatment for 11 cases (11%). No case of anaphylaxis resulted in death. This information is valuable to clinicians who must inform their patients of the potential benefits and risks of treatment.

4. Tolerance mechanisms in Food Allergy

Ohsaki et al. J.Exp.Med January 2018

Explain how breastfeeding can prevent the onset of food allergies in offspring by instructing Treg formation via neonatal Fc receptor (FcRn)–mediated. The translational part of the study shows that Immune Complexes (IC) containing IgG4 and allergen confer protection from food allergy in adult mice in an FcRn-dependent manner. Then gut dendritic cells (DCs) uptake these ICs. Studying the molecular details of the interaction of FcRn with IgG is certainly on the radar of drug companies to improve the half-life of therapeutic antibodies that recycle via FcRn. It might therefore not be too long before we see therapeutic applications of tolerance promoting immune complexes that target FcRn.

IgG antibodies promote food tolerance: Burton et al JACI 2018 141 1 189-201

Using an animal model, shows that food-specific IgG inhibits food allergy by engaging FcγRIIb, a receptor on immune cells. Interaction between IgG and FcγRIIb reduces mast cell activity, blocking anaphylactic shock and limiting IL-4 secretion. These findings suggest that strategies to increase production of food-specific IgG or to activate signaling by FcγRIIb might help restore tolerance in allergic patients and that, when applied prophylactically, might prevent the development of food allergy.

Prevention of food allergy development and suppression of established food allergy by neutralization of thymic stromal lymphopoietin (TSLP), IL-25, and IL-33 M.V/.

Khodoun et al (JACI 2018 141 1 171-179) evaluated the effects of blocking these cytokines in the mouse egg allergy model. Results showed that:

Inhibiting any pro-TH2 cytokine prevents development of egg allergy.

Blocking all 3 pro-TH2 cytokines during the initial weeks of Medium Chain Triglyceride ingestion plus egg white inoculation induces partial tolerance to egg white. Blocking pro-TH2 cytokines suppresses existing egg allergy; all 3 pro-TH2 cytokines must be blocked for maximum and optimal suppression of this disorder.

5. Physiotherapy breathing retraining for Asthma

Burton et al Lancet Resp 2017 13 Dec

In a randomized controlled trial including 655 patients asthmatics 16-70 years, incompletely controlled, between 2012 and 2014, 2 programs of breathing retraining were studied and compared with the usual care group: 3 sessions of face to face group and a self-guided group, delivered by DVD + a printed booklet. The primary outcome was the quality of life after 12 months; the secondary physiological measures of asthma control, patient acceptability and health care costs.

There was no significant differences between the randomization groups in FEV1 or FeNO but a significant better asthma quality of life questionnaire than the usual care group. Such programs can be delivered conveniently, are acceptable, and might reduce health care costs.

6. Can Skin emollients decrease Atopic Dermatitis expression and modulate Atopic March?

A.J.Lowe et al : Annals of All.Asthma.Immunol 2018 Feb 120 2 145-151

In this review, the authors recall the hypothesis that skin-barrier impairment and early-life atopic dermatitis (AD) could play a causal role in the development of sensitization and subsequent food allergies and allergic airways diseases (allergic asthma and rhinitis). They further discuss the potential to target the skin barrier as a means to lower the incidence of allergic disease.

There is a strong link between AD and sensitization, food allergy, asthma, and allergic rhinitis, particularly AD that is severe and commences in the first 6 months of life. There also is emerging evidence that regular use of prophylactic emollients can significantly decrease the expression of AD, at least while treatment continues. Although there is only indirect evidence that early-life emollient use might prevent AD and food allergy, early studies are encouraging. The results of high-quality prevention trials that are in progress are eagerly anticipated. If found to be effective, then neonatal emollient use could be a simple public health measure to lower the incidence of AD, food allergies, and allergic airways disease in future generations.

7. Factors increasing the risk for a severe reaction in anaphylaxis

M.Worm et al Allergy 2018 March Accepted article

To identify and prioritize factors associated with an increased risk of developing severe anaphylaxis, data from the Anaphylaxis Registry (122 centers in 11 European countries) were used in logistic regression models considering existing severity grading systems, elicitors, and symptoms. The authors identified higher age and concomitant mastocytosis as the most important predictors for an increased risk of severe anaphylaxis. Vigorous physical exercise, and psychological burden were more often associated with severe reactions. Additionally, intake of beta-blockers and ACE-I, in temporal proximity to allergen exposition were identified as important factors in logistic regression analysis These data suggest it may be possible to identify patients who require intensified preventive measures due to their relatively higher risk for severe anaphylaxis by considering endogenous and exogenous factors.
A similar investigation in a large population of adolescents (10-14 years) in Melbourne, (V.LMcWilliam et al JACI 2018 141 3 982-990) reveal an alarming high rate of adverse food reactions (547students, among them 93 anaphylaxis episodes). Peanut and tree nuts were the most common triggers, and those with nut allergy were the most at risk of anaphylaxis. Adolescents with asthma and more than 2 food allergies were at the greatest risk.

8. Maternal Asthma severity during pregnancy and risk of offspring Asthma

X.Liu et al JACI 2018 141 886-892

Severe and uncontrolled asthma during pregnancy has been linked to several unfavorable perinatal outcomes. The authors sought to investigate the extent to which offspring asthma is influenced by maternal asthma severity and control during pregnancy and performed a prospective population-based cohort study from Danish national registers, of which 15.014 children were born to asthmatic mothers. Among them, 7.188 children were born to mothers with active asthma during pregnancy. 4 groups were set up, based on dispensed antiasthma prescriptions and on use of medical services: mild controlled, mild uncontrolled, moderate-to-severe controlled, and moderate-to-severe uncontrolled asthma. The outcomes were offspring early-onset transient, early-onset persistent, and late-onset asthma. Prevalence ratios (PRs) of each phenotype of asthma, was estimated, using a log-binomial model with 95% CIs.

Results: Higher prevalence of early-onset persistent asthma was observed among children of asthmatic mothers with mild uncontrolled (PR, 1.19), moderate-to-severe controlled (PR, 1.33), and moderate-to-severe uncontrolled asthma (PR, 1.37) compared with those of mothers with mild controlled asthma. Children of mothers uncontrolled asthma had a borderline increased prevalence of early-onset transient asthma.

Overall maternal uncontrolled asthma increases the risk of early-onset persistent and transient asthma in offspring.

9. Quintupling Inhaled Glucocorticoids to Prevent Childhood Asthma Exacerbations

D. J. Jackson,, N Engl J Med 2018; 378:891-901

Clinicians commonly increase the doses of inhaled glucocorticoids at early signs of loss of asthma control. However, data on the safety and efficacy of this strategy in children are limited.

254 children were studied, 5 to 11 years of age, who had mild-to-moderate persistent asthma and had had at least one asthma exacerbation treated with systemic glucocorticoids in the previous year. They were treated for 48 weeks with maintenance low-dose inhaled glucocorticoids (fluticasone propionate at a dose of 44 µg per inhalation, two inhalations twice daily) and were randomly assigned to either continue the same dose (low-dose group) or use a quintupled dose (high-dose group; fluticasone at a dose of 220 µg per inhalation, two inhalations twice daily) for 7 days at the early signs of loss of asthma control (“yellow zone”). Treatment was provided in a double-blind fashion. The primary outcome was the rate of severe asthma exacerbations treated with systemic glucocorticoids.

Results This rate did not differ significantly between groups. The time to the first exacerbation, the rate of treatment failure, symptom scores, and albuterol use during yellow-zone episodes did not differ significantly between groups. The difference in linear growth between high-dose and low dose group was -0.23cm per year (P=0.06). Conclusions: In children with mild-to-moderate persistent asthma treated with daily inhaled glucocorticoids, quintupling the dose at the early signs of loss of asthma control, did not reduce the rate of severe asthma exacerbations and may diminish linear growth or improve other asthma outcomes and may be associated with diminished linear growth.

10. Quadrupling Inhaled Glucocorticoid Dose to avoid Asthma Exacerbations

Tricia McKeever et al,. N Engl J Med 2018, March 8, 2018; 378:902-910

The authors tested the concept that a plan for patients to manage their asthma (which included a temporary quadrupling of the dose of inhaled glucocorticoids when asthma control started to deteriorate) would reduce the incidence of severe asthma exacerbations among adults and adolescents with asthma.

They conducted a pragmatic, unblinded, randomized trial involving adults and adolescents with asthma who were receiving inhaled glucocorticoids, with or without add-on therapy, and who had had at least one exacerbation in the previous 12 months. They compared a self-management plan (that included quadrupling group) with the same plan (non-quadrupling group), over a period of 12 months. The primary outcome was the time to a first severe asthma exacerbation, defined as treatment with systemic glucocorticoids or an unscheduled health care consultation for asthma.

A total of 1922 participants underwent randomization, of whom 1871 were included in the primary analysis. The number of participants who had a severe asthma exacerbation in the year after randomization was 420 (45%) in the quadrupling group as compared with 484 (52%) in the non-quadrupling group, with an adjusted hazard ratio for the time to a first severe exacerbation of 0.81 (95% confidence interval, 0.71 to 0.92; P=0.002). The rate of adverse effects, which were related primarily to local effects of inhaled glucocorticoids, was higher in the quadrupling group than in the non-quadrupling group.

In this trial involving adults and adolescents with asthma, a personalized self-management plan that included a temporary quadrupling of the dose of inhaled glucocorticoids when asthma control started to deteriorate, resulted in fewer severe asthma exacerbations than a plan in which the dose was not increased.

As suggested by an Australian researcher in his editorial (J.Bardin NEJMP 8March 2018 378 950-950-1) in real-life, clinicians are reluctant to an escalation by a factor of 4 or 5 , of ICS in their patients, due to the risks of severe side-effects.

11. Gamma-tocopherol enriched supplement in Eosinophilic Asthma

A.J Burbanket al JACI April 2018 141 4 1231-1238

Gamma tocopherol (γT), the primary form of vitamin E found in the diet, has anti-inflammatory and antioxidant actions. Previous studies of healthy adults supplemented with γT showed a reduction in airway inflammation induced by LPS. The authors report findings from an early-phase randomized, double-blind, placebo-controlled crossover study of γT supplementation in fifteen adults with asthma, as follows:

Two-week supplementation with γT was associated with reduction in airway inflammatory marker levels, with fewer eosinophils and glycoprotein mucins in induced sputum compared to patients receiving placebo.

The airway neutrophilic inflammatory response to inhaled LPS, in animal models and healthy human volunteers, was diminished after γT supplementation, with fewer neutrophils in induced sputum and a potential protective effect on airway mucociliary clearance.
γT might represent a nonsteroidal additive option for the treatment of asthma.

12. Chronic spontaneous urticaria in children - a systematic review on interventions and comorbidities

H. Cornillier et al P.A.I 2018 29 3 303-310

Chronic spontaneous urticaria (CSU) is not frequent in children. Management guidelines have been developed for adults and teenagers aged 12-18, but data for children under age 12 are limited. This systematic review for original articles published from 2005 to 2016 was performed to assess comorbidities and the efficacy and safety of treatments. 9 reports were included on epidemiologic data (633 children). Only one study allowed for comparison with a control group. Five comorbidities and laboratory anomalies associated with CSU found were atopy (28.1%), positive autologous serum skin test (36.8%), thyroid biologic anomalies (6.4%) and detectable antinuclear antigen (10.4%), seroprevalence for Helicobacter pylori (21.1%), low vitamin D level (69.1%), and psychiatric disorders (70.4%).

On therapeutic point of view, 10 studies (322 children) are included, describing 5 different drug families, mostly H1-antihistamines (n = 297). Cyclosporine was effective and had no adverse effects in 18 children. Omalizumab, montelukast, and cefuroxime were reported in very small series (5, 1, and 1 patients).

In conclusion H1-antihistamines are effective for CSU in children <12 years old, with reassuring safety data at licensed doses.

13. Prevalence and Clinical Characteristics of Chronic Spontaneous Urticaria in European Pediatric Patients

Maria-Magdalena Balp et al Ped:All.Immun May 2018Accepted article

Data on the prevalence and disease management of inducible chronic urticaria (CU) and chronic spontaneous urticaria (CSU) in the pediatric population are scarce. The present study assessed the prevalence of CU (cold, solar, aquagenic), and CSU, and disease management among pediatric patients (0-17 years).

A physician-based online survey was conducted in 5 European countries (United Kingdom, Germany, Italy, France, and Spain) assessing the annual diagnosed prevalence, disease characteristics and treatment patterns in the target population. Results are based on physician responses and analyzed using descriptive statistics. Prevalence estimates were calculated based on the number of CU/CSU pediatric patients seen, treated and referred by the respondents and extrapolated to the total pediatric population from each country.

Across 5 European countries, the one-year (2014) diagnosed prevalence of CU and CSU in pediatric patients was similarly to adult: 1.38% and 0.75% respectively and Angioedema, sign of severity, was reported in 6%-14% of patients. A large proportion of CSU pediatric patients (40%-60%) were treated with 2nd generation of H1-antihistamines at approved dose and 16% to 51% received H1-antihistamines at higher doses. However approximately 1/3 of pediatric CSU patients remained uncontrolled. Other prescribed treatments were oral corticosteroids (10% to 28%) and topical creams (15% to 26%).

In conclusion, this study revealed a prevalence of CSU among pediatric population comparable to adults and suggested an unmet need for approved treatments for inadequately-controlled patients. Harmful (oral steroids) or insufficient (topical creams) medications were frequently used despite of better and guideline recommendations.

14. Novel allergen immunotherapy strategies in Allergic Rhinitis

A.Renand et al JACI 2018 141 5 1750-1760

A recent trial on Sublingual and Subcutaneous Immunotherapy in allergic Grass Pollen continued for 2 years was effective in suppressing the clinical response to nasal allergen challenge. This response was not sustained 12 months after discontinuation of therapy. The authors explored cellular and humoral responses at annual intervals during the trial:

Reductions in numbers of peripheral allergen-specific CD4 T_H2 cells and levels of local nasal T_H2 cytokines closely paralleled inhibition of the clinical response, with rebound at 3 years.

Ratios of allergen-specific IgG_4/IgE along with IgE-inhibitory activity increased and persisted, at least in part, for 3 years.

Rebound of allergen-specific T cells in parallel with the clinical response suggests that restoration of T_H2 immunity abrogated the potential for durable tolerance, whereas persistence of IgE-blocking activity might be an early indicator of a protolerogenic mechanism.

These results suggest that two years of allergen immunotherapy in allergic rhinitis are effective but insufficient for long term tolerance. Novel strategies should target both T and B cells to enhance induction such efficacy.

15. Eosinophilic esophagitis: genetic susceptibility and atopy

L.J.Martin et al JACI 2018 Mai 141 5 1690-1698

Eosinophilic esophagitis (EoE) is associated with atopic diseases. Although there is a strong genetic basis, most EoE genetic risk factors appear to result in a modest increased risk. The authors investigated whether carrying combinations of genetic variants would increase disease risk. Because atopy is in EoE patients, the focus of the investigation was to see the effect of co-existence of risk factors for EoE and atopy. Previous research identified thymic stromal lymphopoietin (TSLP) as a genetic risk factor for EoE and a locus harboring 2 closely spaced genes (IL4/KIF3A) as an atopy risk factor. To summarize the findings:

If either (TSLP or IL4/KIF3A) genetic risk factor was found without the other, there was only a modest EoE risk. Having both genetic risk factors markedly increased EoE risk. This work might help clinicians to better identify subjects at risk for EoE and might provide important clues to customize the treatment.

16. Chronic Inducible Urticaria (CindU): Treatment Options

C.Dressler et al JACI 2018 141 1726-34

Characterized by the appearance of recurrent wheals, angioedema, or both as a response to specific and reproducible triggers, CindU was identified in 30 studies that included patients with cold urticaria, symptomatic dermographism, delayed-pressure urticaria, or cholinergic urticaria.

The authors sought to systematically assess evidence on the efficacy and safety of treatment options. Randomized controlled trials and controlled intervention studies were searched systematically in various databases. Where possible, results were meta-analyzed, by using a random-effects model. Risk of bias was often rated as unclear or high.

Overall, second-generation antihistamines were more effective than placebo, and available data indicate that up dosing might be effective. Omalizumab proved effective in patients with symptomatic dermographism, who did not respond to antihistamines. The available evidence is limited by small samples, heterogeneous efficacy outcomes, and poor reporting quality in many of the studies. A stepwise approach is suggested for the treatment. However, the findings do not allow for drawing specific conclusions for specific subtypes of CindU.

17. Cat exposure in early life decreases asthma risk in genetically susceptible subjects

J.Stockholm et al JACI 2018 141 5 1598-1606

Early-life pet exposure has been studied extensively as a suspected risk factor for childhood asthma. Many observations suggested host genotype-specific effects with most of the studies showing beneficial effect from dog but not cat exposure. The Danish authors report a novel interaction between early-life cat exposure in a cohort of 377 children and genetic variation in the chromosome 17q21 locus, the strongest known genetic risk factor for childhood asthma, as follows:

- Cat exposure from birth attenuated the risk of asthma development during the first 12 years of life in children with the high-risk 17q21 genotype. (SNP rs7216389 variants).
- Increased levels of cat allergens in the children's homes were associated with protection from asthma in children having the high-risk 17q21 genotype. No interaction existed between dog exposure and this genotype.
- Children exposed to cat had reduced risk of pneumonia and bronchiolitis if they had the high-risk 17q21 genotype.

The observed gene-environment interaction suggests a role of early-life exposure to cats in genetically susceptible subjects.

18. Asthma severity, diagnosis criteria, high prevalence in a large random population

R. Mincheva et al JACI 2018 June 6 2256-2264

Severe asthma is notoriously hard to define, The Swedish authors propose a novel definition, based on multiple signs, including daytime and nighttime symptoms, lung function, high degree of medication, (oral corticosteroids) and exacerbations. This algorithm was applied to a large-scale epidemiologic study: A total of 2.006 subjects were carefully phenotyped, the patients being grouped as having 1, 2 or more, signs of severity. The following was concluded:

- Asthma severity phenotypes are exceptionally diverse.
- Asthma severity is present in 13% to 36% of all asthmatic patients,
- A total of 36.2% of asthmatic patients expressed at least 1 sign of asthma severity, and 13.2% had 2 or more signs.
- The group with 2 or more signs was older in age and had higher body mass index, a higher rate of tobacco smoking, and lower lung function.
- Bronchial hyperreactivity, airway inflammation, and sensitization were significantly different among the 3 groups, but the most prominent were smoking and obesity.

In summary, every third asthmatic patient shows at least 1 sign of asthma severity.

19. Asthma Severity: Remission and Outcomes

G.A Westerhof et al JACI 2018

In a recent study on 170 adult onset asthma in Netherland (JACI 2018 January 141 1 104-109) clinical remission is defined as an absence of symptoms ore medication use for 1 year or more and occurred in 16% after a median duration of 45 months. Theauthors also identify nasal polyposis associated or not with bronchial responsiveness, as the main predictive factors for the presence of symptom persistence.

Moreover, in a follow-up of more than a decade B.E.Chipps et al JACI May 2018 141 5 1590-1597 on 341patients enrolled in TENOR II American cohort and representative of the TENOR I group, showed that the most frequent comorbidities were rhinitis (84.0%), sinusitis (47.8%), and gastroesophageal reflux disease (46.3%). Mean percent predicted prebronchodilator and postbronchodilator FEV_1 were 72.7% (SD, and 78.2% respectively).

A total of 231 (72.9%) of 317 patients had positive test responses to 1 or more allergen-specific IgEs. The mean blood eosinophil count was 200/µL. Eighty-eight (25.8%) patients experienced an asthma exacerbation in the prior 3 months requiring hospital attention, oral corticosteroids, or both. More than half (197/339 [58.1%]) had very poorly controlled asthma. Medication use suggested undertreatment.

So TENOR II provides longitudinal data to characterize disease progression and the need for accurate and personalized management.

20. Biologics for Severe Asthma, Role of dupilumab (D)

D is a monoclonal antibody directed against the α-subunit of IL 4 receptor that inhibits IL4 and IL 13 signaling. 2 articles are recently published in the same issue, designed by respected investigators and funded and by pharmaceutical companies:

A) K.F.Rabe et al NEJM 2018 May 20-21

In 210 patients from a multicenter, randomized cohort with glucocorticoid-dependent severe asthma, D reduced oral glucocorticoid use, while decreasing the rate of severe exacerbations and increasing the FEV_1. Transient eosinophilia was observed in approximately 1 in 7 patients.

B) M. Castro et al NEJM 2018 May 20-21

Assigned 1902 patients with uncontrolled asthma treated by subcutaneous D 200 or 300mg every 2 weeks during 52 weeks, and observed a lower rate of exacerbations than those who received Placebo as well better lung function and asthma control. Greater benefits were seen in patients with higher baseline levels of eosinophils. D. belongs to the family of recent new biologics directed against severe Asthma, namely: Mepolizumab and Reslizumab (anti-IL5) Benralizumab (anti-IL5 receptor). However in a small group, these drugs, largely equivalent in effectiveness, have almost no clinical effect and do not render the patients “asthma-free”. More research is needed to practice for them precision medicine.

21. Inhaled combined Budesonide-Formoterol as needed in Mild Asthma

2 trials are reported in the same issue of the NEJM, and funded by a pharmaceutical sponsor:

A) O'Byrne et al NEJM 2018 378 1865-1876

In 3849 patients with mild asthma, as-needed budesonide–formoterol provided superior asthma-symptom control to as-needed terbutaline but was inferior to budesonide maintenance therapy. Exacerbation rates with the two budesonide-containing regimens were similar and were lower than the rate with terbutaline. Budesonide–formoterol used as needed resulted in substantially lower glucocorticoid exposure than budesonide maintenance therapy.

B) E.D Bateman et al NEJM 2018 1877-1887

In 4215 patients with mild asthma, budesonide–formoterol used as needed was noninferior to twice-daily budesonide with respect to the rate of severe asthma exacerbations during 52 weeks of treatment but was inferior in controlling symptoms. Patients in the budesonide–formoterol group had approximately one quarter of the inhaled glucocorticoid exposure of those in the budesonide maintenance group. Finally, the decision belongs to the patients who prefer a total absence of symptoms with a regular treatment or others who accept occasionally mild symptoms but free them from the daily use of inhaler, while preventing loss of lung function and exacerbation.

22. Sjögren Syndrome (SS): Immune signature and prognosis

A French group involved in Immunologic research on viral infections and auto-immunity was interested in the pathogenesis of primary SS. Mouse models and genetic studies suggest the involvement of type 1 and type 2 interferon pathways. Likewise, polymorphisms of the IL-12A gene (*IL12A*), which encodes for IL-12p35, have been associated with SS. The IL-12p35 subunit is shared by 2 heterodimers: IL-12 and 35.

The authors sought to confirm in patients this genetic association.

In 673 patients from 2 French SS cohorts and 585 healthy control subjects, functional studies were performed.

The association of the *IL12A* rs485497 polymorphism and SS was confirmed and an increased serum protein level of IL-12p70 in patients was found in patients carrying the risk allele. Serum levels of IL-12p70 were greater in patients than control subjects, especially in patients with more active disease; conversely, IL-35 levels were decreased in such patients.

In conclusion, serum IL-35 levels were associated with low disease activity, in contrast with serum IL-12p70 levels, which were associated with more active disease. This is an excellent example of the role of immunogenetics in the prognosis of autoimmune diseases.

23. Endocrine-disrupting chemical exposure and childhood allergy

An association of triclosan and paraben chemical exposures with childhood allergy has been found in cross-sectional studies. Triclosan and parabens are chemicals with endocrine-disrupting and antimicrobial properties that are present in a wide variety of personal care and other products.

In the first study using a prospective longitudinal design, the authors performed an ancillary analysis of enrollees in Antenatal Asthma Trial, quantifying triclosan and parabens in maternal plasma during pregnancy and in the urine of offspring at age 3 or 4 years, and serum specific IgE in high risk children: The analysis included 467 Mother-Child pairs.

Results:

1) There was no overall association of prenatal or childhood triclosan or paraben concentrations with asthma, recurrent wheeze, or allergen sensitization at age 3 years.
2) A trend toward an inverse association between T and P exposure and allergic sensitization was even observed.
3) There was evidence of different effects of triclosan or paraben exposure on allergic outcomes between male and female subjects, with higher odds of environmental

sensitization associated with increasing paraben concentration in male compared with female subjects.

This finding warrants further exploration.

24. Polyunsaturated fatty acids in plasma at 8 years and subsequent allergic disease

Polyunsaturated fatty acids (PUFAs) are hypothesized to modulate the risk of allergic disease. However, evidence from previous studies is inconclusive, and limited longitudinal data exist using circulating biomarkers of PUFA intake and metabolism. The Swedish authors aimed to investigate associations between n-3 and n-6 PUFAs at age 8 years and asthma, rhinitis, and aeroallergen sensitization at age 16 years. Proportions of n-3 PUFAs) and n-6 PUFAs (linoleic acid and arachidonic acid [AA]) in blood samples at age 8 years were measured for 940 children from the prospective Swedish birth cohort BAMSE. Allergic disease phenotypes were defined by using questionnaires and IgE measures at the ages of 8 and 16 years. Logistic regression was used to examine potential association.

Results: A higher proportion of total VLC n-3 PUFAs in plasma at age 8 years was associated with a reduced risk of prevalent asthma, rhinitis, and aeroallergen sensitization at age 16 years and with incidence of asthma between 8 and 16 years (adjusted odds ratio, 0.67; 95% CI, 0.47-0.94). AA was associated with a reduced risk of asthma, aeroallergen sensitization, and allergic rhinitis. The findings were most evident for allergic phenotypes of asthma and rhinitis. Additionally, AA was associated with an increased probability of asthma and rhinitis remission between 8 and 16 years of age.

In conclusion: Higher proportions of VLC n-3 and very long-chain n-6 PUFAs in plasma phospholipids at age 8 years were associated with a reduced risk of allergic disease at age 16 years.

24. Standardization of nasal allergen challenges (NAC) EAACI position paper

It is the “gold standard” for the diagnosis of rhinitis or rhinosinusitis, besides clinical history, symptoms, skin tests and IgE, or for initiating specific allergen immunotherapy. or measuring therapeutic success, National recommendations showing, international divergences, 32 members specialists of EAACI, from 15 different countries, decided to initiate a task force to find a consensus in executing a NAC. Apart from indications, contraindications, and preparations for the test procedure, main recommendations are a bilaterally challenge with standardized allergens, with a spray device. An exhaustive list of positivity criteria is given, in form of several tables, for the variety of established subjective and objective assessment methods as well as a schedule for the procedure. A unified protocol is recommended, aiming at eliminating the previous difficulty of comparing NAC results.

Presently, all aspects of NAC, such their potential advantages, as well as their respective drawbacks are studied, taking in account the co-existence of several equally validated methods.

In conclusion, the task force suggests the use of standardized test solutions, to spray 2 puffs (0.1 mL per nostril) bilaterally and to evaluate clinical results, thus providing, a valuable protocol useful for daily clinical practice and epidemiologic studies.

25. Invasive aspergillosis and severe influenza

Invasive pulmonary aspergillosis (IPA) typically occurs in an immuno-compromised host. Recently patients with severe influenza were also reported to develop an IPA. The authors from Belgium and Netherland sought to measure in retrospective multicenter cohort study, the incidence of IPA in patients hospitalized in intensive care units (ICU) and to assess whether influenza was an independent risk factor for IPA. Data were collected from adult patients, older than 18 years, with severe influenza admitted to seven ICU centers for more than 24 h with acute respiratory failure, had pulmonary infiltrates on imaging, and a confirmed influenza infection based on a positive airway PCR test.

Logistic regression analyses were used. Between Jan 1, 2009, and June 30, 2016. IPA was diagnosed in 83 (19%) of 432 patients admitted with influenza. The incidence was similar for influenza A and B. For immunocompromised patients the incidence of IPA was as high as 32% (38 of 117 patients), whereas in the non-immunocompromised influenza case group, incidence was 14% (45 of 315 patients). Only 16 (5%) of 315 patients in the control group (patients with community-acquired pneumonia) developed an IPA. The 90-day mortality was 51% in patients in the influenza cohort with IPA and 28% in the influenza cohort without IPA (p=0·0001) Influenza was found to be independently associated with IPA whatever the sex or use of corticosteroids.

In conclusion Influenza was identified as an independent risk factor for IPA and their association (Infl. + IPA) is a factor of high mortality. The authors suggest for a better outcome a faster viral diagnosis or antifungal prophylaxis.

We must add, in immunocompromised patients, a genetic research, like in a recent French and American article (*N.Hernandez et al J.Exp.Med August 24 2018)* which reports a child with inherited complete IRF9 deficiency who suffered from life-threatening influenza.

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