# Bibliographic updates in Allergology

## 2017

By: Claude Molina and Jacques Gayraud

# Contents

# 1. Fish-oil derived Poly-Unsatured Fatty Acids (PUFA) in pregnancy and wheeze and Asthma in offspring

3 articles are devoted to this topic: 2 are favorable, one is unfavorable.

A. Favorable effects:
H.Bisgaard et al NEJM 2016 December 29
S.Hansen et al JACI 2017 January139 1104-11

a) In this Danish and American double-blind trial among 736 women in the third trimester of pregnancy, n-3 long-chain of PUFA (2,4g/j of fish-oil or placebo olive oil) reduce the absolute risk of persistent wheeze and asthma and infections of lower respiratory tract in offspring (605 children followed 3 years then 2 years) by approximately 7 points or one third.

b) The second article from Danish and Canadian authors: In a randomized controlled trial from 1980 with 24 years of follow-up, including 533 women who received fish-oil during the third trimester of pregnancy, the offspring were invited to complete a questionnaire and attend a clinical examination at age 18 to 19 years.

Maternal supplementation showed, that the probability of having ad asthma medication or lung function outcomes or allergic sensitization was significantly reduced in offspring and confirm the prophylactic potential for long term prevention of asthma or allergy.

B.Unfavorable effects:
H.T.Waldytillake & al, Allergy 26 December 2016 Article accepted

This Australian group hypothesized that n-3 PUFA in breast milk may assist immune and lung development and the aim of the study was to investigate associations between n-3 and n-6 levels in 194 colostrum samples and 118 breast milk, from mothers enrolled in the Melbourne atopy cohort and allergic diseases and lung function in offspring at ages 12 and 18 years.

Higher levels of n-3PUFAs were significantly associated with increased risks of allergic rhinitis and eczema up to 18 years and sensitization and reduced lung function at 12 years.

In conclusion the authors, in spite of possible residual confounding in these associations, the strategy that increase maternal n-3PUFA may not aid in allergic disease prevention.

C.Clinical decision:
R.Ramaswami NEJM 2017 11January

Which of the following options would you recommend for this 30 years woman who is 20 weeks of her 2nd pregnancy, healthy, with a history of well-controlled asthma, and without any ultra-sound screening fetal anomalies. Her 4 years son is frequent seen in the emergency department for persistent wheezing and lower respiratory tract infections? She wants to discuss the risks of similar symptoms in her unborn child.

a) Start n-3 PUFA supplementation, which according to guidelines of FDA administration and a recent published trial on the Web, is a potential therapeutic option at little risk, cost, or inconvenience.

b) Do not start n-3 PUFA supplementation: divergent opinion reflects the difference between clinical decision making, based on inadequate evidence, aims to benefit to individual patient and scientific decision making more rigorous but aiming at population-wide benefit. As long as the family knows that the benefit is unclear it is hard to see the downside to giving fish oil and the first option is recommended.

## 2. Egg-Allergy: prevention in high risk infants with eczema

O.Natsume & al, The Lancet9 December in press on line

It is well known that early consumption of a food allergen is more beneficial than is delayed introduction. The Japanese authors investigated whether or not, early double step in 147 infants with eczema combined with optimal treatment, would prevent egg allergy at 1 year.

In a double blind controlled study they administered orally 50mg of heated egg powder /day from 6 to 9 months of age, then 250mg till 12 months. In a primary analysis 4 (9%) of 47 egg group had an egg allergy compared with 23 (38%) in the placebo group. The risk ratio confirmed the efficacy of this strategy even in high risk infants with aggressive eczema treatment. The only difference is in adverse effects, more frequent in the egg group. This is however a practical approach to overcome an allergic epidemic

## 3. Egg Allergy in infants: How appreciate tolerance

(without the use of challenge test which is often harmful)
2 articles tried to answer:

J. Gradman & al: Ped.Allergy.Immunol 2016 27 825-830
By a long-term follow-up of specific IgE to egg white and ovomucoid and their decrease: study done in 130 Danish infants followed 26 months.

C. Caffarelli & al: Ped.Allergy.Immunol 2016 27871-884
By skin tests to white egg and yolk (ALK extracts) which become negative et when in the same time, introduction of egg provokes only weak reactions: study in 75 Italian infants of average 14 months of age.

## 4. Linking Air Pollution (AP) to Atopic Dermatitis (AD)

T.Hidaka et al Nature Immun2017January 18 64-76
T.Hidaka et al : Nature Immunology 2017 18 64-73

AD is increasing worldwide in correlation with AP. The Japanese authors showed that organic components of pollutants activate the transcription factor AhR. Using AhR-CA mice that develop AD-like phenotypes, they identified Artn keratinocyte specific AhR target gene, whose product artemin is responsible for epidermal innervation that led to hypersensitivity, inflammation and pruritus. In patients with AD, AhR activation and expression of ARTN are positively correlated in epidermis. So AhR in keratinocytes senses environmental stimuli (B.Vaidyanathan et al J ; Exp.Med January 2017) and elicits AD pathology. These researches should be confirmed by epidemiologic studies.

## 5. Skin Microbiome and Atopic Dermatitis

E.A.Kennedy et al JACI 2017 January 139 1 166-172

The early origins of AD involve an interplay between the skin barrier, immune dysregulation and the skin microbiome. Staphylococcus aureus is often associated with flares of AD and it was not known whether this microbe precedes or follows the disease. The authors from Ireland and USA selected in the cohort of Cork, 10 babies and 10 randomly controlled infants with no AD and performed bacterial 16S sequencing and analysis directly from clinical samples at 3 points in the first 6 months of life and at 4 sites (antecubital and popliteal fossae, nasal tip and cheek) relevant to AD. They were able to show that S. aureus did not precede the development of AD and surprisingly several commensal staphylococci present at 2 months were associated with reduced incidence of AD at 12 months suggesting that this genus might be protective and anti-inflammatory.

## 6. Guidelines about starting Inhaled Cortico-Steroids (ICS) treatment for mild Asthma

H.K.Redell et al Lancet 2017 January 389 1066 157-166

These Australian authors aimed to assess the validity of classical guidelines for starting ICS only in asthma with symptoms more than 2 days per week. They perform a post-hoc analysis of the 3years study done in 32 countries with clinic visits every 3 months in patients identified by baseline symptom frequency.

7138 patients were investigated:

- 3577 received once daily inhaled Budesonide 400µg (200 for those aged grouped by more than 2 symptoms days/week or fewer (divided in 2 subgroups: no day to one day, and more than 1 day to 2 days)

Coprimary outcomes were time to first severe asthma event and change in baseline lung after bronchodilator function.
Analysis reveals that time to first severe event was significantly longer across frequency subgroups, for Budesonide versus placebo; similar results were noted for lung function which was higher at 3 years, in the low frequency subgroups.

In conclusion in mild recent-onset asthma once daily low dose Budesonide decreases the risk of severe event-related-asthma, reduces lung function decline and improves symptoms control similarly in all subgroups. These results do not support restriction of ICS to patients with symptoms on more than 2 days per week.

## 7. Proton Pump Inhibitors in the treatment of Chronic Rhino-Sinusitis with nasal Polyp

J.Y.Min et al JACI 2017 January 139 1 130-141

Recent findings suggesting that PPI may modulate expression of eotaxin 3, an eosinophil chemo-attractant, the American and Japanese authors aimed to assess their therapeutic potential in CRSP characterized by tissue eosinophilia and the role of IL 13, cytokine of Th2 nasal inflammation.

Nasal tissues and secretions were measured by multiplex immunoassay and showed increased IL13 and eotaxin 2 and 3 levels correlated with clinical and radiologic scores of severity. Moreover, patients taking PPI had significantly lower levels in vivo eotaxin levels compared with those without PPI. Underlying mechanism reveals that PPI reduce IL13 induced eotaxin 3 expression by non-gastric H-K ATPase, (encoded by a different gene) necessary for IL 13 mediated-epithelial response.

## 8. Chronic Rhino-Sinusitis with Nasal Polyposis and Verapamil

M.M.Miyake et al JACI 2017 2 Article in press

Epithelial P-Glycoprotein (P-gp) is a membrane efflux pump that is overexpressed in CRSwNP and regulate the secretion of Th2 polarizing cytokines. This double blind placebo-control randomized clinical trial of Verapamil® first generation calcic inhibitor and also inhibitor of P-gp, capable of blocking Il5 and IL6, showed that V (80 mg 3 times a day) improve significantly the clinical and radiological scores of treated patients compared with Placebo. However the results are not significant in patients with increased BMI and those with elevated P-gp at baseline. Given that V is cardioactive the risk of high doses limit its use, but monotherapy at low doses is well tolerated, with less side-effects and lower costs. These findings open the door to future researches with calcic inhibitors of new generations.

## 9. Hereditary Angioedema Prophylaxis: Kallicrein Inhibition by Lanadelumab (L)

A.Banerji et al NEJM 2017 376 717-728 (27 Febr)

L. is a new recombinant fully human monoclonal antibody allowing sustained inhibition of kallicrein, implicated in bradykinin mediated angioedema and increased local capillary permeability. It has been tested in a phase 1 b multicenter double blind placebo controlled trial (24 patients & 13 Placebo assigned in sequential dose groups: 30mg, 100mg 300mg 400mg) in 2 administrations 14 days apart. Efficacy was assessed by the rate of attacks: 8 to 50 days) and measurement of plasma levels of cleaved HMW of kininogen. At a dose of 300 and 400mg L reduced kininogen to levels approaching that from normal patients and the 300mg and 400 mg groups had 100% and 88% fewer attacks respectively than the placebo groups. The usefulness of this drug, without significant adverse effects may complete other prophylactic options like C1 Inhibitor (Cinryze) (®) and attenuated androgens such Danazol®.

PS: A new C1 inhibitor, CSL830, a nanofiltered preparation suitable for subcutaneous injection and self-administration has been recently and successfully tested in a phase 3 trial on 90 patients (H.Longhurst and al NEJM 2017 March 231131-1140).

## 10. Anti-Interleukin 31 Receptor A, Nemolizumab (N) for Atopic Dermatitis in Adults (AD)

T. Ruzika et al NEJM 2 Mars 2017 376 826-835

IL-31plays a role in the pathogenesis of AD and more specifically on the occurrence of pruritus. In order to assess the efficacy and safety of N a humanized antibody against IL 31 receptor A, a phase 2, multicenter randomized d.b.p.c 12 weeks trial, was assigned to 264 patients (18 to 65 years of age ) at subcutaneous dose of 0.1, 0.5 or 2mg/kg of body weight every 8 weeks; the primary end point being percentage improvement of the score of pruritus and secondary end-point changes in body surface area of AD.
At all doses, N significantly (30%) and rapidly decreased pruritus. Possible improvement of other symptoms: sleep, quality of life, cutaneous score, is suggested but without statistical comparisons. In spite of the limited length of this trial, this new therapy should be included as a part of a comprehensive approach of different phenotypes of AD and nearby Dupilumab: anti IL 4 and IL 13, already recently studied.

## 11. Hypersensitivity (H) to Aspirin and NSAID and Coronary artery disease: Model of collaboration between allergists and cardiologists

G.Cortelli et al : Allergy 2017 72 498-506

Aspirin (A) is mandatory for patients who need a coronary angiography possibly followed by stenting and may also require dual antiplatelet therapy for 6 to 12 months. In subjects at risk of H. the physicians have to choose between challenge and desensitization. This European multicenter study (10 centers and 310 patients) aimed to establish criteria for eligibility for an A challenge and ensure the best therapy.

217 subjects had histories of H. 119 at a dose lower than 300mg.

163 underwent challenge, 147desensitization.

At the end of this study, the recommendations are as follows: in patients with stable coronary disease and history of non -severe H to A /NSAID a challenge is advisable. Patients with acute coronary disease, especially following doses lower than 100mg should directly undergo desensitization.

## 12. Predictors of adverse effects on Oral Immunotherapy (OIT) for Peanut Allergy

Y.V.Virkud et al JACI March 2017 139 3 882-888

3 studies recruited 104 children assigned to OIT for peanut allergy:

- Increased rates of systemic reactions (42% of subjects) and gastro-intestinal side effects, were observed likely related to dosing.
- Higher rates of these adverse effects were associated with larger skin prick test wheal size (related to gastro-intestinal symptoms) or allergic rhinitis or asthma (predictors of systemic reactions).
- Even graded mild, and declining over time, these adverse reactions need further studies to establish the risks/benefits of OIT for peanut allergy in children

## 13. Omalizumab (O) facilitates rapid OIT for Peanut allergy

A.J.Mac Ginnitie et al JACI March 2017 3 139 873-881

Adjunction of O to OIT for peanut allergy allows more rapid up-dosing and decreases adverse effects. This is the result of a short trial on 37 subjects randomized to O (29) or placebo (8).

O-children treated tolerated higher doses of peanut that the placebo group on initial desensitization day and throughout the study. 23 of 27 O tolerated 2000mg (about 8 peanuts) six weeks after stopping the treatment. 16 of 27 tolerated 4000mg of peanut 33 weeks after stopping. Over all significant reactions occurred on 6 of 8 subjects placebo compared to 4 of 27 O.

## 14. Epicutaneous immunotherapy for the treatment of peanut allergy in children and young adults

S.M.Jones et al JACI2017April 139 4 1242-1252

The authors sought to evaluate the clinical, safety and immunologic effects of this immunotherapy by using Viaskin patches, V 100µg or V 250µg in a multicenter controlled study of 74 participants (age 4-25years) for 52 weeks.

Treatment success (defined as passing a 5044 mg oral food challenge protein or 140-fold increase in successfully consumed from baseline) was achieved in respectively 11 patients (46%), V 100 and 12 patients V 250 (48%) compared with placebo: 3 (12%). It was higher among younger children (4-11 years). Administration was safe, except local mild patch-site reactions. There were significant changes in immune pathways like in other immunotherapies for food-allergy.

In conclusion, this peanut epicutaneous therapy was safe in spite of a modest response after 52 weeks.

## 15. Options in immunotherapy for peanut allergy

Y.Katz, M.R. GoldbergJACI April 2017 139 1135-1136

These pediatricians review all the options for the treatment of peanut allergy, the prevalence of which is increasing and reduces quality of life for both patients and their families. Meticulous avoidance was for many years the only option but do not prevent fatal accidents due to inadvertent consumption (requiring to carry epinephrine auto-injector). Since 2005, protocols of Oral Immunotherapy (OIT) were published but was long, time-consuming with sometimes severe adverse effects and not always sustained desensitization. Indeed in older patients, these adverse effects may be minimized and the treatment protocol accelerated through addition of Omalizumab but at high cost sublingual routes can be used alternately but do not allow a high tolerable dose.

So the novel modality of Immunotherapy by epicutaneous route seems to be an important addition to the growing armamentarium, despite its limitations. There are several encouraging messages from this recent study:

1) There are few adverse effects and they are mild.
2) In youngest children the threshold of reaction to peanut is significantly increased.
3) There was a high rate of adherence to treatment.

It certainly could have a place in providing an initial treatment for severe peanut allergy, avoiding anaphylaxis from accidental exposure and enabling admission to subsequent immunotherapy programs.

## 16. Physical health conditions and quality of life in adults with primary immunodeficiency (PID) diagnosed during childhood

French reference center for PIDs (CEREDIH) study
Barlogis et al JACI April 2017 139 4 1275-1281

Most children with PID now reach adulthood and to investigate long-term morbidity, and their quality of life, the French reference center initiated a prospective multicenter follow-up program.

Among the 889 participants, 329 were adults, 58 undergone stem-cell transplantation; the mean age of participation was 27 years. The major findings are as follows:

- All but 12% experienced a severe (grade 3) or life-threatening condition (grade 4),
- 7,6% of the patients reported a malignancy.
- Adults scored significantly lower for all domains of quality of life.

These findings highlight that these long surviving adults with PID diagnosed during childhood, experienced a heavy burden of health conditions which affect their quality of life and underline the need to closely monitor this vulnerable population.

## 17. Associations between outdoor fungal spores and childhood and adolescent asthma hospitalizations

R. Tham et al JACI April 2017, 139 4 1140-1147

Some outdoor fungi can be associated with asthma exacerbations, little is known about potential interactions with other factors such Rhinovirus respiratory tract infections (HRV) or fungal sensitization. The Australian authors studied the Melbourne cohort of 644 children and adolescents (2-17 years) hospitalized for asthma and collected data on outdoor fungi.

4 allergic species were significantly associated with asthma hospitalizations: Alternaria, and less known species: Leptosphaeria, Coprinus, Drechsfera independent of HRV infection. Moreover, delayed effects were found for fungal exposure up to 3 days before hospitalization.

At last, associations with Alternaria, Coprinus, and Drechsfera were stronger in those sensitized to Cladosporium, probably due to cross-reactivity between fungal species. In conclusion, outdoor fungi can contribute to asthma hospitalization. Is this a special feature of Australasian climate? This requires future researches and closer attention to all environmental factors.

## 18. Symptomatic treatment of pollen-related allergic rhinoconjunctivitis in children: randomized controlled trial.

J. B. Wartna et al, Allergy 201772 4

Although the main symptomatic treatments are intranasal corticosteroids (INCS) (daily or on demand) and oral antihistamines, it remains unclear which treatment provides the best relief of symptoms. Therefore, this study examines whether daily use of INCS is superior to on-demand use or to oral antihistamines on demand.

A single-blinded randomized controlled trial in children (aged 6–18 years) with pollen-allergy is performed. Patients received either INCS daily (fluticasone propionate), INCS on demand (fluticasone propionate) or oral antihistamine on demand (levocetirizine) for 3 months during the grass pollen season. A daily online symptom diary on both nose and eye symptoms was completed. The primary outcome was the percentage of symptom-free days. A total of 150 children were randomized. The percentage symptom-free days was in favour of INCS on demand (30%) compared with INCS daily or with antihistamine on-demand group but not significant). Patients in the INCS on-demand group used on average 61% less fluticasone than patients in the INCS daily group during the study period This trial with three parallel treatment groups shows that INCS daily was not superior to INCS on demand or to antihistamine on demand regarding the number of symptom-free days. An on-demand INCS strategy has the advantage of a lower overall corticosteroid exposure and less costs.

## 19. The gaps in anaphylaxis diagnosis and management by French physicians

G. Pouessel,et al Ped.Allergy Immunol 2017 28 April 288-306

The aim of the current study was to assess physicians' knowledge regarding diagnosis and management of anaphylaxis in children and then to identify causes for the deficiencies. The authors conducted a survey using a two-part questionnaire. In the first part, the questions were based on a clinical scenario involving a 2-year-old child with a peanut allergy: skills on anaphylaxis diagnosis and management were evaluated; in the second part, factors associated with correct diagnosis and management were assessed.

Diagnosis of anaphylaxis, evaluation of the severity of the adverse reactions, and the use of adrenaline were insufficient for the majority of the physicians. Only 19% of the participants had an optimal management step by step from diagnosis to referral to an allergist; 31% of them completed the correct diagnosis and the appropriate treatment with intramuscular adrenaline. Pediatric specialty and CME on food allergy were associated with a better diagnosis, a more frequent use of adrenaline, and a better five-step management.

## 20. Long term consequences of therapeutic intervention in a developing child: early-life antibiotic use and food allergy

J.M.Hascouet & coll : Bulletin Acad.Med April 2017 (in press)
A.G. Hirsch & al. Clin.Exp.Allergy 2017 47 2 236-244

Some perinatal treatments appear to have adverse consequences at adulthood. For example, treatment with broad spectrum antibiotics or for prolonged periods of time, in pregnant mothers or neonates, leads to microbiota alteration which has been associated with an increased risk of allergy and obesity later on. Of note, feeding with mothers' milk allows restoration of physiologic microbiota.

Non-steroidal anti-inflammatory drugs such as ibuprofen use in vulnerable infants with a gender sensibility towards girls might increase the risk of programmed low nephron endowment and premature glomerulosclerosis.

Likewise, antibiotic use is associated with food allergy in a longitudinal data on 30 060 children up to age 7 years from Geisinger Clinic's electronic health records in US. There were 484 milk allergy, 598 food allergy and 3652 other allergy cases.

The acknowledgement of the long-term effects of perinatal care may allow modulating it to reduce adverse consequences at adulthood.

## 21. Early life antibiotic use and the risk of asthma and asthma exacerbations in children

F Ahmadizar, Ped.Allergy.Immunol.2017 Accepted manuscript online: 19 April 2017

The aim of this study was to assess the association between use of antibiotic during the first three years of life and the risk of developing childhood asthma and the occurrence of asthma exacerbations.

Data from four large childhood cohorts were used; two population-based cohorts to study the risk of developing asthma: Generation R (n=7,393, the Netherlands) and SEATON (n=891, Scotland, UK), and two asthma cohorts to assess the risk of asthma exacerbations: PACMAN (n=668, the Netherlands) and BREATHE (n=806, Scotland, UK). Odds ratios (ORs) were derived from logistic regression analysis within each database followed by pooling the results using a fixed or random-effect model.

Results: Antibiotic use in early life was associated with an increased risk of asthma in an analysis of the Generation R and SEATON data. There was no association between antibiotic use in early life and risk of asthma exacerbations later in life in an analysis of the PACMAN and BREATHE.

Conclusion: Children treated with antibiotic in the first three years of life are more likely to develop asthma, but there is no evidence that the exposure to antibiotic is associated with increased risk of asthma exacerbations.

## 22. Controlled trial of early egg intake to prevent egg allergy

D.J.Palmer et al JACI 2017 May 139 5 1600-1607
J.Bellach et al JACI 2017 May 139 5 1591-1599

Two studies, the 1st in Australia, the 2nd in Germany, sought to determine whether regular consumption of egg protein from age 4 to 6 months reduce the risk of IgE mediated allergy in infants at 12 months or not.

- In the 1st study the infants who had hereditary risk, (atopic mother) but without eczema, receive daily pasteurized raw whole egg powder (n = 407) or a color-matched rice powder (n = 413) to age 10 months. All followed an egg-free diet and cooked egg was introduced to both groups at age 10 months. The primary outcome was IgE-mediated egg allergy defined by a positive pasteurized raw egg challenge and egg sensitization at age 12 months.

There was no difference between groups in the percentage of infants with IgE-mediated egg allergy. A higher proportion of participants in the egg group confirmed allergic reaction (25 of 407 [6.1%] compared with 6 of 413 [1.5%]). Egg-specific $IgG_4$ levels were substantially higher in the egg group at 12 months.

The authors found no evidence that regular egg intake from age 4 to 6 months alter the risk of egg allergy by age 1 year.

- In the 2nd German study with similar methods, 406 infants, 4 to 6 months old, were randomized and received egg white powder until 12 months; the primary outcome being sensitization to hen's egg, and the secondary outcome hen's allergy confirmed by food challenge. Among 406 screened, 23infants (5.7%) had hen's egg–specific IgE before randomization. Of the 383 non sensitized infants (56.7% male), 184 were randomized to egg white powder and 199 to placebo. At 12 months of age, 5.6% of the children in the egg group were hen's egg sensitized versus 2.6% in the placebo group and 2.1% had egg allergy versus 0,6 in placebo. So the conclusion is the same as the 1st study. In contrast, it might be dangerous to undertake such investigations, without precaution considering that many 4- to 6-month old infants were already allergic to hen's egg.

## 23. A Clinical trial of intra-dermal and intra-muscular seasonal influenza vaccination in patients with atopic dermatitis

D.Y.M. Leunge JACI 2017 may 139 5 1575-1582

The primary objective of this study was to compare antibody responses to intradermal vaccination in participants with moderate/severe AD with those in nonatopic participants. Secondary objectives were to evaluate the effect of route of administration, Staphylococcus aureus skin colonization, and disease severity on vaccine response.

This was an open-label study conducted in the 2012-2013 influenza season at 5 US clinical sites. A total of 360 participants with moderate/severe AD or nonatopic subjects were assessed for eligibility, 347 of whom received intradermal or intramuscular vaccination per label and were followed for 28 days after vaccination. The primary outcome was the difference in the proportion of participants achieving seroprotection (hemagglutination-inhibition antibody titer ≥1:40 on day 28 after vaccination).

Seroprotection rates for influenza B, H1N1, and H3N2 were not different (1) between participants with AD and nonatopic participants receiving intradermal vaccination and (2) between AD participants receiving intradermal and intramuscular vaccination.

After intradermal, but not intramuscular, vaccination, participants with AD with S aureus colonization experienced (1) lower seroprotection and seroconversion rates and lower hemagglutination-inhibition antibody titer geometric mean fold increase against influenza B and (2) lower seroconversion rates against influenza H1N1 than noncolonized participants with AD.

Conclusion: Participants with AD colonized with S aureus exhibited a reduced immune response to influenza vaccination compared with noncolonized participants after intradermal but not intramuscular vaccination. Because most patients with AD are colonized with S aureus, intramuscular influenza vaccination should be given preference in these patients.

## 24. Churg and Strauss Syndrome (CSS) and Mepolizumab (M)

M. E.Wechsler et al NEJM 2017 376 1921-1932 (18 may)

CSS is an eosinophilic granulomatosis with polyangiitis. M, an anti–interleukin-5 monoclonal antibody, reduces blood eosinophil counts and may have value in the treatment of this syndrome.

In a multicenter, double-blind, parallel-group, phase 3 trial, the authors randomly assigned participants who were taking a stable prednisolone or prednisone dose, to receive 300 mg of M. or placebo, administered subcutaneously every 4 weeks, for 52 weeks. The two primary end points were the accrued weeks of remission over a 52-week period, and the proportion of participants in remission at both week 36 and week 48. The secondary end point included the time to first relapse and the average daily glucocorticoid dose (during weeks 48 through 52). The annualized relapse rate and safety were assessed.

Among 68 participants were assigned to receive M. and 68 to receive placebo. M. treatment led to significantly more accrued weeks of remission than placebo and a higher percentage of participants in remission at both week 36 and week 48. Remission did not occur in 47% of the participants in the M. group versus 81% of those in the placebo group. The annualized relapse rate was 1.14 in the M group, as compared with 2.27 in the placebo group. A total of 44% of the participants in the M group, as compared with 7% of those in the placebo group, had a lower average daily dose of prednisolone. The safety profile of Mepolizumab was similar to that observed in previous studies.

Even so, only approximately half the participants treated with mepolizumab had protocol-defined remission. That is to say that M. may be beneficial for this severe disease.

## 25. Imatinib (I) and Severe Asthma

Katherine N. Cahill, et al N Engl J Med 2017; 376:1911-1920

Mast cells are present in the airways of patients who have severe asthma despite glucocorticoid treatment; these cells are associated with disease characteristics including poor quality of life and inadequate asthma control. Stem cell factor and its receptor, KIT, are central to mast-cell homeostasis. The authors conducted a proof-of-principle trial to evaluate the effect of I, a KIT inhibitor, on airway hyperresponsiveness, a physiological marker of severe asthma, as well as on airway mast-cell numbers and activation in patients with severe asthma.

In this randomized, double-blind, placebo-controlled, 24-week trial treatement, I. was studied in patients with poorly controlled severe asthma whith airway hyper responsiveness despite of receiving maximal medical therapy. The primary end point was the change in airway hyperresponsiveness, measured as the concentration of methacholine required to decrease the forced expiratory volume in 1 second by 20% ($PC_{20}$). Patients also underwent bronchoscopy and bronchial biopsy.

Among the 62 patients who underwent randomization, I. treatment reduced airway hyperresponsiveness to a greater extent than did placebo at 6 months. I. also reduced levels of serum tryptase, a marker of mast-cell activation, to a greater extent than did placebo. Airway mast-cell counts declined in both groups. Muscle cramps and hypophosphatemia were more common in the Imatinib group than in the placebo group.

In patients with severe asthma, Imatinib decreased airway hyperresponsiveness, mast-cell counts, and tryptase release. These results suggest that KIT- dependent processes and mast cells contribute to the pathobiologic basis of severe asthma.

## 26. Systemic innate immune activation in food protein–induced enterocolitis syndrome (FPIES)

R. Goswamiet , JACI June 2017 139 6 1885-1896

Food protein–induced enterocolitis syndrome (FPIES) is a non–IgE-mediated, part of food allergy of infancy, whose pathophysiology is poorly understood. The authors set out to identify and phenotype allergen-responsive cells in peripheral blood of a cohort of subjects undergoing supervised food challenge for FPIES. They profiled antigen-responsive cells in PBMCs by flow cytometry, and examined cells in whole blood obtained before and after challenge by CyTOF, mass cytometry and RNA seq. Results: Using a CD154-based detection approach, they observed that milk, soy, or rice-responsive T cells, and TNF-α–producing $CD154^+$ T cells, were significantly lower in those with outgrown FPIES compared with those with active FPIES. However, levels were within the normal range and were inconsistent with a role in the pathophysiology of FPIES.

Profiling of whole blood by CyTOF demonstrated profound activation of cells of the innate immune system after food challenge, including monocytes, neutrophils, natural killer cells, and eosinophils. Activation was not observed in children with outgrown FPIES. This pattern of innate immune activation is confirmed in a larger cohort by RNAseq. Furthermore,

was observed a pan–T-cell activation and redistribution from the circulation after a positive food challenge but not in those who had outgrown their FPIES.

These data demonstrate a compelling role of systemic innate immune activation in adverse reactions elicited by foods in FPIES. Further investigation is needed to identify the mechanism of antigen specificity of adverse reactions to foods in FPIES.

## 27. Intradermal (ID) grass pollen immunotherapy increases TH2 and IgE responses and worsens respiratory allergic symptoms

Anna Slovick, et al JACI June 2017 139 6 1830-1839

Repeated low-dose grass pollen ID allergen injection suppresses allergen-induced cutaneous late-phase responses comparably with conventional subcutaneous and sublingual immunotherapy. The objective, here, was to evaluate ID immunotherapy in the treatment of allergic rhinitis.

93 adults were randomly assigned with grass pollen–induced allergic rhinitis to receive 7 pre-seasonal ID allergen injections (containing 7 ng of Phl p 5 major allergen) or a histamine control. The primary end point was daily combined symptom-medication scores during the 2013 pollen season (area under the curve). Analysis was by intention to treat. Skin biopsy specimens were collected after intradermal allergen challenges, and late-phase responses were measured 4 and 7, 10, or 13 months after treatment.

Results There was no significant difference in the primary end point between treatment arms. Among secondary end points, nasal symptoms were worse in the intradermal treatment group, as measured based on daily and visual analog scale scores. In a per-protocol analysis intradermal immunotherapy was further associated with worse asthma symptoms and fewer symptom-free days.

ID immunotherapy increased serum Phleum pretense – specific IgE levels compared with those in the control arm. T cells cultured from biopsy specimens of subjects undergoing ID immunotherapy had higher expression of the $T_H2$ surface marker CRTH2 and lower expression of the $T_H1$ marker CXCR 3 respectively. Late-phase responses remained inhibited 7 months after treatment (P = .03).

In conclusion: Intradermal allergen immunotherapy suppressed skin late-phase responses but was not clinically effective and resulted in worsening of respiratory allergic symptoms.

## 28. Benralizumab for patients with mild to moderate, persistent asthma

(In randomised, double-blind, placebo-controlled, phase 3 trial)

2 studies are devoted to Benralizumab (B) which is a humanised, anti-interleukin 5 receptor α monoclonal antibody that directly and rapidly depletes eosinophils, reduces asthma exacerbations, and improves lung function for patients with severe eosinophilic asthma.

- The objective of this first trial (G.Ferguson The Lancet May 2017 on line) was to assess the safety and efficacy of B for patients with mild to moderate, persistent asthma. In this phase 3 trial, were recruited patients aged 18–75 years, weighing at least 40 kg, and with a post bronchodilator reversibility in forced expiratory volume in 1 s ($FEV_1$) of at least 12% at screening. 52 clinical research centres participated in six countries, subcutaneous B 30 mg was injected every 4 weeks for 12 weeks. The primary end point was change from baseline prebronchodilator $FEV_1$ at week 12. Efficacy analyses used an intention to treat approach. Between Feb 2, 2015, and April 24, 2015, 351 patients were enrolled, with 211 (60%) randomly assigned (105 [50%] to placebo and 106 [50%] to B). So B resulted in an 80 mL (95% CI 0–150; p=0·04) greater improvement (least-squares mean difference) in prebronchodilator $FEV_1$ after 12 weeks than did placebo 44 (42%) patients in the B group had adverse events compared with 49 (47%) in the placebo group. The most common adverse events for both groups were nasopharyngitis (eight [8%] patients in each group) and upper respiratory tract infections (five [5%] patients in each group).

This study suggests that active and modifiable disease processes might be ongoing in patients with mild to moderate, persistent asthma receiving ICS. Although the lung function improvement observed does not warrant use of B in this population because it did not reach the minimum clinically important difference of 10%, further studies are necessary to assess this finding.

- The 2nd trial studied the effect of B on oral glucocorticoid sparing in severe asthma P.Nair et al : NEJM 22 Mai 2017 online first. The authors investigated whether B affects the incidence of asthma exacerbations, if it is also effective as an oral glucocorticoid–sparing therapy in patients relying on oral glucocorticoids to manage severe asthma associated with eosinophilia. In a 28-week randomized, controlled trial, B was administered at a dose of 30 mg subcutaneously either every 4 weeks or every 8 weeks versus placebo. The primary end point was the percentage change in the oral glucocorticoid dose from baseline to week 28. Annual asthma exacerbation rates, lung function, symptoms, and safety were assessed.

Of 369 patients enrolled, 220 underwent randomization and started receiving B or placebo. The two B dosing regimens significantly reduced the median final oral glucocorticoid doses from baseline by 75%, as compared with a reduction of 25% in the oral glucocorticoid doses in the placebo group. The odds of a reduction in the oral glucocorticoid dose were more than 4 times as high with B as with placebo. Among the secondary outcomes, B administered every 4 weeks resulted in an annual exacerbation rate that was 55% lower than the rate with placebo), and B administered every 8 weeks resulted in an annual exacerbation rate that was 70% lower than the rate with placebo; there was no significant effect of either B regimen on the forced expiratory volume in 1 second ($FEV_1$), as compared with placebo. Frequencies of adverse events were similar between each B group and the placebo group. So B showed significant, clinically relevant benefits, as compared with placebo, on oral glucocorticoid use and exacerbation rates. These effects occurred without a sustained effect on the $FEV_1$.

## 29. Knemometry (K) and inhaled corticosteroids (ICS) in children with Asthma

B.Chawes et al JACI 2017 August 140 2 431-436

Assessment of effects of exposure to ICS is often done by measuring 24h urine free-cortisol excretion. K assessing short-term lower-leg growth rate is a more rarely used alternative.

The primary aim of this randomized study was to compare the sensitivity of these 2 techniques in 60 children aged 5 to 12 years for evaluating these effects. The findings suggest that K is a more sensitive pharmacodynamic measure that cortisol urine excretion and that a parametric determination of lower leg growth rate, increase the sensitivity of the method.

## 30. A single intervention for cockroach control reduces asthma morbidity in inner cities

F.Rabito et al JACI August 2017 140 2 565-570

The single use of use of an insecticidal bait in the home of asthmatic children living in inner cities of New-Orleans was tested in a randomized study, during a 12 months period, to examine the impact on cockroach counts and reduction of asthma outcomes. A strategic placement of baits (Kitchen and toilets) a visit 6 times/year, asthma symptoms assessed every 2 months in 102 children aged 5 to 17 years realized a different approach than the multifaceted and traditional cockroach abatement. The findings showed that this single, inexpensive, of low toxicity alternative intervention lead to a sustained elimination of insects over 12 months and a significant improvement of asthma outcomes.

## 31. Penicillin Allergy (P.A). new approaches

BMJ 2017 358J. 3402

It is the most commonly noted drug allergy and it is necessary to distinguish patients at low and high risk of having a true P.A.

· The risk factors: frequent exposure to antibacterial, female sex, age, atopy.

· Different types of reactions: immediate (IgE dependent) rare, non immediate (urticaria, angioedema , Stevens-Johnson, anaphylaxis.

· Methods of diagnosis: clinical history, skin-tests and oral provocation (mainly in children and in specialist allergy centers).

The aim is also to exclude hypersensitivity to β-lactams and cross reactivity with other antibiotics: Cephalosporins 1$^{st}$ and 2$^{nd}$ generation (10%) 3$^{rd}$ (2 to 3%) due to similarity in the side chain of the molecules.

Alternatives include tetracyclines, metronidazole, macrolides, quinolones, …often with adverse effects and more expansive.
Inappropriate labelling: in case of true allergy could result in a severe reaction. Otherwise, incorrectly labelled P.A. may lead to emergence of multi-resistant pathogens, long inpatient stay in hospital, mortality and treatment costs.

## 32. Tezepelumab (Tz) in adults with uncontrolled Asthma

J.Corren et al: NEJM 2017 377 936-946

A new monoclonal antibody specific for the epithelial-cell-derived cytokine thymic stromal lyphopoietin (TSLP) was tested in a randomized trial including patients with moderate to severe asthma.

3 doses were used: 70mg every 4 weeks (145 patients) 210mg (145) 280mg every 2 weeks (146) during 52 weeks and compared with placebo (148 patients): the primary end point was the annualized rate of exacerbations.

Among patients treated with long-acting βagonists and medium to high-doses of inhaled corticoids, those treated by Tz had significantly lower rates of exacerbations than those who received Placebo. These findings were independent of baseline blood eosinophils counts but with reduction of serum IgE levels and FeNO . This highlights the potential pathogenic role of TSLP across different asthma phenotypes and the advantage of targeting this broadly active cytokine rather inhibition of a single downstream pathway.

## 33. Difficult and multiple treatments of Severe Asthma (SA)

E.Israël and H.K.Reddel NEJM 2017 7 Sept 377 965-976

The authors distinguish difficult to treat asthma which remains uncontrolled despite treatment with high doses of inhaled corticoids and SA which include exacerbations, poor asthma control, lung function impairment and exclude asthma improved with optimal adherence, inhaler technique and treatment of co-existing conditions (e.g. sinusitis, tobacco or occupational exposure). Patients with SA make up 3% to 10% of adults with asthma and accounts for more than 60% of the costs associated, primarily with medications. Before deciding whether a patient needs biologic add-on expansive therapies, it is necessary to understand the pathobiology of Asthma and its various inflammatory phenotypes:

a) Persistent type 2 eosinophilic inflammation. It includes many clusters (allergic aspergillosis, aspirin exacerbated respiratory disease or late onset asthma with high body mass index). The new therapies have been proposed Anti-IgE: Omalizumab (Xolair®) Anti-IL5 : Mepolizumab® approved in USA and Europe , but also reslizumab benralizumab , Anti-IL 4 and IL 13 : Dupilumab.

b) Neutrophilic and mixed inflammation: coexisting with sinus infections suggesting macrolide therapy; Anti-TSLP (Tezepelumab). Other pathways adaptive or innate are also in progress and may lead to a more personalized treatment.

## 34. Influenza vaccine in egg-allergic recipients: Task force on practice parameters in USA

Allergy/Immunology PubMed 2017. Health Ministry :France

A large number of studies have reported inactivated influenza vaccine IIV to be safe for egg-allergy recipients. Special precautions such as pre-vaccine skin testing or stepwise challenge are unnecessary and may constitute a barrier to immunization. It is even the case for the live-attenuated influenza vaccine LAIV, recommended once the concerns regarding its efficacy have been resolved. So vaccine providers should not ask about the egg allergy status of recipients on influenza vaccine which can be administered in France by pharmacists or nurses. A 3rd type of vaccine, given by inhalation is available but not recommended by the French authorities.

PS. A IIV delivered by dissolvable microneedle patch is used in England, the safety, immunogenicity and acceptability of which is attested by a controlled trial.

## 35. Azithromycin for 48 weeks in persistent asthma

P.G.Gibson et al : The Lancet 2017 390 659-668

420 Adults with uncontrolled persistent asthma despite medium-to-high dose inhaled corticosteroids plus a long-acting bronchodilator were assigned to receive Azithromycin 500mg (213 patients) or placebo (207 patients) 3 times a week for 48 weeks, in order to prevent exacerbations, in a randomized trial from Australia and New-Zealand. Between 2009 and 2015, Azithromycin reduced asthma exacerbations compared with placebo, and significantly improved quality of life. Diarrhea was more common in treated patients (34% versus 19%).

In conclusion: Azithromycin during a long period might be a useful add-on therapy in persistent asthma.

## 36. From wheezing to Asthma: Risk factors in children

M.Lukkarinen et al: JACI 2017 140 988-995

The Finish authors sought to identify risk factors, at the 1st severe wheezing episode, for current asthma 7 years after and separately for atopic and non-atopic asthma.

127 steroid-naive children were followed and all clinical factors were analysed: At study entry, median age was 11 months, 17% were sensitized, 98% were virus positive. At 8 years 37 had current asthma: atopic 19, non-atopic 18.

The risk factors for atopic asthma were: sensitization ($p \leq .001$) eczema ($p \leq .014$) wheezing with rhinovirus ($P \leq .035$).

For non-atopic asthma, the risk factors were: 1st wheezing due to respiratory syncytial virus / rhinovirus negative P=.001) at age less than 11 months (P=.007) parental smoking (P=.028).

So diverse phenotypes and mechanisms can be predicted by clinical markers at the time of 1st wheezing episode suggesting different early intervention strategies for secondary prevention of asthma.

## 37. Severe Nasal Polyposis (SNP) and Mepolizumab (M)

Cl. Bachert et al JACI 2017140 1024-1031

Patients with eosinophilic SNP require surgery. The European authors sought to assess the efficacy and safety of M. versus Placebo. 105 adult patients received 750 mg of M (or placebo) every 4 weeks for a total of 6 doses; the primary end point was the number of patients no longer requiring surgery at week 25 of a composite of endoscopic nasal polyp score; changes in nasal symptom severity were secondary end-point. A significantly greater proportion of patients in the M. group no longer required surgery (30% vs 10%: 16 vs 5). A significant improvement of polyposis severity was observed in M. group compared with placebo. M. safety profile was comparable.

In conclusion M. reduced need for surgery in eosinophilic and non-eosinophilic SNP.

## 38. Novel formulation of inhaled sodium cromoglycate (PA101) in Chronic Cough (CC) and Interstitial Pulmonary Fibrosis (IPF)

S.S.Birring et al : The Lancet Resp.Med 2017 sept. Online first

In a randomized, double blind, proof of concept phase two trial, the authors aimed to test efficacy and safety of this PA101, delivered via a high efficiency eFlow nebuliser that achieves drug deposition in the lung, in 24 patients with IPF +CC. A similar study was designed in 27 patients with Chronic Idiopathic Cough (CIC) the 2 cohorts coming from 7 centres in UK and the Netherlands The primary end-point was change in daytime cough frequency (from acoustic recording).

The findings showed in patients with IPF that PA 101 reduced daytime cough frequency by 31% at day 14, compared with placebo.

By contrast no benefit was observed in the CIC cohort. The drug was well tolerated in the 2 cohorts. The anti-tussive mechanism of the drug is still under study.

## 39. Occupational Asthma

J.D DEWITTE: 24 Octobre 2017; In press: Bulletin de l'Académie Nationale de Médecine

The term "work-related asthma" encompasses both asthma caused by work (i.e. occupational asthma) and pre-existing or coincident asthma exacerbated by non-specific stimuli at work, the latter condition commonly referred to as "work-exacerbated asthma". Occupational asthma may result from immunologically mediated sensitization to a specific substance at work (i.e. "immunologic"). In France the 5 most frequent allergenic substances are: flour, then isocyanates, latex, aldehydes and persulfates. It is important that occupational asthma be recognized clinically because it has serious medical and socioeconomic consequences. The author studies the diagnostic value of the available methods which include an appropriate clinical history, the use of specific immunology and measurement of inflammatory markers, and various methods of relating functional changes in airway caliber to periods at work.

## 40. Reactive Airways Dysfunction Syndrome or Brooks syndrome

J.D DEWITTE: 24 Octobre 2017; In press: Bulletin de l'Académie Nationale de Médecine

Exposure(s) to high concentrations of irritant compounds, best typified by Brooks in 1986 , modified by Bardana in 1999, include 7 criteria: absence of atopy, unique and massive exposure to gaz, fumes or vapors, and lead to asthma-like symptoms, beginning early (24h ) after exposure, not lasting more 3 months, absence of eosinophilia or smoking, lymphocyte inflammation (broncho-alveolar lavage). We must bring closer the symptoms observed among workers of World Trade Centers in New-York after the terrorist attack of 11 September 2001 which last still 6 months later. There are few studies on the follow-up of this syndrome identity of which is based on responsible irritant agents.

## 41. Occupational Allergic Dermatitis in Bricklayers and Wood construction workers

C.Geraut: 24 Oct. 2017 In press in Bulletin de l'Académie Nationale de Médecine Paris France

The building and public works sector covers many activities with multiple skin hazards responsible for contact dermatitis due to cement, acids, solvents and paints, various adhesives and glues including epoxy and other very allergenic resins, carcinogenic hydrocarbons, wood dust, vibrations and dust of free silica responsible for scleroderma in stone cutters. The link with the job is based on epidemiological, scientific and clinical data

mainly in the workplace with detailed and precise analysis of the work conditions. Bricklayers, carpenters, cabinet makers, asphalt workers, engine drivers and stone masons are concerned. Prevention is essential.

## 42. Influenza in Asthmatics

J.Schwarze et al: Allergy Nov 2017accepted articles

Task force Influenza in Asthma EAACI: Chrysanthi Skevaki

This is a comprehensive review, including scientists from more than 20 European countries of influenza burden in asthmatics. A significant variation in reported rate of viral detection and in its likely role in asthma exacerbations is underlined. The strongest evidence of an association was seen in studies of children. The coverage of vaccination, although recommended in all European countries, varied between regions. Limited data suggest a good seroprotection, seroconversion, and efficacy, mainly in asthmatic children, more controversial in adults. However, the safety of vaccination in all asthmatics is confirmed. Future research on anti-viral drugs is needed.

## 43. Immune mechanisms of respiratory viral infection in Asthma

Farne ,S.Johnston Current Opinion in Immunol 2017 48 31-37

The severity of respiratory viral infections in asthma is the result of a dysregulated immune response. Excess type 2 inflammation and growing production of Interferons are the 2 main characteristics of this phenomenon. Moreover, the role of epithelial derived cytokines (IL 25, IL33, TSLP) in orchestrating type 2 immunopathology, including type 2 Innate Lymphoid cells (ILC2s) must be emphasized.

## 44. NUT Co Reactivity - Elimination Recommendations

Arnon Elizur,et al Allergy 2017 11 Nov Accepted Articles

To examine the co-incidences of allergies among tree-nuts and improve diagnostic testing to minimize the need for OFC, the Israeli pediatricians took charge of eighty three patients prospectively evaluated for walnut, pecan, cashew, pistachio, hazelnut and almond allergy. Standardized skin prick tests (SPT) using finely ground tree-nut solution and basophil activation tests (BAT) were performed. Patients underwent OFC for each tree-nut they eliminated.

While most patients were sensitized to 5-6 tree-nuts, over 50% were allergic to only 1-2 tree-nuts. The highest rate of allergy in sensitized patients was observed for walnut (74.6%) and cashew (65.6%). The rate of co-allergy for most tree-nuts was < 30%. Knowledge

of co-incident allergies in these pairs along with the combination of SPT and BAT correctly distinguished allergic from tolerant patients forwalnut (87%), pecan (66%), cashew (71%) and pistachio (79%).

In conclusion, these data should assist in differentiating between allergic and tolerant patients, decrease the need for OFC and allow for appropriate elimination recommendations.

## 45. Lip Food Challenge as alternative to Open Food Challenge

C.Venter et al Ped All. Immun 2017 28 7 707-711

The British pediatricians of the Isle of Wight, using the method of French allergists Rance & Dutau and A. Monneret-Vautrin, performed a Lip Food Challenge (LFC) in many children from birth cohorts followed until 11 years. Skin prick-tests to common food allergens (milk, egg, cod sesame, wheat and peanut) were evaluated. Then 112 LFCs took place. Four cases although positive were excluded as parents decline to continue the process. So108 LFC were followed up by an open food challenge. A positive labial reaction was noted in 9 challenges. All resulted in positive oral food challenge (OFC). A positive predictive value of 100%, a negative predictive value of 72,7% with 100% specificity were calculated. Side effects of LFC were minimal: urticaria (3 cases), with lip edema (2), rash, rhinorrhea. These data, despite very limited and including only four food allergens, prove that LFC is highly indicative of a positive OFC (but a negative LFC does not rule out a positive OFC). In conclusion LFC is feasible, reliable and safe.

## 46. Immune Mechanisms of Food Allergy

Turcanu et al Curr.Op.Immunol 2017October 48 92-98

Environmental factors, dual exposure to allergens, hygiene hypothesis and local microbiota may explain worldwide increase in food allergies. The tolerance is driven by effects of microbiota on gut immune responses whereas skin exposure to foods may promote allergy. As proved by recent studies (Learning Early on Peanut Allergy - LEAP), early intervention by introduction of peanuts in the infants diet, reduces the window-of-risk when children are not protected by tolerance. It conveyed more information on evolution of IgE and IgG4 antibodies responses to food allergens over time. Prevention studies require long-term immunological and clinical follow-up.

## 47. Risk of Asthma: Lessons from Amish and Hutterite Children

C.Ober et al Current Op.Immunol 2017 October 48 51-60

It is well known that, since the publications of Erika Von Mutius, children who grow up in traditional farm environments are protected from developing asthma mainly by activating innate pathways, and distinct immune cell phenotypes. Moreover, the 17q21 asthma locus confers both protection and risk, depending on exposures. This 'farm effect' can be largely explained by the child's early life contact with farm animals, in particular cows, and their microbes. The recent studies of the authors further demonstrated that although Amish and Hutterites are very similar with respect to ancestry, many lifestyle factors, and farming practices, profound differences exist in the levels of house dust endotoxin, in the prevalence of atopy among school children, and in the proportions, phenotypes, and functions of immune cells. These findings like many previous studies in European farm children have advanced our understanding of the asthma-protective 'farm effect'.

## 48. Atopic Dermatitis and Psoriasis: Similarity and Difference

E.Guttman-Yassky et al Current Op.Immunl 2017 October 48 51-60

Psoriasis and atopic dermatitis (AD) are common T-cell mediated inflammatory diseases of the skin that can be treated by specific cytokine antagonists or broader immunosuppressive drugs. The diseases are similar in that epidermal keratinocytes respond to T-cell derived cytokines by altering growth and differentiation responses. When studied across European-American populations, psoriasis and AD display differing T-cell polarity and different arrays of cytokines. Psoriasis is a disease largely driven by Th17 T-cells and associated IL-17 activation, while AD has a strong Th2 component associated with IL-4 and IL-13 over-production, and both diseases have activation of Th22 T-cells and Th1 pathways with increased IL-22 and IFNγ production, respectively. AD is a disease frequently associated with increased IgE production and over allergies or asthma, most likely due to increased Th2 activation, which is largely lacking in psoriasis. Hence, psoriasis and AD can be viewed as distinct diseases with differing clinical, tissue, and molecular disease phenotypes, but this view does not account for specific subtypes of AD, including Asian-origin, intrinsic, and pediatric AD, that have a prominent IL-17 component and also tissue patterning that overlaps with distinctive psoriasis histopathology. Hence, when considering the range of AD phenotypes, a case can be made that psoriasis and AD exist across a spectrum where polar T-cell axes can be variably present and create some overlapping disease characteristic. So it is necessary to personalize therapies and target multiple T-cell axes to attain similar disease improvement.

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