Bibliographic updates in Allergology

2013

By: Claude Molina and Jacques Gayraud

Contents

Letter to the reader

Dear colleagues and readers,

As we begin this New Year with a new series of Updates, we would like to thank you for your loyalty and the friendly interest many of you have expressed.

During this past year, we have produced 50 one-page Updates on a wide range of practical allergology subjects, 9 on asthma (3 on inhaled corticosteroids), 7 on food allergy, 6 on environmental factors, 5 on nutritional factors, 6 on organ allergy (digestive tube, eye, skin, and so on).

We have tried to stick to practical information, often original, sometimes anecdotal, while doing our best to avoid general overviews and suggesting that those who wished to go further on the subject refer to the paper in question.

We intended to turn these BUAs into *training* tools, trying with our colleague and friend Luis Taborda to prepare MCQs on the topics treated. But it soon became obvious that the authors' opinions were often too specialised or personal to be considered as generally applicable.

However, consulting the UEMS/EAACI questionnaires showed us how accurate, varied and high quality the answers were supposed to be, and also how necessary it was for new allergists trying to qualify or for those looking to update their knowledge, to have a clear idea of the latest findings in Immunology and more generally in biology or even genetics.

That is why we will try from time to time to propose such subjects in our BUAs, in the style of: "*All you wanted to know about… without ever daring to ask*".

A final, but often repeated desire for more interactivity, not only amongst ourselves but also with the whole allergist community, will be realised with the creation of a real Forum in the, we hope, very near future.

Such are our plans. We are now looking forward your suggestions.

Claude Molina & Jacques Gayraud

1. Father Christmas's reindeer and nasal popyposis

Theme: ENT Allergology
Key words: Reindeer nose – Human nose – Nasal microcirculation – Nasal polyposis

In a surprising publication entitled "*Why Rudolph's nose is red*", a group of Dutch and Norwegian researchers, alluding to *Santa Claus* and his legendary sleigh pulled by Rudolph and several other reindeer through Northern Europe's frozen plains, wanted to understand why in the legend as well as in reality the reindeers' noses were red (*A.M.Van Kuyjen et al BMJ 2012 17 December e8/311*).

They thus compared, *in vivo*, using a high technology video-microscopic system, the nasal microcirculation of 2 reindeers to that of the nasal septal mucosa of 5 healthy volunteers and a patient with grade 3 nasal polyposis. In this way they managed to evaluate vascular density and flow index, as well as reactivity to some local drugs (vasoconstrictor or anaesthetic) and perform an accurate statistical analysis.

The researchers found many similarities between healthy humans and reindeer. Analyses, confirmed by the first-ever biopsic studies, show hairpin-like capillaries rich in red blood cells with a perfused vessel density, as well as crypt or gland-like structures.

But what comes out of this research is that the vascular density of the reindeer's nasal mucosa is 25% higher that the healthy human being's, which explains the reindeer's legendary luminous red nose (and also antler ends). This enables these animals' nasal mucosa to protect, under extreme polar conditions, their brain temperature.

The authors remind us on this occasion of all the other nasal functions, i.e. humidification, filtration, inflammation control, oxygen dispensation to cells, and response to allergens. On top of that, this delicate technique reveals the functional aspect of nasal microcirculation which even makes it a hemodynamic marker usable in intensive care.

Finally, nasal polyposis (one case only, but an advanced one) reveals the microvasculature irregularity with total absence of hairpin-like capillaries and gland-like structure.

2. Winter hay fever: a Christmas gift for Swiss school children

Theme: ENT Allergology
Key words: Winter hay fever – Alder pollen – Global warming

A Swiss doctor from Grabs (a small village in Eastern Switzerland), with the help of Zurich allergist colleagues, reported the unusual observation in school children of the area of a rhinitis close to hay fever but occurring in winter (*M.Gassner et al NEJM 2012 December 21 on line*).

They consequently gathered all data on allergic manifestations of the past 25 years among 15-year-old school children in the small village of Grabs, as well as the specific IgE antibodies to 103 molecular allergens (using ImmunoCAP ISAC), that is from 54 students in 1986 and 46 in 2006. In 2010, they retested 12 of them (then +/-39 years old) for various

common inhalant allergens. At the same time atmospheric pollen levels were measured with the use of Hirst-type pollen traps.

Already in 2006, they had observed IgE antibodies to the main allergen of alder trees (*Aln gl*) in 10.9% of healthy subjects, but these were not seen with pollen of other trees. Besides, among the 12 former students retested, three of them had become sensitized to alder. Similarly, although none of the children reported having had allergic symptoms between 1983 and 1986, 6 students had such symptoms in 2006 and their rhinitis was attributed to a common cold.

The explanation came from the observation around Christmas of 2011 of large amounts of alder pollen in the trap. Indeed, just over a decade ago, 96 hybrid trees of the Alder family, with high winter resistance, had been planted along a main boulevard in Grabs, where children walk or ride the bus on their way to school. Changing temperatures and street lighting may have influenced the release of pollens from these trees in winter (*Alnus x spaethi, A. japonica x et A.subcordata*).

That is why the authors entitled their study "*Hay fever as a Christmas gift*".

3. Severe allergic reactions to exposure to Methylisothiazolinone (MIT)

Theme: Allergen – Skin allergy – Respiratory allergy
Key words: Methylisothiazolinone – Contact eczema – Asthma – Cosmetics – Paints

Chemicals such as cosmetics or preservatives usually cause allergic manifestations through direct contact: the result is allergic contact dermatitis, a type IV immune reaction. The inhalation of other industrial chemical allergens such as isocyanates may cause severe reactions, but only rare skin ones.

Now, it appears that a preservative, MIT, recently introduced in marketed cosmetics and paints in Europe, and hitherto mostly responsible for dermatitis, is also causing respiratory allergic reactions, sometimes severe, when inhaled (*M.Dirgaard Ludov et al BMJ 2012 December 4*). Hence, in Denmark, allergic reaction to this compound in patients with eczema rose from 1.4% in 2009 to 3.1% in 2011 (55 positive reactions out of 2470 patch tests). Half these cases had been exposed to MIT via cosmetics, and over one third via paints. Among the latter, eczema, sometimes accompanied by asthma, had occurred at home after use of paint or after working or staying in a recently painted place. Dermatitis was located on uncovered skin (face and neck) or in the popliteal fossa. Some cases required hospitalisation.

The authors then inventoried 17 paint brands whose MIT concentration ranged from 10 to 300 ppm, and in an experimental study observed that emissions from painted glass plates were measurable for nearly 26 days.

In the 80's, MIT was marketed in proportions of 1/3 with its chlorate derived product (even more responsible for sensitization) and the combination of both was considered as the main cause of preservative contact dermatitis.

MIT on its own has been regulated since 2000 in paints and lacquers for professional use and the first observations of this type of allergy were issued in 2004. For cosmetics, concentration was limited to 15 ppm, but since 2005 in Europe and the USA a maximum of

100 ppm has been tolerated. And yet, MIT is not regulated for domestic cleaners, which means that it is difficult for the consumer to detect MIT presence or concentration.

Knowing the health hazards of this exposure to airborne allergens in many environments, the authors ring alarm bells for European authorities to reduce authorised concentrations, or even ban some products.

4. Respiratory symptomatology and menstrual cycle (MC)

Theme: Asthma
Key words: Menstrual cycle – Asthma – Tobacco – Overweight

Variations in respiratory symptomatology (RS) as a function of the menstrual cycle are the object of an important paper by Northern authors (*F.Macsali et al AJRCCM 2012 29 November ahead of print*) concerning 3926 women aged 20-44 from Sweden, Norway, Denmark and Estonia, whose questionnaire answers were analysed by chronobiology methods, along with stratification by BMI, smoking and asthma status.

These were women with a regular MC of 28 days on average, taking neither contraceptive nor hormones, with whom RS was recorded daily between the 1st day of the last menstruation and the 3 last days of the MC. The originality of this study comes from the use of the 'cosinor' methodology to describe the RS rhythm. We know that the MC comprises a 1st oestrogenic phase of 10-14 day follicular maturation followed by ovulation with a 0.5° central temperature increase, then the 2nd luteal phase with progesterone secretion and decrease in FSH and LH ending with menstruation at the dip of the hormonal secretion.

Since hormonal factors are linked to metabolic, and smoking has an anti-oestrogenic effect, it was important to take these factors into account and above all to know whether some patients had been diagnosed as asthmatic.

The following was observed, with significant rhythmic oscillations for each symptom and each subgroup:

• Wheezing was at its highest from day 10 to 22 of the MC, with a drop-in frequency at the time of ovulation and in almost all subgroups.
• Shortness of breath was highest from day 7 to 21 with a drop at mid MC in several subgroups.

• Coughing peaked just following putative ovulation for asthmatics, smokers and those who are overweight (BMI ≥23kg/m²).

While these variations were observed in all groups, it is among asthmatics that therapy should be considered most carefully, as this would imply adjusting the treatment on an individual basis, taking into account chronobiological variations of each patient's MC, to be monitored over several months.

5. Smelly biomarker for 'Neutrophilic' asthma

Theme: Asthma
Key words: Hydrogen sulphide – FEV1 – Neutrophils – FeNO

Sulfide hydrogen (H2S), well known terrible smelly gas, produced by many cell types in the lungs, has been recently discovered as capable of inducing vascular smooth muscle relaxation and being an anti-inflammatory and anti-oxidant agent.

J.Saito of London Brompton Hospital (*et al JACI 2013 131 1 p.232-4*), in search of new bio markers, attempted to measure its levels in the serum and supernatants from induced sputum in asthmatic patients. The very sensitive technique used required several adjustments before being considered as reliable because levels (between 10 and 100µmol/L) evaporate rapidly after sampling.

40 asthmatics and 15 healthy controls were the object of the preliminary study:

- 23 asthmatics of an average age of 47 years: severe asthma (SA) requiring *per os* and inhaled corticosteroids, in association with long-term agonist β2.
- 17 asthmatics of an average age of 36 years, suffering from moderate asthma (MA) controlled by inhaled corticosteroids.
- controls had an average age of 40 years.

Results were as follows:

• There was no significant difference in healthy subjects' and asthmatics' saliva. But provoked sputum and serum revealed significantly higher levels in SA and MA than in controls.

• Besides, there was an inverse correlation between sputum H2S and FEV1, and also a negative one with reversibility to albuterol, two signs of persistent airway obstruction.

• There was a positive correlation between sputum H2S and the percentage of sputum neutrophils, but not with macrophages and eosinophils.

• Finally, an inverse correlation was observed between sputum H2S and FE NO, the atter usually considered as an expression of eosinophilic asthma.

Overall, after multiple linear regression, it appears that sputum H2S levels (but not the serum ones) are associated to sputum neutrophilia, decrease in FEV1, bronchospasm irreversibility to agonist β2 and increase in BMI, all signs pointing to the neutrophilic asthma of an aging and overweight subject; contrary to eosinophilic asthma, moderate and reversible to albuterol.

Thus, H2S could be considered as a bio marker for the neutrophilic asthma phenotype. An assumption to be confirmed on larger cohorts, as well as the necessity of specifying the possible origin of sputum H2S (bacterial flora of deeper airways?).

6. Statins (S) and allergy

Theme: Anti-allergic therapeutics
Key words: Statins – Asthma – T CD4 lymphocytes – IL10 interleukin

Statins, well-known and widely-used cholesterol-lowering agents and inhibitors of the A-reductase coenzyme 3HMG, also have anti-inflammatory properties. Moreover, as recently shown in a Taiwan study, they act as inhibitors to airway hyper-responsiveness in asthmatic mice sensitized to ovalbumin and treated per os with Pravastatine et Atorvastatine (*Chin Fen Huang et al, Annals of Allergy, Asthma Immunol 2013 110 1 11-17 et Editorial de J.L.Rosenberg*).

Closer to clinical considerations, a Thaï study analysed in vitro by flow cytometry the effect of an association of Simvastatine and Fluticasone on asthmatics' T CD4 cells incubated with dentritic cells. They observed that the T regulators: Treg / Th 17 ratio was high and significantly more so than when each product was taken alone. A simultaneous increase in IL10, explains the reduction of airway inflammation. Conversely, high Th17 levels are apparently linked to severe and neutrophilic asthmas (*K.Maneechotesuwan et al, Clin & Exp.Allergy 2013 43 212-222*). Other statins, such as Fluvastatin and Lovastatin have similar properties, always observed *in vitro*.

On clinical point of view (JL.Rosenberg), the results are more limited and often contradictory. While the association of S and corticosteroids appears beneficial among the obese and hypercholesterolemic asthmatic, this needs to be confirmed by numerous therapeutic trials.

These studies nevertheless have drawn attention to the lipidic metabolism and its role in lung physiopathology.

However, there is drawback as concerns side-effects of S. since several of them have induced anaphylactic reactions. Thus, with the 37-year-old US patient suffering from family hypercholesterolemia (F.S Khan et al JACI 2013 131 1 234-236) a Rosuvastatine (Crestor®) desensitization protocol was successfully performed in 72 h, the initial 0.01mg dose having enabled him to tolerate 9 months later the 20mg dose per *os*.

7. Natural history of infant cow milk allergy

Theme: Food allergy
Key words: Allergy prediction – Cow milk – Specific IgEs – Skin prick tests – Atopic dermatitis

In a multicenter study by US paediatricians (Baltimore, New-York, Denver, Little Rock, Chapel Hill (*R.Wood JAC I 2013 1 in press*) a cohort of 3-15 month-old infants was followed in two categories:

- the first group was composed of infants with an obvious clinical history of milk allergy (as well as egg allergy for some of them) with a positive prick test to the trigger food;
- the second was composed of children suffering from moderate to severe atopic dermatitis (AD), with positive prick test to milk or egg.

Only the children with a clinical history of milk allergy were enrolled and followed over a long period in order to assess the natural evolution of this allergy towards its resolution, the time taken to achieve it and hence the possibility of safely ingestion the food again.

Out of 293 infants, 244 milk-allergic were followed for over 5 years (66 months). Allergy resolved in 154 subjects (52,6%), i.e. a little over 1 in 2 and on average around the 63rd month. Through statistics and a large number of biological parameters (mononuclear stimulation and PCR analysis), the authors tried to specify the predictive factors of allergy persistence, among which 3 emerged with a strong probability (P≤ 0.001):

- Specific IgE levels at baseline
- Skin test wheal size
- Severity of AD

The chances of resolution are then associated with a low level of specific IgEs, a small size skin test wheal and a mild AD. They are generally higher in girls. It should also be noted that 20% of those children, still allergic, could tolerate cooked milk products. However, no other biological criteria (IgG4 or IgE/IgG4 ratio, Fox P3, GATA 3, IL10, IL4, IFNγ) or mononuclear stimulation testing turned out to be resolution predictors.

This once again emphasizes the superiority of "good old" clinical practice over the most sophisticated biological tests, and this diagnosis triad constitutes a precious predictive tool for paediatricians and families with a view to a safe milk ingestion.

8. Kiwi fruit allergy (KA) in Europe

Theme: Food allergy
Key words: Kiwi – Skin prick tests – Specific IgEs –Molecular allergens – Iceland

A relatively frequent and not just anecdotal aetiology, KA was the theme of a European survey in the framework of the Prevall study, gathering 311 subjects in 12 different countries, among which France (Strasbourg), and 4 climatic regions throughout Europe.

They sought to elucidate European geographic differences, both in clinical terms and diagnostic methods, possible cross-allergies, prognosis and severity factors (*Thuy-Le et al JACI 2013 131 164-171*).

Two varieties of K are known. The most common, the object of the study, is the green variety, *Actinidia deliciosa* cultivar Hayward, whose extract includes several allergens, the 6 most representative of which were tested with ImmunoCap: *Act d1, Act d 2, Act d 5, Act d8, Act d 9 et Act d 10*, along with the total extract. The other variety, *Actidinia Chinensis* cultivar Hort 16 A, is less common.

Clinical signs were very varied, going from oral irritation (the mild form, 87% of cases) to moderate forms (digestive troubles) and to anaphylactic shock and occurring between 15 and 60 minutes after ingestion in 92% of cases. There were no challenge tests, the clinical and biological signs being evocative enough, whether it be mono-sensitization or association with sensitization to birch pollen or latex.

As for diagnosis, the comparison of skin prick-tests and I°cap with the 6 allergens shows a clear superiority of the biological test, sensitivity climbing from 20% for skin tests and the total extract I°cap, to 65% for the 6 molecular allergen I°cap.

As to sensitization, it varies according to region:

- 32% of the patients living in Iceland were *Act* d1 (Actinide) sensitive.
- Those from central and western Europe and eastern Europe were sensitized to *Act* d8 (a class 10 protein, 58% and 44% respectively)
- Those from southern Europe, were mainly sensitized to *Act* d9 (profiline, 31%) and to *Act* d10 (a lipidic transfer protein, 22%).

Severity factors are independently represented, by residence in Iceland and by *Act* d1 sensitization. Although independent (P=0.003), their association is even more significant (P≤ 0 .001).

Finally, the treatment, obviously only by eviction, is not always straightforward, due to cross-sensitizations and risks of "hidden" foodstuffs.

9. Proton-pump inhibitors (PPIs) and asthma

Theme: Asthma treatment
Key words: Proton-pump inhibitors – asthma – gastroesophageal reflux – pneumonia

Commenting on a recent publication by J.G.Mastronarde *et al* (*NEJM 2009 9 April 360 1487-1499*) which reported that Esomeprazole lacked efficacy over poorly-controlled asthma, several specialists are now contesting some of these conclusions (*C-S Hsu et J-H Kao, NEJM 31 January 2013*) and are looking again at the issue of PPIs and asthma.

Recalling the high prevalence of asymptomatic gastroesophageal reflux in these patients, they state that acid reflux by pH monitoring as observed in the quoted study, only represents a sub-group of subjects and is not representative of the patients at large. This only means that acid reflux is not a likely cause of these poorly controlled asthmas. However other factors such as Body-mass index, age, sex, smoking status, have not been explored sufficiently to justify the authors' conclusions.

Similarly, J.Lenglinger from Vienna believes that only endoscopy with biopsy can reveal an asymptomatic reflux requiring PPI treatment.

Besides, M.P.Wise *et al* (from Cardiff) state that, if PPIs reduce both the volume and acidity of gastric contents, they do not prevent a more or less bacteria-enriched pulmonary microaspiration and are then often associated with pulmonary complications and at the least an inflammation which may explain the lack of efficacy of treatment.

In his response, R.A.Wise from Baltimore (USA), one of the leaders of the initial survey, confirms the frequency in these refractory asthmas of asymptomatic reflux, actually also found in other respiratory affections (cystic fibrosis or interstitial fibrosis) and interpreted as a consequence of alterations in pulmonary mechanics. Is it really necessary, in such cases, to perform an endoscopy with biopsy given the risks and cost involved? The author does not think so and suggests looking firstly for other possible causes of failure of the asthma treatment (obesity, age, drugs). As for the risk of infectious complications or

pneumonia, due to PPIs and aggravating asthma, he had no confirmation of it despite a wide-ranging random survey of 412 patients.

He nevertheless admits the possibility of harmful as well as beneficial effects of gastroesophageal acid suppression.

On the whole, it appears that unless there is a strong suspicion of reflux, PPIs do not improve this poorly-controlled asthma and could even worsen their evolution.

10. Mechanisms of tolerance (T) to allergens

Theme: Immunology
Key words: Tolerance – Allergens – TH2 lymphocytes – T regulators - TGFβ - Ig G1 – IgG4 – Specific immunotherapy – Epitopes – Recombinant allergens – Toll-like receptors

In the framework of the immunology topics planned for our BUAs, this one is analyzed in several recent papers that we shall briefly summarize, within the strict limits of a usual item.

- a European paper, by the C.M.Akdis group (*O.U Soyer et al: Allergy 2013 68 2 16- 170*), a supplement to his excellent contribution in *Nature Medicine* (*2012 18 5 736-746*);
- and an American one, by the Woodfolk group (*J.Wisniewski et al Clin.Exp.Allergy 2013 43 164-176*).

Tolerance can be defined with Medawar as the state of indifference or non-reactivity towards a substance (here, the allergen) which should normally induce a response. Recent advances in immunology and molecular biology have identified the mechanisms that in allergic diseases do away with or reduce the inflammation initiated by the differentiation of T cells, particularly Th2, following the presentation of the allergen to dendritic cells. Regulatory cells (T.reg) play a pivotal role in inhibiting Th2-mediated inflammation through cytokines (IL 10 and TGFβ) or antibodies (IgG1, IgG4) targeted by introduction in the body (injection, ingestion or inhalation) of allergens during specific immunotherapy (SI) and inhibiting the IgE-allergen binding.

But other cells (Th1, Th17, even Th9 or Th22), pro-inflammatory with their cytokines, mediators, transcription factors (Fox p3), surface molecules (CD), can also modulate the immune response. Incidentally, for about ten years, biological drugs (e.g. monoclonal antibodies) have replaced chemical ones.

The efficacy and safety of this Tolerance can be improved in 6 ways (Akdis):

1. By short-circuiting the IgE-allergen link through fragmentation of the allergen and use of linear peptide epitopes of T cells;
2. By using recombinant allergens;
3. By associating allergens with innate immunity stimulators such as Toll-like receptors (TRL 4);
4. By varying allergen administration: subcutaneous, sublingual, epicutaneous, intra-lymphatic (lymph-node);

5. By merging allergens with immunity modifiers such as FcγRIIb which inhibits basophil and mastocyte degranulation;
6. By associating SI with monoclonal antibodies (e.g. Omalizumab) to avoid the anaphylactic risks of rush-treatment;

Finally, we should emphasize the possible role of the intestinal microbiome and the discovery of tolerance markers which open up new therapeutic targets.

11. Asthma risks for children born after infertility treatment

Theme: Asthma – Prevention
Key words: Asthma – Infertility – In Vitro Fertilization IVF – Assisted Reproduction Technique – ICSI: Intra Cytoplasmique Sperm Injection

This is the subject of a major British prospective and randomized study (*C.Carson et al Hum. Reprod. 5 December 2012 on line*) on a cohort of more than 18,000 children recruited at 9 months and followed-up to 5 and 7 years of age. It was predominantly focused on children born after ART (Assisted reproduction Techniques) either IVF or ICSI.

Several birth categories were analysed: planned, unplanned, welcome or not, those with a prolonged (over a year) time to conception (TTC) and the ovulation induced, IVF or ICSI. Asthma, wheezing and use of anti-asthma medications were taken into account; a total of 13,041 children aged 5 (72%) and 11,585 aged 7 (64%) were included.

Statistical results show that, compared with planned children acting as control, children born from subfertile parents were significantly more likely to experience asthma or to be taking anti-asthmatics respectively at 5 and 7 years of age, this being particularly true with singleton children born after treatment for maternal infertility.

True, the latter are relatively few in number (104 subjects) but all the possible confounders were analysed, and data weighted for non-response to minimize selection bias.

On the whole, and given the Scandinavian bibliographical references with similar observations, the researchers are convinced that the treatment of maternal infertility is a factor favouring childhood asthma.

12. Intralymphatic (IL) specific immunotherapy (SI) of pollen allergy

Theme: Therapeutic – Immunotherapy
Key words: Intralymphatic specific immunotherapy – Pollen allergy

This is a Swedish pilot study intended to determine whether this SI mode is a valid and harmless alternative to the classic technique of pollen rhinitis treatment which requires, as we all know, a number of subcutaneous injections (around fifty, according to the researchers), normally continues for 3 to 5 years and at a significant cost.

The IL technique consists in injecting into a superficial inguinal lymph node, possibly guided by ultra-sound, 3 times at approximately 4-week intervals, a dose of about 1000 Units of aluminium-hydroxyde absorbed depot allergens, either grass of birch pollen.

A first 'open' test on 6 patients, intended to check the safety, feasibility and benefits of the technique, was followed by a 2nd controlled and random test on 15 patients, including 8 Placebo.

In addition to the clinical examination with scores, the classic protocol of course included: possible side-effects monitoring, skin prick tests, nasal provocation tests, blood paarameters (specific IgEs, IgG4 but also immuno-cytochemistry aiming at T lymphocyte activation), cytological (inflammatory cell content) and biological (cytokines) study of nasal lavage fluids.

At the end of the study, it appears that IL treatment is perfectly tolerated, that its clinical efficacy is significant (despite the small number of subjects), and that, biologically as well as classically, it induces an initial increase in the IgE levels (but not IgG4), together with an activation of the peripheral T lymphocytes (CD69 and CD98 expression), an improvement in the nasal cytological inflammation and a decrease in IL8 levels.

As a conclusion, IL immunotherapy constitutes a beneficial advance, from all clinical, biological, and socio-economic points of view (4 injections only as opposed to €9,000 for the conventional technique).

13. Childhood obesity (O) and asthma (A)

Theme: Asthma – Allergy paediatrics
Key words: Obesity – Asthma – Asthma control – Home pollution

Two major studies focus on this association: a US one (*L.N.Borrell et al JACI Feb 7 2013 ahead of print*) focused on ethnic and environmental factors, and a European one on the chronology and compared development of these two entities (*D.Rzehak et al JACI 2013 a.o.p*).

In America, 2,174 children, aged 8-19, from across the USA, Mexico and Puerto Rico, and suffering from A and O, were examined in order to determine how efficiently they are controlling their A, particularly how they respond to inhaled corticosteroids. Only 17.6% of cases were found to be under control (383 subjects: 192 boys and 191 girls), 48.9% were partly under control (1,063 subjects: 605 boys, 458 girls) and 33.3% were poorly controlled (403 boys and 325 girls).

After adjusting for all confounders (passive smoking, recruitment season…), O children had a 33% greater chance of having worse asthma control than their normal weight counterparts. However, for girls, African-Americans had lower odds of worse asthma control than Latino-Americans.

The longitudinal European survey concerned 12,050 children belonging to 8 cohorts from different countries and suffering from A and allergies; its aim was to study A incidence as a function of weight gain profile: 3 categories were analysed according to WHO criteria:

- One, normal
- One with early and rapid weight gain in the first 2 years of life
- One with progressive weight gain from age 2 to age 6

After adjusting for different child development factors, it appears that rapid weight gain in the first 2 years is the most predictive risk factor for A, and this up to age 6.

Finally, a 3rd study of 148 A and O children, aged 5-17 and predominantly African-American (*KD Lu et al JACI Feb 2013 aop*), points to an increase in the sensitivity to home and urban pollutants (PM 2.5 and NO2) in A and O subjects, and also that a control of home pollution is also beneficial for O.

14. Late-onset asthma (LOA) and metabolism of NO

Theme: Asthma
Key words: Late-onset asthma – NO (Nitric Oxide) – FENO (Fractional Exhaled Nitric Oxide) – ADMA (Asymmetric Dimethyl Arginine)

Late-onset asthma (LOA) is today considered as a particular phenotype, clinically severe, with a neutrophilic inflammatory profile, often occurring in obese persons, and responding little to inhaled corticosteroids. It thus differs from early-onset A (EOA) in young children, which is rather atopic and eosinophilic.

The recent multicentre US study (*F.Holguin et al AJRCCM 2013 187 2 153-159*) adds a new, metabolic, dimension concerning arginine, a NO substrate amino acid, whose synthesis is thus diminished because of its methylation.

155 subjects aged 18-69, belonging to a cohort of severe As, 73% women and 27% men but 47% obese were the object of the study:

- One group suffering from LOA (76 cases)
- Was compared to the EOA group (79 cases)

Given the known association between weight gain (frequent in LOA) and FENO decrease caused by the increase in ADMA plasmatic concentration and the decrease in the L-arginine/ADMA ratio, the research aimed to verify whether this mechanism was comparable in the 2 A groups.

Statistical results show that the ADMA average plasmatic concentration is indeed high in LOAs (and not in EOAs) whereas that of L-arginine was lower. And such a decrease in the L-arginine/ADMA ratio is associated with persistent respiratory symptoms, lower FEV1 and lung volumes, and lower IgE levels, which are all markers of LOA.

All in all, the study confirms that the L-Arginine/ADMA ratio may account for the inverse relationship between IMC and FENO, and that its decrease which reduces NO synthesis strips the latter from its protective role on the respiratory function.

The resulting conclusion in practice would be to treat these LOAs by L-Arginine or L-citrulline so as to restore the NO metabolism, but the first trials have so far not been convincing.

15. Allergenic extracts and their regulation: the French exception

Theme: Therapeutic – Immunotherapy
Key words: APSI (Allergens Specially Prepared for Individuals) – AFSSAPS (Agence Française de Sécurité Sanitaire des Produits de Santé) – APSI Group

Like all medicines, allergenic extracts (AEs) have required a marketing authorization since 2001 in Europe. Two categories must be distinguished: usual, industrially produced allergens (APs), and "named patient products" (NPPs) specially prepared for an individual person by medical prescription.

They are regulated at the national level. In France, and in line with EU guideline, AFSSAPS (the French Agency for Health Products' Safety) has introduced new requirements for all APs:

- For each one a detailed technical file must provide all the pharmacologic, toxicological and clinical data supporting its quality and security but also its diagnostic and therapeutic interest.
- The selection process first began by defining a list of relevant aeroallergens (pollens, dust mite, pets, fungi) and creating an ASPI/NPP work group composed of the main allergist organisations (teachers, scientific societies, continuing education institutions, trade unions) as well as representatives from the 2 AP manufacturers.
- For an allergen to be authorized, it must be validated first by the ASPI/NPP group then by the two expert AFSSAPS Commissions.

The methodology is based on 5 assessment criteria, of which 2 are compulsory: evidence of the patients' sensitivity to the allergen and proof of their exposure to it. A first list of 84 APs was drawn up and 73 retained; then in 2008 and given the absence or insufficiency of valid published studies, only 66 were authorized (of which 29 were validated by scientific studies establishing their efficacy) and about 1/3 standardised. This strict French process, similar to that in the USA, has not been adopted by all European countries. But it guarantees that our APs are clinically relevant and safe, before a consensus on their standardisation.

16. Recombinant Allergens (RA) in Paediatrics

Theme: Allergens
Key words: Recombinant allergens – Major allergens

The identification of allergenic components with the techniques of molecular biology and selective IgE reactivity to allergens (major or minor) represent significant breakthroughs towards the personalised diagnosis and treatment for allergic patients (*R.Coudert et J.Just Bulletin de l'Acad. Nle Médecine Mars 2013 sous presse*).

In this way, it is possible to make out several molecular families and to characterize the main epitopes as follows:

1) Thermoresistant LTPs (*Lipid Transfer Protein*), present in raw or cooked fruit and vegetables (eg. *Ara h 9*) and responsible for sometimes severe respiratory and food allergies, mostly observed in Southern Europe.

2) Thermolabile PR-10s (*Pathogenesis Related proteins*), responsible for oral syndrome and cross-allergy (eg. apple-birch).

3) Profilines: minor allergens, in pollens and plants, often without clinical consequences.

4) Tropomyosin: a muscular protein, frequent in invertebrates (shrimp, dust mites, eg. *Der P 10*), responsible for cross-allergy between dust mites, shell-fish, and snails).

Identifying the specific major allergen in children may help to avoid sometimes hazardous provocative testing; this is the case for peanuts, where simple sensitivity to *rArah 2* confirms the diagnosis.

As for prognosis, the association between *Der p1* and *Der p2* predicts a good efficacy of dust-mite immunotherapy (inversely not recommended if sensitivity to *Pen a 1*, the shrimp tropomyosin, is also associated).

Several attempts at immunotherapy with RAs have been successfully performed (Birch, Timothy, Cat) but the high heterogeneity of molecular profiles (*S.Tripodi JACI 2013 129 3 834-839*) and changes in pre-clinical IgE response over time (*L.Hatzler JACI 2013 130 4 894-901*), make 'customised' allergenic preparation and its validity quite risky.

17. Biomarkers of Omalizumab (O) potential efficacy in severe allergic asthma

Theme: Severe Asthma – Treatment
Key words: Omalizumab – FE NO – Severe allergic asthma – Blood eosinophilia – Periostin

In severe allergic, primarily Th2-weighted asthma (A), American and European specialists recommend the use of one of 3 dosages of O (75, 150 or 300 mg), in a single 4-weekly injection. In France, only the 75 and 150 mg doses are authorised. In order to avoid useless and costly treatments, the role of biomarkers (BMs) likely to predict O's efficacy is analysed in the following paper (*N.A.Hanania et al AJRCCM 7 March 2013 on line*).

850 patients, aged 12-75 and suffering from severe allergic asthma were enrolled (427 asthmatics and 423 placebo), in an American multicentre randomised study. 3 BM were used at the beginning of the treatment: FeNO for 397 patients (46.4%), blood eosinophilia for 797 (93.8%) and Periostin (P) for 534 (62.8%). The objective was to assess reduction in A exacerbations during treatment (48 weeks, on age- and weight- adjusted US established doses), BMs were divided in 2 subgroups: low and high level.

Compared to placebo, the 3 high level BMs revealed O's clear efficiency in the reduction in A exacerbations.

Comparing the two subgroups statistically showed high level BM superiority over low:

- for FeNO : 53% vs 16% (P : 0.001)
- for blood eosinophilia: 32% vs 9% (P: 0.05)
- for P dosage: 30% vs 3% (P: 0.07)

True, there was no significant difference between the 2 subgroups at the end of treatment as to the patients' quality of life and A symptomatology, with the 3 BMs expressing airway inflammation.

But, if one looks at the action mode of monoclonal antibodies, FeNO would be the best marker for O assessment (anti-IL4 and anti-IL5), whereas P, the marker for eosinophilia and IL13 action, would be more sensitive to Lebrikizumab.

It should be noted (with *N.C Thomson et al JACI 2013 1008-1016*) that all inflammatory biomarkers are clearly reduced in current smokers with severe asthma.

18. Omalizumab (O) in the treatment of Chronic Urticaria

Theme: Skin allergology
Key words: Omalizumab – Chronic urticaria

Two papers deal with this theme: a Canadian one (*C.H.Song Ann. Allergy Asthma, Immunol. 2013 113-117*), an open trial on 16 patients, and an American one (*M.Maurer et al NEJM 2013 368 924-935*), a randomised multicentre trial on 323 patients.

All the authors agree on the definition, i.e. eruption of hives and itching for over 6 weeks uncontrollable by antihistamines. O efficacy was assessed using 7-day activity scores and itch-severity scores.

- In the Canadian trial, O (not reimbursed by the State for this indication) was administered every 2 to 4 weeks at 150mg doses. A remission was obtained with 10 patients, 6 after the 1st injection, 2 after the 3rd and 2 after the 6th. Failure or cessation of O in 2 cases. In the long term: 3 were asymptomatic 1 year after the last dose, 1 after 9 months; 7 continued treatment every 4 to 8 weeks; 3 had stopped completely. On the whole, a mixed result.

- In the American trial, 323 patients aged 12-75 (average 42), 85% white, 41% suffering from Angioedema; High level of IgE (average 78 UI),), received 3 subcutaneous injections every 4 weeks at age-, height- and weight-adjusted doses (82 at 75mg, 83 at 150mg, 79 à 300mg and 79 placebo); they were monitored for 16 weeks, with daily and weekly electronic itch-severity scores (0 to 21, average 14 in the 4 groups).

Primary end-point: After 12 weeks, decrease in itch-severity score by at least 5 points, and in hives number and size; Statistics revealed a significant decrease for the 150 and 300mg groups (P = or ≥0.001).

Secondary end-point: proportions of remission (free of hives and itching) In post-hoc analyses, the results are: 10% for placebo, 18% for the 75mg group, 23% for the 150mg and 53% for the 300mg group; therefore, clinical improvement depending on the dosage in both analyses; however, a maximum of side effects at 300mg.

That is to say that O's place remains to be defined in the treatment of Chronic Urticaria.

19. Role of Th17 and IL17 in Allergo-Immunology

Theme: Immunology
Key words: Th17 lymphocytes – IL17A and IL 17C interleukins – auto-immunity – CD24 – Allergic alveolitis – Respiratory infection

As a lymphocyte subpopulation, newly identified in the CD4+ Th framework, Th17 cells seem to play an important role in the mechanism of allergic and auto-immune (AI) diseases. Moreover, they are co-responsible for the release of Interleukins 17, a family of 6 components from IL17A to IL17F, with 17A and 17C the most important.

1) TH17 and AI: Increased incidence of AI is due to the joint action of genetic and environmental factor. A remarkable US-German paper (*M. Kleinewierfiled et al Nature on line March 2013*) showed, in cell culture and on a murine experimental Encephalomyelitis (an animal model for Multiple Sclerosis MS,), the pivotal role of Th17cells. Indeed, high salt-concentration in mice, whether metabolic or food-induced, worsens Encephalitis since nervous tissues are invaded by TH17s which release pro-inflammatory cytokines: IL147A, GM-CSF, IL2 TNFα. The paper's authors carefully avoid extrapolating to humans the relationship between hyper salted diets (Western fast-food) and occurrence of AIs such as MS and Psoriasis but suggest clinical trials of food salt reduction in individuals at risk for developing AI disease.

2) IL17A and hypersensitivity pneumonitis (HP): In a murine model of HP provoked by *Saccharopolyspora rectivirgula*, cause of Farmer's Lung disease, still frequent in Canada, the authors (S.A Hasan et Al JACI 2013 on line) show that IL17A is crucial for the development of lung fibrosis, which is significantly attenuated by depletion of neutrophils. Moreover Monocytes/Macrophages and Neutrophils (and not Lymphocytes) are the main cells-type that expressed IL17A in experimental HP.

3) IL17C and lung infection: (*P.Pfeiffer et al AJRCell Molecul.Dec 2012*) IL17C enhances inflammatory response of the lung epithelium of mice infected with *Pseudomonas aeruginosa*, an innate immune response, suppressed by cigarette smoke, one of the mechanisms explaining the harmful effects of smoking.

20. Infections and asthma

Theme: Asthma – Infection
Key words: Infections – Asthma – Microbiome – Vitamin D

As recalled in an excellent review by T.T.Hansel et al (*The Lancet 2013 381 March 9 861-871*), the respiratory tract is literally 'bombarded' by bacteria and viruses (in addition to dusts and allergens). It adapts its response with Dendritic, Epithelial and Lymphocyte cells. It is well-known that one healthy adult harbours an estimated 100 trillions of bacteria which can today be identified through genomic methods (16 S ribosomal subunit sequence): The microbiome is mainly located in the colon but also present in the respiratory system.

In asthmatics, the mucosal immune response is variable. The authors categorise it according to the '7 ages of asthma' (A) with its consequences on practical points of view:

1) Already in the foetus, although maternal exposure to bacteria and farm dusts has a protective effect against-asthma, vitamin D deficiency in the mother may cause 'wheezing' in the new-born (NB) that some paediatricians hesitate to label as asthma.

2) At birth, the NB already carries approximately one hundred bacteria in the colon and the umbilical cord contains an increased concentration of Th2 chemokines. In a recent Danish study in 662 subjects, the authors found a colonisation of neonates airways by *Moraxella Catarhhalis* and *Hemophilus Influenzae*, (*N.V Folsgaard et al AJRCCM 2013 6 589-595*) which is associated with inflammatory immune response and may result in chronic inflammation.

3) During infancy (up to 18 months), SRV (*Syncitial Respiratory Virus*) is the major cause of bronchiolitis, leading often to future A.

4) During early childhood (up to 5 years), virus and allergens account for the classical atopic march towards asthma.

5) During later childhood and adolescence (6 to 16), children are vulnerable to viruses responsible for persistence of A, but also to *Mycoplasma Pneumoniae* and *Chlamydia Pneumoniae* which justify the use of macrolides.

6) In adults, the respiratory microbiome is abundant and diversified, but it is RHV (*Respiratory Human Virus*) which is the major cause of A exacerbations.

7) Finally, in elderly subjects, the range of concomitant diseases causes a loss of lung function and vulnerability to bacterial and viral infections, justifying recommendation of influenza vaccination in this age group. The authors conclude that these advances in the role of microbes in asthma may allow personalised treatment in the near future.

21. Testing children for allergies

Theme: Paediatric allergology **–** Allergy diagnosis
Key words: Skin tests – IgE – Allergist – Primary Care Physicians – Molecular biology – Challenge test – Eczema – Urticaria – Respiratory allergy – Gastro-intestinal symptoms – Anaphylaxis

In an important review, the Geneva university hospital team (*P.A.Eigenmann et al Ped. AllergyImmunol 201324 3 195-2009*), in collaboration with 13 paediatric centres in Europe, points out his large experience in this field. Recalling the need for close collaboration between Allergists and Primary care Physicians who are the first to confront the symptoms and often diagnose allergy in their young patients, the authors put forward a number of recommendations, particularly for skin tests (prick and intradermal) which are difficult to interpret before the age of 2 and must be used in correlation with clinical relevance. The same can be said of the biological tests: particularly total and specific IgE whose sensitivity and specificity must be defined before any therapeutic decision.

At that time, Allergists comes in to confirm a diagnosis by molecular biology techniques (Immuno-Cap) looking for recombinant allergens, or through challenge tests, a core activity of Pediatric Allergist trained physicians, which in well-equipped centres are safe and lead to either the confirmation or the elimination of the diagnosis, thus avoiding useless

treatments or, in the case of **f**ood allergy, excessive and sometimes unpleasant eviction measures.

The paper then reviews the different symptoms which justify the use of tests (who does what, when and how?).

- For skin manifestations:

Eczema: Think of food allergy, the most frequent allergens in Europe being eggs, milk, peanuts, wheat, fish and soybeans; beware of skin tests made with raw extracts, which often generate false positive results.

Urticaria: Either acute within 2 hours of the suspected trigger factor, for which skin and IgE tests can be sufficient, or chronic, seldom allergic or specialist-relevant (medication?).

- Respiratory manifestations: Rhinitis and conjunctivitis, either seasonal (role of pollens, different according to areas) or perennial, with coughing and wheezing (dusts, dust mites, fungus) that are difficult to treat and need other procedures but should be differentiated from asthma.

- Gastro-intestinal disorders: with colic and other digestive symptoms. In excessive, inconsolable crying infants, consider cow's milk allergy**.**

- Finally, special cases of Anaphylaxis by allergy to hymenoptera (bee or wasp) or even to latex, anaesthetics or antibiotics: they call for hospitalisation in reference centres.

22. Food challenge (FC) in children sensitised to peanuts/treenuts

Theme: Paediatric allergology – Allergy diagnosis
Key words: Food challenge – Peanut – Hazelnut – Atopy – Specific IgE

Food challenge is at the very heart of the paediatric allergist's field.

When carried out in double-blind placebo-controlled testing, it is the gold standard of the diagnosis. It supplies conclusive confirmation, leading to appropriate and customised therapy.

But, even in expert hands and harmless in principle, it is time-consuming and anxiety-causing in the young patient and his/her family. It can then sometimes be replaced by an 'open' test. On the other hand, it can be the solution for a child without yet clinical signs but with a high IgE level.

This is the situation described by the Lausanne and Geneva Swiss paediatricians concerning peanut and tree nut allergy in children (*S.Ludman et al Ped.Allergy.Immunol May 2013 276-28*), who attempted to clarify the risk factors in case of accidental ingestion, given that tolerance to these allergens develops with age and that 1 child in 2 with a ≤ 5 kU/l specific IgE level, and after 4 years has a 1 in 2 chance of becoming tolerant.

The retrospective study concerned 98 children aged 9 to 13 who had never ingested peanuts or hazelnuts and who had undergone a FC: 47 to peanut and 51 to hazelnut, with 29 positive, 67 negative and 2 inconclusive. The whole set of data on family history, patients' personal history, extra examinations, and possible associated allergies, were subjected to a multivariate logistic regression analysis.

The results were the following:

- The association of maternal atopic history and a specific IgE ≥ 5 kU/l induces a significant increase the risk in the likelihood of positive FC.

- After adjusting for age, this positive FC probability in 3-year-old children is 67%, 5 times more frequent than in older subjects.

- As for other factors, such as patient's atopy, type of food allergen (peanut or tree nut), other associated allergy**,** or severity of previous food reactions, there was no significant association.

These results should help the allergist, for each particular case, to decide on a FC or not. As concerns the test technique and although there are no standard rules, it seems that it is similar in Switzerland and United Kingdom (St Thomas Hospital) where the allergen (peanut/tree nut) dose used is twice as large (*S. Ludman, Allergy 20132 68 539-541*) with similar outcomes.

It must be emphasised that these trials were performed between 2005 and 2011, a period during which using Immuno-cap looking for recombinant allergens was not yet common. We know they can set guidelines and sometimes eliminate the need for FC. However, we must interpret IgE reactivity to these components (cf *Aalberse et al Allergy 2013 in press*) whose heterogeneity is well-known, taking account of their clinical relevance and remembering that evolution of sensitivity towards clinical manifestation, is a slow and progressive process.

23. Dry Night Cough (DNC) as allergy marker in pre-school children

Theme: Paediatric allergy – Respiratory allergy
Key words: Night cough – Asthma – Atopy

In a first epidemiological study on a cohort of infants from the Paris area (*PARIS: Pollution and Asthma Risk in Infants Study*) the authors (F. Rancière et al Ped.Allergy.Immunol 2013 24 131-137) had observed a frequent association between DNC and allergic manifestations.

To confirm this hypothesis, they undertook a new trial by following the cohort of 3840 infants from birth to age 4 between 2003 and 2006 with this methodology:

- parental questionnaires of the ISAAC type;

- blood markers of atopy at 18 months of age: total and specific IgEs ≥ 45 kUI, blood eosinophilia ≥ 470/µl and more recently for some subjects ImmunoCap Phadiatop);

-presence of a DNC without infection, with or without wheezing.

The whole set of data gathered from 1869 infants was submitted to a series of statistical analyses. It should be noted that 4 infants on 10 having presented at least one DNC episode between 1 and 4 years.

Three types of trajectory were identified:

- a 1st group (72.4%): never or infrequent pattern, this group being then used as control
- a 2nd group (8.8%): transient pattern, with moderate DNC occurring in year 1 but cured by year 4
- a 3rd group (18.8%): rising pattern, with DNC starting at year 2 and persisting at age 4, or beginning later but still present at age 4

The statistical study reveals in group 2 a high proportion of smoking mothers, without any marker of atopy. In group 3, apart from a frequent family history of allergy**,** there is a significant association between DNC and atopic markers at 18 months (high IgE and sensitisation to respiratory and/or digestive allergens) and presence in the fourth years of clinical allergic manifestations, mainly eczema and pollen rhinitis.

Thus, while wheezing is regarded by English-language publications as predictive of allergy and sometimes asthma, DNC in itself, without infection or wheezing, is shown here to be an excellent risk-marker for allergic morbidity.

24. Antihypertensive medication use and anaphylaxis (A)

Theme: Allergy and anti-hypertensive medications (AHT)
Key words: Hypertension – Anaphylaxis – Beta-blocker – Diuretics – Angiotensin-converting enzyme inhibitors – Angiotensin-receptor blockers – Calcium channel blockers

Following several papers on A in patients treated both by Angiotensin-converting enzyme (ACE) inhibitors and venom immunotherapy, or patients taking β-blockers and contrast products, the authors from Mayo Clinic Emergency Department in Rochester USA (*S.Lee et al JACI 2013 131 1103-8*) conducted a retrospective study on subjects over 18 who had consulted the department for an A episode between 2008 and 2011 and who were being treated for hypertension (AHT).

302 patients were enrolled, of which 204 females (68%), with an average age of 44; they were clustered in 3 groups according to their A severity:

- group 1 (55 cases, 18%): hypotension, hypoxia or syncope
- group 2 (139 cases, 46%): signs and symptoms involving 3 or more organ systems (pharynx, lungs, digestive tract, excepting AHT-linked heart disease)
- group 3 (57 cases, 19%): the most severe cases with hospitalization (intensive care for 17)

The anti AHT involved, ranked by order of frequency, were:

- β-blockers (BB): 49 cases
- Diuretics (D): 48 cases
- ACE inhibitors: 34 cases
- Calcium channel blockers: 22 cases
- Angiotensin-receptor blockers: 8 cases.

The trigger allergen was food (82 cases, 27%), medication (78 cases, 26%), bee or wasp venom (29 cases, 10%), a contrast product (17 cases, 6%), latex (2 cases, 1%), and no particular factor identified for the remaining cases.

Several statistical analyses of single and multiple logistic regression were performed. After adjusting for age, gender, trigger factor and pre-existing lung disease, it appears that BBs, ACEs and Ds are significantly associated with A symptoms of group 2 (odds ratio 2.8, CI 1.5-5.2, P=.0008) and 3 (odds ratio 4.0, CI 95% 1.9-9.8, P=.0001).

NB: the conjunction of 2 or 3 anti-AHTs, including CCBs, is also associated with A severity.

The authors tried to clarify the mode of action of these hypotensive drugs: role of bradykinine for ACEs, cardio-vascular co-morbidity accounting for the need to associate several anti-AHTs (at least two are usually recommended). But what clinicians must retain from this interesting study is that the subjects under anti-AHT treatment run a severe A risk, regardless of age, gender or allergic trigger factor.

25. Risks of stepping down Inhaled Corticosteroids (IC) in stabilised asthma (adults and children)

Theme: Asthma – Allergy treatment
Key words: Stabilised asthma – Inhaled corticosteroids – FEV1 – Peak expiratory flow – Adults – Children

The Mayo Clinic's respiratory-allergists (*M.Rank et coll JACI2013 131 3724-729 e2*) addressed this issue through a meta-analysis of the numerous papers in English on the subject. Two independent readers went through the full-texts and summaries of the major international data banks, up to 21st January 2012, i.e. 1798 papers, 172 full-texts, out of which 7 were selected which satisfied the chosen criteria: random studies, follow up at least for 3 months after stepping down ICs, and a clinical lung function check-up by FEV1 and Peak Expiratory Flow (PEF).

It is, first of all, necessary to define what is meant by stable asthma (A). According to common guidelines, it is a well-controlled A, with no exacerbations for one year, and treated by low doses of ICs.

The study encompasses papers which compared patients who had stopped their treatment with those who continued for 6 more months. (NB: the authors do not distinguish those who progressively stepped down ICs and those who stopped at one go).

Gathering all the available statistics, they calculated that the relative risk of an exacerbation within 4 months of stepping down by comparison with those who continue is 2.35 (P≤ .001). The absolute risk is 0.23 (P≤ .001).

At the end of the study, patients who stopped ICs show a significant decrease in their FEV1 (130 ml, P≤ .003) and their PEF (18L: min, P≤ .004) and a slight increase in their symptomatic score (P≤ .001).

So, the authors conclude that in stabilised asthmas, those who stop the regular treatment by ICs show an exacerbation risk compared to those who continue.

The same author (*M.Rank et al: Annals of All. Asthma Immunol. 2013 in press*) gets to less negative outcomes when he turns to children.

In a retrospective study on 477 children aged 5-18, observed between 2009 and 2011, following US paediatric recommendations, and after statistical treatment, they noted that those who tried to stop taking ICs did so successfully in approximately 3 cases out of 4.

NB: the season to avoid when stopping ICs is autumn.

The authors consequently conclude that stepping down the treatment of stable A in children is frequently successful; a slightly different conclusion from that made in adults.

26. Th17/IL17, severe asthma and vitamin D

Theme: Asthma – Severe asthma
Key words: Severe asthma – Vitamin D – Lymphocytes TCD4, Th17 – Interleukins IL17, IL22

We already drew attention (September 2012 BUAs) to the advantage of checking vitamin D blood levels (25 OH D3) in allergic and asthmatic patients. More recently (April 2013 BUAs) we recalled the role of TH17 and IL17 in Allergo-Immunology. This issue has again been addressed by a group of London researchers (*A.M.Nanzer et al JACI 2013 in press*) who, assuming the role of TH17 in severe, steroid-resistant (SR) asthma (A) and the benefit brought about by vitamin D3 in enhancing anti-inflammatory action of steroids, performed on asthmatic culture cells a series of *in vitro* investigations intended to determine IL17A levels.

28 patients of an average age of 50, 18 suffering from severe asthma defined by their resistance to steroids (SR) and 10 sensitive to steroids (Ss) according to usual criteria (BTS), as well as 10 healthy controls, gave blood samples (after a 2-week weaning from steroids). The T CD4 lymphocytes isolated were put in culture and submitted to a range of tests (flow cytometry, PCR, cytokine levels). It appears that:

1. SRAs cell cultures synthesize IL17 and IL22 to significantly higher levels (7 times as much) than Ss and controls; these cytokines can be found in the culture supernatant.

2. Steroids added to the cellular environment do not inhibit IL17A and IL22 synthesis in SR A or Ss A, unlike controls.

3. Vitamin D (1α,25(OH)D3) inhibits IL17 and IL22 expression in SRA and SsA cultures, irrespective of steroid addition.

These observations, together with a number of clinical and experimental references exposed in papers, justify the use of vitamin D3 in the treatment of severe asthma, particularly to enhance action of steroids.

27. Dupilumab (D) in eosinophilic asthma (EA)

Theme: Asthma – Severe asthma
Key words: Dupilumab – Eosinophilic asthma – Interleukins IL4, IL3

A new monoclonal antibody (MA) targeting the alpha subunit of Interleukin-4 receptor, inhibiting both IL4 and IL13, was the topic of a US multicentre study (Pittsburgh, Denver and Los Angeles Universities) (*S.Wenzell et al NEJM 2013 29 May online*). It concerns moderate-to-severe EAs with high eosinophil levels (≥ 300/ml in blood and ≥ 30% in sputum), treated for at least 1 year and poorly-controlled by Fluticasone (F) and Salmeterol (S).

Among 491 patients, 52 aged 18-65 were enrolled (and 52 in the placebo group). D was administered by subcutaneous injections of 300mg once a week for 12 weeks, while F was stopped at week 4 then S between weeks 6 and 9.

The first endpoint was the occurrence of an A. Exacerbation (Ex), the second, was a range of measures of A. Control, during the trial period, and the third,the study of D feasibility and tolerability.

• At the end of the treatment there were 3 Exs in the treated group (6%) versus 23 (44%) with placebo, corresponding to a significant 87% reduction; Any one of them required hospitalisation.

• Clinical monitoring included symptomatic score, morning and evening peak-flow measurement, frequency of nocturnal awakenings. The results were significantly favourable to D, especially for morning peak-flows. FEV1 showed a 200ml average increase, much appreciated by patients with marked initial lung obstruction.

• On biological level, a large number of Th2-type inflammatory markers were compared: FENO, IgE, CCL 17 and 26, all clearly reduced by D, with the paradoxical exception of eosinophils.

• As for tolerability, it was satisfactory albeit with some more frequent reactions in group D (such as nausea, nasopharyngitis, headaches, or injection-site reactions).

True, as pointed out by M.E. Wechsler's critical review in his Editorial, it is not yet the magic potion, and length of the trial was limited. However, and compared with the other active MAs, particularly targeted on IL13 (Lebrikizumab, Tralokizumab), D active both on IL4 and IL13 deserves further investigation.

28. Occupational asthma (A) in cleaning workers

Theme: Asthma – Occupational allergy
Key words: Occupational asthma – Cleaning staff – Total IgEs – FEV1 – FeNO

A joint study by Spanish and Canadian authors (*D.Vizcaya et al Respir.Med May 2103 5 673-83*) of 42 cleaning workers suffering from A and recent respiratory symptoms, carefully selected, compared to 53 healthy controls, of the same age, sex and social condition, clarified their functional and biological characteristics.

These cleaners were 93% female, average age 42 years, recruited in Barcelona within 37 cleaning companies, between 2008 and 2009. Before clinical examination, the

questionnaire covered symptoms, personal history, and above all information on cleaning products used at work as well as at home. A complete table presents 10 varieties: bleach, detergents, degreasers, waxes, polishes, limescale removers etc.

The study measured FENO, FVC and FEV1, and its reversibility post-bronchodilators, and, in serum, total IgE, pulmonary surfactant protein D and the 16kDa Clara cell secretary protein, as well as in exhaled breathe condensate, 10 interleukins, 2 growth factors, cys-leukotrienes, and 8-isoprostane.

The statistical study by multivariable logistic regression analysis showed:

• A high prevalence of atopy (42% vs 10%) as well as a level of total IgE 2.9 times higher in As than in controls; worth noting however was the lack of eosinophilia.

• A slight decrease (8%) in FEV1 under bronchodilators, asserting the low reversibility of these Asthma of adult onset; Moreover, the high FENO observed in patients and controls is not discriminating.

• Respiratory biomarkers did not reveal any significant association, thus excluding the role of impaired permeability of the alveolar epithelial barrier or of oxidative stress. Among cleaning products, irritants and sprays were most used by As at work (although their domestic use could have been an extra risk factor). The same can be said of glass cleaners, polishes and multi-use products (of various chemical compositions).

• All these informations deserve to be taken into account in the field of occupational safety, socio-economic point of view and also public health

29. Occupational asthma and skin tests

Theme: Occupational allergy
Key words: Occupational allergens – Skin tests – Standardisation

An EAACI Task-Force gathering 15 allergist centres in 6 European countries (Germany, Austria, Spain, France, Italy, Poland) undertook a detailed investigation on the value of skin prick-tests (SPT) in IgE-dependant occupational allergies (OA) (*V.Van Kampen, F.deBlay et al Allergy 2013 68 651-658*).

It is obvious that this value depends essentially on the quality of the allergenic extracts (AE) and of which depend confirmation of occupational origin of the disease and all the forensic and socio-economic consequences, from prevention to possible compensation and possible unemployment.

116 bakers, 47 farmers, 33 latex-allergic patients (mostly health professionals) of an average age of 48 were selected, 89 suffering from asthma.

Allergenic extracts from 7 European producers were used. The main allergens were: wheat flour, rye flour, soy, storage mites, animals' hair (cow) and latex. Respective AE content in proteins and antigens were estimated.

SPTs ≥ 1,5mm were considered as positive. The basic reference was specific IgE values. Sensitivity (S), specificity (Sp), Youden Index (computed from these two values) were calculated, as well as predictive SPT positive and negative values with the different solutions.

The conclusions, also published in the same journal (*Allergy 580-584*) reveal a very high disparity of manufactured AEs in their protein and antigen contents, even with an overall Sp of about 80%, the richest content solutions giving the best results. But, wheat and soy flour

AEs for bakers and farmers showed a low sensitivity and a wide variability between manufacturers. The highest consistency was obtained with the latex allergen.

The authors recommend using simultaneously solutions from different sources, until the occurrence of hypothetical standardisation.

At the same time, it should be noted that in 10 cases of severe work-related asthma (2 farmers, 2 bakers, 2 vets and 4 persons allergic to chemicals) a successful treatment, by Omalizumab, made it possible for 7 of them to maintain their activity with a significant improvement (*F.Lavaud et al Allergy 2013 Mai 651-658*).

30. Red meat allergy: an enigma lastly solved?

Theme: Food allergy – Allergen
Key words: Red meat – Alpha Gal – Ticks

The T.A.E Platts-Mills team was among the first to identify, in patients having shown severe allergic reactions after ingesting red meat (beef, pork or lamb), the presence of IgE against the carbohydrate epitope: galactose α1,3-galactose (*α-Gal*). The same IgEs were observed in patients treated with Cetuximab.

Later on, an association between meat allergy, tick bites and *α-Gal* IgE was observed in Australia, in the USA (in the Rocky mountains) and more recently in Spain and Sweden. Swedish researchers of the M. van Hage school (*C.Hamsten et al Allergy 2013 68 549-552*) have just demonstrated the presence of *α-Gal* in the gastro-intestinal tract of the *Ixodes ricinus* tick.

So they studied the serum of 4 patients having presented allergic reactions, both severe and late (urticaria, anaphylaxis), to red meat ingestion (beef), and they observed in them the presence of high levels of α-Gal IgE (≥ 100 kA/L in two of them) while the control serum of an atopic subject having eaten chicken was negative for both *α-Gal* and beef. Moreover, *Ixodes ricinus* extracts inhibited patients' IgE response. And finally, cross-sections of tick intestine revealed the presence of mono and polyclonal antibodies against *α-Gal*.

The study authors conclude that it is the 1st time that the epitope was detected in the *Ixodes ricinus* gastro-intestinal tract. Moreover, red meat allergic patients have a strong IgE response to beef and *α-Gal* epitope but also a clear response to *I.ricinus*, regardless of this epitope. It is likely that in Europe, following global warming, an increase in the rodent and deer (tick vectors) populations may induce higher risks of meat allergy.

31. Children's non-atopic asthma (A) and exposure to molds (M) in rural and urban dwellings

Theme: Asthma – Allergens
Key words: Asthma – Molds – Rural environment – Urban environment

The role of Ms in A is well known but disputed. The originality of the study reviewed here (*M. Flamand Hulin et al Péd. Allergy.Immunol. 2013 24 345-351*) lies in the assessment of exposure to Ms no longer visually or by spore count, but by emission of microbial volatile

organic compounds (MVOCs). The Fungal Index (FI) established and validated by the CSTB (*Centre Scientifique et Technique du Bâtiment*), is the result of emission of MVOCs ranked by their synthetic origin and on the basis of 19 different chemical markers.

The study of A in children from the Clermont-Ferrand area and diagnosed at least one year before included: detailed questionnaire, history, clinical examination and skin tests according to the ISAAC protocol (International Study of Asthma and Allergies in Childhood) with respiratory function tests and assessment of FI at home in apartments or farms during one week in spring.

In all, 95 children living in an urban (U) or rural (R) environment were monitored: 44 asthmatics (51 controls), with roughly the same proportion of boys and girls, and an average age of 12. 46% of the urban children were atopic, with sensitization to home allergens. In the rural environment only 20.8% were atopic, and only 1 with sensitization to *Alternaria*.

The results were as follows:

- 60% of homes were contaminated by Ms (19% through the naked eye, 58.5% through the FI); 65% of rural homes were contaminated vs 50% of urban ones.
- Exposure to Ms was observed in 70.5% of A children vs 49% in controls; The risk was higher in R than in U areas (p=0.1077) but the relationship between exposure to M and A was only significant in non-atopic children (10 times higher risk than in atopic: p=0.0581); Moreover, asthmatic children living in urban contaminated dwellings, screened at hospitals, had a higher proportion of blood neutrophils and a slightly reduced FEV1 (17.8%) than non-exposed ones.

These findings:

1) Confirm the correlation between exposure to Ms (attested by FI) and A, particularly in rural-dwelling living children.
2) Suggest a non-atopic mechanism, which is not in contradiction with the common concept of rural environment protection from allergy and A.
3) Are based on a small number of cases and therefore need to be confirmed by further research.

32. Sun exposure and atopy

Theme: Atopy
Key words: Atopy – Eczema – Rhinitis – Sun exposure – Vit.D

A group of Australian paediatricians and epidemiologists (*A.S.Kemp Péd. Allergy. Immunol 2013. 24 5 493-500*) who have been following a cohort of children since birth, attempted to specify the role of ultraviolet ray exposure in childhood or in adolescence on occurrence of allergic diseases.

In 415 subjects followed since 1988 up to the age of 16 (Tasmanian cohort), sun exposure duration was recorded through parental reports: first at the age of 1 month, then in summer holidays and week-ends, at the age of 8 and 16, then discriminated into 3 categories of daily durations: low, average, high (over 4 hours per day).

At the same time levels of vitamin D25(OH)D were measured and melanin density was checked by spectrophotometer.

An ISAAC type questionnaire (International Study of Asthma and Allergies in Childhood) recorded clinical manifestations of eczema, asthma or pollinosis (which in Australia concerns rye grass pollen), whereas sensitization to other respiratory allergens was detected by specific IgEs.

The findings were as follows:

Firstly, a good correlation appeared between the 3 estimations of daily duration of sun exposure in childhood and adolescence.

Besides, it was observed that:

1) Daily sun exposure of 4 hours and more in adolescence, especially during summer holidays and to a lesser extent on summer week-ends, is associated with significantly reduced eczema.

2) The same can be said of pollen rhinitis the incidence of which is significantly lower, more so during holidays than at week-ends.

3) On the contrary, this exposure at 8 or 16 years of age had no effect on sensitization to inhalant allergens.

4) There is no association between serum vitamin D levels and allergen sensitization.

On the whole, increased sun exposure during summer holidays in adolescence is associated with reduced eczema and rhinitis risk, independently of measured vitamin D levels. But there is no difference in inhalant allergen sensitization or asthma. However, the authors do not recommend this practice, (not without risks), for the improvement of incidence or prevalence of allergic diseases**.**

33. Recent advances on blood and sputum eosinophils (E)

Theme: Cytology – Physiopathology
Key words: Eosinophil –Eosinophil peroxidase(EPX)

Eosinophils are key-cells in allergic reaction; several interesting papers on the subject can be found in the journal *Allergy* of July 2013 vol.7. Among others, we selected that written by the Brazilian team of *M. I. Muniz-Junqueira (911-920)* which studies the correlation between the morphological modifications of blood Es and the severity of childhood asthma.

55 asthmatics aged 2-13 were monitored, 40 exacerbations, 15 symptom-free asthma and 15 healthy controls. The changes observed were isolated or associated: pseudopods, cytoplasmic vacuoles, release of a small moderate or large quantity of granules, cell spreading, free granules. It appears that such modifications are statistically more frequent in asthma exacerbations.

Reduced cell density should be added to this list, as already revealed in the 1980-90s by the works of A. and M. Capron's team who stressed the interest of these modifications, hypodense E. being an activation marker.

A Canadian-American study (P.Nair et al Allergy August 2013 early view) brings to our attention the development of an ELISA-type technique to detect sputum EPX (*Eosinophil peroxidase*), another eosinophilia marker, which will prevent tedious cell counts.

Thus, in 30 asthmatics tested, EPX levels statistically correlated with sputum E percentage (rs=0.84 P≥0.001). Moreover, whereas other granular proteins (ECP and EDN)

could be detected even in neutrophilic asthmas or COPDs, EPX, which did not increase in such cases, seemed specific to eosinophilic airway.

In addition, EPX was detected in the course of allergenic provocative tests (10 cases) whereas counts decreased dramatically after anti-IL5 treatment (Mepolizumab) for hyper-eosinophilic manifestations.

Finally, as for technical aspect, EPX levels obtained by simple noncentrifuged filtration correlated perfectly with those measured in cytocentrifuged prepared sputum supernatants (rs=0.94).

The authors consider then that this is a reliable, reproducible, simple marker of Es, specific to sputum and eosinophilic asthma airways.

34. Are eosinophils (E) essential? Consequences of their absence

Theme: Cytology – Physiopathology
Key words: Eosinophil – Monoclonal antibodies

An apparently incongruous question, which G.J.Gleich et al. (*Allergy vol 68 n°7 July 2013 829-835*) attempt to answer on the basis of several clinical observations and experimental studied.

Attention was first drawn to the subject in 1955 following the observation of a 50-year old man suffering from a benign thymoma associated with agammaglobulinemia and in whom medullar biopsies and circulating blood tests had shown the total lack of Es but the presence of basophils. Except for infectious episodes due to immunoglobulin deficiency, the lack of Es was not accompanied by any specific symptoms. Such was also the case in other similar observations in the 1960-70s. The mechanism of this anomaly was never elucidated.

Whether due to a deficiency with dysgammaglobulinemia or in allergic diseases (severe asthma, urticaria, rhinitis), the lack of Es which is clinically not very frequent (a Pittsburg University study in the 1980s only detected 24 cases out of 24 300 patients) does not seem responsible for the risk of malignant tumours nor for auto-immunity.

The same was true in experimental studies of guinea pigs (treated by E anti-serum) or mice treated by anti-IL5 monoclonal antibodies (MAs). Even in animals infected by parasites such as Schistosoma, Strongyloides or Trichinella, defence mechanisms are not affected and E does not then appear necessary for animals' maintenance of homeostasis, health or longevity.

In these conditions, the authors are not surprised by the fact that MAs are well tolerated. Such is the case of Mepolizumab in some observations even over 6 years. This is less obvious with Relizumab and Benralizumab (anti- α chain of the IL5 receptor).

In fact, these conclusions should be tempered by the small number of clinical observations of eosipenia. They must not forget the fundamental role played by E in parasitosis and as effective cells in **allergic reactions**, through the cytotoxic mediators released by the granules.

The interest of this paper resides essentially in the confirmation of a good tolerance of MA in hyper-eosinophilia syndromes where collapsing E levels are no longer to be feared.

35. Recent advances on the Churg-Strauss (CS) syndrome

Theme: Severe Asthma
Key words: Asthma, Churg-Strauss syndrome, ANCA, Hypereosinophilia, Vasculitis

CS syndrome is an eosinophilic granulomatosis associated systemic necrotising vasculitis clinically characterized by severe asthma and eosinophilia. *Manuéla Latorre*, of the Junior Members group (*JMA*) of *EAACI Milano 2013* points out the two principal clinical aspects of the disease:

1) Eosinophilia prominence, in adolescents,
2) Vasculitis prominence, in older patients.

Both cases are characterised by a difficult to treat asthma, nasal polyposis with chronic rhinitis, high proportion of blood eosinophilia, (commonly over 10%), and in sputum (which appears to be an excellent monitoring marker).

On Biologic point of view, neutrophilic anti-cytoplasmic antibodies (ANCA) are found more frequently in adults, mainly if musculoskeletal or multiorganic manifestations exist.

Histologically, all cases present necrotising vasculitis and eosinophil-rich granulomatosis, involving upper airways and peripheral nervous system, less frequently involving heart, skin or digestive tract.

Regarding pathogenesis, the disease seems triggered in some cases by exposure to allergens or drugs, but a genetic factor of predisposition is recognized; a Th2 response is also observed (IL4, IL5, IL13 cytokines). As to eosinophils, they are activated, have a prolonged lifespan, which is probably the cause of tissue damage by release of their granule proteins.

Anyway, CS syndrome is a severe disease which is often complicated with thromboembolism. Average life expectancy was estimated at 8-9 years in a small study group of Australian patients (*AF. Whyte et al Intern.Med 2013 43 7 784-90*).

The treatments hitherto proposed are above all glucocorticoids and immunosuppressants such as cyclophosphamide or azathioprine, but some trials with anti-IL5 monoclonal antibodies, namely mepolizumab, supplemented with the B-cell-depleting agent rituximab, have lead to symptom regression, but with no definite conclusion regarding their long term effects (*A.Vaglio et al Allergy2013 68 3 261-73*).

36. Allergic reactions to vaccines

Theme: Allergy to vaccines
Key words: Vaccines - Vaccine constituents

The reluctance shown by many adults, for themselves and their children, toward vaccination in general, comes from the presumed risks of side-effects, among which allergic reactions, albeit relatively rare, come high. What is the reality? This is the question R.Wood attempts to answer (Pédiatric allergy and Immunol 2013 24 521 26).

Like all medications, any vaccine is likely to provoke an anaphylactic reaction; but statistically speaking, these reactions vary from 1 in 50 000 doses to 1 in 1 million doses. The timing and variety of symptoms already distinguish between immediate and delayed allergy.

In fact, it is rather the vaccine constituent that the microbial components which usually causes these reactions; the author quotes the following:

1) Gelatine (measles, rubella, mumps).

2) Egg protein (influenza, yellow fever).

3) Milk casein (anti-diphtheria and anti-tetanus vaccines).

4) Preservatives (Tiomersal, Aluminium, usually responsible for delayed local reactions).

5) Latex (syringe or medical equipment).

6) Traces of antimicrobials.

7) Yeasts (hepatitis B and papillomavirus).

The clinical approach to these reactions is based on classical algorithms, depending on the urgence or not of vaccination, subject's age, first vaccination or booster shot, patient's history (allergic or otherwise), intensity of symptoms on previous vaccinations.

The allergist may thus need to carry out vaccine or constituent skin tests; biological tests will complete the information (in the known allergic subject: gelatine, egg). He may also have to divide the vaccine into 2 or 3 doses.

Finally, new developments are likely to arise; there are influenza vaccines without egg protein (Optaflu, Flublok) which have been validated by European and US authorities. With regard to this, the author underlines the specific guidelines for the administration of influenza vaccine to egg allergic patients i.e. the care that should be taken with adults or children who have shown + severe reactions to egg, thus requiring medically administered injections; and, in any case, avoid inhaled vaccines (which contain egg traces) since data on their harmlessness are still lacking. Moreover, the author recognizes that these recommendations may change over the coming years.

37. Health, economic and environmental impacts of rehabilitating asthmatic children's homes (simulation model)

Theme: Allergy and indoor environment
Key words: Housing – Asthma – Indoor air quality – Combustion pollutants

This original article uses environmental, statistical, medical and economic techniques to compare a complex system, that is, the evolution of asthma in children and its consequences, according to building interventions aimed at improving the quality of indoor air and reducing energy costs (M.P Fabian et al JACI 2013 early view).

The study concerns asthmatic children living in Boston in low-income families whose + polluted housing required energy-saving interventions. At the same time the effect on asthma improvement was evaluated, together with the reduction in health care costs

(provided by medical insurance in the USA: Medicare, Medicaid), all of which was compared to the cost of these interventions.

The method consisted in perfecting a pediatric asthma simulation model, validated by data from other papers. It is classified as moderate or severe according to FEV1, daily symptoms, evolution, medication given and any hospital admissions. Then follows indoor air pollutants evaluation: combustion pollutants: NO2, particles under 2,5µg (PM 2.5), cockroach allergens (Bla g 1 et 2 often found when pets lived in the home) and damp (witness of fungi).

The characteristics of the housing were then analyzed with a view to improving quality and conformity with public regulations and energy saving measures.

These interventions could be isolated or form part of a bundle: replacing gas stoves by electric ones, repairing kitchen exhaust fans, eliminating pets and smoking in the household, fitting high-efficiency particle filters, double-pan windows, weatherization of the building, (partially financed by the US government); outcome of asthma symptoms and costs of health care were evaluated according to each intervention.

Among others, results showed that elimination of pets (responsible for reduction in cockroach allergen concentration), associated to the repair of kitchen exhaust fans, produced a drop-in asthma exacerbation of 7 to 12% with one to three-year payback periods. Many other examples are quoted (together with their estimation in monetary terms). In this way the housing rehabilitation program (aiming at improved insulation) has indeed led to a 20% increase in the frequency of asthma symptoms due to a rise in damp level from 19 to 67%, but this was mitigated by repairs to air vents in the kitchen and bathroom, and by elimination of pollution sources such as the replacement of gas stoves.

The findings of this simulation model which can be applied to other populations, means that the savings from each intervention can be calculated, and its efficiency evaluated.

After consideration of these different examples (in this case young asthmatic living in deprived housing conditions), it is clear that physicians must not only take into account the treatment of the patient but also look at patient environment, particularly indoors, and the economic and health impact of interventions aimed at improving it. Assistance from public authorities is justified since they too are interested in the air quality in more salubrious housing and in energy savings. This work bridges the gap between clinical and environmental health sciences.

38. Neonatal health of infants born to mothers with asthma

Theme: Asthma- Atopy
Key words: Newborns – Maternal asthma

Maternal asthma is the most common chronic affection during pregnancy, labor and delivery with a frequency which almost doubled between the 1990s and the 2000s (P.Mendola et al JACI 2013 August in press).

It is well known, for many years, that maternal asthma has been the cause of risks of obstetrical complications (pre-eclampsia, placenta abruption, pulmonary embolism) as well

as premature birth, loss of weight and size for the newborn, and increased frequency of hospital admissions, intensive care, malformations, perinatal mortality.

A group of US gynecologists from 12 clinical centers, including 19 hospitals in 9 US districts, undertook an extensive retrospective study using the 2002-2008 US survey on 225512 newborns (NB) with a recorded birth after the 23rd week of gestation. 17044 of them, born to asthmatic mothers, were compared to as many non-asthmatic mother NBs, using logistic regression statistical methods: adjusted odds ratios with a 95% confidence interval (CI).

The methodology consisted in recording the data on the number of weeks of gestation, all the classical manifestations observed in the previous epidemiological studies, i.e.: respiratory complications (apnea, tachypnea, asphyxia and respiratory distress), cardiac manifestations, intra cerebral hemorrhage, enterocolitis, as well as prematurity and perinatal mortality (death between the first and third week).

The findings:

1) Firstly, and contrary to previous studies, which linked the frequency of perinatal complications to preterm delivery, this was only significant after the 33rd week of gestation, that is, between the 33rd and 37th week.

2) The risk of neonatal complications is statistically higher among newborns with asthmatic mothers than with controls, after adjustment for delivery method and the mother`s clinical and demographic factors.

3) The most frequent complications noted: undersized NBs, admission to NICU, hyperbilirubinemia, jaundice and respiratory complications as well as intra-cerebral hemorrhage and anemia, less frequently and among at-term NBs.

It should be noted that the risks of jaundice observed in many other statistics and which were considered as the effect of corticoids administered to the mother, have not been observed here; there was no sex-related increased risk either.

The authors finally point out the statistical power of their study, higher than all those previously published. Admittedly its limitation was the lack of precise information on the characteristics of the maternal asthma, exacerbation risks, and treatment; it should be noted however that, a poorly controlled asthma leads to an increased risk of prematurity and undergrowth; in other words, is efficient treatment is the safest security of a favourable evolution of the NB's health.

To conclude, the authors point out that maternal asthma is significantly associated with prematurity and undersized NBs and that complications (respiratory and jaundice primarily) are more frequent in NBs with asthmatic mothers even among at-term deliveries.

39. Immunity receptors and upper airways

Theme: Immunology
Key words: Immuno-receptors – Upper airways – Bitter taste receptors

Among the natural or adaptative immunity receptors, the most well known are the Toll-like receptors (TLR) expressed in the cilia cells of the upper airways. They play an important role in recognizing microbials (TLR4 for Gram (-) bacterial polysaccharides, TLR2 for Gram + peptidoglycans and lipoteichoic acid.

But a new class of receptors has recently emerged: the T2R bitter taste receptors.

In the January 2011 BUA we mentioned the subject, these receptors intended to play a defensive role against the ingestion of toxic substances, these new receptors were observed in the airways (A.Deepak et al. Nature Med 16 Nov 2011 1299-1304), which could mean that when activated, they triggered a bronchial spasm, protective factor against atmospheric pollution.

More recently a group of US authors (American journal of Rhinology et allergy: R.J.Lee et N.A.Cohen 2013 27 283-286) has pointed out the presence of these receptors (T2R) in sino-nasal cavities and suggest that their essential role was to neutralize bacteria. As there are 25 isoforms, the group tested several of them on cultivated nasal mucous biopsies from 56 patients with chronic rhinosinusitis (CRS), in order to study their neutralizing role on Pseudomonas aeruginosa.

Whereas T2R 19, 30 and 46 are ineffective, T2R38 appears to be the most important in the struggle against microbial flora, particularly Gram-, by means of biochemical mechanisms leading to activation of cilia cells and secretion of NO. But the authors go even further, knowing that T2R38 is encoded by the gene TAS2 R38 which includes two polymorphisms, depending on the position of aminoacids: an active haplotype, due to the proteins (Proline, Alanine, Valine, PAV) and a non-functional haplotype (Alanine, Valine Isoleucine AVI). Thus PAV/PAV homozygotes present greater defense against germs and are known as super tasters (as opposed to non-tasters).

The authors therefore put forward the hypothesis that patients suffering from CRS react differently to treatment according to genotype, and in a pilot study of 26 subjects they observe, after genotyping, that the only PAV/PAV homozygote subject reacted favorably to the medical treatment, whereas surgery proved necessary for the 9 PAV/AVI and the 4 AVI/AVI subjects.

The small number of cases rules out formal conclusions, but our attention is now drawn to the importance of genetic studies in treating CRS.

In conclusion, this mucociliary clearance function, due to bitter taste receptors, is crucial both in treating and preventing upper airway infections. Moreover, the well-known role of activators as flavor enhancers (natural sugars, saccharine) could help us understand the importance of these substances in empirical treatment of some cases of rhino-pharyngeal chronic cough.

40. Onset and development of allergy-like respiratory symptoms in preschool children

Theme: Atopia
Key words: Allergic pathway - Preschool children - Night cough – Parental smoking – Allergens – Atopia – Antibiotherapy.

Following up on the epidemiological study of a cohort of Parisian preschool children (the PARIS cohort, Pollution and Asthma Risk in Infant Study), the French authors, whose recent night cough study we analysed (BUA May 2014), have attempted to understand the onset and evolution of allergic type symptoms, identifying different phenotype trajectories in these children aged 3 months to 4 years (F.Rancière et al ,of the group I.Momas : Allergy 2013 68 1158-1167). The children were examined several times between 2003 and 2006.

From the whole cohort of 3840 children, the authors selected 2522 for this new study. A series of relevant statistical tools were used with the aim of overcoming researchers' subjectivity. K-means algorithm (a sort of data partitioning/clustering) while associating these phenotypes with IgE sensitization, and multinomial statistic regression for risk factors studied, Details of symptoms and their evolution are presented in many statistical tables.

The authors thus isolated four phenotypes: 2 transient (T), 2 persistent (P). Using a control group with few or no symptoms at all (1236 cases, i.e. 49%), they observed that the 2 T phenotypes were marked: T1 essentially by rhinitis in 295 children, i.e. 11%, and T2 by wheezing, essentially nocturnal, in 399 cases i.e. 15%. As for the two P phenotypes: P1 was characterized by rhinitis with cough in 234 subjects, and P2 by dermatitis in 308 cases (12%).

At the final age-4 examination, the authors noted, taking these phenotypes and corresponding risk factors, that for T1 the greatest risk factor is parental smoking. According to statistics, T2 mainly concerns boys, and the risk factor is day-care attendance source of promiscuity and probable exposure to infection risks.

As for the two other phenotypes, P1 and P2, these are considered as the result of exposure to allergens, either respiratory (dust mites in the bedding, fungi) or food allergens, but they are also associated with family **allergy** history essentially parental, and with high frequency stress. All these factors point to later development of allergic reactions. As for atopic dermatitis, which like P1 is accompanied by high IgE levels and often hyper eosinophilia, it has its own risk factor: the frequency of maternal antibiotic treatment during pregnancy.

Thus, the two transient phenotypes could be interpreted as expression of irritated airways associated with infection in a smoking environment.

On the other hand, the two phenotypes P1 and P2 with permanent symptoms both present IgE sensitization, which appears to correspond to the classic atopic march: evolution from dermatitis to asthma during the child's growth (11% of cases, which is equal to the prevalence of asthma in French school-age children). Also, in these statistics, the authors confirmed the importance of psycho-social factors and the protective role of breastfeeding in the development of allergy.

41. Asthma in school-children and psychological problems (behavioural problems)

Theme: Asthma – Allergy and psychology
Key words: Asthma – Psychological factors – Internalizing – Externalizing problems

The relationship of asthma (A) to psychological problems is an ongoing subject of controversy: are these the cause or the consequence? The extensive multicentre work carried out by the French team (I. Annesi-Maesano et al. Allergy Oct 2012 68 1471-1474) in six cities: Paris, Marseille, Clermont-Ferrand, Strasbourg, Bordeaux and Reims, has provided an original contribution to the discussion. 6880 children with a mean age of 10.4, attending 108 schools and 409 classes in the two last years of primary school, (CM1 CM2 in France) took part in the survey.

This included 2 components:

- an internationally recognized psychological questionnaire (SDQ) with 5 items and several scales, dividing subject behaviour in 2 types: internalizing (emotional) problems or externalizing (conduct problems) and 3 categories: normal, borderline and abnormal;
- a parental ISAAC type questionnaire to detect A cases in this general population and to classify them in 4 categories: early onset, current, moderate and severe.

The detailed statistical analysis, after elimination of confounding factors, revealed that:

- children with abnormal behaviour, either due to emotional (I) or conduct problems (E) are more asthmatic than others (significantly higher prevalence $P \leq 0,05$)
- among these asthmatic children, 15% of **I** presented abnormal and 10% borderline conduct, whereas 14% of **E** presented abnormal and 5% borderline conduct; in all cases, conduct abnormalities were significantly associated with early, generally moderate asthma;
- in addition, borderline conduct subjects were found to be negatively related to parents' knowledge on how to prevent asthma attacks;
- overall, some causes of these conduct abnormalities are: family difficulties, insufficient treatment (not the case here), and stress which provokes type Th2 immune reactions.

42. Statins and Asthma

Theme: Asthma – Allergy treatment
Key words: Asthma – Statins – Asthmatic exacerbation – Corticosteroids

At a time when the extensive use of cholesterol-lowering statins (S) is questioned in the treatment of cardiovascular diseases, the work of a Boston team (S.M.Tse et al AJRCCM 2013 4 October in press) brings a timely contribution, underlining the anti-inflammatory role of these drugs and their interest in preventing exacerbations of adult asthma.

The research objective was to examine the effect of Statins on asthma exacerbations using a large cohort from five major sites, including health data from a population of over 1 million subjects who were monitored from 2004 to 2010.

Methodology: Statin users aged over 31 years (around 8000 asthmatic subjects) were identified and observed over a 2-year period and - after adjusting for age, anti-asthma treatment, season, demographic factors and co-morbidity – compared to an approximately equal number of non-users.

Asthma aggravations were divided into 3 groups: need to prescribe oral corticosteroids (other than inhaled), hospital or doctor's visit, emergency admission to hospital.

All these data were analysed by logistical regression. After adjustment for confounding factors, results were as follows:

- the use of Statins was significantly associated with a reduction in emergency hospitalisations; the same was true of the need for extra per os corticosteroids;

- however, no difference was observed for asthma-related doctor's visits or simple hospitalisation.

In conclusion, among Statin users with asthma, this treatment is associated with reduced risks of emergency hospitalisation or oral corticosteroids dispensing.

43. Lipids and allergy

Theme: Asthma – Allergy treatment
Key words: Lipids – Sphyngo-lipids - Lysophosphatidic acid – Asthma – Magnesium

The role played by lipid mediators is well known; these are derived from arachidonic acid which, under the influence of Phospholipase releases the two main types of allergy mediators: prostaglandins via Cyclo-oxygenase and Leucotrienes via Lipo-oxygenase.

Attention has recently been drawn to Sphyngo-lipids (S) and their role in genetic predisposition to asthma. Metabolism of these lipids is related to modifications in magnesium homeostasis and, as there is an association between S and bronchial hyper-reactivity, it has been suggested (B.D.Levy NEJM 2013 5 Sept 976-77) that genetics may account for the variable reactions observed in the treatment of serious forms of asthma by intravenous magnesium injections.

However, another lipid mediator well known in oncology, LPA (Lysophosphatidic acid) today appears as an important mediator of allergic reactions, particularly in the airways, as is underlined in the paper published by G.Y.Park et al (AJRCCM October 15 2013 188 928 – 940).

In this mixed study, both experimental and clinical, the authors recall that Lysophatidylcholine (LPC) releases, under the influence of Lysophospholipase D (LPD) also known as Autotaxin (ATX), LPA which binds specific receptors resulting in an array of biological actions: cell proliferation, migration, survival, differentiation, explaining its function in the pathogenesis of asthma.

To prove it, the authors used broncho-provocation on volunteers suffering from moderate asthma caused by common allergens (dust, ragweed, Aspergillus) and observed in the broncho-alveolar lavage fluid a remarkable increase in LPA, enriched in its two polyunsaturated metabolites LPA 22.5 and 22.6. At the same time ATX concentration was also higher.

Using a murine asthma model, the same authors demonstrated that transgenic mice with a high ATX level had more severe asthma, whilst blocking the enzyme activity and knocking down the LPA receptor caused attenuation of bronchial inflammation and Th2 cytokines.

In conclusion, the ATX-LPA lipidic pathway appears to have a prominent role in certain asthma phenotypes, which would explain the evermore widely recognized link between asthma and obesity.

These mediators probably also play a role in the bronchial remodelling of certain forms of asthma.

Finally, in so far as they also play a role blocking tumour growth, some anticancer drugs may also be beneficial in allergy.

44. Ten-year follow-up and evolution of three European asthma cohorts

Theme: Asthma – Epidemiology
Key words: Asthma phenotypes – Allergic asthma – Non-allergic asthma

An impressive epidemiological study, covering several thousand European asthmatics and using the 'cluster' statistical method together with 'latent transition analysis', allowed a large international team (France, Germany, Sweden, Italy and Spain) to establish the trajectory and 10-year evolution of several asthma phenotypes.

3320 adults were recruited in three cohorts: the European Community Respiratory Health survey (ECRH), the Swiss cohort study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA), and a more recent European cohort on Genetics and Environment (EGEA) (Anne Boudier Inserm Paris et al. AJRCCM 2013 188 5 550-560), all three cohorts being followed up after 10-12 years from 1990 to 2012, i.e. 58% from first diagnosis and 42% during follow-up.

The asthma model was based on standard protocols and usual questionnaires filled in by the patient: 1) Level of symptoms (low, moderate, high), 2) Importance of the allergy factor as shown by skin tests and IgE levels, 3) Pulmonary function: FEV1, and in certain cases testing for bronchial hyperactivity.

7 asthma phenotypes were categorised as follows:

A. Allergic asthma with few symptoms, often untreated (21% of cases)
B. Non-allergic asthma with few symptoms (17%)
C. Non-allergic asthma with strong symptoms (8-12%)
D. Non-allergic symptomatic asthma (18% with bronchial hyper reactivity)

E, F, G. Allergic asthma with moderate symptoms.

Statistical results show that:

- After 10 years, the different phenotypes are extremely similar, with 2/3 of subjects remaining in the same category.

- Allergic asthmas A, D, E, F show great stability.

- Transition from moderate asthma to a strong and severe symptom phenotype is more frequent in non allergic asthma: the 3 corresponding phenotypes (B,C,D) are usually observed in elderly subjects, often obese, female, with high co-morbidity.

In conclusion the interest of this survey resides essentially in its statistical robustness and the use of new epidemiological tools in the search for greater understanding of adult asthma and its long-term evolution.

45. Contrasts in the effects of yeast and fungi in triggering infant asthmatic wheezing (AW)

Theme: Asthma allergens

Key words: Asthma – Fungi – Yeast – Bronchial wheezing – Indoor air quality

It is known that exposure to fungi often causes wheezing in infants (AW) either through irritation or allergy, but little is known of the different effects of indoor and outdoor fungi.

For this reason, a group of Boston researchers (B Behbod et al Allergy 2013 68 11 1410-1418) observed a cohort of 499 at-risk infants, aged 2 to 3 months, cultivating yeast and fungi in the bedroom and also in indoor and outdoor air dust.

AW diagnosis and its characteristics (intensity and frequency) were determined by bi-monthly parental phone questionnaire; samples, cultures and concentrations being carried out through usual techniques defining an exposure index and highlighting the fungi responsible.

The data were statistically analysed according to fungi concentrations and adjusting for possible confounding factors, such as season, infant birth weight, smoking and/or maternal mould sensitisation, and child exposure to home allergens.

Findings show that:

AW risks at one year are significantly positively associated with the indoor dust Alternaria, and Cladosporium. These risks are also associated with indoor air concentration of Penicillium and outdoor Cladosporium levels.

In contrast, indoor dust yeast concentration was associated with a reduced AW risk. They therefore reveal as protective.

Finally, frequent wheeze was borderline associated with dust and indoor air yeasts.

As for Alternaria, this was only associated with AW in children with maternal mould sensitization.

In conclusion, while AW levels were high during exposure to different types of mould considered as irritant or allergenic, indoor yeasts and unicellular moulds were associated with strong protection against AW.

Molecular microbiological studies on immunity may perhaps elucidate the contrasting effects of moulds on infant wheezing, which often leads to asthma.

46. Role of long-acting anticholinergics in complementary Asthma treatment

Theme: Asthma
Key words: Beta 2 mimetics – Inhaled corticosteroids – Anticholinergics

Although asthma in adults is often treated by inhaled corticosteroids (IC) associated with long-acting sympathomimetics salmeterol type (S), the exact role of anticholinergics, also long-acting bronchodilators, type tiotropium (T), remains unclear (currently contested in COPD treatment).

This is what a group of researchers (SP Peters et al du NIHLBI JACI 2013 132 5 1068 1074) sought to clarify, with a view to defining the interest of T (Spiriva ®) as an alternative to S when added to ICs. Their aim was to describe the different responses of asthmatics to each of the two products and to pinpoint the predictors of a positive clinical response.

The classical methodology included a double-blind three-way crossover trial, randomized in 3 groups, on 210 adults whose symptoms where inadequately controlled on a low dose of inhaled corticosteroids (80 µg beclometasone, twice a day). Three groups were identified: one with a double dose (160 µg), a second associating IC and S (50 µg twice a day) and a third group with IC+T (18 µg each morning via Handihaler). Each treatment covered 14 weeks preceded by a 2-week trial period.

In these 210 patients, aged an average 42 years, 32% male, 87% atopic, with an asthma history of roughly 14 years (FEV1 approximately 70% +/- 15% of the predicted level), the clinical efficiency was assessed according to the classical main criteria: morning Peak Expiratory Flow (PEF), number of symptom-free days, FEV1 response to a short-acting bronchodilator (albuterol or ipratropium, I), and lastly cholinergic tone measured by the lower resting heart rate

Overall, results revealed that, while approximately equal numbers of patients showed a differential response to S and T in terms of morning PEF (90 and 78 respectively) and of symptom-free days (49 and 53 respectively), a greater number of subjects showed a positive response with an FEV1 higher for T (104) than for S (62). Besides, paradoxically it is an acute response to a short acting bronchodilator: albuterol (Salbutamol ®) rather than to I , which made it possible to predict significantly a positive clinical response to T, for both FEV1 and PEF. The same is true for the 'bronchial obstruction' factor as revealed by the FEV1/Forced Vital Capacity ratio. As for the cholinergic tone, a high level is also a predictor of positive action of T.

Conversely, ethnicity, sex, atopy, IGE level, sputum eosinophil count, FeNO, asthma duration, and body mass index were not statistically predictive factors.

In conclusion, these findings show that the clinical response to T associated with IC in the treatment of moderate asthma may be favourable and represents a worthwhile alternative to S; Among predictive factors, the role of the short-acting β2 mimetic and the presence of a confirmed airway obstruction deserve to be mentioned.

46. Lung CT scan in asthmatics – A new approach to bronchial remodelling

Theme: Asthma
Key words: CT scan – Asthma – Airway remodeling – Trapping

A group of English radiologists and pneumologists led by S.Gupta (JACI 2013 Nov in press) studied the computed tomography (CT) of asthmatics' proximal airways through analysis of their quantitative clinical, functional, and radiological data, and also using new statistical tools (cluster analysis and 'fractal geometry').

The aim of the study was to explore the notion of airway remodeling and air trapping, and to try to determine new asthmatic phenotypes according to airway structure. 65 asthmatics – 48 with severe and 17 with moderate asthma – were compared to 30 healthy subjects through usual tests. Demographic data were similar as regards age, sex, asthma duration, and socio-professional factors.

CT scanning and detailed statistical analysis, together with careful study of the structures, was carried out on the lung right upper lobe (RUL) considered by the authors to be surrogate of the whole bronchial tree.
The table of findings and detailed radiological illustrations revealed:

1. Compared to controls, all asthmatics, however severe their asthma, showed a significant decrease in the RUL lumen volume but with no systematic modification of wall volume. This means that it may be a simple bronchial change in calibration, not necessarily with thickening of wall or smooth muscle.

2. Air trapping measured by lung density expiratory/inspiratory ratio was statistically greater in asthmatics than in controls. There was no evidence of emphysema.

Moreover, comprehensive analysis revealed three asthma phenotypes:

- Cluster 1 is characterised, as always in asthmatics, by an increase in lung volume with lumen dilation, but associated with severe air trapping and notable wall thickening (11 cases); this is a severe form.

- In cluster 2 there is no proximal airway remodeling, nor air trapping; this group (34 subjects) corresponds clinically to moderate asthma.

- Finally, cluster 3 associates severe air trapping and bronchial lumen narrowing (17 patients); this is a severe asthma with poorer lung function.

As a conclusion, quantitative CT scanning appears to be an interesting diagnostic tool discriminating asthma phenotypes through lung structure figures and offers new therapeutic possibilities.

47. Herpes and atopy

Theme: Atopy – Infectiology
Key words: a,β,y herpes virus - Cytomegalovirus – Eczema

In a recent article (JACI 132 6 1278-12 86) D.Dreyfuss, a paediatrician at Yale University USA, recalls that herpes family viruses are indisputable components of the human microbiome. The persistence and latency of the infection act on the genome, and are consequently able to modulate immune response, particularly atopic predisposition. There are three groups of these double stranded DNA virus:

α) Essentially HSV1, HSV2 and HSV3 or Zoster, responsible for skin or mucous lesions of the herpes Zoster type, usually benign, and latent mostly in neurones.

β) Cytomegalovirus, HSV5, V6 or V7, latent mostly in macrophages and lymphocytes.

γ) Epstein-Barr Virus (EPV), latent in lymphocytes and coding for a protein resembling to IL10 but with Th2 type action; it should be noted that when the virus infects pre-existing atopic lesions there is a risk of severe eczema; conversely, an early infection may have a protective effect.

With examples of his personal experience, the author demonstrates the various aspects observed during viral infection which may modify the clinical picture in an atopic subject. One case describes an adult with history of allergy, where contact with a necklace was assumed to be the cause of a vesicular skin rash. In fact, the presence of hemidermatome lesions revealed that this was a reactivation of herpes Zoster which resolved spontaneously.

In a second case; an adolescent suffered from eczema herpeticum which could be taken for an atopic dermatitis or contact allergy, but which, due to simultaneous mouth and eye mucous symptoms, led to the diagnosis of virus reactivation, and required rapid acyclovir treatment in order to avoid complications such as corneal scarring or vision loss.

As concerns cytomegalovirus, whose ocular and skin manifestations may suggest the severe drug-induced syndrome known as DRESS (Drug Réaction Eosinophil Systemic Symptoms), an early infection should be sought with high virus IgM levels, or a reinfection with high IgG levels. Antiviral therapy is indicated.

Finally, in the case of maculopapular skin rash, which would point to atopic dermatitis or a reaction to antibiotics, a recent EBV infection (early high IgG and IgM levels with EB nuclear antigen negativity) should be suspected. These lesions may resorb spontaneously, or more rarely call for corticosteroid and anti-viral therapy.

Finally, it should be remembered that the Kaposi sarcoma virus (HSV8), mostly observed in immunodeficient or AIDS patients, is responsible for severe skin lesions.

In conclusion, the author draws attention of allergists to the atypical presentation of these viral lesions in the atopic patient.

Also known as Hereditary Quincke Oedema, HAE is a autosomal dominant disorder characterized by repeated attacks of swelling of the skin (not itching), gastrointestinal tract, genital organs and above all larynx (with risks of asphyxiation), due to a hereditary absence or low levels of the complement C1 esterase inhibitor (C1 INH) which also plays an important role in regulating the fibrinolysis and triggers the release of bradykinin.

Although a rare disorder, it has been the subject of many recent publications including A.Banerji Annals of Allergy, Asthma Immunol. 2013 111329-336, JA.Bernstein and Jonathan American Journal of Rhinology and Allergy 2013 27 6522-527, as well as the American Guidelines (JACI 2013 131 6 1491^{e} by BL.Zuraw and JA. Bernstein).

Three varieties can be differentiated according to C1 INH level and activity:

- Type 1: total absence of C1 INH (roughly 50% of diagnosed patients, usually between 10 and 20 years of age);

- Type 2: C1 INH present in plasma but non-functional (15%); these two types are caused by a mutation of SERPIN G1 gene;

- Type 3: merely symptomatic, but ill-defined, present in the family history, and often affecting women; it should be distinguished from drug-induced HAE (angiotensin –converting enzymes).

Among factors which trigger these attacks, one should note traumatism (even benign) and surgical operations (on the airways in particular), which should be preceded by short-term prophylaxis. The use of IV plasma-derived C1 INH concentrated extracts is recommended at least 6 hours before the operation.

As for long-term prophylaxis, it is obvious that danazol type androgens are the best treatment for these patients, in terms of efficacy, cost and easy administration (to be avoided however in children and pregnant women).

As for other products such as bradykinin antagonist icatibant, or kallicrein inhibiting ecallantide, these may reduce the duration or severity of attacks; they may be of use in acute cases but are very costly and likely to entail side effects.

In Europe and France, where the disease is extremely rare, there is a risk of diagnosis failure, but its frequency is likely to increase with the mixing of populations.

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

Claude Molina
claude.nelly.molina@orange.fr

Jacques Gayraud
Jacquesgm.gayraud@gmail.com

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