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Review of
EAACI 2017
Helsinki, Finland

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Front cover and contents photograph: Helsinki, Finland, home of EAACI 2017. *© Andrey Korolev / 123rf.com*

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Welcome

Hello and welcome to *EMJ Allergy & Immunology 2.1*, which provides a plethora of content from this broad and exciting field. Inside, readers will find a comprehensive review of the European Academy of Allergy and Clinical Immunology (EAACI) congress 2017, this year held in the beautiful city of Helsinki, Finland. As part of this review, we showcase a selection of abstracts presented at the event, with the summaries written by the authors themselves. We also feature interviews with several members of our Editorial Board, who share their wisdom on this fascinating discipline. Finally, the latter half of the journal is dedicated to a collection of stunning peer-reviewed articles, spanning a variety of topics from the use of emerging technologies in allergen immunotherapy management to the microbiological biohazards associated with occupational allergies.

> “Following the congress review, there are five intriguing interviews for you to peruse, covering a range of topics, from a personalised approach to immunotherapy to the state of allergy in Malaysia.”

Embodying the motto ‘On the road to prevention and healthy living’, this year’s EAACI congress was at its progressive and informative best. Our Congress Review section features highlights from the event, including a call to action aimed at policymakers throughout Europe, summaries of two engrossing Pro-Con debates, and several insightful ‘Year in Review’ discussions on topics such as gut and skin immunology.

Following the congress review, there are five intriguing interviews for you to peruse, covering a range of topics, from a personalised approach to immunotherapy to the state of allergy in Malaysia. Next comes our gripping selection of abstract reviews. In such a broad and varied discipline, it is no surprise that the topics here are equally plentiful, ranging from the creation of a complete chronic urticaria medical history checklist to a discussion on the incredible phenomenon of thunderstorm-related asthma.

Arriving at our articles section, this edition’s Editor’s Pick is an article by Uzunoglu, who presents a comprehensive evaluation of the microbiological hazards that relate to occupational allergies, highlighting the importance of a multidisciplinary approach. Additionally, Anagnostou assesses the progress of oral immunotherapy for food allergies and Melioli et al. discuss the use of emerging technologies in allergen immunotherapy management. These are merely a small selection of the papers contained within the journal.

No matter your professional background, this year’s edition of *EMJ Allergy & Immunology* is sure to captivate and inform. We hope you enjoy reading it and that it serves to guide and inspire you in your clinical practice and research. Finally, we look forward to seeing you next year at the EAACI congress 2018.

Spencer Gore

Director, European Medical Journal

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Foreword

Prof Dr Jacques Bouchard

Associate Professor of Clinical Medicine, Laval University, Québec City, Québec, Canada.

Dear Readers,

It is with great pleasure that I introduce you to this year's edition of *EMJ Allergy & Immunology*.

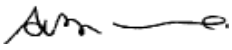
Following the excitement of the 61st Annual Meeting of the European Academy of Allergy and Clinical Immunology (EACCI) congress in June, this latest eJournal provides an excellent summary of the event, aimed at keeping you up to date with the ground-breaking research that was presented over 5 days in Helsinki, Finland. By including the key details from poster presentations and discussion sessions, this review will allow you to revisit your favourite highlights or catch up on what you missed from the largest allergy congress in the world. For those of you who would like to delve further into the fascinating world of immunology, I encourage you to continue to the Abstract Reviews section, which provides a more detailed summary of a selection of the abstracts presented at the congress, written by the researchers themselves.

Moving on, you will find a collection of inspiring interviews with some of my colleagues who explain why they are so passionate about their work in the field of allergy and immunology. They answer questions relating to their past experiences and future aspirations, and I am sure you will enjoy learning more about the professional and personal lives of some of the top experts in this field.

The final section of this eJournal comprises a selection of peer-reviewed papers submitted by leading allergy and immunology specialists. I believe these original reviews are an important aspect of the eJournal and are not to be missed, as they provide an opportunity to prompt discussions and debates amongst yourself and colleagues regarding the very latest discoveries. Although all papers are of outstanding quality, my particular favourite is the paper titled 'Microbiological Biohazards Associated with Occupational Allergies', by Uzunoglu. This unique review summarises the main pathogens that are known to contribute to the development of occupational allergies, and concludes with a discussion around the importance of managing these agents.

I would like to thank you all for your contributions to this latest version of *EMJ Allergy & Immunology*, making it a fascinating and inspiring read that I hope you enjoy and recommend to friends.

Kind regards,



Jacques Bouchard

Associate Professor of Clinical Medicine, Laval University; Head of the Medicine Department, La Malbaie Hospital, Québec City, Québec, Canada.

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Includes a selection of the latest articles for allergy & immunology, neurology, innovations, and more.

FEATURE

‘Vaginal Rejuvenation’ and the Regulation of New Technologies: Controls Are Still Lacking

- Antonios Antoniou, Ahmed Yassin

Featured inside:

ARTICLES

Editor’s Pick: A Regenerative Biology View on Artificial Tissue Construction and Three-Dimensional Bioprinting: What May We Learn from Natural Regenerative Phenomena?

- Henrik Lauridsen

Efficacy of the Artificial Urinary Sphincter ZSI 375 for Treatment of Post-Radical Prostatectomy Incontinence in Patients with Intrinsic Sphincter Deficiency: A Preliminary Study

- Alejandro Carvajal Obando et al.

Digital Technology Healthcare Solutions in an Era of Moving Populations and Chronic Illnesses: Are We Being Realistically Smart?

- Judith Ansaa Osae-Larbi

Comprehensive Assessment and Pharmacotherapy of Patients with Chronic Pain Syndrome Due to Diabetic Neuropathy and Postherpetic Neuralgia

- Katarzyna Rygiel

Benchmarking Outcomes That Matter Most to Patients: The Globe Programme

- Andre G. Dias et al.

Epithelial-Mesenchymal Transition in Docetaxel-Resistant Prostate Cancer

- Camila Libardi do Amaral

Concerns About the Use of Non-High-Density Lipoprotein Cholesterol as a Lipid Predictor

- William E. Feeman, Jnr.

Occupational Allergy

- Stacey E. Anderson et al.

And, even more...

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EAACI ANNUAL CONGRESS 2017

MESSUKESKUS CONGRESS CENTER,
HELSINKI, FINLAND
17TH–21ST JUNE 2017

Welcome to the European Medical Journal review of the 61st European Academy of Allergy and Clinical Immunology Annual Congress

The largest allergy congress in the world was this year hosted in the scenic city of Helsinki, Finland. The congress theme was 'On the road to prevention and healthy living', encapsulating the passion of the European Academy of Allergy and Clinical Immunology (EAACI) to create a better quality of life and lower disease burden for their patients.

The city of Helsinki provided the perfect setting for the congress, being known the world over for its modernity and its association with scientific prowess. The most recent Thomson Reuters list of Highly Cited Researchers was furnished with no fewer than 10 representatives of the University of Helsinki, out of the 17 researchers featured from across Finland. In 2015, a team, headed by Prof Kari Alitalo at the University of Helsinki, reported the discovery of lymphatic vessels in the brain, which has been hailed as one of the most significant scientific findings of the year. Indeed, this discovery has changed the way that we think about neurological diseases by showing the connection between the brain and the lymphatic system. Helsinki is also famous for its world-class research in climate change; the University of Helsinki was this year chosen as the prestigious headquarters of the Integrated Carbon Observation System (ICOS), and this will be closely followed in 2021 by the Aerosols, Clouds, and Trace Gases Research Infrastructure Network (ACTRIS). These are just some of the impressive accolades boasted by the beautiful city that attendees were encouraged to explore alongside the jam-packed scientific programme.

Continuing the theme of academic and scientific excellence, the EAACI congress utilised the very best in technological support. Audio accompaniments to poster sessions were available via an app, while delegates were also able to earn CME credits simply by entering the room in which a session was being held without the need to scan in. A computer chip synced with an attendee's badge registered via wireless sensors mounted throughout the venue, offering attendees a convenient and fast way to earn CME credits and enjoy the congress without waiting in line to scan in.

The programme offered attendees the chance to take part in all aspects of allergy and immunology research and practice, and with such a broad range of activities, talks, and sessions to attend, there really was something for everyone. Postgraduate sessions offered medical students the opportunity to learn more about the practice of allergy and immunology, with training courses offered on topics such as managing drug hypersensitivity, adult food allergy, and 'omic' technologies; attendees could also take a short course in leadership to offer career advice and progression. Pro-Con debates featured throughout the event, and you can read about some of these in more detail in the following congress review, courtesy of our congress reporters. The schedule was peppered with symposia addressing a plethora of important issues in allergy and immunology, including treatment of rhinosinusitis, environmental and climate impact on allergic disease, and the much-anticipated Women in Science symposium.

> "We are a young academy facing a generational change, as well as generational and gender opportunities"

Women in science is a subject of great importance for EAACI; EAACI president Prof Antonello Muraro was keen to note the achievements of EAACI in advocating for greater progression for women in science as well as the academy's commitment to encouraging young talent in her presidential message in the congress newsletter. She explained: "EAACI now has 10,000 members and more than half of them are women. Our biggest group is the Junior Members assembly. We are a young academy facing a generational change, as well as generational and gender opportunities." She was also optimistic and passionate about the future of the society: "EAACI is definitely the place to be if you have ideas and want to make them happen. The passion and vision are there, and I very much hope and wish that the academy's members will continue to enjoy working together in the coming years."

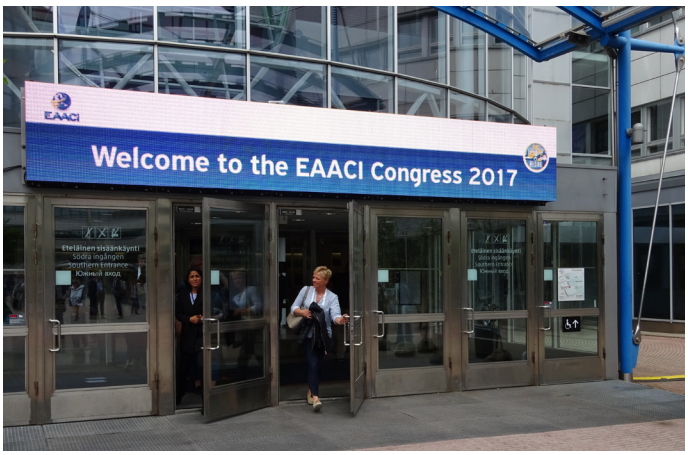
The opening ceremony welcomed attendees with a rousing rendition of classical piano by well-known Helsinki-born jazz musician, Iiro Rantala. Following this, Prof Muraro addressed delegates alongside Prof Antti Lauerma, the EAACI Congress 2017 Chair. Prof Lauerma talked of the journey to arranging the congress, explaining that: "Every member can suggest a topic or session" so that "The whole programme over the 18 months is the result of our membership's suggestions." It is this enthusiasm and hard work that makes EAACI arguably one of the most inclusive European congresses.

Another exciting and much-anticipated aspect of the congress was the poster presentation and discussion sessions. Posters and oral presentations were displayed throughout the event and prizes were awarded each day to the most impressive. The winners included studies on management of drug allergy, anaphylaxis, drug allergy: diagnosis, biomarkers in asthma, and insect venom allergy, with winners hailing from all four corners of the globe. Presenters of a selection of abstracts have provided the European Medical Journal with exclusive summaries of their research for your reading pleasure. Simply proceed to our Abstract Reviews section to learn about just some of the ground-breaking research that was presented at the congress, whether you are looking back on the congress or catching up on what you missed.

EAACI 2017 was certainly a congress to remember. We hope you will enjoy our independent review of the event and look forward to seeing you at next year's event in Munich, Germany!

Call to Action: Allergy and Asthma

AN ISSUE especially promoted at the EAACI congress 2017 was the political Call to Action for European nations: 'United action for allergy and asthma'. This Call to Action had been launched prior to the congress, on 25th April 2017. EAACI was one of three co-founders of this initiative. The other two founders were the European Federation of Allergy and Airways Diseases Patients' Associations (EFA) and the European Parliament Interest Group on Allergy and Asthma. The co-founders intend that this initiative will kickstart an advocacy campaign that is European in scope to generate action to tackle two of the most prevalent chronic conditions in Europe: allergy and asthma (currently there are >220 million patients across Europe with allergy and asthma).



The Call to Action in Europe will focus its attention on both EU and national policymakers. Its overall goal is "to unite all strategic parties in Europe to address allergy and asthma through a collaborative and holistic approach, supporting patients' rights." Policy recommendations will be provided to stakeholders at all levels, ranging from patients to the European Parliament and EU member states.

> "Change is possible, it needs to happen now, let us unite to drive positive change together."

Furthermore, it is hoped that, under the aegis of the Call to Action, increased collaboration between European countries can be fostered. This collaboration would involve better promotion of allergy and asthma programmes, greater support for the collection of public health measures, and increased co-ordination to monitor allergy and asthma-related trends across Europe. Another goal is for European countries to increase expenditure and investment on campaigns to prevent and detect allergy and asthma. These would include training programmes and awareness campaigns targeted at healthcare professionals.

It was noted at the EAACI congress that the first stage of the campaign was to collect signatures from all interested parties in order to show both support and the need for greater development in monitoring, preventing, and treating allergies and asthma. This signature-gathering stage culminates on 30th September 2017. Speaking at the launch event for the Call to Action, Sirpa Pietikäinen, Co-Chair, European Parliament Interest Group on Allergy and Asthma, offered an inspiring message, stating: "Change is possible, it needs to happen now, let us unite to drive positive change together."

Pro-Con Debate: Macrolides Should be Considered for the Treatment of Asthma

THE MODERATOR Dr Ömer Kalayci (Turkey) introduced the two participants in the first of the Pro-Con debates that took place at the EAACI Congress on Sunday 18th June. In favour of the motion 'Macrolides should be considered for the treatment of asthma' was Dr Michael Edwards (UK), and opposing was Prof Vibeke Backer (Denmark).

Before the debate began, the audience was asked to vote on the motion put forward, utilising the EAACI Congress smartphone app. This vote found 78% in favour of considering macrolides for the treatment of asthma.

Dr Edwards began by defining what he meant by the word 'consider'. "We should consider macrolides for the treatment of asthma. What I am not saying is that macrolides should replace inhaled corticosteroid therapy," he clarified. Dr Edwards then presented a number of published studies that showed the potential for this type of treatment. With regard to stable asthma, he outlined the results from 11 adult and 3 paediatric trials. Of the 11 adult studies, 10 met their primary endpoint, and just over half met their primary endpoint plus at least one secondary endpoint. Additionally, two-thirds of the paediatric trials included in his analysis supported the use of macrolides in stable asthma.

> "We have reasons for optimism. Clinical trials do show an effect."

He then discussed the role of macrolides in reducing asthma exacerbations, introducing four studies that achieved positive results. In one, for example, there was ~40% reduction in severe asthma exacerbations through treatment with the macrolide azithromycin.

Finally, Dr Edwards displayed several studies showing the effects of macrolides in young children (aged 1–3 years) with asthma-like symptoms. In these there were excellent reductions in conditions such as lower respiratory tract infections; additionally, some particularly interesting information to emerge was that azithromycin, an antibiotic, is effective in viral disease. "Azithromycin may be doing something that we do not completely understand," mused Dr Edwards.

He concluded with a positive message tempered by the need for greater understanding: "We have reasons for optimism. Clinical trials do show an effect. I think we need to consider what is the correct trial design and to look for a macrolide effect in asthma. And I think part of the reason is the challenges associated with designing the correct trial, because we do not understand the underlying biology very well."

Prof Backer then made her counter-arguments. She began by pointing out that the data regarding macrolides in asthma are currently very limited. She also reminded the audience that quality of life is one of the most salient issues for asthma patients, and with regard to this particular measure, a number of studies had failed to show a positive effect. Indeed, there was consistently no difference in the medium effect between macrolides and placebo.

Similarly, the Danish professor discussed several studies that did not display any impact between patients on placebo or treated with macrolide in relation to mortality rates. An exception to this was in open label trials, when the patient knew they were receiving the treatment. In conclusion, Prof Backer was unequivocal: "My conclusion is there is no effect of macrolides in asthma treatment."

In a 2-minute rebuttal, Dr Edwards then conceded that many more studies were required to fully understand everything that macrolides are actually doing, while reiterating what he saw as their great potential in contributing to the treatment of asthma. Prof Backer was not to be moved from her confirmed position, however, that macrolides should never be considered for asthma treatment.

To end proceedings, Dr Kalayci asked the audience to re-cast their votes. There was a narrowing of the gap from the first vote, with 63% in favour and 38% against, which brought the session to a close.

Pro-Con Debate: Can Drug Provocation be Done Without Skin Testing First?

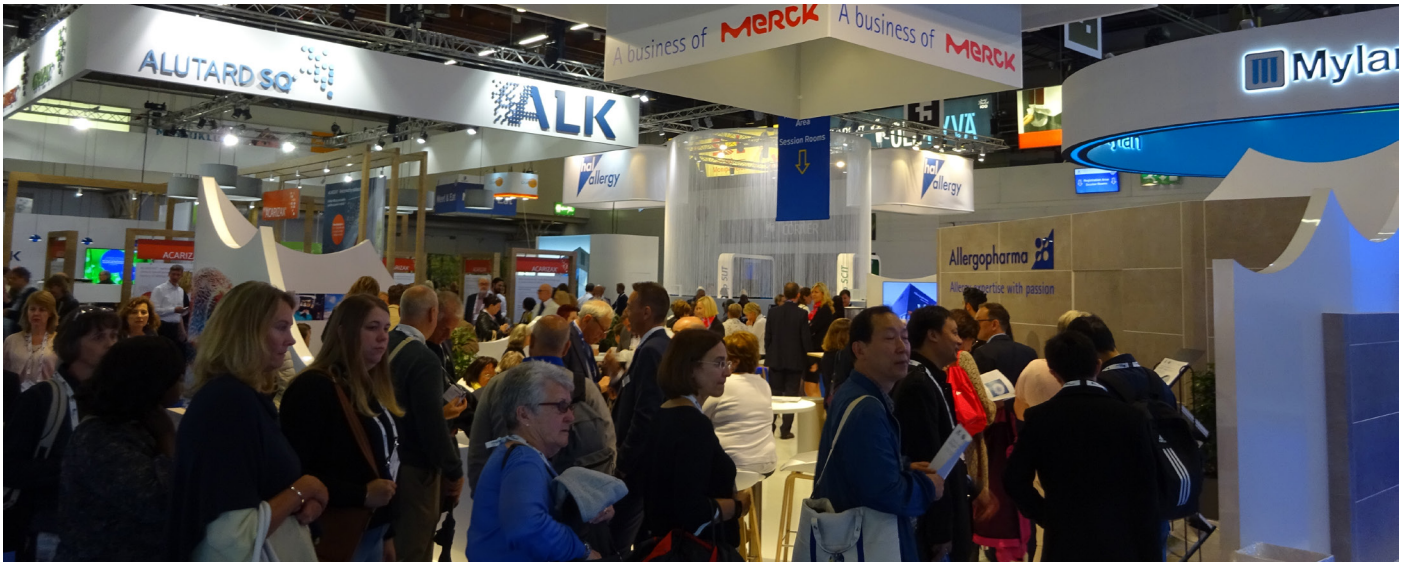
ANOTHER of the exciting Pro-Con debates that featured throughout EAACI 2017 focussed on the topic of drug provocation and skin testing; views on whether skin testing prior to drug provocation is necessary were discussed. The session was chaired by Prof Andreas Bircher (Switzerland), with Dr Lene Heise Garvey (Denmark) advocating the position that skin testing is not strictly necessary before drug provocation and her opponent Dr Knut Brockow (Germany) defending the need to perform the tests.

The discussion was lively and informative, with speakers drawing on both personal experience and published studies to demonstrate their points. Prof Bircher opened the session by introducing the topic and reiterating that although drug provocation certainly could be done, the real question was should it be done. He began by asking the audience to participate in the live vote via their smartphone app to agree or disagree with the statement 'Can drug provocation be done without skin testing first?' and remarked that the results came out close to 50/50, setting the scene for a passionate debate.

As a consultant allergist in Copenhagen, Denmark, Dr Heise Garvey explained that her clinic performs 10–20 provocations per day. She began by defending the statement as the pro side of the debate, concentrating her argument on antibiotics as the most common cause of drug allergy. She acknowledged the tremendous pressure on healthcare professionals to see more patients in a shorter amount of time, as well as the need to reduce the number of tests being taken and the number of visits per patient to the clinic, something which also benefits the patient. However, she pointed out that what is always paramount is the safety of the treatment for the patient.

Dr Heise Garvey talked about the European Network for Drug Allergy (ENDA) guidelines and described their recommendation for skin testing in every patient as "elaborate." She named a number of studies that looked at the possibility of drug provocation without prior skin testing, which found that skin testing had not been necessary, and also described the Australian Allergy Society's guidelines, which had begun to look at the options for drug provocation without skin testing.

At Dr Heise Garvey's clinic, she reported the rate of presenting anaphylaxis as between 2% and 3%, with most patients presenting with minor rashes. She explained that, as an allergist, it is her responsibility to minimise the risk of anaphylaxis; however, this risk can never fully be eliminated, and as such even full skin testing cannot completely remove the risk of anaphylaxis with drug provocation. For this reason, her clinic undertakes risk evaluations for every patient before recommending only the highest-risk patients for skin testing prior to drug provocation. The results of this process on 1,913 drug provocations have recently been accepted in EAACI and Practice digital edition, in which IgE tests were performed after penicillin exposure. Two hundred and eleven (11%) of these patients tested positive, of whom 43 (20%) had immediate reactions, and one had anaphylaxis which was treated in the usual manner.



For the con side of the argument, Dr Brockow began by commending Dr Heise Garvey on a well-argued point but admitted he was critical of the arguments put forward. He agreed with Dr Heise Garvey on the need for safe, reliable, and easy testing methods and believed that skin testing was the better of the two options: skin test or drug provocation. There is a reason that drug provocation is the last step in drug allergy testing, he said, as a positive skin test can eliminate the need for difficult drug provocation. Dr Brockow acknowledged the need to carefully select patients for skin testing to maximise the benefits and conceded that in some cases the skin test was not particularly helpful. He drew on published studies from central Europe on paediatric populations in which skin testing improved the accuracy of diagnosis of drug hypersensitivity and emphasised the importance of detecting this ahead of speeding towards drug provocation which, particularly for paediatric patients, can be very unpleasant.

Dr Brockow was passionate about ensuring the patients' safety and comfort being the most important priority, and the responsibility of the clinic, and, as such, he recommended against drug provocation without prior skin testing due to the risk of anaphylactic shock and anaphylaxis. He concluded with a reiteration of the fact that skin tests are an easy and quick way to eliminate the dangers associated with drug provocation, and that specificity depended largely on the drug in question, sensitivity was better for immediate rather than non-immediate hypersensitivity reactions, and skin testing was for screening rather than exclusion of drug hypersensitivity. In short: better safe than sorry!

In the second audience vote, the results had been influenced by the heated debate. Audience members had gone from being torn between the two viewpoints to now agreeing with Dr Heise Garvey, with a greater majority taking the pro side of the debate.

Year in Review – Immunology: Skin Immunology

DURING the engrossing 'Year in Review – Immunology' session at the EAACI Congress, which took place on Monday 19th June, Prof Jan Gutermuth (Belgium) took to the stage to showcase what he regarded as the stand-out studies from a year notable for many breakthroughs and discoveries in skin immunology.

The dermatologist immediately described his excitement at the advancements currently taking place. "It is a very rewarding time in dermatology and allergology, because especially in our field, we have been infamous for just using steroid creams, but now we are moving to precision medicine," he said.

> "It is a very rewarding time in dermatology and allergology, because especially in our field, we have been infamous for just using steroid creams, but now we are moving to precision medicine."

"We have highly coded new therapies, which target the immune system like the biologicals, but also [new therapies targeting] small molecules are coming. I think this is maybe unseen, but in the last years it has been happening in our fields."

Prof Gutermuth then presented the first study of his talk: a very important one that analysed the differences in the immune system between females and males. This is an area that has been somewhat neglected according to Prof Gutermuth, who cited the fact that just 3.3% of immunological studies assess the potential of sex bias, and that only in 40% of manuscripts do we know the sex of the used cells. It is well known that females have a much stronger immune system than males, with males two-times more likely to develop, and die from, cancer, for example. However, 87% of those diagnosed with autoimmune diseases are female, which Prof Gutermuth suggested could be a trade-off for having a stronger immune protection. "So, the big question of course: when we compare female and male cells and outcomes, is it triggered by hormones? Or may there be other factors working which are independent from hormones?" he asked.

The study displayed significant cellular differences between males and females in a variety of conditions, providing increased understanding in this area. It was discovered, for instance, that there is higher expression of the VGLL3 gene in females and VGLE3 is the sex-bias transcription factor that regulates a number of genes associated with autoimmunity. Such discoveries are likely to provide the basis for further research.

The Belgian professor later went on to look at a condition that had seen major advancements recently: atopic dermatitis. A number of new therapies have been developed for these patients, whose biggest issue is often the time lost to treatment. One of the studies he selected for presentation looked at transepidermal water loss in newborns: a big risk factor for the development of atopic dermatitis. Encouragingly, this analysis found that daily emollient treatment can reduce the incidence of atopic eczema by a massive 30–50%, which is a very effective, as well as simple and cheap, solution.

Prof Gutermuth concluded by stating that there was much hope for the future for further treatments for atopic dermatitis, with the development of drugs in the T helper Type 2 pathway a particularly interesting area to look out for in the near future.

Year in Review – Immunology: Gut Immunology

A review of some of the most recent developments in the understanding of gut immunology was provided by Dr Calum Bain (UK) during the 'Year in Review – Immunology' session on Sunday 18th June at the EAACI Congress. He chose to focus his analysis on the role of dendritic cells (DC) in gut immunology, a topic that has seen an enormous amount of interest in recent times.

> "The power of transcriptional profiling has revealed markers that we were not aware of until just a couple of years ago, and this opens the possibility of being able to deliver antigens to specific DC subsets under defined conditions."

He began by reminding the audience of the vast size of the gastrointestinal tract, and that the intestine is constantly exposed to many different antigens, e.g. dietary and commensal microbiota. Therefore, the gastrointestinal immune system needs to differentiate between them, which is a fine balancing act. "DC play a key role in determining tolerance versus immunity," stated Dr Bain.

The Scotsman then described the evolution in knowledge that has been seen recently in regard to the role of DC: "Over the last couple of years and especially over the last year, there has been an explosion of interest in working out exactly what different DC do, and different studies here, including those of our own, show that the DC pool in the intestine is incredibly diverse. And [there have been] other seminal studies showing that identifying unique transcription factors in DC populations and the origin of these cells, all of which are known to derive from commitment pre-DC precursors, that arrive from the gut mucosa and mature locally to give rise to mature functional DC. This work argues against the earlier idea that CD103-positive DC are hardwired to give rise to regulatory cells and they showed that CD103 DC also prime effector T cells."

He went on to describe recent work by himself and his colleagues on the role of tumour necrosis factor (TNF)-β in regulating different aspects of DC biology. "We have contributed to this in different ways, but most recently by looking at the role of TGF-β receptor signalling and showed that this plays a role in controlling the homeostasis of DC populations in the intestine," he said.

One particularly important advancement Dr Bain also described was the ability to align DC subsets across tissues and species through the use of powerful techniques, specifically mice and humans; this is certainly a progression that will improve understanding in studies to come.

Dr Bain was able to sum up the presentation with a message of optimism for the future. "The power of transcriptional profiling has revealed markers that we were not aware of until just a couple of years ago, and this opens the possibility of being able to deliver antigens to specific DC subsets under defined conditions," he declared. "This would revolutionise the way that we introduce antigens into the system, and if we understand better the way in which DC decide whether to mount a tolerant response versus a protective immune response, perhaps we could use antigens to deliver these markers specifically to DC subsets."

Alcohol Hyper-Reactivity in Chronic Airway Inflammation

DR ELS DE SCHRYVER (Belgium), spoke at a session at the EAACI congress on alcohol hyper-reactivity in chronic airway inflammation. The talk began with Dr De Schryver briefly expounding on the vast history of alcohol, noting that it has been used by humans since the prehistoric era for a variety of cultural, religious, and medical reasons. In this session, the impact of alcohol on airways was in the spotlight.

The audience were invited to ponder the case of a patient who reported drinking a glass of wine and then sneezing, coughing, and wheezing. This then led to consideration of previous studies that had investigated alcoholic drinks and asthma: a topic that has been examined a number of times.

The first study Dr De Schryver reported on was an historical one from 1983.[1] The study authors utilised a questionnaire to find out the impact of alcoholic beverages on 168 asthmatic patients. Of this group, 32.1% reported that at least one type of drink worsened their symptoms, while 23.2% stated that alcohol could improve symptoms, especially in severe cases. The drinks that were commonly reported as worsening symptoms were wines, beer, and whiskey, while the drinks stated to improve symptoms were typically whiskey and brandy. Another questionnaire that was answered by 366 patients recruited from the Asthma Foundation of Western Australia aimed to further examine anecdotal reports that alcoholic drinks triggered asthmatic responses.[2] The authors collected data on the frequency and characteristics of asthmatic reactions, in addition to investigations of other food sensitivities and allergies. They concluded that alcoholic drinks, wines in particular, were strongly associated with triggering asthmatic responses. Building on this, it was suggested that many of these responses were likely to be as a result of sensitivity to the sulphite additives in wines.

Dr De Schryver went on to discuss the findings of several other studies that linked alcohol with respiratory symptoms. These included two questionnaires carried out in Sweden with 9,316 and 228 respondents,[3] respectively, and a Danish questionnaire with 4,242 responses.[4] Both of these questionnaire-based studies provided evidence linking alcohol to worsened respiratory symptoms in various respiratory conditions.

Having talked over a number of studies linking alcohol to the worsening of symptoms in various respiratory conditions, Dr De Schryver next provided the details of a study she had carried out with colleagues to investigate this association in greater detail.

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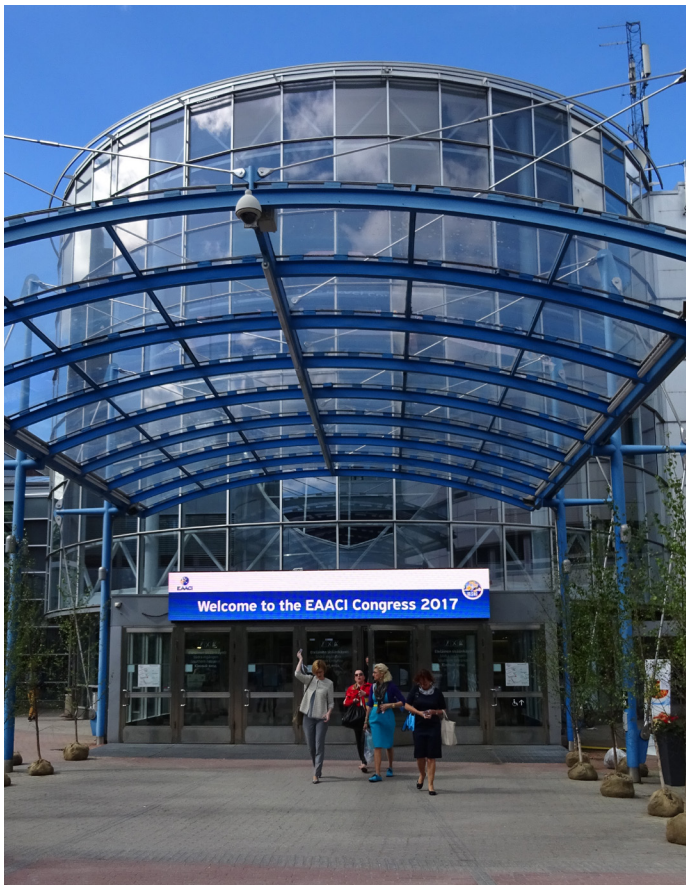


Nasal Hyper-Responsiveness to Alcohol

IN THE NEXT section of her talk, Dr De Schryver expanded on a study she had carried out with her fellow researchers. To begin, Dr De Schryver discussed the context of the study by noting that there has been shown to be an association between chronic respiratory inflammation and alcoholic drinks. More specifically, patients with chronic upper airway disease often reported a worsening of their symptoms upon imbibing an alcoholic beverage or two. This then begged the question of whether it was the alcoholic component of such a beverage that was causing the reaction or whether it was another component altogether. Dr De Schryver gave the example of wine as a case in point. She stated that there were >400 components in wine that have the potential to induce an allergic response, including spices and sulphites.

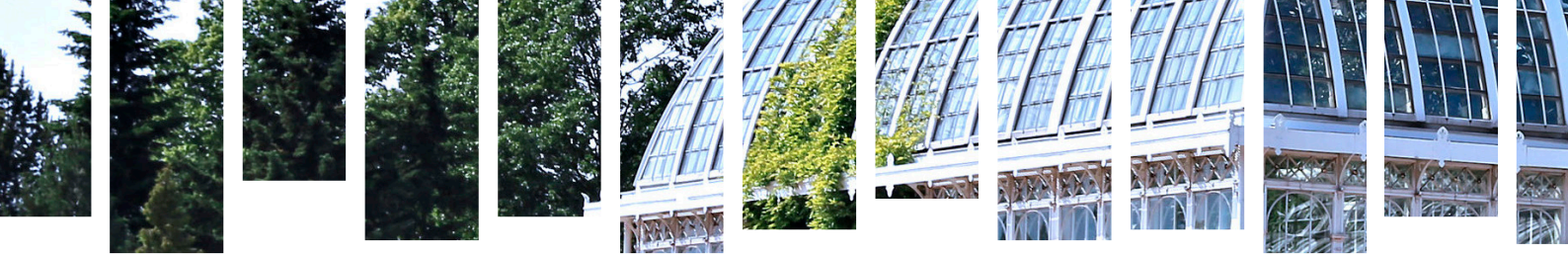
Therefore, Dr De Schryver and her fellow researchers designed a test to isolate the influence of alcohol. The study's participants were 34 chronic rhinosinusitis with nasal polyps (CRSwNP) patients and 14 healthy controls. Participants began by sniffing 15% ethanol five times. Then participants were given 60 mL of 15% ethanol and, finally, 120 mL of 15% ethanol. There was a wait of 10 minutes after each step. After the 10-minute period had elapsed, nasal responsiveness was measured. A variety of outcome measures were collected in order to study whether the alcohol had caused a response. These included the determination of a total nasal symptom score (patients were scored from 0–3 for itching, sneezing, rhinorrhoea, and congestion) and an anterior rhinomanometry to evaluate nasal airflow.

The results found that 35.3% of CRSwNP patients had a positive test result (a respiratory response was provoked) after drinking 15% ethanol. This was in comparison to 7.1% of the control group. Furthermore, when a control test was conducted utilising pure water, only 5.8% of CRSwNP had a positive test result, compared with 7.1% of the control group.

In order to investigate what happened if the nasal inflammation was taken out of the equation, a small follow-up test was conducted. Six of the patients with CRSwNP and a positive test result agreed to take a course of oral steroids to treat their nasal inflammation. These 6 patients were given Medrol for a period of 20 days in decreasing doses (32 mg for 5 days, 16 mg for 5 days, and 8 mg for 10 days). After the treatment period, the test with 15% ethanol was repeated again, and only 1 patient had a positive response to the test.

Dr De Schryver summed up the findings of the study, stating: "I think we can state now that alcohol itself can induce a nasal hyper-responsiveness, at least in certain populations with nasal inflammation. And then secondly, alcohol hyperactivity is probably due to the underlying autoimmunity. So, the inflammation is the cause of the hyper-responsiveness."

> "I think we can state now that alcohol itself can induce a nasal hyper-responsiveness, at least in certain populations with nasal inflammation."



Amir Hamzah Abdul Latiff

Consultant in Clinical Immunology, Allergy and Paediatrics, Allergy and Immunology Centre, Pantai Hospital, Kuala Lumpur, Malaysia; President, Malaysian Society of Allergy and Immunology (MSAI); Board Member, Asia Pacific Association of Allergy, Asthma and Clinical Immunology (APAAACI).

Q: We understand that you specialise in clinical immunology and allergy, more specifically specialising within the paediatric population. What made you pursue a career in this area?

A: My first speciality was in general paediatrics and I had completed a Master's programme in Malaysia for that specialisation. The Master's programme was considered an exit examination in Malaysia and, on passing it, a specialist would then be gazetted as such after 6 months. As part of any Master's clinical and medical programme, a thesis was required, and I chose to look into the immunological aspects of childhood steroid-sensitive nephrotic syndrome. My initial interest in pursuing paediatric nephrology, as a subspecialty in paediatrics, was eventually superseded by my interest in clinical immunology from the aforementioned thesis. Hence, my interest to pursue clinical immunology in paediatrics in the first instance eventually lead to an opportunity to delve into the full (and separate) speciality of clinical immunology and allergy in the UK, 2 years after completing my Master's programme.

Q: Could you give us a brief overview of what your role as the President of the Malaysian Society of Allergy and Immunology (MSAI) entails? What are your main responsibilities?

A: My role as President of the MSAI entails both administrative and educational roles, and these are not necessarily separate from each other. With the assistance of an executive committee and the MSAI secretariat, I work towards achieving the aims and objectives of the MSAI, including promoting the highest possible standards of teaching, study, and research among those engaged in the practice of allergy and immunology, in the best traditions of medicine and medical ethics; co-operating with local medical bodies, allied corporations, and universities in pursuing MSAI's objectives; and publishing newsletters and educational materials.

My main responsibilities are to ensure that a stream of continuing medical education (CME) programmes, in various forms of symposia, workshops, and round table discussions, are churned out as frequently as possible throughout the society year. This also engages various key players from the industry to help organise CME programmes that encompass both allergic diseases and primary immunodeficiency diseases (PID). The latter has become a personal mission of mine, as great efforts are being generated to increase the awareness of PID amongst the public and healthcare professionals alike. Hence, much support is given to the Malaysian Patient Organisation for Primary Immunodeficiency (MyPOPI) in their annual activities, which have included a road show, a charity walk, family days, and talk shows on both the radio and the television.

Q: Some of your most recent publications have been focussed on the EAACI/GA²LEN/EDF/WAO guideline; could you tell us a little more about this guideline? How important is the collaborative development of guidelines such as this one?

A: It was a privilege to be on the expert panel for the 4th edition of the EAACI/GA²LEN/EDF/WAO guideline on urticaria in 2012, and thus one of the co-authors of the 2013 update published in 2014. The panel has been meeting every 4 years since the first meeting in 2000, with the 5th edition (for which I continued to be on the expert panel) recently concluded in December 2016, and is awaiting publication. In both meetings, I represented the MSAI and we endorsed the guideline, as had many other sister societies from various parts of the world. It is truly a global and multinational

guideline, as great efforts have been made to streamline the management of chronic urticaria using a common language and utilising the GRADE system in making judgements about quality of evidence and strength of recommendations.

It is indeed refreshing that not only are key opinion leaders (KOL) contributing towards the development of such guidelines, but these KOL are also representing their national societies. This reflects a regional effort amongst nations from various regions of the four corners of the world. This will create a unified attempt to streamline the management of many immune-mediated diseases via a common networking platform.

Q: How useful are patient registries at determining the pathology and characterisation of these sorts of conditions?

A: There are several specific objectives that make PID patient registries useful, such as connecting affected patients, families, and clinicians by having registry meetings, which provide an opportunity to talk and share personal experiences. The advent of social media has increased patient involvement in these types of activities by encouraging patient forums and dialogues, and assisting with recruitment for research and support. Patients and families often want to connect to advocate support of patient services, and financial support for patient care and research. Similarly, physicians or paediatricians and other clinicians may want to connect with each other to learn more about PID and possible treatment options. Registries offer access to essential information and to experts in PID to assist healthcare providers with advising and counselling patients.

“There are several specific objectives that make PID patient registries useful, such as connecting affected patients, families, and clinicians by having registry meetings, which provide an opportunity to talk and share personal experiences.”

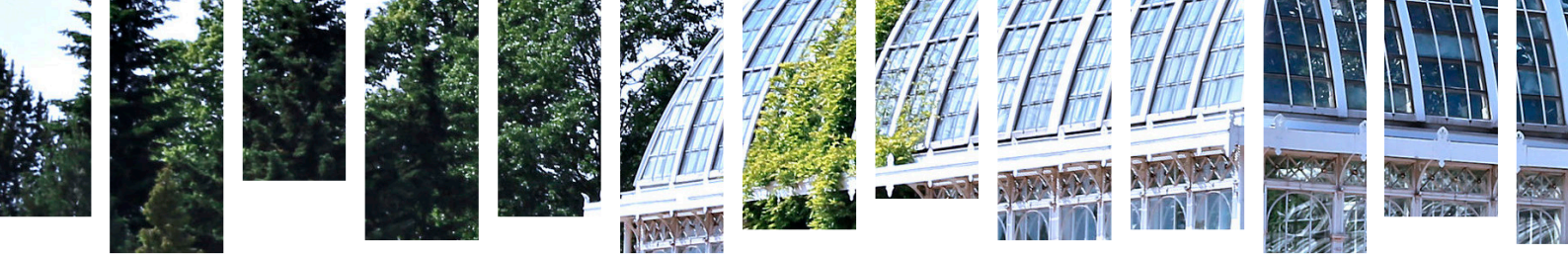
“The focus on epidemiological studies is unlikely to shift...”

Patient registries allow us to learn the natural history, evolution, risk, and outcomes of PID. Typically, uncommon diseases such as PID are described in a general way, based on their symptoms at the time of diagnosis. With refinement in diagnostic techniques, including genetic and biochemical testing, classical disease descriptions are broadened and diseases are better described in terms of specific outcomes.

Another use of patient registries is to support research on the genetic, molecular, and physiological basis of PID, and to further research features of disease, both clinical and basic. Clinical research depends on having a representative population for determining the timing and frequency of natural events and complications, such as the development of autoimmune complications, unusual infections, and related or unrelated malignancies. Thus, uncommon diseases, such as PID, would benefit from patient registries by having access to a comprehensive database that is adequate enough to address critical questions.

Q: What is the main focus of your current research? Is this focus likely to shift in the coming years?

A: The ongoing research in collaboration with other academician paediatric immunologists is mainly focussed on PID, particularly the continued efforts to determine the prevalence of PID, as well as enhancing diagnostics in Malaysia. The same concept goes towards establishing the prevalence of allergic diseases in Malaysia, as previous data are now more than a decade old, and I believe there is a rise in prevalence of various allergies since then. In addition, I plan to undertake research into the difference in sensitisation to common mites: *Dermatophagoides pteronyssinus*, *Dermatophagoides farina*, and *Blomia tropicalis* in Malaysia. The focus on epidemiological studies is unlikely to shift in the coming years, but spin-off studies will be considered along the way, mainly in molecular diagnostics and allergen-specific immunotherapy.



Q: How important are events such as the annual European Academy of Allergy and Clinical Immunology (EAACI) Congress to immunologists and allergists?

A: Such events are important as they give the opportunity for allergists and immunologists from various parts of the world to meet annually, in person, as part of their educational and research networking, and to connect with the industries that manufacture and supply various pharmaceutical and diagnostic products.

Q: In your opinion, what do you think will be the biggest challenges and obstacles for immunologists in the next 5 years?

A: This really depends on where immunologists practice, in which areas of interest they are clinically oriented and conducting research, and is thus influenced by the socio-economic circumstances and the needs of the communities and countries. In Malaysia, where clinical immunology and allergy is not entirely recognised as a sub-specialty or branch in medicine by the government, the biggest challenge would be gaining that recognition. Tremendous efforts have been made in the last 10 years, by myself and others fully trained in the field of clinical immunology, to negotiate this recognition for the betterment of the overall management of patients with primary immunodeficiency's in particular, and addressing the increasing prevalence of complex allergic diseases. Certainly, there have been small steps from the health authorities to discuss the recognition of the field and I hope it will progress rapidly in the next few months.

Q: What would you say your proudest career achievement has been so far?

A: I have yet to find my proudest career achievement, as I continue to just focus on the jobs in hand, particularly as President of the MSAI, where the previous objectives and missions mentioned need my attention. Nonetheless, I felt very proud to have been the Chair of the Joint Congress of the Asia Pacific Association of Allergy, Asthma and Clinical Immunology and Asia Pacific Association of Pediatric Allergy, Respirology & Immunology (APAAACI and APAPARI) 2016, held in Kuala Lumpur, where the MSAI was the organiser and host. I had an excellent team to support me amongst the MSAI Exco and Secretariat and, along with the local professional conference organisation, managed to deliver a very successful congress.

Another proud moment is the newly formed Allergy & Immunology Centre in Pantai Hospital, Kuala Lumpur, Malaysia, that I assisted the hospital in developing; I am currently the Lead Clinician of this Centre of Excellence. This is the first of its kind in the private healthcare sector in Malaysia, and I envisioned this as an integrative centre for clinical and laboratory services, plus a hub for patient education in all things allergy and immunology.

Q: What guidance would you give to emerging clinicians or researchers with an interest in allergy and immunology?

A: The main advice I would give to young specialists with an interest in allergy and immunology is to gear themselves up for a joint effort with me and others, advocating to establish and gain recognition for this field to be another much-needed subspeciality in Malaysia. Plans would be initiated for them to embark on a 2-year fellowship-training programme locally, with an extension of the programme for a placement in distinguished training centres abroad for a year. Overall, this will need lots of commitment and dedication, but, with the ultimate aim of providing optimal care for patients with complex allergic diseases and PID in particular, it will be a journey worth enduring.

> "The main advice I would give to young specialists with an interest in allergy and immunology is to gear themselves up for a joint effort with me and others, advocating to establish and gain recognition for this field to be another much-needed subspeciality in Malaysia."

Nicola Jay

Consultant Paediatrician Allergy and Asthma, Sheffield Children's Hospital, Sheffield, UK; Council Member, British Society for Allergy and Clinical Immunology (BSACI), Royal College of Paediatrics and Child Health (RCPCH), Paediatricians in Medical Management, and Yorkshire and the Humber Clinical Senate.

Q: Could you describe for us what your duties and responsibilities are as Consultant Paediatrician at Sheffield Children's Hospital (SCH), Sheffield, UK?

A: SCH is a children's hospital in the north of England which serves an ethnically diverse population. As a consultant, I have clinical responsibilities including allergy clinics (general, immunotherapy, and drug allergy) with the aim of ensuring a holistic approach to managing atopic conditions to minimise the impact on children and ensure their future entitlement in life. Training the next generation of paediatricians, as well as taking part in research, helps ensure a commitment to continuing care and enhancement of care. I am also a consultant appraiser/mentor and a personal/academic tutor to medical students. To help others see their value in a profession that can be stressful is extremely rewarding.

Q: What strategies could be undertaken to ensure that children and their parents are better equipped to deal with allergic conditions in the paediatric population, thus reducing the need for hospital care?

A: Providing patient-centred care where we listen to what our children and families need has demonstrated success with improved outcomes. We need to enquire about our families lives and work with them to provide advice and care that they can commit to, rather than healthcare professionals (HCPs) 'telling' them what to do. When we empower individuals to take responsibility for their own health we can ensure sustained impact from a young age.

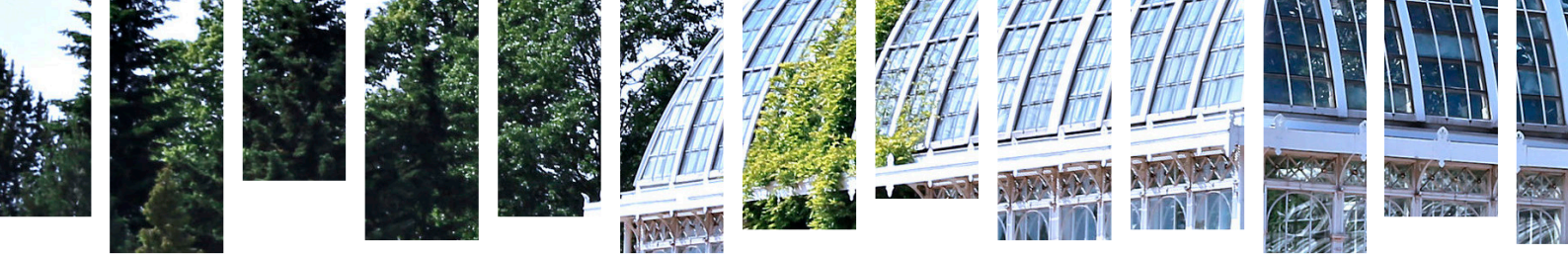
> "To help others see their value in a profession that can be stressful is extremely rewarding."

Q: Are there any variations in the prevalence and type of allergic conditions faced among different ethnicities? What are the reasons for this, and how does this disparity affect the care clinicians provide?

A: At the moment we do not have enough information to say whether the prevalence of atopic conditions is different, dependent upon ethnicity. What we do know is that, as for most conditions, the black and minority ethnic (BME) population have poorer outcomes for atopic conditions such as asthma. From a local project, we have found that children from the BME population have a delayed presentation to the allergy clinic with a greater number of atopic conditions with increased severity at presentation. We are currently concentrating on two areas to understand why: a community project looking at mothers' views in the South Asian community; and a hospital-based project looking at access to care within clinics, e.g. appropriate communication tools.

Q: How has the field of allergy and immunology changed since you began your career? What are some of the most notable developments you have witnessed?

A: Most definitely attempts at prevention of allergy with the landmark Learning Early About Peanut allergy (LEAP) study as well as the Enquiring About Tolerance (EAT) study, which have enhanced our knowledge significantly. The active management of food allergies with use of desensitisation as well as use of immunotherapy to prevent the future development of atopic conditions are the areas of notable development and need to be developed alongside the preventative measures.



Q: What would you say are the biggest challenges allergists and immunologists may face over the next decade?

A: The allergy 'epidemic' continues to explode across the world and we need to gain a better understanding of why. Research is central to providing answers and we need to ensure any trials developed address important issues. As always, monetary constraints are at the forefront of people's minds, however we need to remember that treatment strategies are usually more expensive than prevention.

Q: Following on from this question, in what ways could policymakers and funding bodies assist allergists in tackling this challenge? What would your ideal strategy to tackle this challenge look like?

A: We need to ensure that allergy and immunology are highlighted as significant health problems across the world, with large organisations such as the European Academy of Allergy and Clinical Immunology (EAACI) being at the forefront in Europe, attempting to influence parliamentary committees. Funding bodies need to commit to prevention and management strategies, translating excellent research into clinical practice. As a group we also need to work more closely together, developing databases based on outcomes and sharing what works well. I am a great believer that any child who starts a new treatment, especially those that modulate the immune system, should have information collected to ensure best outcomes. We are at our best for patients when we work together.

Q: Please tell us a little about the BEEP study that you are part of. What do you hope will be the eventual outcome following publication of the results?

A: The Barrier Enhancement for Eczema Prevention (BEEP) study is being led by Prof Hywel Williams in Nottingham, UK and is a randomised multisite study with a control group, attempting to see if the use of emollients from birth can prevent eczema. I became involved towards the end of recruitment, when it was decided to observe whether there is a difference in food allergy and aeroallergen sensitisation in the two groups, and 1,395 families took part. It is extremely exciting to be part of a larger group developing research aimed at potentially preventing atopic conditions in children, the Holy Grail for all allergists.

Q: You have previously been involved in a frontline scheme to better educate primary healthcare providers about allergic conditions. Could you describe for us the intended benefits of such a scheme?

A: The allergy epidemic has exploded in the last decade causing significant morbidity in our patient population. Addressing the present gap in knowledge of primary care HCPs in the management of atopic conditions is of paramount importance, to ensure the delivery of earlier and more comprehensive treatment, to minimise health inequalities and prevent disease progression. Looking after patients closer to home, within local communities, also helps develop support networks.

Q: As a council member of the Yorkshire and the Humber Clinical Senate, what do your roles involve? How useful are such regional bodies?

A: Clinical Senates were established in England to be a source of independent strategic advice when any NHS organisation is considering change. I have the pleasure of meeting with a multi-professional group as part of the council, which is the 'steering group' of the senate, to consider how best to review requests for our involvement. Many requests are from other areas of the country and as such provide assurance to stakeholders. With the development of sustainability and transformation partnerships (STPs) in England, the senates are considered to be a prime resource for this purpose.

> "Clinical Senates were established in England to be a source of independent strategic advice when any NHS organisation is considering change."

Q: What advice would you give to young medical students considering specialising in the field of allergy and immunology?

A: Go for it! It is a fast-moving world that rewards the curious, with so much still to be done. There are opportunities for all, whether you prefer research or being more patient-facing; with the ability to significantly improve the quality of life in a vast proportion of the world's population. There are leadership opportunities to work across boundaries as in the Finnish Asthma/Allergy programme that has demonstrated what happens when we work together.

Enrico Heffler

Personalized Medicine: Asthma & Allergy Clinic Unit, Humanitas Clinical and Research Center, Department of Biomedical Science, Humanitas University, Milan, Italy.

Q: Could you tell us more about your daily roles and responsibilities as Assistant Professor in Respiratory Medicine at the Humanitas University in Milan, Italy?

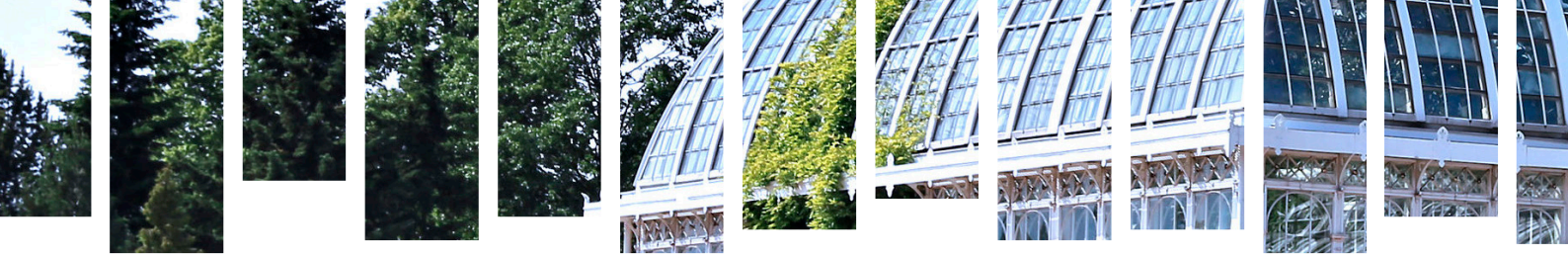
A: My position as Assistant Professor implies different duties. In particular, I have three big areas that I must cover: the clinical part (my patients are mainly the most severe allergic patients), teaching and tutoring for medical students, and clinical and translational research, mainly in the fields of severe asthma, nasal polyposis, urticaria, and systemic mastocytosis.

Q: In the last 10 years, there has been some adjustment in relation to asthma guidelines, whereby there has been a shift in the approach to treatment and management; however, asthma control is still insufficient. Could you tell us a little about the changes made to these guidelines? In your opinion, why is asthma so difficult to control?

A: Asthma guidelines, about 10 years ago, changed their approach to treatment and management of asthmatic patients, pointing the attention to the concept of 'asthma control', more so than 'asthma severity'. Even if these two concepts may seem very similar, they have totally different meanings: asthma severity reflects a sort of snapshot of the clinical situation of a patient before an adequate treatment, whilst 'asthma control' refers to the different clinical and functional outcomes after a period of adequate treatment. This revolutionary change in the vision of asthma allowed clinicians to be more precise and focussed on asthma therapies. Unfortunately, despite the wide diffusion of asthma guidelines, only a minority of clinicians strictly follow them, with the result of poor mean asthma control in all epidemiological studies. This is possibly due to several complex factors that characterise asthma, such as the difficulty of correctly using the inhalation devices, the tendency of patients affected by chronic diseases not to properly follow the prescribed treatments for long periods of time, the negative influence of some relevant comorbidities (e.g. nasal polyposis, obesity, etc.), and finally the intrinsic corticosteroid resistance of some patients.

Q: Following on from the above question, do you think there could be additional changes made to these guidelines to further aid and optimise asthma control?

A: I think that international guidelines should promote and increase the interaction between primary care doctors (general practitioners and paediatricians) and asthma specialists (allergists or pneumologists), to create hub-and-spoke networks that may facilitate a holistic approach to the asthmatic patient. Moreover, greater levels of attention and ability of doctors to be emphatic with patients will surely help to motivate them to adhere to the prescribed treatment.



Q: One of your most recent publications is a comprehensive review of current knowledge on the role of microRNA (miRNA) in asthma, particularly their potential as biomarkers for severe asthma. Could you tell us more about this research?

A: The article summarises the current knowledge on miRNA in asthma, with a special focus on severe asthma. miRNAs are small, endogenous RNA molecules that may inhibit translation and promote mRNA degradation of several proteins. miRNAs function in post-transcriptional regulation and control physiological and pathological processes in various diseases, including asthma. Therefore, they seem to be perfect biomarkers of different molecular/biological processes underlying the asthma pathogenesis. Unfortunately, the technical method used to assess miRNAs in different tissues is still expensive and carries a certain degree of difficulty, therefore limiting, for now, the use of miRNAs as biomarkers in clinical practice. I hope, and am quite confident, that in the near future this technical problem will be overcome.

Q: Is there a specific area of research that you have not had a chance to explore thus far that you would like to investigate in the future?

A: In my clinical practice, I take care also about patients with a rare disease called mastocytosis in which mast cells (the main effector cells of allergic reactions) are upregulated in terms of activity and number, giving a variety of symptoms that range from typical cutaneous involvement (i.e. the so-called urticaria pigmentosa) to a systemic form characterised by multi-organ involvement and often severe recurrent anaphylaxis. I would like to have more time to dedicate to the research of mechanisms of activation and inhibition of mast cells in these patients.

Q: You are actively involved in the activities of multiple societies, including but not limited to, Secretary General of the Società Italiana Allergologia Asma Immunologia Clinica (SIAAIC) and Board Member of the European Academy of Allergy and Clinical Immunology (EAACI). How do you maintain the right balance between these activities and your scientific research and practice?

A: It is a hard job, but someone has to do it! Joking aside, I think that my involvement in national and international scientific societies allows me to create scientific networks that are useful for the research part of my job, therefore I consider the societies themselves part of my scientific engagement.

Q: How important is the annual EAACI congress to allergists and immunologists? Is there anything in particular you hope to take away from this year's event?

A: The EAACI congress is the biggest (both in terms of participants and scientific level) worldwide event in allergy and clinical immunology, therefore I think it is somehow mandatory for all scientists and clinicians in this field to attend. It is an event that successfully mixes sciences with 'political affairs' and leisure. I hope to bring home new scientific collaborations, new friends, and novel information mainly on two topics: severe asthma and severe chronic spontaneous urticaria.

Q: In recent years, there have been a number of collaborative initiatives, including the International Collaboration in Asthma, Allergy and Immunology (iCAALL) whereby the American Academy of Allergy, Asthma & Immunology (AAAAI), the American College of Allergy, Asthma & Immunology (ACAAI), the EAACI, and the World Allergy Organization (WAO) joined forces with the aim of increasing awareness to positively impact diagnosis and treatment of these conditions. How crucial are projects such as these in advancing the field?

A: These collaborations are crucial for Allergy and Clinical Immunology as a scientific field, because they produce important milestone papers and statements for some of the most crucial clinical problems of our field. Moreover, a collaboration among different societies is always an occasion to create new visions on scientific and political issues.

> "...my involvement in national and international scientific societies allows me to create scientific networks that are useful for the research part of my job..."

Q: What, in your opinion, is currently the greatest challenge for those studying in the field of allergy and immunology?

A: We are now entering an era of new biological treatments, which promises to treat patients according to their phenotype/endotype. The big new challenge will be to translate into clinical practice the so-called 'personalised' approach to patients, including the use of (non-invasive) predictive biomarkers for choosing the right treatment for the right patient.

Q: What guidance would you give to emerging clinicians, researchers, or students with an interest in allergy and asthma?

A: I always say to my students that allergy and clinical immunology is one of the most exciting and complex of clinical and scientific fields, because most of the new discoveries are somehow related to the immunological mechanisms of diseases. I think this is a great motivation for future scientists and clinicians.

> "The EAACI congress is the biggest... worldwide event in allergy and clinical immunology, therefore I think it is somehow mandatory for all scientists and clinicians in this field to attend."

Maria Jose Torres

Head, Unit of Allergic Diseases, Malaga Regional University Hospital; Associate Professor of Medicine, Malaga University; Vice Director, Institute of Biomedical Research in Malaga (IBIMA), Malaga, Spain.

Q: Could you tell us about your role as Head of the Unit of Allergic Diseases at Malaga Regional University Hospital? What are your main duties and responsibilities on a day-to-day basis?

A: My main role is to organise the clinical service portfolio, the management and communication with the hospital director, and also research, management, and teaching. My main duties are: i) to offer the best clinical attention to patients on a short waiting list while trying to prioritise urgent pathologies; ii) to manage the costs and objectives of the unit and to liaise with the directors of the hospital; iii) to organise teaching for the medical school students, the PhD students, and the research fellows in training; and iv) to organise research in the different clinical and basic research lines.

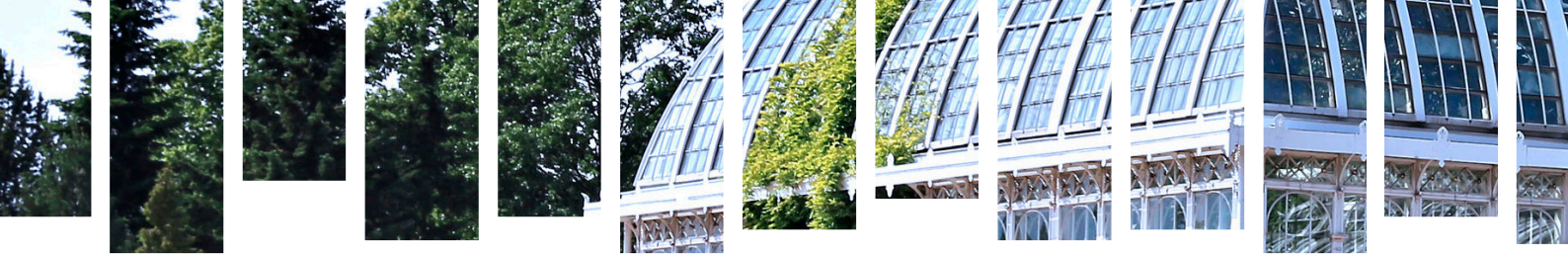
> "One of the most important measures is to identify patients in the acute phase of the allergic reaction..."

Q: What are the main roles and functions of the Institute of Biomedical Research in Malaga (IBIMA), of which you are Vice Director? What have been its greatest achievements since you began working at this institution?

A: IBIMA is a new research institute that includes groups from two different hospitals and universities (technology, psychology, and the medical school). The main achievement has been to bring together groups with different scopes, with the sole objective of improving medical knowledge. We have increased the number of publications, the impact factor, and the number of European projects in recent years.

Q: Have you noticed any trends in the amount of allergic reactions to medicines and foods in recent years? If so, what are the main reasons for this?

A: Yes, in recent decades there has been a great increase in the prevalence of allergic reactions to drugs and foods. Regarding allergic reactions to



drugs, one of the main reasons is the increase in drug consumption and the wide array of clinical compounds included, such as new radiocontrast media, biological drugs, and chemotherapy drugs. The incidence of food allergy has also increased, and this has been associated with a multitude of environmental factors, including hygiene habits, antibiotic use, caesarean births, exposure to certain chemicals, ultraviolet light, lifestyle changes, and the Western diet. Changes in environment and nutrition can result in a dysbiosis of the skin, gut, and lung microbiota, and result in changes in microbial metabolites, which may generate epigenetic modifications.

Q: Do you believe that there are any extra governmental regulations that could be put in place to reduce the amount of allergic cases caused by drugs and food?

A: One of the most important measures is to identify patients in the acute phase of the allergic reaction, and have a well-trained allergist evaluate and diagnose them as soon as possible following the allergic episode. Although allergy is a prevalent disease, and food and drug allergies are a global health problem, this speciality is not well-known by the medical community. For this reason, it is necessary to teach physicians to deal with this type of reaction during and after medical school. It is important to increase patient education to avoid self-prescription and to help them understand the differences between allergy and intolerance, among other aspects.

Q: Are the causes and treatment of allergies a particularly fast-growing area of medical research? How far has our understanding grown since you first began working in the field?

A: Research performed in genomics, the microbiome, immunology, proteomics, and metabolomics has completely changed the approach to allergic patients in recent decades. Now it is clear that allergic diseases need to be stratified and endotypes need to be defined as the diagnosis and treatments differ. Molecular diagnosis of patients is now used by many allergists to diagnose patients, and immunotherapy and biologicals are widely used for treatment.

Q: You have undertaken a lot of research into the development of the hapten-transport molecule for the study of hypersensitivity to beta-lactams, and into other drugs for their application in tests that determine the presence of immunoglobulin E antibodies specific to these drugs. What has been the most notable finding you have made in this area to date, and what impact has it had on clinical practice?

A: One of the main important discoveries is that there are many endotypes among patients allergic to beta-lactams: those allergic to all beta-lactams, those allergic only to one group (penicillin or cephalosporin), or those allergic just to one drug (amoxicillin or clavulanic acid). This means that the more selective the reaction is, the more therapeutic alternatives the patient has, and this is critical in an era when bacterial resistance has increased dramatically. We have also demonstrated that beta-lactam allergy differs among countries, and this is directly related with its consumption. Regarding diagnosis, we have made great improvements in *in vitro* diagnosis, especially in basophil activation tests and the use of nanostructures.

Q: Do you believe that there are any particular areas in allergy and immunology that are currently under-researched?

A: Yes, we need to understand why a patient becomes allergic, the reasons for the increase in allergic diseases, and which habits, even after pregnancy, need to be modified to decrease this epidemic.

Q: In your view, what is the biggest challenge currently facing allergologists, and what steps need to be taken to overcome it?

A: There are two big challenges: i) allergic disease has almost turned into an epidemic in the last few decades, especially in developed countries; and ii) the knowledge, diagnosis, and treatment has changed greatly. Therefore, a large number of well-trained allergists are needed to diagnose and

treat these patients, because nowadays many patients are not diagnosed, or are incorrectly diagnosed, and cannot benefit from specific treatments that could modify their disease.

Q: In 2011, you received an award from the Fundación Salud 2000 for the study of allergic reactions to drugs and nanomedicine. Could you describe the impact that this work has subsequently had?

A: With this study, we have been able to improve the *in vitro* diagnostic methods in patients with beta-lactam allergy. We have built nanostructures that are bound to beta-lactam that emulate what happens *in vivo* with beta-lactam-protein adducts. *In vitro* diagnosis of beta-lactam allergy is important because it is safe for the patient, is cheaper for the health system, and can be completed within 24 hours.

Q: What advice do you have for medical students thinking about beginning a career in the field of allergy and immunology?

A: Future allergists have to deal with a speciality where both clinical and basic science is completely inter-related. The same clinical picture can have many causes and different mechanisms. Moreover, it is a challenge because in many cases the allergy disease starts in childhood and continues throughout life but with different clinical pictures, so patients need to be followed. Also, the environment is critical and several factors need to be known: where we live, which pollens we are exposed to, what we eat, which drugs are most often consumed, etc.

Antonio Musarra

Head of Allergy Unit, Health Care Service, Scilla, Reggio Calabria, Italy.

Q: Please tell us a little about your career so far. What were your first steps towards working in allergology and how did you become Head of Allergy Unit, Health Care Service, Scilla, Italy?

A: After my degree, while I was training in a paediatric ward, taking care of and treating children with respiratory disorders, I decided to specialise in allergology. After my specialisation, my career started as a territorial specialist. Ten years ago, in order to carry out a second level of allergy diagnosis and treatment, I thought it was necessary to create an allergy unit in a hospital in my region. So, with a bit of difficulty, I started putting some ideas together regarding an Allergy Unit in the Hospital in Scilla, and I was appointed Allergy Unit Head by the Director of the Agency of the Healthcare System.

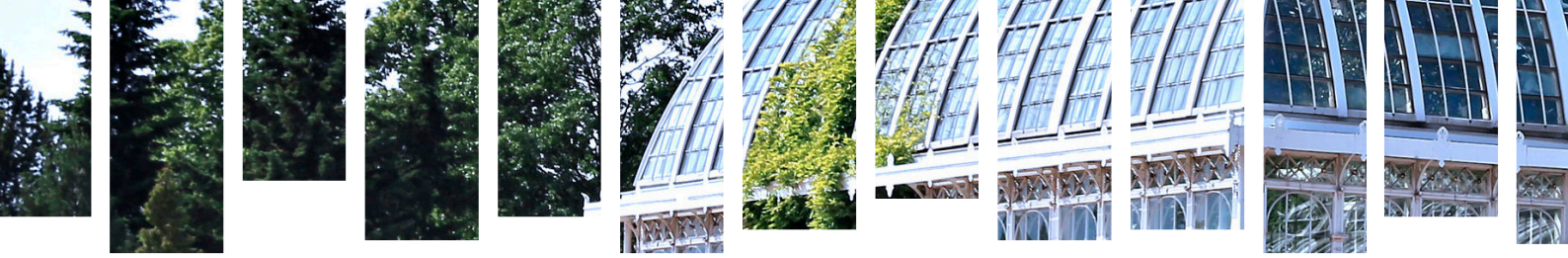
> “In the last decade, I have noted an overall increase in allergic patients...”

Q: What aspect of your career as a clinician and as a researcher do you find most fulfilling and why?

A: As a clinician, I find it very gratifying to apply the most appropriate diagnostic tools and treatments in the different fields of allergic diseases; as a researcher, I can evaluate epidemiological data, new drugs and their efficacy, difficult cases, and new biomarkers.

Q: Have you noticed any recent patterns or trends in terms of either the number of allergy patients or the types of allergic conditions that you treat on a day-to-day basis? If so, are there any obvious reasons for this?

A: In the last decade, I have noted an overall increase in allergic patients, especially patients with chronic allergic rhinitis, drug allergies, and severe food allergies. Rhinitis is frequently unrecognised by physicians and trivialised by patients. Consequently, the patients think that they do not need medication. Most patients sought



medical help only when allergy symptoms became intolerable. Regarding drug allergies, it is probable that the progressive increase in drug consumption is the main cause of increased drug allergic reactions.

Q: Are there any allergies that are particularly common or prominent in Italy? What are the main reasons for this?

A: In recent years, ragweed allergy has represented a challenge for Italian allergists, mainly in northern Italy. Instead, the most prevalent allergen sensitisation in the Mediterranean area in southern Italy is towards *Parietaria*, which is responsible for chronic allergic respiratory conditions in this area. Meteorological factors, especially high temperature, could be correlated. Regarding food allergies in southern Italy, there was a huge increase in lipid transfer protein allergies, a pan-allergen in plant-derived foods. Lipid transfer protein is a potentially severe food allergy.

Q: In a paper that you contributed towards in 2011, it was concluded that environmental factors play a significant role in the onset of respiratory allergies among migrants in Italy, who have a higher rate of monosensitisation and more severe asthma/rhinitis than is seen in Italians. Has this research led to any changes in the way healthcare is administered and medical advice provided to migrants in Italy?

A: Unfortunately, it has not. In relation to this problem, no changes to the healthcare system have been adopted. In Italy, an awareness campaign on allergic diseases in general is increasingly needed for all allergic patients, including migrants.

Q: Could you briefly describe the method of allergen component-resolved diagnostic testing and the extent to which it has improved allergy diagnosis in comparison to previous methods of diagnosis?

A: Component-resolved diagnosis (CRD) utilises purified native or recombinant allergens to detect immunoglobin E (IgE) sensitivity to individual allergen molecules, and has become of growing importance in clinical investigation of IgE-mediated allergies. Until now, *in vitro* allergy diagnostics were based on detecting specific IgE (sIgE) sensitivity to total extracts which contained a series of allergenic and non-allergenic components. CRD can determine the precise allergy profile of each individual patient. In patients showing multi-sensitisation using traditional extracts, CRD can discriminate genuine sensitisations from sensitisations caused by cross-reacting molecules. CRD is useful in respiratory allergy, food allergy, latex allergy, and hymenoptera venom allergy.

Q: You have recently contributed towards a recommendation document for the use of molecular diagnostics in allergic diseases. Could you describe the main recommendations and explain in what ways this will help clinicians in the diagnosis of allergic diseases?

A: The main objective of the recommendation document is to provide pathologists and clinicians with information and algorithms enabling the proper use of second-level diagnostics. The document describes how to use CRD in polysensitised patients with respiratory allergy to prescribe the correct allergen immunotherapy. It also suggests a diagnostic algorithm for patients with food allergy to identify the risk of severe allergic reactions, and a diagnostic algorithm for patients showing poly-sensitisation to hymenoptera venoms in order to prescribe the appropriate venom immunotherapy. It also suggests interpretative reports to explain the clinical significance of the test results.

Q: How do you believe the use of allergen component-resolved diagnostic testing methods will evolve in the future? What needs to be adapted to make this method more effective?

A: I believe that molecular diagnostic dissemination will positively impact the perception of allergy at the global level, significantly changing the approach to allergic patients. Furthermore, this new tool could help to drive clinicians toward a precision medicine in the field of allergology. CRD represents a scientific revolution, and to make this method more effective, medical

education and training programmes are needed for allergy specialists.

Q: What would you say is the largest challenge facing allergologists at present? What steps can be taken to overcome this?

A: At this moment, the largest challenge for allergologists is facing the 'allergic epidemic', both in reality and in its perception as such by patients. To do this, and to improve co-operation and co-ordination between scientific societies in the promotion of allergy and asthma programmes, an adequate number of specialists are necessary. Our duty is to improve prevention and diagnosis to achieve early detection and effective treatment, to invest in awareness campaigns for civil society, patients, and healthcare professionals, and to involve politicians and decision-makers in these actions.

Q: Finally, what advice would you give to medical students about to begin a clinical career in allergy and immunology?

A: Allergology and immunology are fascinating and attractive specialties for medical students. They are constantly evolving and stimulate interest in research. My advice for those who want to take up this type of career is to not give up when there are difficulties in the choice they must make. Being that allergic diseases are increasing and are widespread, a good specialist and researcher can surely find a correct collocation if they do their job with passion and conviction.

FUTURE OF THE ALLERGISTS AND ALLERGEN SPECIFIC IMMUNOTHERAPY (FASIT) MEETS EAACI

This company-sponsored symposium took place on 20th June 2017 as part of the European Academy of Allergy and Clinical Immunology (EAACI) Congress in Helsinki, Finland

Chairpersons

Ulrich Wahn,[1] Marek Jutel[2]

Speakers

Marek Jutel,[2] Jörg Kleine-Tebbe,[3] Oliver Pfaar,[4,5] Piotr Kuna[6]

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3. Allergy & Asthma-Center Westend, Berlin, Germany

4. Department of Otorhinolaryngology, Head and Neck Surgery, Universitätsmedizin Mannheim, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany

5. Center for Rhinology and Allergology, Wiesbaden, Germany

6. Medical University of Łódź, Łódź, Poland

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MEETING SUMMARY

The symposium provided a flavour of key presentations and issues discussed at the 2017 Future of the Allergists and Allergen Specific Immunotherapy (FASIT) workshop held in Hamburg, Germany. Prof Wahn explained that the FASIT meeting brought together basic scientists, clinicians, and practitioners to brainstorm issues around allergy. Prof Jutel considered FASIT presentations exploring how precision medicine can be used to select optimal patients for allergen immunotherapy (AIT). He outlined the role of phenotypes and endotypes, reviewed some biomarkers that are currently under validation, and considered the role of adjuvants. Prof Kleine-Tebbe considered a number of promising Phase II studies that have failed to be translated into successful Phase III studies. Factors influencing results, he said,

include high placebo effects, natural variability of the environment, patient heterogeneity, and the use of different endpoints for Phase II and III trials.

Prof Pfaar considered whether allergen exposure chambers (AEC) are at a stage to be used for Phase III (pivotal) trials in AIT. He provided an overview of the history and advantages behind these facilities and reported the regulatory view. Prof Pfaar reported a recently published Position Paper from the European Academy of Allergy and Clinical Immunology (EAACI) addressing the current status of allergen chambers and setting the 'frame' for further developments, such as clinical validation. The position paper included the views of all relevant stakeholders, including clinicians, chamber operators, and regulators. In the second part of his talk, Prof Pfaar reviewed the introduction of paediatric investigation plans (PIP), which are required for allergen products prior to receiving marketing authorisation and considered the methodological problems for fulfilling these regulatory demands. Finally, Prof Pfaar called for further consultation and collaboration between all parties involved in AIT regarding possible improvement of PIP.

Prof Kuna highlighted the European Union (EU) Directive 2001/83EC, which threatens both allergy diagnostics and the entire discipline of allergology. The directive states that allergens should be considered as drugs, and makes no distinction between allergens used for therapeutic procedures and those used for diagnostic purposes. The cost of obtaining and keeping marketing authorisations for test allergens is expensive. Already there are signs that allergen testing has been reduced in Europe. Prof Kuna concluded that it is essential for all stakeholders (authorities, allergists' societies like the EAACI, the European Medicines Agency (EMA), European legislators, and allergen manufacturers) to come together to ensure the continued availability of *in vivo* allergen diagnostic tests in the EU.

Introduction

Professor Ulrich Wahn

Prof Wahn explained that Allergopharma (Reinbek, Germany) invites international leaders in the allergy field to come together to discuss important immunotherapy issues. The initiative led to the first FASIT workshop in 2006, with meetings now held regularly. Allergists, said Prof Wahn, provide holistic overviews of various chronic (allergic) diseases, summarised as atopic syndrome. They evaluate triggers and causes of allergy, provide evidence-based recommendations on environmental control, prescribe pharmacotherapy, give advice on prevention, and educate primary care physicians. AIT is a "game changer", said Prof Wahn. It not only offers symptom relief, but modifies disease. FASIT, bringing together basic scientists and clinicians, provides a platform for research updates and opportunities for informal brainstorming around immunology and its clinical and regulatory requirements.

Europe as a continent, said Prof Wahn, illustrates how diverse the practice of immunotherapy can be. Data from the World Allergy Organization (WAO) in 2010 showed that in the UK just 1,700 specific immunotherapy treatments have been applied compared to 700,000 in Germany, 500,000 in France, 380,000 in Italy, and 350,000 in Spain.[1] Even for countries strong in AIT there is variation in the way treatment is delivered. Subcutaneous immunotherapy (SCIT) dominates in Germany and Spain, while sublingual immunotherapy (SLIT) dominates in France and Italy. FASIT provides the forum for debating differences in practice. FASIT, Prof Wahn concluded, stands for progress, innovation, and open discussion.

New Promising Perspectives in Allergen Immunotherapy

Professor Marek Jutel

The concept of personalised medicine, Prof Jutel explained, offers promise to develop tools predicting who will respond to therapies, thereby creating the opportunity of targeted treatments. The ideal approach involves identifying the phenotype (defined as visible properties), exploring the endotype (pathogenic mechanisms), and optimising the treatment for the patients (theratype) (Figure 1). Precision medicine in AIT helps selection of the optimal patient and therapy to reduce trial-and-error prescribing and control the overall costs.

One study showed certain endotypes (namely high or low expression of monocyte chemotactic protein-1 [MCP-1], eotaxin, and IL-8) distinguish patients according to disease severity (whether mild, moderate, or severe) in eosinophilic asthma.[2]

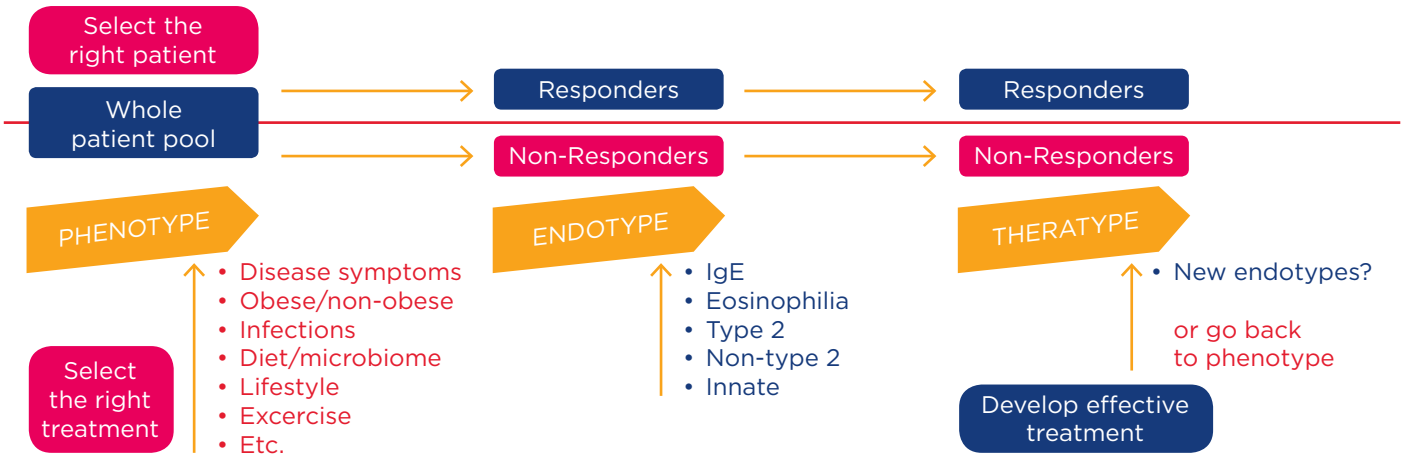

Figure 1: Personalised and precision approach for treatment of allergic patients.
Jutel M. FASIT "Asthma phenotyping and endotyping - precision medicine".
Ig: immunoglobulin.

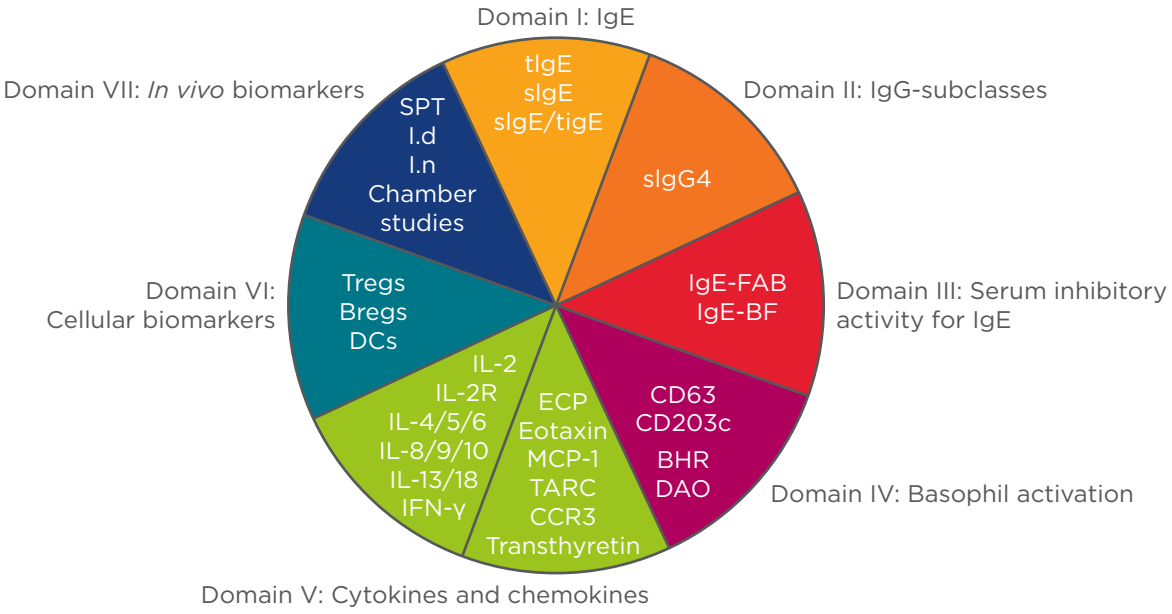

Figure 2: Domains reviewed by the EAACI Biomarkers task force.[3]
Each biomarker was assessed on the basis of its utility as a surrogate/predictive marker of efficacy in clinical trials and for monitoring the response of patients in clinical practice.
Ig: immunoglobulin; tIgE: total IgE; sIgE: specific IgE; sIgE/tIgE: specific IgE/total IgE ratio; Tregs: T regulatory cells; Bregs: B regulatory cells; DCs: dendritic cells; SPT: skin prick test; Id: intradermal; In: intranasal; IL: interleukin; IFN-γ: interferon gamma.
Shamji M. FASIT 2017 "Biomarkers in Allergen Immunotherapy".
Adapted from Shamji et al.[4]

Biomarkers, Prof Jutel said, can be used to link endotypes to clinical AIT phenotypes, leading to improved patient stratification.[3]

An EAACI task force, led by Mohamed Shamji, recently assessed a range of biomarkers for utility as surrogate/predictive markers of efficacy for clinical trial use and monitoring of individual patient responses.[4] The task force, which reviewed seven domains of biomarkers (Figure 2), concluded that intracellular expression of fluorochrome-labelled diamine oxidase in basophils might be suitable as a biomarker for efficacy and tolerance after AIT. Furthermore, they concluded differential expression of DC2 (GATA-3, CD141, and RIPK4) and DCreg (C1QA and FcγRIIIA) cell markers following SLIT to likely be associated with efficacy.

Other studies suggested additional biomarkers for AIT efficacy. In one study, Shamji et al.[5] showed that functional assays of inhibitory immunoglobulin (Ig)G_4 and IgE-blocking factors were more useful surrogates of clinical response than IgG_4. In a second study, Shamji et al.[6] found expression of fluorochrome-labelled diamine oxidase (DAO) in whole blood basophils was significantly higher among patients who achieved successful AIT (both SCIT and SLIT) for seasonal allergies. Gueguen et al.[7] showed that a combination of five markers (C1Q, CD141, FcγRIIIA, GATA3, and RIPK4) correlated with AIT SLIT clinical efficacy.

In real life, said Prof Jutel, factors such as obesity, diet, the microbiome, lifestyle, and exercise all influence efficacy. One factor is histamine, the effect of which on immune regulatory cells has been known for several decades.[8-10] In a recent study, Barcik et al.[11] found levels of the histamine secreting bacteria *M. morganii* in the human gut microbiome correlated with asthma disease severity (mild, moderate, or severe). On the basis of such observations, Barcik et al.[11] speculated that increased levels of bacterial derived histamine in asthma patients contribute to histamine-related pathologies.

There is also evidence that diet influences microbiome composition. In controlled feeding studies, Wu et al.[12] showed that microbiome composition changed detectably within 24 hours of initiating a high-fat/low-fibre or low-fat/high-fibre diet, but that enterotype identity remained stable.[12] Such data indicate that enterotype states are associated with long-term diet.

When Prof Jutel investigated the gut microbiome for patients from different European areas, he was able to predict whether the subject was obese or not, and found that different asthma endotypes also correlated with microbiome composition (unpublished data).

Ultimately, improved understanding of pathophysiology of allergic diseases in individual patients, said Prof Jutel, should make it possible to design better vaccines. At FASIT, Carsten Schmidt-Weber reviewed adjuvants and immune modulators considered attractive prospects for AIT. These included chitin-based adjuvants (engaging mitochondrial stress pathway), mRNA vaccinations, vaccination-driven antibody responses dependent on the microbiome, functional hydrogels and 'doped' nanoparticles, and JAK kinase inhibitors.

When patients are found to be non-responders, Prof Jutel concluded, a new approach could be taken to analyse phenotypes to consider whether any additional factors (such as obesity or the microbiome) might be affecting immunological mechanisms.

Molecular and Other Approaches for Allergen Immunotherapy: The Peril of Phase III Trials

Professor Jörg Kleine-Tebbe

For AIT, said Prof Kleine-Tebbe, some successful Phase II trials have failed to translate into positive Phase III trials. First, he considered evidence for T cell epitope trials. It was Phil Norman, he said, who first showed T-cell reactive treatment peptides (using two peptides of 27 amino acids from major cat allergen Fel d 1) improved human allergic responses to cats.[13] The concept was taken forward by Circassia Pharmaceuticals, plc. (Oxford, UK), who developed Cat-SPIRE®, a new class of synthetic peptide immune-regulatory epitopes (involving seven synthetic peptide T-cell epitopes with short sequences derived from Fel d 1). A study of Cat-SPIRE demonstrated improvements in the primary endpoint (total rhinoconjunctivitis symptoms) after both 1 and 2 years of treatment.

For the study, subjects were exposed to cat allergens in environmental exposure chambers before and after treatment with Cat-SPIRE delivered intradermally over 3 months.[14,15] However, in the following Phase III Cat-SPIRE field study, involving 1,409 cat-allergic subjects, Cat-SPIRE did not meet the primary endpoint (a combined score of symptoms and allergy medications).[16] Such data illustrate how one of the biggest hurdles for AIT treatments, said Prof Kleine-Tebbe, is the transition from Phase II to Phase III studies. A key difference is that Phase II studies might take place in environmental exposure chambers or employ various *in vivo*-challenge models, while Phase III studies take place in the field.

Notably for Cat-SPIRE, said Prof Kleine-Tebbe, there was a considerable placebo effect (58.5%), which set a high bar for any therapeutic intervention. A range of factors, he explained, contributed to placebo effects, including regression to the mean, the Hawthorne effect (which could mean that observing patients in itself changes the outcome), variable exposures, and subjective expectations.

A recent publication argued that placebo effects in acute pain and a range of clinical conditions activate brain regions associated with self-generated emotion, self-evaluation, thinking about the future, social cognition, and valuation of rewards and punishment.[17] A conjugated Amb a 1–toll-like receptor 9 agonist vaccine (TolambaTM) for ragweed-allergic subjects suffering from rhinitis also failed to translate from Phase II to III trials.

In the Phase II trial, the AIT vaccine (compared to placebo) reduced allergic rhinitis symptoms during the 2001 ragweed season (peak season, p=0.006) and maintained effects during the 2002 ragweed season (peak season, p=0.02).[18] However, the subsequent Phase II/III trial involving 738 ragweed allergic subjects failed to show an effect over placebo.[19] Also, in some instances where early studies have proved positive there was no further development, including recombinant birch pollen major allergen Bet v 1-vaccine and a mixture of five recombinant grass pollen allergens.[20,21] Considering evidence for the recombinant B cell epitope based vaccines, Prof Kleine-Tebbe said that less studies have been undertaken than for T cell epitopes. One randomised double-blind placebo controlled AIT study in a chamber showed a small decrease in nasal and ocular symptoms and titrated skin prick testing in comparison to placebo.[22] Field trials are planned.

Potential reasons for negative results in AIT Phase II/III trials, said Prof Kleine-Tebbe, include low pollen counts and selecting the wrong patients for the study. For example, the inconclusive results obtained in a study of grass SCIT by Prof Kleine-Tebbe were attributed to very low grass pollen count that season.[23] In another study, subjects showed considerable pre-seasonal symptoms and no increase during the main grass season suggesting symptoms reported were not primarily reflecting grass pollen exposure.[24] Such studies raise questions around how far Phase III trials can be considered reliable or to truly represent real life situations. That is not to say that there have not been AIT treatments shown to be positive in both Phase II and III trials. One example is SQ-standardised grass allergy immunotherapy with SLIT tablets, which was found to be effective after 1 year of treatment,[25] and after 3 years of treatment and a further 2 years of follow-up.[26]

Summarising his data, Prof Kleine-Tebbe said factors influencing results include high placebo effects, the natural variability of the environment (i.e. unpredictable pollen seasons), whether field studies represent the real world, patient heterogeneity, and the use of different endpoints in Phase II and Phase III trials. The FASIT delegates had identified steps to improve the design of trials, including introduction of a standardisation approach where patients are exposed to allergens in chambers to distinguish allergic from sensitised patients, removal of high placebo responding patients (if that is ethically valid), and introducing the same efficacy parameters in Phase II and III trials. Individual patient data and presentation of results in more detail would provide valuable information beyond simply reporting primary endpoint results.

With Phase III trials, Prof Kleine-Tebbe said, it was only when "every wheel" of the complex "study machinery" moved in the same direction that positive results could be achieved.

The Use of Allergen Immunotherapy in Europe: Regulatory Aspects and Call for Harmonisation

Professor Oliver Pfaar

Prof Pfaar considered two issues debated at FASIT: i) whether AEC were ready for Phase III trials, and ii) whether it was realistic to conduct childrens' studies in the face of PIP?

In 2008, the EMA provided guidelines for the clinical development of AIT products for allergic diseases. The guidelines stated that clinical efficacy in Phase III (pivotal) trials must be demonstrated under natural exposure of the respective allergens which evoke symptoms.[27] However, such a nature-based approach has methodological problems, with Prof Pfaar outlining examples of the unpredictability of natural allergen exposure. The high variability of pollen exposure is illustrated by a study comparing pollen counts in Paris (France) and Copenhagen (Denmark) in 2007 and 2008.[27] The results showed that pollen seasons start earlier in Paris than Copenhagen, and additionally that there were striking variations of pollen levels in Paris between the same months in 2007 and 2008. The consequence, said Prof Pfaar, is that findings would most likely be very different for trials conducted in Paris and Copenhagen and in different years. Another example is a post hoc analysis of data collected over six trials and six grass pollen seasons by Durham et al.,[28] which showed that the

magnitude of the treatment effects of grass SLIT were greater for higher pollen exposures.[28] In another study, the HIALINE working group[29] found that allergen release per pollen (potency) varied substantially, ranging from <1–9 pg of Phl p 5 per pollen. Such variation was in addition to natural variations in pollen count. The bottom line, said Prof Pfaar, is that nature is beyond our control and allergen exposure cannot be predicted or controlled. But attempts have been made to 'control nature'. In the 1980s, Prof Friedrich Horak developed the first Allergy Provocation Chamber (the Vienna Challenge Chamber) to improve controllability of allergen exposure. Over the years, several AEC have been introduced worldwide, with designs ranging from fixed chambers with large capacities, to mobile chambers.

Advantages of chambers include the possibility to expose patients to defined levels of allergen that control factors including particles/m^3, the temperature, air-pressure, and humidity. Other advantages include the absence of confounding allergens, no bias rescue-medication intake, no impact of personal context (outdoor versus indoor activities), and easy collection of biological samples. Additionally, lower numbers of subjects are needed than in field trials, which has an ethical benefit and results in cost savings.[27,30]

EMA guidelines state that AEC (as with other challenge methods) can be used for analysing primary endpoints in Phase II studies, such as dose range findings, 'proof-of-concept', or 'onset of action' trials.

But for pivotal Phase III trials, the guidelines emphasise that: "Provocation tests in allergen chambers are deemed to be promising tools for the evaluation of efficacy, however the results of such provocations have to be validated in comparison with clinical symptoms by natural exposure before such tests could be used as primary endpoints."[31] However, Prof Pfaar added, no clear further guidance about this validation procedure is given in the EMA guideline. The EAACI therefore recently set up a task force initiative bringing together academics, regulators, and chamber operators to consider technical prerequisites, model validation, and comparability with field trials.[32]

Regarding technical prerequisites, the group recommended validation of the allergenic exposure (including at least pollen grain counts and distribution), the use of GMP-grade allergens when processed material is mandated by local regulatory authorities, control of the chamber environment, standard operating procedures for cleaning facilities after each exposure, standard operating procedures for chamber operation, and logging of data for each exposure session.

For model validation, the group considered there should be evaluation of the outcomes of the plateau phase of the challenge, justification of single versus serial challenges, justification of low versus high dose challenges, disclosure of general patient selection criteria to assure appropriate patient selection and safety, use of standardised and clinically relevant outcomes, and reporting and justification of the calculation of the effect size of the intervention.

For comparability of allergen chamber trials with field trials, the group considered that direct comparison was not possible as natural allergen exposure cannot be determined and rescue medication is allowed in field trials. Indirect comparisons of effect size, however, are possible when allergic subjects with comparable clinical characteristics are evaluated. Most importantly, the panel concluded that hybrid trial designs that correlate AIT treatment effect sizes (demonstrated under natural exposure during the season) with those demonstrated under AEC challenges in the same patient population are feasible and may represent an option.

Looking into his crystal ball, Prof Pfaar foresaw a future where clinical validation chambers would be used in Phase III trials. For this vision to be realised, collaboration between chamber operators, academics, and manufacturers of AIT products will be needed.

The EMA/PDCO (Paediatric Committee) Standard Paediatric Investigation plan for Allergen Products for Specific Immunotherapy (Revision 4), which came into force in 2009, is now mandatory before companies submit marketing authorisation.[33] The PIP specified that separate dose-finding AIT studies are not required in children, but proof of long-term efficacy is.

Marketing authorisation applicants have to select one allergen product of their portfolio which will be evaluated for long-term disease modifying efficacy in adults and children (3-year treatment and 2-year post-treatment follow-up). Once long-term efficacy of the selected product has been

established in adults and children, development of all other products will depend on the proposed marketing authorisation application (treatment of allergic symptoms, sustained clinical effect, and long-term efficacy/disease modifying effect).

Prof Pfaar reviewed the FASIT debate around whether long-term efficacy studies are really realistic for children, which at the FASIT meeting was moderated by Prof Matthias Kopp. He gave the example of the GAP trial by Erkka Valovirta, where, after 7 months of screening, recruitment of 812 children at 101 centres in 11 countries was achieved.[34] While a "big job with a heavy work load", said Prof Pfaar, the GAP study does in principle demonstrate the feasibility of PIP studies in SLIT. There has, however, been no single published trial for SCIT meeting the PDCO criteria. The FASIT panel assessed the co-operation of ethical committees in approving SCIT trials and concluded that the willingness of parents to enter their children into 5-year placebo controlled SCIT studies was low.

Long-term studies in children, said Prof Pfaar, were needed but raised issues over whether it was ethical to deprive children (in the placebo arm) of known treatment benefits for long periods of time. Therefore, he considered what should be viewed as the best 'realistic' grade of evidence for AIT clinical efficacy in the paediatric population. Many unresolved issues exist, including ideal clinical endpoints and whether biomarkers might be used. Currently, Prof Pfaar concluded, there is a kind of 'paralysis'/reluctance among researchers, manufacturers, experts, and authorities with regard to designing proper clinical studies in children. Prof Pfaar ended his presentation with an urgent call for further consultation between all parties involved in AIT.

How Can we Offer High Quality Diagnostics for Our Patients in the Future?

Professor Piotr Kuna

One of the major issues discussed at FASIT 2017, said Prof Kuna, was the threat facing diagnostics from EU legislation. The consequences, he said, placed the entire medical discipline of allergology (allergy) in peril. During the FASIT meeting, Prof Torsten Zuberbier and Prof Ludger Klimek gave an overview on the current situation.

The situation was due to the consequences of the EU directive 2001/A3/ EC article 1 4b, which states allergens in general should be considered as drugs, falling under relevant national and European legislation.[35] Unfortunately, the directive made no distinction between allergens used for therapeutic and diagnostic purposes. The bottom line, said Prof Kuna, was that allergens used for diagnosis need to obtain marketing authorisation, and are required to demonstrate safety, sensitivity, and specificity in clinical trials. Furthermore, during routine clinical use, regular dossier updates are required showing handling of variation processes, ongoing stability testing, and periodic safety update reports.[35,36]

Such legislation, he added, will apply to a range of diagnostics including prick tests, prick to prick tests, intracutaneous tests, nasal provocation tests, challenge tests (e.g. food), and patch tests. Skin provocation tests, he said, represent the cornerstone of the diagnosis of Type 1 allergies. They are safe, fast, and inexpensive, and furthermore clinicians have had decades of experience using them. Modern laboratory allergy diagnosis can be considered to add to *in vivo* tests, but do not replace them. An online survey of an EAACI Task Force led by Vicky Cardona and Ludger Klimek, conducted in 2017, questioning representatives from 31 national EAACI-affiliated societies about allergy diagnosis, demonstrated skin tests are preferred to *in vitro* tests. Results showed that 90.3% of respondents preferred skin tests for respiratory allergy, 64.5% for food allergy, 58.1% for insect venom allergy, 54.1% for atopic dermatitis, and 58.1% for urticaria.[37]

Already, consequences from the legislation are being observed. Since 2004 France has lost two-thirds of prick test diagnostics; in 2013 alone, Germany lost 443 authorised diagnostics; and, in the Netherlands, only six authorised diagnostic tests are currently available.[38] Estimates for the German Health system, suggest totally replacing allergy diagnosis with laboratory diagnosis (such as basophil activation tests) would increase costs by a factor of 3.5 to 5.[38]

Obtaining marketing authorisation for *in vivo* tests is also likely to be expensive. Estimates taking into account clinical development costs, Phase I, II, and III trials and PIP testing, suggest the total cost per skin prick registration would be a minimum of €385,000. Such expenditure would result in street prices of €1,500 for rare allergens and >€60 for

more frequently used allergens.[39] To ensure continued availability of *in vivo* allergy diagnostics, said Prof Kuna, all stakeholders (EAACI, manufacturers, the EMA, and national regulators) need to come together to resolve the issues. The EAACI has established a task force to consider the issue of allergy diagnostics and is approaching the EU commission in an attempt to change European legislation.

The EAACI has also proposed that manufacturers should consider 'exchanging' rare allergens so that they are not all faced with supporting all allergens in all markets. Without *in vivo* allergen diagnostic testing, Prof Kuna concluded, the allergy community will not exist. Either amendment to the current legislation or the introduction of new legislation, he said, will be needed to save the discipline.

Conclusion

The FASIT meetings, said Prof Wahn, ensure conversations do not remain as just academic discussions in ivory towers, but are shared widely throughout the world. The aim, he said, was to develop the best possible immunotherapy for patients and ensure a future for both patients and allergists. He gave credit to Allergopharma for providing a platform to enable speakers to address important issues and discuss the future of allergology.

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CONTROVERSIES ON SPECIAL PRODUCTS FOR MANAGING COW'S MILK PROTEIN ALLERGY IN INFANTS: SAFETY AND SUITABILITY

This symposium took place on 18th June 2017 as a part of the European Academy of Allergy and Clinical Immunology (EAACI) Congress in Helsinki, Finland

Chairpersons

Antonella Muraro,[1] Arne Høst[2]

Speakers

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MEETING SUMMARY

The aim of the symposium was to share learnings from the recently established European Academy of Allergy and Clinical Immunology (EAACI) Task Force on special products for cow's milk protein allergy (CMPA), with the intention of providing an overview on controversies regarding extensively hydrolysed formulas (eHFs), their utility, and the validity of the definition 'special products for CMPA'.

Dr Rosan Meyer opened the symposium by discussing the evidence for appropriate dietary management in CMPA, emphasising the importance of breastfeeding and dietary management of breastfed children with CMPA, hypoallergenic formula, and the current controversies and debate around formula choice. Dr Martinas Kuslys covered the current interpretations and ranges for definitions for eHFs, and presented data from an analytical programme that aims to improve understanding of the wide range of commercially available formulas, with the objective of defining eHFs in a more consistent, meaningful, and practical way. Prof Antonella Muraro and Prof Arne Høst closed the session with a discussion around the need for updated guidelines to ensure safe products for infants with CMPA, summarising some of the issues with currently available hypoallergenic formulas.

Welcome and Introduction

Professor Antonella Muraro and Professor Arne Høst

The EAACI Task Force on products for CMPA was established in 2016, with the objective of addressing the need for improved knowledge regarding treatment of infants with CMPA. The symposium speakers are members of the EAACI Task Force, which aims to better define eHFs through a collaboration between academia and industry. The ultimate goal is to provide clarity in the field and to offer safe and suitable solutions, and advice for daily clinical practice.

Choosing the Most Appropriate Dietary Management for Infants with Cow's Milk Protein Allergy

Doctor Rosan Meyer

There are currently two existing definitions for 'hypoallergenic formulas'.[1,2] The first definition for specialty infant formulas with reduced allergenicity is based arbitrarily on a content of <1% immune-reactive protein of total nitrogen, while the second is based on the product being tolerated by at least 90% of infants (with 95% confidence interval) with documented CMPA. A key feature of the second definition is the recommendation that after a successful double-blind challenge, clinical testing should also include an open challenge, using an objective scoring system to document allergic symptoms during a 7-day period. A controversial aspect of the first definition is the lack of supporting evidence that the <1% threshold would prevent a clinical reaction. Therefore, there has been a drive by official bodies for hypoallergenic formulas to be tested in clinical trials and to comply with the second definition.

There is a lack of consistency around the definition of the Dalton size of peptides in eHF. A proposal used in many guidelines[1,3] dictates that the product should have free amino acids and peptides <1.5 kDa in size. This proposal may have originated from a study of peptide lengths in commercially available formulas, in which significant amounts of peptides of molecular weights (MWs) >1.5 kDa were not detected in any of the tested feeds.[4] The study authors did not recommend using >1.5 kDa as a cut-off, they simply reported that the formulas they tested did not contain significant amounts of larger proteins; however, various subsequent publications have featured it as a recommendation. Interestingly, a review of clinical studies of different formulas found that Dalton size alone does not predict clinical outcome.[5]

eHFs are suitable for most infants with CMPA,[6] and can contain protein derived from casein, whey, or rice. Casein-based eHFs were one of the first established hypoallergenic formulas (>60 years ago), while whey-based eHFs have been available since the early 1990s, and can contain lactose. Many casein and whey-based eHFs are well-established and tested products. However, many products currently available on the market have not been subjected to rigorous testing. Extensively hydrolysed or partially hydrolysed rice formulas are relatively new, and are not available worldwide. Rice-based eHFs have undergone testing according to the EAACI guidelines in two studies.[7,8] However, limited data exist on the effect of rice-based formulas on growth and its nutritional adequacy, with only a small number of studies available, featuring low numbers of patients. A question also remains over the presence of arsenic in rice-based formulas.[9]

Amino acid-based formulas (AAF) contain proteins only in the form of individual amino acids, and none are based on any cow's milk proteins. Generally, AAFs are reserved for the subgroup of patients with the most severe cases of CMPA[6] as they are considered the only truly non-allergenic formulas, with products available for infants both <1 year and >1 year of age. A recently submitted systematic review concluded that the following conditions warranted the use of AAF: failure on an eHF, eosinophilic esophagitis, faltering growth and multiple food eliminations, and anaphylaxis.[10]

Lactose has numerous benefits as an ingredient in formula. Historical fears regarding the risk of adverse reactions to lactose, as expressed in a 1999 joint statement of the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) and European Society for Paediatric Allergology and Clinical Immunology (ESPACI),[2] have been reassessed. More recently, ESPGHAN stated that: "adverse reactions to lactose in CMPA are not supported in the literature, and complete avoidance of lactose in CMPA is no longer warranted. eHFs containing purified lactose are now available and have been found safe and effective in the treatment of CMPA".[11]

It is important to note that lactose is the main source of carbohydrate in breast milk.[12] Given

that in non-immunoglobulin (Ig)E-mediated gastrointestinal allergies, breastfeeding is strongly recommended,[13] concerns over lactose seem unfounded. In addition to the positive impact of lactose on taste, lactose has a beneficial effect on the gut microbiota and metabolome in children with CMPA,[14] and has also been shown to improve the absorption of calcium and zinc.[15]

The need for a multidisciplinary approach in managing CMPA is summarised by a statement from the Italian Society of Paediatric Nutrition/ ItalianSociety of Pediatric Allergy (SINUPE/SIAIP) Allergy and Immunology Task Force:[16] "the interaction of the nutritionist, dietitian, nurses, allergologist and, whenever possible, psychologist, is the most successful way to ensure both growth and health of allergic children". Dietitians, as part of a multidisciplinary team, are known to improve parents' experience, reduce the number of appointments, and increase cost efficiency.[17] Dietary counselling has also been proven to result in a significant improvement in anthropometric and laboratory biomarkers of nutritional status of allergic children.[18]

In summary, there are several factors which need to be taken into consideration when choosing the most appropriate dietary management for infants with CMPA. Many guidelines exist for the management of CMPA, which recommend eHF for most cases as first-line formula, and AAF for the severe spectrum of CMPA.[6] When making the choice, it is also important to consider not only the nutritional status of the child, but also whether the hypoallergenic formula has been tested in children with CMPA as required by EAACI guidelines, if growth and nutritional adequacy data have been published, and if the micronutrient content is suitable for the child. For example, medium-chain triglycerides can optimise absorption of lipids in patients with malabsorptive disorders, and the addition of iron in follow-on formulas and formulas suitable for >1 year can be considered. The addition of vitamins, prebiotics, and probiotics, as well as taste and flavour additions, are also important to consider.[19,20] Practicalities, such as local availability, the reimbursement environment, and cost of formula must also be taken into account. The age of the child can also impact formula choice and taste acceptance, and religious and other dietary considerations (e.g. presence of multiple food allergies or being vegan/vegetarian) may restrict the formula choice further.

Not All Extensively Hydrolysed Formulas Intended for Cow's Milk Protein Allergy are the Same

Doctor Martinas Kuslys

Although the ultimate goals of all eHFs are the same, to be well-tolerated by most infants with CMPA and to be nutritionally complete with similar taste and consumption properties to regular formulas, recent publications have highlighted the chemical heterogeneity of eHFs.[21,22] Currently, eHFs can be characterised by either chemical analysis[3,23] or by the desired clinical outcome.[11,24,25]

Chauveau et al.[22] analysed the peptide profiles of three whey-based eHFs. Each peptide profile was found to be different. Two were found to have residual whey peptides, recognised by specific IgE, and two had residual caseins.[22] The authors concluded that: "the degree of hydrolysis and the size of residual peptides of each eHF should be known by practitioners".[22] In another study, four peptide profiles were tested from four batches of several commercially available casein-based eHFs and each was shown to be different. The authors concluded that dissimilarities in peptide profiles of the products may be related to the differences in their overall functionality.[21] These functional differences have also been observed in clinical practice. Although these observations cannot be generalised for all eHFs, in a study of 49 children with CMPA, half were found to have incomplete resolution of symptoms following whey-based eHF treatment.[26] Surprisingly, few eHF products have been shown to be efficient in terms of both allergy and growth.

Samples of commercially available eHFs from 12 countries (sourced from 11 major suppliers) were analysed with a clear focus on suitability for the management of CMPA. The programme consisted of internal investigations at the Nestlé Research Labs, Switzerland and external investigations at Neotron SPA, Italy and was conducted in accordance with accepted international testing standards. Only eHFs based on cow's milk proteins and marketed for the management of CMPA in infants were included. Although the MW distribution of hydrolysates can be used as an indicator of the degree of hydrolysis, several other parameters should be used to characterise eHFs. Quantification of residual proteins is also important as values reflect both the design of

the formula and the quality management in production. The analysis comprised of osmolarity, nitrogen fractions, lactose content, total and free amino acids, β-lactoglobulin, and casein content and included sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) and size exclusion-high-performance liquid chromatography (SE-HPLC) for peptide profiling and MW distribution analysis. The results focussed on three main aspects: peptide profiling and MW distribution, and both β-lactoglobulin and casein content by enzyme-linked immunosorbent assay (ELISA).

Significant variation in the peptide MW distribution was found, and the percentage of peptides with MW >1.2 kDa varied from 1–36%. Similarly, β-lactoglobulin levels were found to vary by more than two-orders of magnitude. eHF samples were grouped into two categories; 20% of investigated samples had non-measurable β-lactoglobulin content (lower than or at the limit of quantification [LoQ]: 0.010 mg/kg), and 80% of samples had β-lactoglobulin content >LoQ, with high variability from 0.020–36 mg/kg.

Casein concentrations also displayed a similarly wide variation. With 83.3% of samples having non-measurable casein content (≤LoQ: 0.2 mg/kg), and 16.7% having casein content >LoQ, with high variability from 0.3–1.1 mg/kg. Figure 1 displays these data and highlights the importance of using a combination of analytical methods when carrying out assessments of formulas. The results suggest that a high degree of hydrolysis is desirable, but further quality control elements are needed to ensure consistently clinically safe products.

It has been recognised by EAACI that not all eHFs are clinically tested or fit for their intended purpose.[6] The wide variation of the degree of hydrolysis in commercially available eHFs reflects the lack of alignment for the definition of 'extensively hydrolysed'. The high variability of commercially available eHFs and wide interpretation of the definition of eHF results in some products which are perhaps incorrectly labelled as 'extensively hydrolysed' and may be unsuitable for CMPA management. In 2010, the Spanish Food Standards Agency (AESAN) disclosed that milk protein had been found in samples of baby milk that had been marketed as being suitable for infants with milk allergies, leading to a product recall.[27] These findings highlight that the degree of hydrolysis alone, is not sensitive enough to characterise eHFs. It is recommended that actionable guidelines should be introduced and implemented to better define eHFs, and to provide guidance on conducting clinical trials.

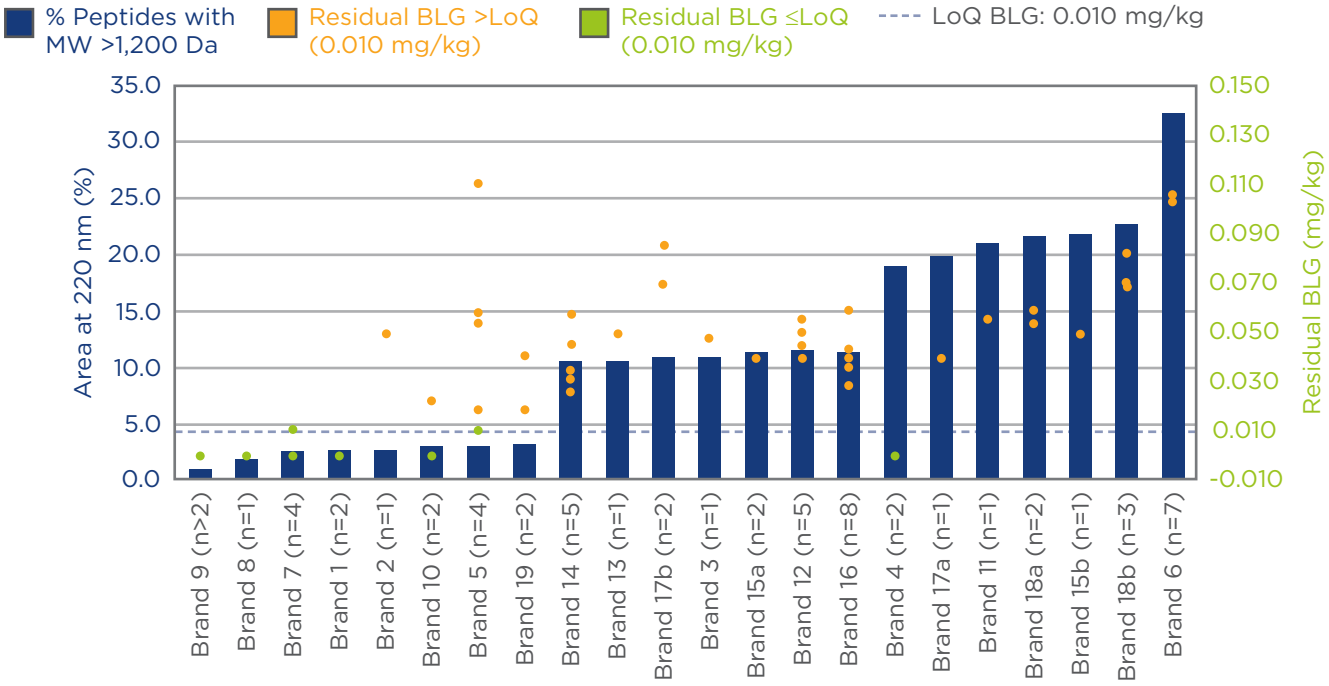

Figure 1: A combination of analytical methods; assessing formula suitability for the management of CMPA. BLG: β-lactoglobulin; Da: Dalton; LoQ: limit of quantification; MW: molecular weight; CMPA: cow's milk protein allergy.

New Guidelines Ensuring Safe Products for Infants with Cow's Milk Protein Allergy: Update from the EAACI Task Force on Special Products for Cow's Milk Protein Allergy

Professor Antonella Muraro and Professor Arne Høst

At present, not all commercially available products for infants with CMPA are safe and effective, since some contain a substantial proportion of high MW peptides, with a variable degree of residual antigenicity and allergenicity.[28-30] The criteria for hypoallergenic formulas recommended by EAACI in 2004 states that hypoallergenic formulas should have 90% clinical tolerance (with 95% confidence interval) in infants with IgE-mediated CMPA. Furthermore, the formula should be investigated in at least two centres with consecutive patients representing both IgE and non-IgE-mediated CMPA.[31] Casein hydrolysates,[32,33] whey hydrolysates,[34-37] and amino acid mixtures[35,38-41] have been shown to meet these criteria; however, there have been reports of allergic reactions to formulas labelled as 'eHF',[22] suggesting they do not meet these criteria and are neither safe nor effective.

The degree of hydrolysis and content of β-lactoglobulin has been investigated in a range of products.[30,42,43] Currently, there is no unanimous agreement on the criteria for eHF classification. Products can only be defined as non-allergenic if they are pure amino acid mixtures, all others, even those labelled as hypoallergenic, contain residual allergenicity and may induce allergic reactions.

Reduction of allergenicity can be achieved through several processes which can be combined, such as, enzymatic hydrolysis, heat treatment, and ultrafiltration. Hypoallergenic formulas can contain residual antigenicity due to inadequate hydrolysis and filtration, the presence of peptides with cow's milk protein (CMP)-derived epitopes, the aggregation of smaller peptides, and the cross-reaction of epitopes with those of CMP. Contamination and inclusion of other antigens can be introduced during production or packing processes, and from carbohydrate and lipid sources, which may explain batch-to-batch variations. Many products defined as 'hypoallergenic' have also undergone changes in their chemical composition, such as the addition of probiotics and prebiotics, long-chain polyunsaturated fatty acids, and other additives. It is unclear how these changes impact the 'hypo-allergenicity' as evaluated in the initial product.

Numerous tests are available to determine the antigenicity of cow's-milk-based formulas, including: physicochemical tests, which allow formal titration and an estimate of the percentage of hydrolysis, SDS-PAGE for MW determination, immunoblotting, inhibition ELISA and radioimmunoassay (using sera from sensitised patients), and animal models of anaphylaxis.

Future developments in the field should include industry-wide agreements on standards for preclinical testing, and quality control and assurance. Careful clinical testing, should also be carried out for quality assurance of each new 'hypoallergenic' product before its launch in the market. Strict criteria should be established with requirements for informative labelling on all products, and a European database of products for CMPA should be created, allowing information on adverse reactions to be collected.

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RAPID DESENSITISATION FOR THE MANAGEMENT OF HYPERSENSITIVITY REACTION TO BIOLOGICALS: INFLIXIMAB AND ADALIMUMAB IN INFLAMMATORY BOWEL DISEASE PATIENTS

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The introduction of biologicals for the treatment of inflammatory bowel disease (IBD) is an important therapeutic tool, but their usefulness is limited in patients with hypersensitivity reaction. Rapid desensitisation (RD) is used to overcome this problem.[1] The aim of our study was to evaluate RD safety and efficiency for the management of hypersensitivity reaction to infliximab (INX) and adalimumab (ADL) in IBD patients.

The study population consisted of 50 IBD patients, with a mean age of 40 years (17–64 years). The group consisted of 40 women (80%). We examined patients from September 2012–December 2016 in a prospective manner. Of the 50 individuals studied, 45 (90%) had Crohn's disease, 4 (8%) had ulcerative colitis, and 1 (2%) had IBD in undifferentiated form. A total of 19 (38%) patients had adverse reactions to INX, 16 (32%) to ADL, and 15 (30%) to both INX and ADL.

The stratification of patients according to Pichler's classification[2] of adverse reactions to biologicals revealed that 7 (14%) of the patients had type alpha, 27 (54%) type beta, 14 (28%) type gamma, no patients had type delta, and 2 (4%) had type epsilon. For allergology work-up, skin prick tests with undiluted and intradermal tests with 1/10 and 1/100 dilution were carried out with INX and ADL.[3] Both tests were evaluated at 20 minutes for immediate reactions and at 24, 48, and 72 hours for late reactions. Skin tests were positive in 5 (10%) patients. A basophile activation test (BAT) was carried out according to known methodology in used concentration. For INX: 25, 10, 5, and 2.5 µg/mL and for ADL: 125, 50, 25, and 12.5 µg/mL. BAT was positive in 7 (17%) patients. Anti-INX and anti-ADL antibodies were not detected. RD was indicated when skin test and/or BAT were positive and/or based only on a clinical course of adverse reaction.

RD was performed in 20 (40%) patients, with INX in 8 (40%) and with ADL in 12 (60%) of those patients. For RD, we used the previously published protocols.[1,4] Montelukast, anti-H1 and H2 blockers, and systemic steroids were used for the premedication. All procedures (skin and blood tests, desensitisation) were carried out with the informed consent of the patients. Successful RD was performed in 16 (80%) patients. In four (20%) patients RD had to be stopped early due to adverse reactions (dyspnoea and exanthema in two patients, decrease of C3 and C4 complement proteins in one, and flu-like syndrome in one).

In conclusion, RD is an effective method in people with an allergic reaction to biologicals because it allows the return of these drugs for IBD treatment.

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HYPERSENSITIVITY TO NATURAL RUBBER LATEX GLOVES AMONG ALBANIAN DENTAL STUDENTS

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Keywords: Questionnaire, allergy diagnostic tests, natural rubber latex, dental students, allergy symptoms, latex exposure duration.

Latex allergy is a common occupational disease among healthcare workers who use latex gloves.[1-3] Diagnosis of latex allergy is determined by analysis of personal history, physical examination, skin prick, patch, and challenge tests, or specific IgE determination, while self-administrated questionnaires are used to assess data about natural history, risk factors, etc.[4-7] The main aim of this study was to determine the prevalence of allergy to latex gloves among dental students and the role of exposure duration in latex allergy.

In this prospective study, a total of 240 students completed a self-administered questionnaire providing information about gloves, working habits, signs and symptoms related to glove use, precautions taken to minimise it, etc. The students were separated as non-exposed, shortly-exposed, and longer-exposed to natural rubber gloves during school practice. The challenge and patch tests were performed through latex gloves, and the skin prick test for latex, pneumoallergens, and trophoallergens with commercial extracts.

The questionnaire items and diagnostic tests revealed that one-quarter of the participants were suspicious of latex glove hypersensitivity.

Table 1: Reactions to latex exposure.

Type of reaction to latex exposure	Non-exposed (n=33)	Shortly-exposed (n=136)	Longer-exposed (n=71)	Total (N=240)	p
Suspected adverse reactions	6 (18.2%)	26 (19.1%)	28 (39.4%)	60 (25%)	0.002
Irritant skin reactions	5 (15.2%)	16 (11.8%)	25 (38.2%)	46 (19.2%)	0.0002
Allergic skin reactions	1 (3%)	15 (11%)	19 (26.8%)	35 (14.6%)	0.002
Internal organ allergic reactions	1 (3%)	4 (2.9%)	4 (5.6%)	9 (3.8%)	0.5

Table 2: Correlation between latex exposure duration and other study variables.

Variables	Frequency (%)	r	R^2	p
Previous reports of latex allergy	24 (10.0)	0.196	0.104	<0.001
Regular use of latex gloves	227 (94.6)	0.320	0.002	<0.001
Assisting colleagues who use latex gloves	195 (81.3)	0.361	0.007	<0.001
Hand erythema during work	23 (9.6)	0.132	0.133	0.018
Previous surgical interventions	57 (23.8)	-0.027	-	0.625
Irritant dermatitis after hand wash/washout procedures	33 (13.8)	0.104	-	0.063
Irritant disorders after hand disinfection procedures	26 (10.8)	0.114	0.005	0.040
History of additional allergic pathologies	42 (17.5)	0.118	-	0.034
Family history of allergic diseases	63 (26.3)	-0.003	-	0.956
Smoking tobacco	65 (27.1)	-0.065	-	0.243
Immediate erythema after using latex gloves	31 (12.9)	0.145	0.078	0.009
Eczema or cracked skin within 2 days after using latex gloves	34 (14.2)	0.217	0.071	<0.001
Concentration disorders after use of latex gloves	46 (19.2)	0.085	-	0.125
Recent problems in concentration level after use of latex gloves	27 (11.3)	0.134	0.026	0.016
Regular use of latex-free gloves	146 (60.8)	0.055	-	0.321
Adverse reactions after use of latex-free gloves	2 (0.4)	-0.093	-	0.095
Attenuation of adverse symptoms after use of latex-free gloves	102 (42.5)	0.067	-	0.229
Sneezing, eye itching, and/or nasal congestion after latex exposure	13 (5.4)	0.033	-	0.550
Breathlessness attack after latex exposure	6 (2.5)	0.159	0.070	0.004
Facial itching, angioedema, or erythema after latex exposure	12 (5.0)	0.074	-	0.186
Breathlessness attack after toy balloon blowing	5 (2.1)	0.104	-	0.061
Additional allergic reactions non-related to latex	28 (11.7)	-0.047	-	0.401
Visit in emergency services after latex exposure	17 (7.1)	-0.067	-	0.230
Previous positive allergy tests	13 (5.4)	0.048	-	0.384
Previous food allergies	37 (15.4)	0.043	-	0.422
Latex wheal	5/18 (27.8)	0.130	-	0.295
Latex flare	6/18 (33.3)	0.126	-	0.302
Suspected adverse reactions	60 (25.0)	0.179	0.033	0.001
Irritant skin reactions	46 (19.2)	0.163	0.001	0.003
Allergic skin reactions	35 (14.6)	0.171	0.007	0.002
Internal organ allergic reactions	9 (3.8)	0.140	0.046	0.012

Their mean value for skin reactions, such as contact urticaria, irritant, or allergic dermatitis, was between 10% and 14%, while for non-cutaneous symptoms the mean value was <5% (Table 1). The average latex exposure was estimated to be ˜214±71 hours (SE), with a maximum of 11,500 hours. The correlation between studied variables and the time exposure to latex gloves revealed weak-to-moderate relations with respect to reported latex allergy, eczematous reactions, hand erythema after glove wearing, irritant reactions during wash/washout procedures, recent concentration problems during usage of latex gloves, or dyspnoea attack during latex exposure (Table 2). In general, the students who experienced latex exposure for >2 years during their school practice have shown a two-fold positive response for statements or diagnostic tests on latex gloves hypersensitivity

(Table 1). Additionally, the Kendall's tau coefficient progressed from the non-exposed group to the longer-exposed group for the majority of items. Logistic regression analysis revealed an association between different questionnaire items and positive allergy tests among suspected and diagnosed cases of latex allergy, but not with control tests, including between the positive patch test and presence of non-cutaneous symptoms. Sensitisation to aeroallergens and trophoallergens was shown in 38% and 12% of subjects, respectively.

This study reinforces the notion that it is essential to recognise which professionals are sensitive to latex in order to provide appropriate treatment and to establish adequate prevention.[3] Due to the relationship between allergic reactions to latex gloves and some medical histories during school practice, it is necessary to undergo pre-matriculation evaluation and periodic health surveillance of dental students.[8] A positive history of allergic and irritant symptoms, determined by a questionnaire, was a significant predictor of a positive response to latex antigens.[5] This, in combination with positive diagnostic tests, confirms suspected latex allergy, especially when pathology is already established. This study also demonstrated that latex allergy patients are more predisposed to be sensitised to aeroallergens and trophoallergens compared to the general population. This predisposition can be considered an important risk factor for the development of food allergy and respiratory allergic diseases.[3,7] Moreover, our findings suggested that respiratory exposure plays an important role in the interaction between different mechanisms during sensitisation processes, and that questionnaire statements about latex allergy in combination with positive diagnostic tests can be reliable in the identification of allergic subjects.[9,10]

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SKIN PRICK REACTIVITY TO 80 DIFFERENT ALLERGENS AMONG 144 MEDICAL STUDENTS IN BIRJAND, IRAN

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Keywords: Allergy, allergen, Birjand, skin prick test, student.

BACKGROUND

Allergic disorders are among the most prevalent health problems around the world, particularly in low and middle-income countries.[1] Allergies impose a high economic burden and have a significant negative impact on patients' quality of life, especially in students when allergies interfere with academic life.[2] Allergens are the most common trigger of allergic symptoms and the pattern of sensitisation varies in different societies because of lifestyle and genetic background. Identification of the prevalent allergens in each area and the general population has an important role in the prevention and management of allergic disorders. Since Iran has a high population diversity, as well as different geo-climatic conditions, we aimed to evaluate the skin sensitivity of medical students in Birjand, Iran by using 80 different allergens.

SUBJECTS AND METHODS

Medical students were randomly selected and provided informed consent to participate in the study. Demographic data and the presence of different allergic disorders amongst the students were evaluated using a questionnaire. Skin prick tests were performed with 80 different extracts, including foods, pollens, and indoor allergens.

RESULTS

There were 144 medical students (mean age: 21.1 years; range: 19-30 years; male/female ratio: 0.63) enrolled in this study. The prevalence of asthma, allergic rhinitis, and eczema was 2.77%, 40.00%, and 12.50%, respectively. At least one positive reaction was seen in 58% of the participants, and more than half were polysensitised. The most common allergens were *Salsola kali* (48.61%), a mixture of common weed pollens (45.38%), *Chenopodium Album* (40.97%), and a mixture of tree pollens (29.86%). They also were the most potent allergens and had the largest mean wheal size (29.5, 15.3, 11.8, and 9.9 mm^2, respectively). Tomato, orange, walnut, mustard, and pomegranate were the most prevalent food allergens (4.86%, 3.47%, 3.47%, 3.47%, and 3.47%, respectively). There was no significant difference in sensitisation between males and females.

DISCUSSION

The results of this study showed high, medium, and low prevalence of allergic rhinitis, eczema, and asthma, respectively, which is similar to the results of other reports from this area that studied the general population.[3,4] In the case of prevalent aeroallergens, weed pollens, particularly Russian thistle and Lambs quarter, were the most common and potent allergen, in concordance with the results of another study in the region.[5] Skin sensitivity to indoor allergens, particularly mites and moulds, was quite low, which can be explained by the geo-climatic situation of Birjand. Two other studies have also confirmed the lack of mite growth in Birjand[6] and in many other parts of Iran.[7] In the case of food allergens, the pattern of sensitisation differed from the results of most other studies in Iran, which report both cow's milk and egg as the frequent food allergens in children.[8]

CONCLUSIONS

The results of this study confirmed high rates of allergic rhinitis and skin sensitisation to plant pollens, particularly weeds and grasses, while the sensitivity to indoor allergens and food allergens was low.

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RAGWEED POLLEN ALLERGY: PATTERNS AND CROSS-REACTIVITY

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Keywords: Ragweed allergy, ISAC microarray, cross-reactivity, allergic rhinoconjunctivitis, immunoglobulin E (IgE).

Allergic rhinoconjunctivitis is a Th2-type inflammatory disease of the nasal mucosa and the conjunctiva, mediated by immunoglobulin (Ig)E antibodies. The prevalence of allergic rhinitis in Europe is ˜25.0%,[1] ranging from 17.0% (Italy) to 28.5% (Belgium).[2] Inhaled allergens are an important factor in morbidity, and they may severely affect quality of life. Over recent decades, a matter of particular concern has been *Ambrosia* (ragweed) pollen, its presence in the air being determined by the plants dispersing it and the meteorological processes that alter pollen release, dissemination, transport, or deposition on surfaces.[3] The aim of this study was to determine the impact of ragweed pollen on allergic patients from western Romania.

A total of 97 subjects were recruited prospectively between August and November 2013, in an observational cross-sectional study. Of the 97 individuals, 84 with positive skin prick test (SPT) to ragweed pollen extract and 13 negative controls were included. Patient evaluation was performed by SPT with a panel of 18 standard inhaled allergens. Specific serum IgE to 176 allergens was determined by using the ImmunoCAP ISAC microarray (Phadia AB, Uppsala, Sweden).

Mean patient age was 31.2±8.9 years, with a mean allergic disease age of 3.62±3.15 years. Of the patients, 40% were male. Patients with a positive SPT to ragweed pollen extract totalled 84. Most patients (73%) had moderate-severe intermittent allergic rhinoconjunctivitis, and 25% of them also had allergic asthma. Out of the 84 patients with a positive SPT to ragweed pollen extract, 90% also had increased specific serum IgE levels to the major ragweed allergen, Amb a 1 (5% Class 1, 35% Class 2, and 45% Class 3) (Figure 1).

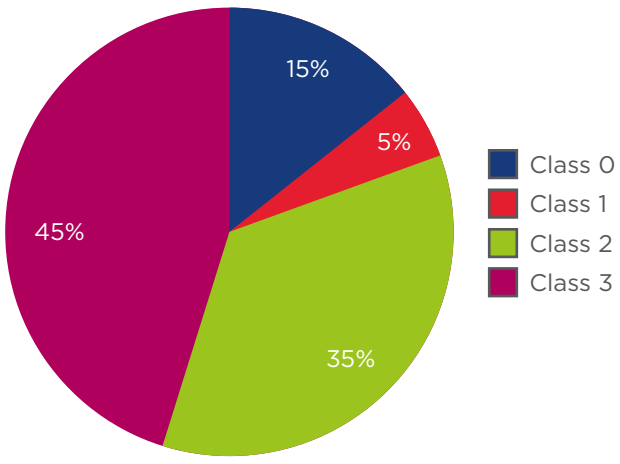

Figure 1: ImmunoCAP ISAC microarray results.

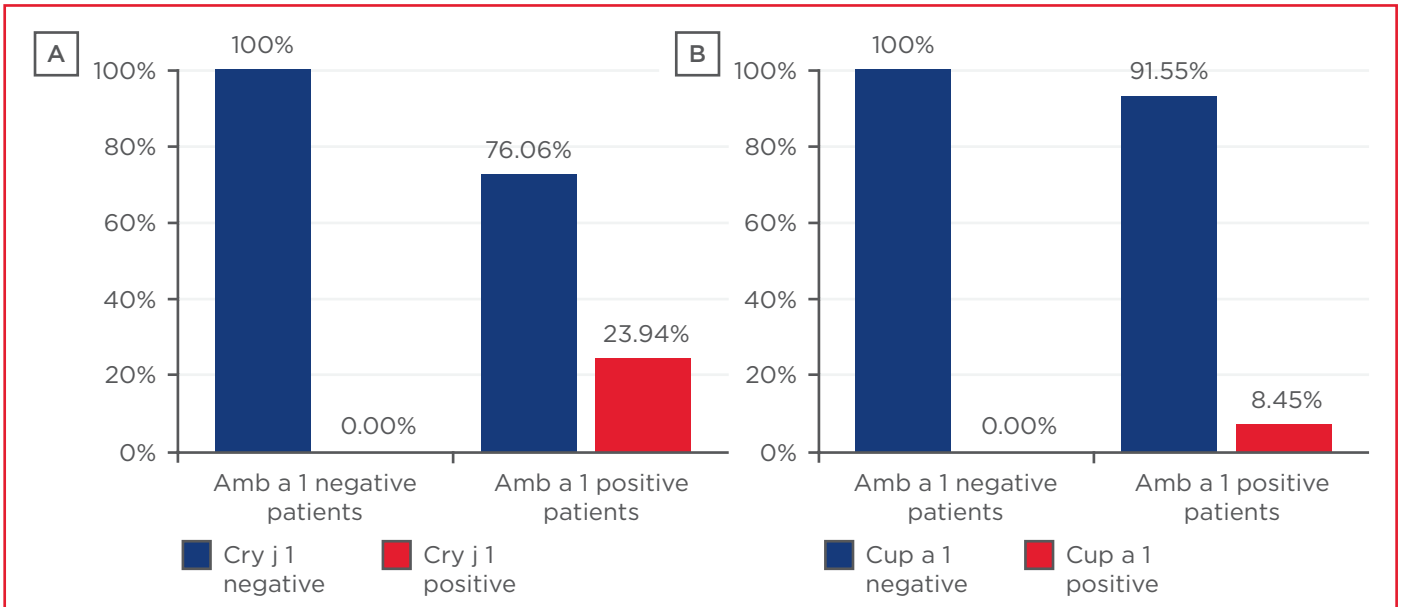

Figure 2: Potential cross-reactivity between Amb a 1 and other allergens from the same family for both Amb a 1 positive and negative patients.
A) Cross-reactivity between Amb a 1 and Cry j 1; B) Cross-reactivity between Amb a 1 and Cup a 1.

Among the patients who were tested for multiple allergens by SPT, the majority (78%) were polysensitised. Polysensitised patients were mostly sensitised to other pollens (cereals, *Artemisia*, birch, and oak), house dust mites (*Dermatophagoides pteronyssinus, Dermatophagoides farinae*), and pet dander (dog, cat). The sensitivity and specificity of the ImmunoCAP ISAC microarray (Amb a 1) versus SPT (ragweed pollen extract) was 85.88% (95% confidence interval [CI]: 76.63–92.48%), and 90.91% (95% CI: 58.67–98.49%), respectively. IgE class did not correlate with SPT response class. We investigated potential cross-reactivity between Amb a 1 and other allergens from the same family, from species not present in the local, indigenous flora: Cry j 1 (Japanese cedar) and Cup a 1 (Arizona cypress). Cry j 1 specific IgE were identified in 24% of the Amb a 1 positive patients, as opposed to none of the Amb a 1 negative patients, which was a statistically significant difference ($p<0.05$). Cup a 1 specific IgE were identified in 8% of the Amb a 1 positive patients, as opposed to none of the Amb a 1 negative patients, which was statistically insignificant ($p>0.05$) (Figure 2). A moderate correlation was found between the self-reported evaluation score (on a scale 1–10) and a computed symptoms score (total symptoms a patient presents), by using Spearman's rank correlation coefficient (0.584), which was extremely significant ($p<0.0001$), meaning that the patients' estimate of disease severity correlated well with the number of symptoms. All patients with a disease history older than 15 years had developed allergic asthma.

There was a small fraction of patients that were allergic to minor ragweed pollen allergens and they were not identified by standard *in vitro* diagnostic procedures. Component-based diagnosis using microarrays is needed for the selection of the appropriate allergen source for specific immunotherapy. Appropriate therapeutic measures need to be taken in order to prevent progression of allergic inflammation from rhinoconjunctivitis to bronchial asthma.

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POLLEN ALLERGY POTENCY FOR THE MAIN URBAN PLANTS

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Keywords: Pollen, allergy potency, allergy risk, exposure, sensitisation, species.

Pollinosis, or respiratory allergy due to pollen grains, is a real pathology for 20–30% of the European population. Before illness prevails, there is a period of sensitisation due to pollen exposure of the population, particularly among children, the elderly, and the very frail. For this reason, it may be very important to decrease the risk of sensitisation by pollen in proximity of these people, such as in public gardens, schools, and hospitals.

It is necessary to truly understand the difference between the allergy potency of a pollen grain, and the allergy risk due to the pollen. The allergy potency is the capacity of the pollen grain to produce immunoglobulin E in a large part of the population. It is an exposure index corresponding to the level of allergen contained inside the pollen grain, in the micro-cytoplasmic particles or around the exine of the pollen grain. The allergy potency of a pollen grain is the same regardless of the localisation of the source plant. For instance, birch pollen is a pollen grain which contains a large amount of Bet v 1 in any country from Finland to the south of Spain. This also applies to other trees such as olive, cypress, grasses, and ragweed.

The allergy risk due to pollen is a health impact index corresponding to the capacity of the amount of pollen to cause allergy to sensitise an individual to a place. Allergy risk is dependent on the allergy potency of the pollen grain, the amount of pollen, the localisation of the population, and the meteorological conditions.

Table 1: Allergy potency for main trees.

Trees		
Species	**Family**	**Allergy potency**
Maple*	*Aceraceae*	Moderate
Alder*	*Betulaceae*	High
Birch*		High
Hornbeam*		High
Hop-hornbeam		Low or negligible
Hazel*		High
Baccharis	*Asteraceae*	Moderate
Cade	*Cupressaceae*	High
Common cypress		High
Arizona cypress		High
Juniper		Low or negligible
Thuja*		Low or negligible
Locust (robinia)*	*Fabaceae*	Low or negligible
Chestnut-tree	*Fagaceae*	Low or negligible
Oak*		Moderate
Beech*		Moderate
Walnut*	*Juglandaceae*	Low or negligible
Paper mulberry	*Moraceae*	High
White mulberry		Low or negligible
Ash*	*Oleaceae*	High
Olive-tree		High
Privet*		Moderate
Pine*	*Pinaceae*	Low or negligible
Plane-tree**	*Platanaceae*	Moderate
Poplar*	*Salicaceae*	Low or negligible
Willow*		Moderate
Yew	*Taxaceae*	Low or negligible
Japanese red-cedar	*Taxodiaceae*	High
Linden*	*Tiliaceae*	Moderate
Elm*	*Ulmaceae*	Low or negligible

*Several species; **The pollen of the plane trees is weakly allergenic. On the other hand, the microneedles contained in the waders resulting from the degradation of the female heads of the previous year are very irritating.

Table 2: Allergy potency for main grasses.

Grasses		
Species	**Family**	**Allergy potency**
Chenopod*	*Chenopodiaceae*	Moderate
Burned soda (prickly saltwort)		Moderate
Ragweed*	*Asteraceae*	High
Mugwort*		High
Daisy*		Low or negligible
Dandelion*		Low or negligible
Mercury*	*Euphorbiaceae*	Moderate
Plantain*	*Plantaginaceae*	Moderate
Grasses*	*Poaceae*	High
Sorrel* (Rumex)	*Polygonaceae*	Moderate
Neettle*	*Urticaceae*	Low or negligible
Pellitory*		High
Reed canary-grass	*Poaceae*	High
Reed grass		Moderate
Tufted hairgrass		High
Sand ryegrass		Moderate
Fescue*		High
Oatgrass		High
Hare's-tail		Moderate
Giant feather grass		Moderate

*Several species.

For our example, the allergy risk due to birch pollen exposure is very high in Finland and nul in the south of Spain.

For all these reasons, the French aerobiology network (RNSA) provided some tables with the allergy potency (high, moderate, low, or negligible) of the main trees, grasses, and herbs that are commonly planted in urban areas (Table 1, Table 2). It is very important that landscape gardeners take into account these lists before choosing the different species for public or private gardens for the health of the users.[1,2]

It is interesting to see that similar publications of exposure index in Granada, Spain estimated an exposure index for different public gardens with the number of plants and their respective allergy potency.[3] On the same topic, during 2 years (2015–2016) the aerobiological information systems and allergic respiratory disease management (AIS LIFE) and RNSA located some Sigma-2 like pollen traps in gardens in Paris and Lyon, France. These proximity pollen traps evaluate the allergy potency of different gardens and create an index of exposure risk with reference to the number of species, allergy potency, and the annual number of pollen grains of each.[4,5]

The recommendations are as follows: plants with low or negligible allergy potency can be freely planted, those with moderate potency should only be planted in very few numbers, and those with high potency should not be planted.

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DOES LEUKOCYTE TELOMERE LENGTH PLAY A ROLE AS A CANDIDATE BIOMARKER FOR PRENATAL STRESS EXPOSURE AND THE RISK OF ATOPIC DERMATITIS DEVELOPMENT?

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Keywords: Atopic dermatitis, prenatal stress, telomere length, birth cohort, oxidative stress.

According to the Development Origins of Health and Disease (DOHaD) theory,[1] maternal prenatal stress is one of the key factors that affect the offspring's risk of non-communicable diseases (NCD).[2] Allergy is one of the representative NCD in children. Recent epidemiology studies indicate that maternal prenatal stress increases the risk of allergic diseases in offspring.[3,4] No biomarker, however, is available, meaning that the exposure to stress or the possibility of allergic diseases development cannot be estimated. On the other hand, oxidative stress increases when subjects are under psychological stress[5] and this elevates the risk of contracting NCD.[6] Oxidative stress is thought to also be involved in allergic disease pathogenesis.[4] Recently there have been clues that the leukocyte telomere length (LTL) shortening reflects the exposure to cumulative oxidative stress.[7] Telomeres, the protective nucleoprotein structures with a variable number of a tandem repeat sequence that envelops the ends of linear chromosomes, are known to shorten with cell division.[8] The LTL shortening is accelerated by oxidative stress and inflammation.[9] This study aimed to verify whether maternal prenatal stress reduces the LTL in offspring, and whether the offspring's LTL shortening is associated with the state of atopic dermatitis. If an association was shown, it would implicate that LTL shortening themselves, or other factors that can shorten the LTL, i.e. oxidative stress, is largely involved in the pathogenesis of prenatal stress inducing development of the offspring's atopic dermatitis.

We selected a Korean birth cohort that demonstrated a good association between the prenatal maternal stress and offspring's atopic dermatitis development.[10] Among subjects whose cord blood and 1-year peripheral blood were both collected, 4 groups were selected according to both the level of prenatal maternal stress and later development of atopic dermatitis (high stress with later atopic dermatitis [HSWD], high stress without atopic dermatitis development [HSOD], low stress with later atopic dermatitis [LSWD], and low stress without atopic dermatitis development [LSOD] group). We evaluated cord blood and 1-year peripheral blood-LTL by measuring the mean terminal restriction fragment length using commercial kits from each group and compared them according to time points and groups.

A total of 68 subjects were sampled (22, 14, 13, and 18 for the HSWD, HSOD, LSWD, and LSOD groups, respectively). The mean 1-year peripheral blood LTL was significantly shorter than that of cord blood, which means that 1 year is a sufficient time to evaluate the change. When we divided groups according to the prenatal maternal stress, LTL were shorter in high stress groups than low stress ones, regardless of atopic dermatitis development both in cord blood and 1-year peripheral ones; this implies that prenatal stress certainly affects LTL shortening and the effect persists during the initial developmental period after birth. On the other hand, when groups were divided according to atopic dermatitis development, cord-blood LTL were not different between groups and 1-year peripheral-blood LTL presented only marginal difference between those that developed atopic dermatitis and those that did not. This demonstrates that LTL shortening is not a causal factor for developing atopic dermatitis. When we subdivided the comparison into each subgroup, the LTL did not shorten in the LSOD group, whereas in the LSWD group, LTL significantly shortened during 1 year after birth, which indicates that LTL shortening was prominent with the atopic dermatitis development.

In conclusion, prenatal stress results the LTL shortening; this may not be the causal, but the associated, factor of atopic dermatitis development. These results collectively indicate that the LTL shortening, a marker for oxidative stress exposure,

reflects the complicated pathogenesis of prenatal stress associated with offspring's atopic dermatitis development.

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YOGHURT CULTURE *LACTOBACILLUS DELBRUECKII* SUBSP. *BULGARICUS* MODULATES THE SECRETION OF TYPE 1 AND 2 T HELPER AND REGULATORY T CELL-RELATED CYTOKINES BY PERIPHERAL BLOOD MONONUCLEAR CELLS FROM PATIENTS WITH ATOPIC DERMATITIS

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Keywords: Atopic dermatitis (AD), probiotics, *lactobacillus bulgaricus*, Type 1/Type 2 T helper cells (Th1/Th2), regulatory T cell (Treg) cytokines.

ABSTRACT

Introduction: Atopic dermatitis (AD) is an inflammatory skin disease which may arise due to the imbalance between Type 1 T helper (Th1), Type 2 T helper (Th2), regulatory T cell (Treg) cell-related immune responses. Evidence suggests that appropriate stimulation with probiotics may correct the skewed immune response in children with AD. The aim of this study was to determine the effects

of the yoghurt culture *lactobacillus delbrueckii* subsp. *bulgaricus* on the secretion of Th1/Th2/Treg-type cytokines by peripheral blood mononuclear cells (PBMCs) from children with AD.

Methods: *L. Bulgaricus* was cultivated on MRS agar broth. The PBMCs from 20 children with AD were separated by Ficoll-Hypaque centrifugation and co-cultured with different intensities of ultraviolet to kill bacteria in RPMI-1640, plus 10% fetal calf serum for 48/72 hours. The levels of interleukin (IL)-10, IL-4, IL-12, and interferon gamma (IFN-γ) were measured in the supernatant of PBMCs by enzyme-linked immunosorbent assay. RNA extraction and real time reverse transcription polymerase chain reactions were used to measure Foxp3 mRNA expression.

Results: *L. bulgaricus* significantly upregulated the secretion of IL-10, IL-12, and IFN-γ, whereas it reduced the secretion of IL-4 by PBMCs at both incubation times of 48 and 72 hours and both bacteria-to-PBMCs ratios 100:1/50:1, compared to controls ($p<0.05$). There were no significant differences between incubation times of 48 and 72 hours regarding the secretion levels of IL-12, IFN-γ, and IL-4; however, the secretion level of IL-10 by *L. bulgaricus*-stimulated PBMCs at the incubation time of 72 hours, and in the presence of a bacteria-to-PBMCs ratio of 100:1, was significantly higher than the incubation time of 48 hours and in the presence of a bacteria-to-PBMCs ratio of 50:1 ($p<0.0001$ and $p<0.001$, respectively). Neutralisation of IL-10 by the anti-IL-10 antibody increased the secretion levels of IL-12 and IFN-γ at the incubation time of 72 hours, compared to 48 hours, and at a bacteria-to-PBMCs ratio of 100:1, compared to 50:1. The expression level of Foxp3 mRNA by *L. bulgaricus*-stimulated PBMCs, as correlated to IL-10 secretion, at an incubation time of 72 hours and in the presence of a bacteria-to-PBMCs ratio 100:1, was significantly higher than 48 hours and in the presence of a bacteria-to-PBMCs ratio of 50:1 ($p<0.01$ and $p<0.05$, respectively).

Discussion: These data show that *L. bulgaricus* may modulate the secretion of Th1, Th2, and Treg-related cytokines in AD patients. It seems that the activity of Treg cells, after 72 hours of stimulation or at a bacteria-to-PBMCs ratio of 100:1 by *L. bulgaricus*, dominates the effector T cells. The Th1 and Th2 cells do not secrete more cytokines after the 72 hours incubation time and at a bacteria-to-PBMCs ratio of 100:1, compared to 48 hours and a bacteria-to-PBMCs ratio of 50:1. Therefore, the potential therapeutic use of *L. bulgaricus* for treatment of AD should be considered for further investigation.

A COMPLETE CHRONIC URTICARIA MEDICAL HISTORY CHECKLIST

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Keywords: Chronic urticaria (CU), checklist, medical history, chronic spontaneous urticaria, chronic inducible urticaria.

Chronic urticaria (CU) (>6 weeks) is classified in two subtypes: chronic spontaneous urticaria and chronic inducible urticaria. In ≤90% of the chronic spontaneous urticaria cases, the search for underlying causes is not successful in routine clinical practice. Patients with CU are a challenge for physicians. A thorough medical history and physical examination to identify all possible eliciting factors and causes are important for the diagnosis. Existing international guidelines are

usually generalised and not very useful for clinical practice and an oriented medical history in the first doctor–patient meeting.

The aim of this study was to provide a checklist and a collection of items that should be included in a correct medical history, allowing physicians to quickly and easily identify the mean characteristics of the disease and the possible eliciting factors, to enable an accurate diagnosis and management of the disease.

First, we conducted a literature search for relevant studies of CU until December 2016 using MEDLINE, the Cochrane Library for systematic reviews of databases, and the PubMed search engine. A total of 82 articles were found and all items to be incorporated into the first checklist were discussed.

A checklist was developed and a collection of items essential for anamnesis and diagnosis of CU and typical symptoms or characteristics according to CU subtypes was compiled. The items of the checklist included time of onset of disease, duration of wheals, onset of lesions after the trigger, symptoms onset, shape, size, colour, and distribution of wheals, associated angioedema, associated subjective symptoms of lesions, stimuli (such as physical, food, drugs, infection), diurnal and nocturnal variation, evaluation of the activity with UAS7 and the urticaria control test, and laboratory results, including complete blood count and others.

Being confronted with a patient with urticaria can be frustrating for both patient and physician. As lesions may persist, eliciting factors are confusing, and this could lead to a misdiagnosis of the disease. This checklist and collection of items can help focus, orientate, and save time in a medical consultation, aiding physicians to diagnose and manage CU more accurately.

Further research is recommended to validate this tool, which needs to be adapted to the context and reality of each country, depending on the most frequent aetiology of CU. Furthermore, this checklist could be useful as a means of consultation using, for example, a smartphone.

STUDY OF MODIFIED SKIN PRICK TEST WITH 140 ALLERGENS IN SINGLE SITTING IN CASES OF SEVERE PERSISTENT ALLERGIC RHINITIS

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Keywords: Modified skin prick test (MSPT), severe persistent allergic rhinitis, World Allergy Congress (WAC).

When allergen detection is not possible by a patient themselves or from their previous history, the next step is allergy testing. When allergen avoidance is not practical, immunotherapy becomes important. A person can be allergic to anything in the world, from the sun above to the earth below.

India is a large country with a population of approximately 1.2 billion, low socioeconomic status, a low literacy rate, and large numbers of fauna and flora and, hence, a large number of indoor and outdoor allergens.

Case history alone often leads to misdiagnosis of rhinitis. Nearly 65% of patients are prescribed antihistamines for their reported allergic rhinitis; however, they have symptoms that are not caused by this condition.[1-3] In such a situation, it becomes very difficult and impractical to test allergens from the patients by history alone or with a fixed panel of allergens pertaining to the local area. This is for several reasons: allergic patients are travelling across countries, new sensitisations are being discovered in relation to climate change, and cross-reactivity may be unsuspected.

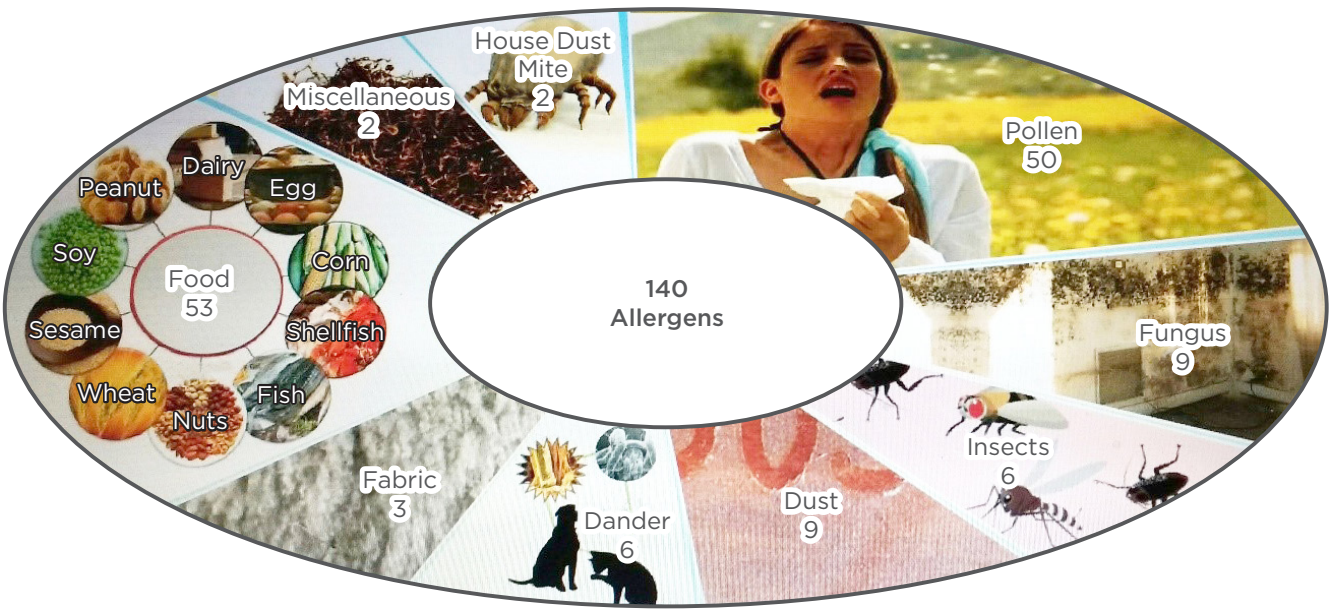

Figure 1: Common allergens of central India.

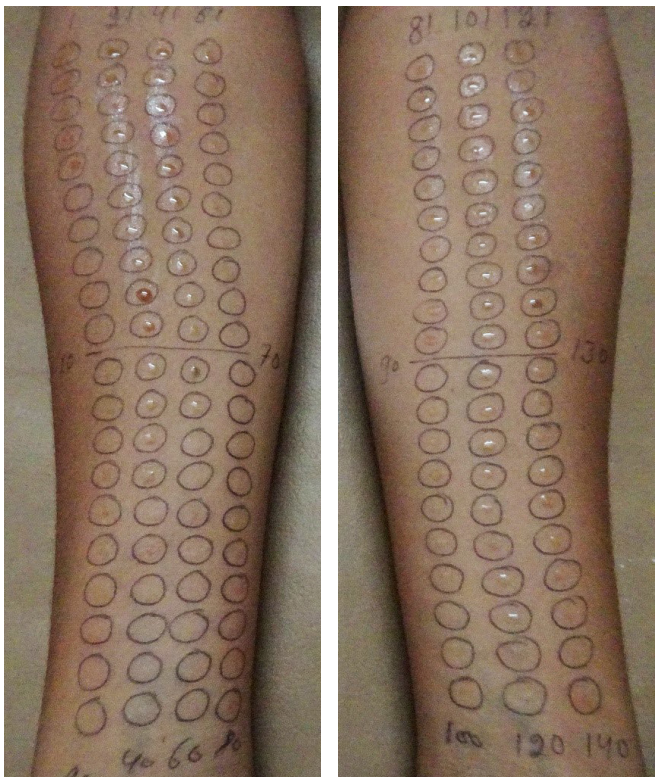

Figure 2: Modified skin prick test with 140 allergens. Demonstration of allergen placement.

An allergy test was carried out by a modified skin prick test (MSPT) method for 140 common allergens of central India (Figure 1).[4] A total of 810 patients from 6–63 years of age participated. The MSPT was carried out on the volar aspect of both forearms, spaced at a distance of 1.2–1.5 cm between two allergens to accommodate 140 allergens.[5] This compared to a paper by Welsh et al.[3] Of the 810 patients, only 10 showed overlapping of induration for 2–3 allergens, which were tested just above the cubital fossa in the same sitting (Figure 2).

Discussions were held with patients regarding their MSPT results, causative allergens, and exposure details. Surprisingly, a correlation between MSPT results and history could be established retrospectively, which may have been missed due to a more limited number of allergens and history of correlation of symptoms before allergy testing. In the discussed MSTP method with 140 allergens, an accurate diagnosis of severe persistent allergic rhinitis could be made saving time, energy, and money compared to current testing.

When this abstract was presented at the EAACI congress, several questions were asked by attendees:

Q: Is the MSPT economically viable?

A: It is believed that, yes, this method of allergen detection is economically viable.

Q: How easy was it to use the template to mark out 140 allergens?

A: This is a matter of practice only.

Q: Was serum-specific IgE collected before immunotherapy with MSPT began?

A: Serum-specific IgE was not collected because IgE and skin prick test do not have the same biological and clinical relevance and are not interchangeable.[3]

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LEUKOTRIENE RECEPTOR ANTAGONISTS IN MANAGING SEVERE UNCONTROLLED ASTHMA

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Keywords: Asthma, therapy, leukotriene receptor antagonists, inflammatory mediators, interleukin (IL)-5, IL-13, eosinophils.

INTRODUCTION

Asthma is a chronic inflammatory disease where >100 powerful inflammatory mediators are associated with airway hyper-responsiveness, mucus hypersecretion, activation of fibroblasts, hyperplasia, and hypertrophy of airway smooth muscle.[1] Cytokines are involved in this inflammation. The cells that produce cytokines include B cells, T cells, dendritic cells, natural killer cells, cytotoxic T cells, T helper cells (Type 1 and 2), endothelial cells, mast cells, plasma cells, progenitor cells, bone marrow cells, thymus cells, and tumour cells, together with fibroblasts, leukocytes, monocytes, and macrophages. Type 2 T helper cells produce granulocyte macrophage colony-stimulating factor (GM-CSF) and interleukins (IL), including IL-4, IL-5, IL-9, IL-13, IL-25, IL-31, and IL-33, which are responsible for chronic eosinophilic inflammation, the type of inflammation that is characteristic to allergic diseases such as asthma. This complex pathophysiological process leads to the clinical manifestation of asthma with recurrent episodes of wheezing, breathlessness, chest tightness, and coughing.[1-4]

Severe asthma is defined as "asthma which requires treatment with high-dose inhaled corticosteroids (ICS) plus a second controller (and/or systemic

corticosteroids) to prevent it from becoming 'uncontrolled' or which remains 'uncontrolled' despite this therapy."[5] Uncontrolled asthma is defined as at least one of the following: poor symptom control, frequent, severe, and serious exacerbations, and airflow limitation. If patients do not use preventive anti-asthma treatment, it can cause irreversible airway remodelling.[5]

Table 1: The descriptive statistics for IL-5, IL-13, and eosinophils in asthma patients treated with ICS/LABA plus montelukast.

ICS/LABA + montelukast	IL-5 before therapy	IL-5 after 6 months of therapy	IL-13 before therapy	IL-13 after 6 months of therapy	Eo before therapy	Eo after 6 months of therapy
Mean	9.24	3.35	1028.21	252.21	0.0497	0.0245
Standard deviation	5.39	4.02	621.02	427.23	0.0590	0.03
Range	0.02–20.18	0.01–12.40	67.35–2,444.65	0.40–427.23	0.00–0.22	0.00–0.15
Median	7.58	1.32	757.15	81.04	0.03	0.02
25–75% percentiles	5.28–13.41	0.27–5.07	623.27–1514.29	2.97–217.72	0.01–0.05	0.00–0.03

IL: interleukin; ICS: inhaled corticosteroids; LABA: long-acting beta-antagonists; Eo: eosinophils.

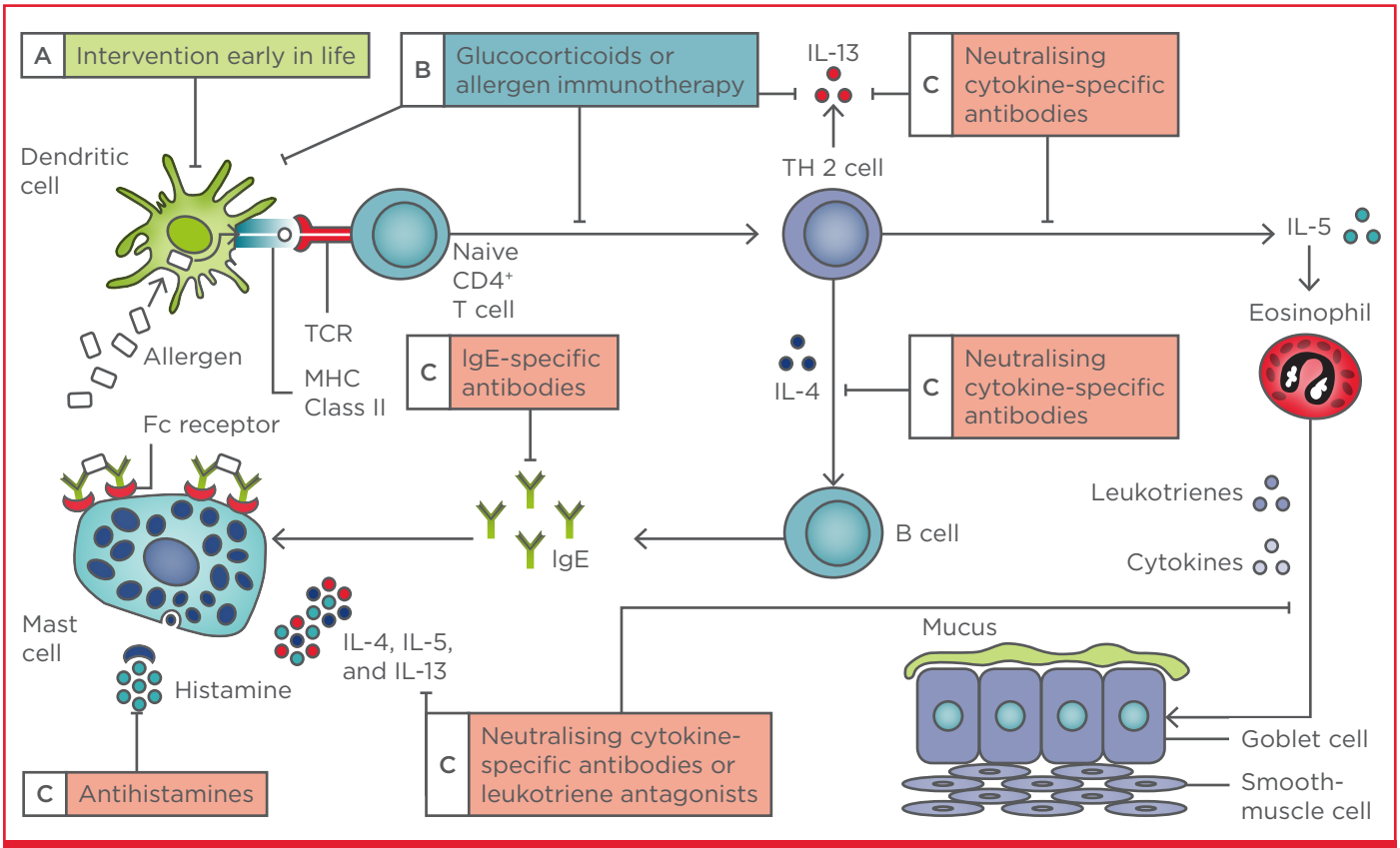

Figure 1: The allergic pathway and potential points of intervention.
TCR: T cell receptor; MHC: major histocompatibility complex; IL: interleukin; TH 2: T helper cell Type 2; Ig: immunoglobulin.
Adapted from Hawrylowicz CM, O'Garra A.[4]

OBJECTIVES

The aim of this study was to determine the effect of adding montelukast to combined therapy (ICS/long-acting beta-agonists [LABA]) in patients with severe uncontrolled asthma by analysis of the serum level of IL-5, IL-13, and eosinophils, and the symptom score.

METHODS

In this study, we included 29 patients that were treated with ICS/LABA (500/50 µg twice daily) plus montelukast (10 mg daily). In each patient, we measured the serum levels of IL-5 and IL-13 by the enzyme-linked immunosorbent assay (ELISA) method at the Institute of Immunobiology and Human Genetics, Faculty of Medicine, Ss. Cyril and Methodius University of Skopje, Skopje, Macedonia. The number of eosinophils was obtained using visual examination of a peripheral blood smear at The University Clinic for Haematology, Skopje, and by assessing symptom scores with 5-point Likert scale of breathlessness at the beginning and after 6 months of therapy. The reference values for IL-13 are 0–6.9 pg/mL, for IL-5 are 0 pg/mL, and are 0.58–0.66% for eosinophils.

RESULTS

The results were statistically analysed according to the Wilcoxon Paired Test, using a significance value of $p<0.05$ and a high significance value of $p<0.01$. The obtained results of IL-5, IL-13, and value of eosinophils showed that the levels before the start of therapy were much higher and treatment of ICS/LABA plus montelukast reduced these values with statistical significance (IL-5: $Z=4.64$; $p=0.000004$; IL-13: $Z=4.7$; $p=0.000003$; eosinophils: $Z=2.99$; $p=0.0028$; $p<0.05$). Symptom score results also showed statistically significant improvements ($Z=4.54$; $p=0.000006$) after 6 months of therapy (Table 1).

CONCLUSION

Combination therapy with ICS/LABA represents the gold standard in the treatment of asthma. It is a safe and effective treatment that is recommended by the Global Initiative for Asthma in the treatment of uncontrolled, severe, and persistent asthma in Steps 3 and 4 of treatment.[1] Combination high-dose of ICS/LABA generally provides additional benefit for patients, but it is well recognised that not all patients will achieve well-controlled asthma despite an appropriately high dose of ICS or ICS/LABA combination therapy. In such patients, there is a need for additional add-on therapy, such as treatment with a leukotriene receptor antagonist (Figure 1). The addition of this treatment to patients whose asthma was considered to be insufficiently controlled resulted in a significant clinical improvement in asthma control, pulmonary function, and quality of life, and the dose of ICS/LABA was able to be reduced.[6-9] This suggested that these markers of inflammation are important for monitoring disease evolution and success of therapy in patients with asthma.[10]

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THUNDERSTORM-RELATED RESPIRATORY ALLERGY

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On Monday 21st November 2016 in Melbourne, Australia, there was a very unusual weather occurrence of wind and torrential rain combined with a high pollen count, which sent high quantities of pollen allergens across the city. Hospitals were swamped with emergency patients affected by severe asthma attacks (>8,500 patients across Monday night and Tuesday, with 9 fatalities). Firefighters and police officers were called in to help physicians and paramedics respond to thousands of calls from citizens with breathing problems. The event caused many people, including those who had no history of asthma, only of hay fever, to experience frequent and severe breathing difficulties.[1]

Thunderstorms have been linked to asthma epidemics, especially during the pollen seasons, and there are descriptions of asthma outbreaks associated with thunderstorms[2-10] in several cities, typically Australian ones and most commonly in Melbourne (where two other outbreaks occurred in 1992). A large increase in the number of visits for asthma at the emergency departments has been observed in other cities, including Birmingham and London, UK and Naples, Italy, all of which coincided with a heavy thunderstorm during the spring.

Thunderstorm-related asthma is a dramatic example of the allergenic potential of pollen antigens and how pollen allergic patients who encounter an allergenic cloud of pollen are at higher risk of having an asthma attack. Pollen grains can be carried by thunderstorms at ground level, with the release of allergenic biological aerosols of paucimicronic size, derived from the cytoplasm of pollens (ruptured or not), that can penetrate deep into lower airways. In other words, there is evidence that during wet conditions or thunderstorms, pollen grains, in part after rupture by osmotic shock, release their contents into the atmosphere, including respirable, allergen-carrying cytoplasmic starch granules (0.5–2.5 µm)[11] or other paucimicronic components that can reach lower airways, inducing asthma reactions in pollinosis patients.

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EDUCATION IS KEY! CALL FOR ACTION!

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I have been asked to share my opinion about the diagnostics of anaphylaxis and how to treat it. As you probably know, anaphylaxis is the extreme outing of an allergic reaction and is likely if any one of three criteria is fulfilled (Figure 1).[1] Assessing anaphylaxis is hard to do because you must first assess or establish the eliciting condition. The European Academy of Allergy and Clinical Immunology (EAACI) has produced guidelines for allergic conditions to help clinicians establish the correct diagnosis and treatment for that condition.[2] Although anaphylaxis may occur with different allergic conditions, one of the major eliciting factors for anaphylaxis is food, and food has been the main immunoglobulin (Ig)E-mediated cause for anaphylaxis hospitalisation in recent years.[1,3] These guidelines are instrumental in the education of anyone dealing with patients at risk of anaphylaxis.

It might be hard to diagnose patients with an allergic condition that may have the potential of anaphylaxis, and it all starts with the medical history. Listening to the patient telling their story about the reason why they are consulting their family doctor, you need to know what to ask and how to interpret the answers; I know that is not an easy task. Then, when you have concluded that it could be an allergic condition that is causing your patient's complaints, you might decide that you need to perform some additional analytical tests. Therefore, you tell him or her that you want some allergy tests performed, and it is here that misunderstandings may begin. The term 'allergy test', in this situation, is inaccurate and might set the patient on the wrong foot. The tests you are considering performing are tests which indicate the presence of antibodies to certain allergens, and, simply said, the result can be positive or negative. The absence of antibodies will "indicate that the patient does not have an allergy, but the presence of antibodies does not indicate an allergy, only sensitisation!"[4] But just telling the patient that the result, as such, of the 'allergy test' (for a specific allergen) is positive might let the patient believe that he or she is allergic to that allergen, and that might not always be true.[5,6] Therefore, I would stress banning the term 'allergy test' and calling it as it is.

1. Acute onset of illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g. generalised hives, pruritus or flushing, swollen lips, tongue, or uvula), and at least one of the following: a) respiratory compromise (e.g. dyspnoea, wheeze or bronchospasm, stridor, reduced peak expiratory flow, hypoxaemia), b) reduced blood pressure or associated symptoms of end-organ dysfunction (e.g. hypotony [collapse], syncope, incontinence).
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours): a) involvement of the skin or mucosal tissue (e.g. generalised hives, itch or flush, swollen lips, tongue, or uvula), b) respiratory compromise (e.g. dyspnoea, wheeze or bronchospasm, stridor, reduced peak expiratory flow, hypoxaemia), c) reduced blood pressure or associated symptoms (e.g. hypotony [collapse], syncope, incontinence), d) persistent gastrointestinal tract symptoms (e.g. crampy abdominal pain, vomiting).
3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours): a) infants and children: low systolic blood pressure (age specific) or >30% decrease in systolic blood pressure, b) adults: systolic blood pressure <90 mmHg or >30% decrease from that person's baseline.

Figure 1: Criteria for an anaphylaxis reaction recognition.
Adapted from Sampson et al.[1]

The outcome of these tests is only valid in the diagnosis of the condition in relation to the medical history, and should be tests to confirm or disprove your suspicion. If you are not sure or in doubt, the only true means of telling whether a patient with a suspected food allergy truly has a food allergy is the use of oral food challenge under strict supervision, which is currently seen as the gold standard.[7]

How does this help us in assessing the diagnosis of the risk of anaphylaxis? That is difficult to say. The outlined procedure will help us in assessing whether a patient does have a food allergy but says nothing about the risk of anaphylaxis. So, how can we assess if an allergic patient is at risk of anaphylaxis? One way (and please note that it would be ethically questionable), is to perform an oral challenge, but then not to stop at the first signs or symptoms, but to proceed until the patient shows severe symptoms. The question is, do we want to go that way? What is the advantage or disadvantage for the patient? Does the outcome of this single test predict future outcomes? So, I ask the reader, can we genuinely advise the patient that he or she is at risk of anaphylaxis? In practice nowadays, we encounter a definite diagnosis of a true food allergy based on a severe allergic reaction or anaphylaxis in the medical history, and the concluded advice is that the patient is also at risk of anaphylaxis in the future. If the patient is lucky, they will get an adrenaline auto-injector prescribed, for the first aid treatment should an anaphylaxis occur, and advice to then call an ambulance. If the patient is lucky, they will also be educated in when and how to administer an adrenaline auto-injector and is instructed on how to avoid the eliciting allergen.

Unfortunately, it all comes down to luck. I know I am generalising, but the fact is that allergists in many countries are too few and only a few medical specialists are also experienced in allergy and anaphylaxis. Recently it was shown that "the primary care doctors expressed self-declared gaps in knowledge in most manifestations of allergy with a correspondingly high self-expressed educational need."[4] This realisation makes me both anxious and glad, as these doctors are the first in line to help the growing number of people with allergies; it makes me anxious because it shows that the knowledge of allergies is lacking and glad that they are willing to educate themselves. We know that knowledge is lacking in the majority of medically educated health professionals. Did you know that, for instance, in the Netherlands medical students in their 6-year education to be a basic doctor only get an average of 16–24 hours' education on allergy! So, allergy, although a rising societal medical problem (some even say it is the 21st century epidemic), is hardly the focus of education policy makers!

But even after the basic medical education, students need to specialise themselves in an area of medical interest, and what do we see? The specialities focus mainly on organ systems, like internal medicine, otorhinolaryngology, dermatology, gastroenterology, respiratory medicine, cardiology, etc. Allergy is, in many countries, a subspeciality and first you should complete a primary speciality. Due to the length of medical education the decision to also choose an allergy subspecialty is only taken by the totally committed.

Another problem is that allergy is a 'holistic' condition; by this I mean that the symptoms that arise from an allergic reaction may appear in different organ systems, sometimes simultaneously, and are thus not restricted to one organ system. The only other 'holistic approach' speciality is paediatrics. We still have a long way to go and hopefully the education of policy makers will enable them to realise that allergy should have a prominent place in the medical curriculum.

There is a growing interest in allergy research. Researchers are considering the mechanisms of the immune system and try to find out the basics of the allergy mechanism. They have succeeded greatly in disclosing which different cells play a role in that mechanism. But why someone is sensitised and someone else not, given the same circumstances and conditions, has still not been explained. In my opinion, for these disclosures to happen it may still take a long time. I was told, when my child had an anaphylaxis in 1994, that it would probably take some 10–15 years before a cure would be available, and, although research has progressed a lot since, 23 years later there still is no cure. I do admit, at this moment there seems to be a positive effect due to food allergen immunotherapy, but that is still in an experimental stage and not in daily clinical practice.[8] We must continue on this path, as people at risk of anaphylaxis are looking out for these kinds of therapies because living with allergies and the risk of anaphylaxis reduces their quality of life immensely. Policy makers should allocate public funds for clinical and societal research and not have the impression that the problem is not so

great because only a limited number of fatalities occurred compared to other conditions or diseases. Focussing only on fatalities does not reflect the impact of the problem. They should consider the hospitalisations and reduction in quality of life.

What is, then, my message to the world? Until there is a cure, education is key. Education not only for the medical professional on how to guide and educate their allergic patients, but also for parents and the patients themselves on how to deal with this condition and the risk of anaphylaxis. This will raise their quality of life through the knowledge that their condition is manageable and they can take control. They need to know that, in general, the risk of anaphylaxis is due to the eliciting allergen entering their body, they need to know what they react to, and what the allergens are that might cause anaphylaxis. The parents need to know the assessed real risk and not the perceived risk, as the perceived risk may become the projected anxiety in the allergic child, thus developing an anxiety disorder.[9]

Education in the manageability of their allergy requires the correct information provision and the skill to communicate it to the social environment. This will allow the allergic individual to fully participate in society, with some restrictions, but no limitations.

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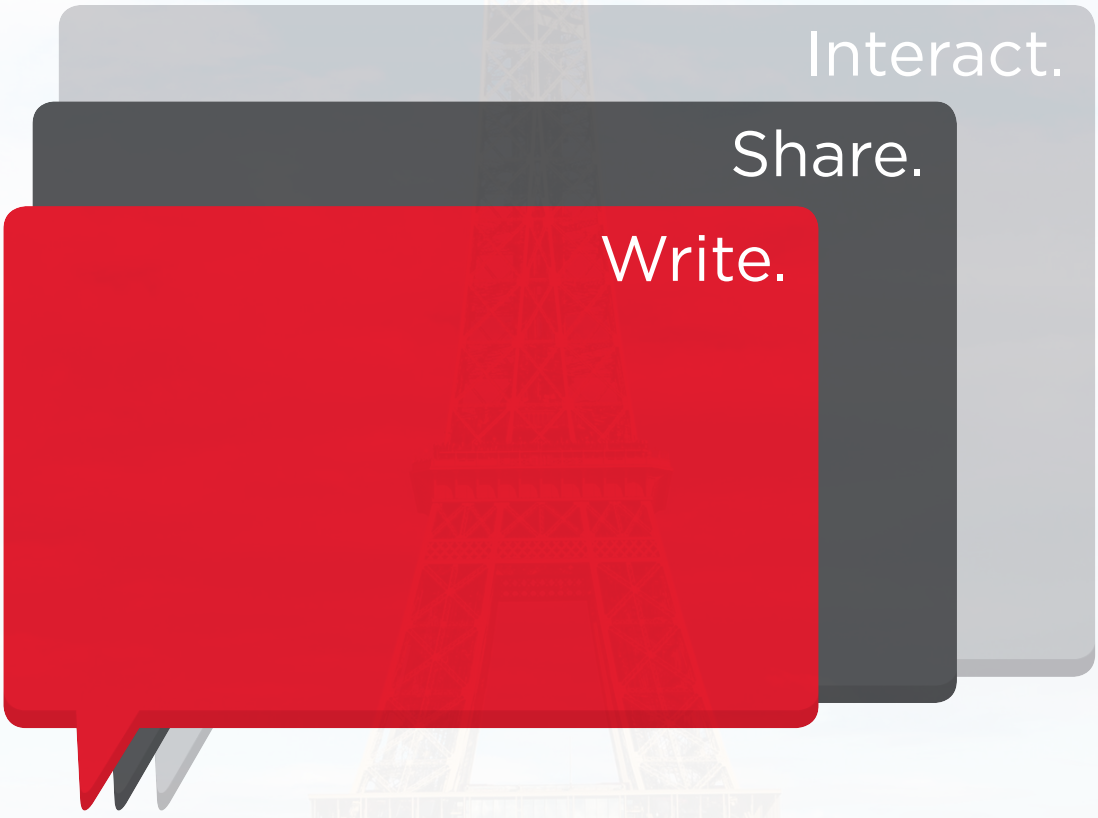

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EDITOR'S PICK

My Editor's Pick for this edition of *EMJ Allergy and Immunology* is the article provided by E. Uzunoglu, which offers a fascinating overview of the microbiological hazards that are connected with occupational allergies. Uzunoglu accurately highlights the importance of a multidisciplinary response to occupational disease, making this a captivating read that provides topical recommendations.

Prof Dr Jacques Bouchard

MICROBIOLOGICAL BIOHAZARDS ASSOCIATED WITH OCCUPATIONAL ALLERGIES

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ABSTRACT

Microbiological occupational allergens usually originate from a part or products of bacteria, fungi, or arthropods. They may be harmful on their own or their impact may come from cross-reactions of their substance. It is mostly the respiratory system, conjunctiva, and skin that are affected. This short review clarifies the microbiological biohazards associated with occupational allergies.

Keywords: Occupational hazards, bioaerosols, mycotoxins, endotoxins, fungi, arthropods.

INTRODUCTION

Occupational allergies are a group of immunologic disorders that are caused by workplace allergens. They are socioeconomically important diseases that may cause workforce loss, morbidity, and mortality. Therefore, early diagnosis and detection of allergens are important.[1] Allergies resulting from these biological agents mostly affect the respiratory tract, conjunctiva, and/or skin. They usually cause allergic rhinitis, allergic asthma, toxic or hypersensitivity pneumonia, allergic alveolitis, farmer's lung, conjunctivitis, and dermatitis.[2,3] There are several biological hazards that cause occupational allergies, such as toxins, body fluids, virulence factors, or whole cells of bacteria, fungi, plants, and animals, including arthropods.[2,4,5] The majority of the allergen biohazards are mostly in bioaerosol and/or droplet form. Bioaerosols are organic dusts originating from toxins or the main components of bacteria or fungi, faeces, the bodies of mites and insects, pollens, and different proteins from mammals. In recent years, researchers have focussed on this subject due to a great deal of workers being exposed to these dusts. Bioaerosols are the major allergic risk factors in agriculture and the agricultural industry, waste recycling, food processing, the detergent industry, laboratories, libraries, and medicine. Although there is great awareness about bioaerosols, the pathogenesis and dose-dependent effects are still unclear.[2,3] There is no specific classification for allergen biohazards. According to the Haz-Map database,[6] infectious occupational biohazards are classified into six categories: contact with infected living animals; contact with contaminated animal products; tick, flea, or mite bite; contact with human or animal waste; contact with an infected patient or blood; and raising dust containing pathogens. However, this classification does not exactly fit to the

microbiological biohazards associated with occupational allergies. In this paper, a short review will be given of different microbiological biohazards in workplaces that cause occupational allergies.

BIOHAZARDS ORIGINATING FROM BACTERIA

Endotoxin

The major allergen originating from bacteria in workplaces is endotoxin, which is a lipopolysaccharide (LPS) gram negative molecule. The outer cell membrane of gram negative bacteria is made up of a high molecular weight, heteropolymeric substance. Its main components are O-antigen, core polysaccharide, and lipid A molecules. It is a highly conserved layer among different gram-negative species and its immunological effects are attributed to Lipid A moiety. The destructive effects of the LPS molecule was first shown in 'Monday asthma' of cotton workers in the 1960s.[7] To date, a long list of occupations have been reported, such as herb processing, grain and vegetable agriculture, wood processing, waste collection and sorting, cucumber and tomato nurseries, swine farms, sewage, and so on.[2,3] A possible explanation for the pathophysiological mechanism is the adjuvant-like effect of endotoxins on airway inflammation after contamination with water, food, and other products.[7]

In the USA, a national survey about endotoxin has shown that LPS is an allergen which exacerbates asthma symptoms.[8] Eisenbarth et al.[9] reported that low concentrations of LPS were enough for development of airway hypersensitivity in mice. Moreover, Strohmeier et al.[10] found that allergised mice without a LPS receptor did not develop airway hyper-responsiveness. However, there is a paradox in the literature about the immunological benefits and harmful effects of LPS. According to the 'hygiene hypothesis', it is considered that a lack of microbial exposure might be a risk factor for allergic diseases. In this theory, LPS exposure protects the individuals against Type 1 hypersensitivities, by switching T helper Type 2 (Th2) cells into Th1 cells. Briefly, innate immune cells recognise LPS and produce cytokines that influence development of adaptive immunity. Among these cytokines, interleukin (IL)-12 stimulates T cells to switch to effector T cells that primarily secrete interferon (IFN)-γ. There is a positive feedback between innate and adaptive immunity cells and this IFN-γ augments IL-12 response by stimulating antigen-presenting cells of innate immunity. Both IL-12 and IFN-γ inhibit Th2 cytokine production (e.g. IL-4, IL-5, and IL-13) and help to develop Th1-type immune response instead of the Th2-type that protects against atopic diseases.[7]

Although the hygiene hypothesis considers LPS as a protective factor against allergy development, studies are still unclear. LPS of bacteria may have pro-inflammatory properties that induce respiratory symptoms. In addition, depending on the duration of exposure, dosage, and environmental and genetic factors, the responses of the workers may vary.[7] Therefore, more systematic studies defining both genetic and environmental factors are needed.

Peptidoglycan

Peptidoglycan (PGN) is a cell wall component of almost all bacteria, but predominantly gram-positives. It is a polymeric substance, made up of (1,4) linked N-acetylglucosamine and N-acetylmuramic acid. Bacterial PGN is one of the main components of bioaerosols and there is evidence suggesting that PGN causes bioaerosol-induced inflammation especially in humans working in livestock farm houses. In a clinical study, it was shown that swine dust containing PGN caused acute inflammatory reactions by increasing fever and blood granulocyte concentration in swine farmers.[11] Both *in vivo* and *in vitro* studies showed that PGN is a mast cell stimulator via toll-like receptor (TLR) dependent mechanisms.[12] Inhalation of this substance may trigger TLR-2, increase the influx of mast cells into the alveolar compartment and/or gastrointestinal tract, and cause production of different pro-inflammatory cytokines and chemokines such as TNF-α, granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-1, and IL-5.[13] On the other hand, there are also studies supporting the hygiene hypothesis and demonstrating that PGN can decrease both mast cells development and the number of mature mast cells by apoptosis, like LPS. It is estimated that the environmental exposure to PGN also protects from both asthmatic symptoms and bacterial infections like the endotoxin component of bacteria.[11]

Other Virulence Factors

Several molecules like toxins or peptides of bacteria also augment inflammatory reactions in sensitised individuals. Among these, *Staphylococcus aureus* has the leading role with its numerous virulence factors.[5] Methicillin-resistant *S. aureus* (MRSA) is a causative agent of severe health problems in

healthcare workers and animal farmers. They are at risk of both nasal and skin infection with MRSA strains.[14,15] In the Netherlands, there is a high MRSA colonisation rate (29.0%) among pig farmers compared to the general population (0.1%).[15] *S. aureus* infection increases the severity of the atopic skin diseases due to its virulence factors, such as superantigens, Panton-Valentine Leukocidin, protein A, lipoteichoic acid, and many others. These virulence factors cause T cell, mast cell, and macrophage activation, and cytokine release.[16] Therefore, physicians have had a tendency to add antibiotics to their prescriptions in patients with atopic skin disorders. In a study from Germany, 13.5% of the nurses who were suffering from occupational skin disorders were also infected with MRSA. Hand eczema was significantly more frequent and severe in MRSA carriers than in non-carriers. According to the results of the dermatology studies, it seems that the best treatment method for the occupational allergic skin disorders is taking precautions against MRSA infection among healthcare workers.[17]

BIOHAZARDS ORIGINATING FROM FUNGI

A single fungal cell can produce >40 proteins that can cause allergy.[18] Both the molecules they produce and the allergic fragments they carry in their structures can cross-react with each other.[18] To date, 112 genera of fungi are thought to be a source of allergens. Potential allergens are from three major classes: Ascomycota, Zygomycota, and Basidiomycota. Ascomycota is the largest group and includes the most common allergic genera *Alternaria*, *Cladosporium*, *Penicillium*, and *Aspergillus*. Yeasts have been also reported as the cause of allergic diseases. Ascomycetes and Basidiomycetes also have yeast forms. *Candida albicans*, *Malessezia furfur*, and *Saccharomyces cereviseae* are the most common species that cause allergic diseases.[19]

Any fungus found in the environment may be an opportunistic pathogen in an immunocompromised patient. Clinical manifestations of fungi may vary from infection in allergic bronchopulmonary disease to active infection.[20] Allergy to fungi generally occur as immunoglobulin (Ig)E-mediated, Type I hypersensitivity. This atopic condition can manifest as asthma, rhinitis, conjunctivitis, urticaria, or atopic dermatitis. Fungi also cause Type II hypersensitivity that arises secondary to mannan, a polysaccharide which is present in *Candida* and *Aspergillus* cell walls and Type III hypersensitivity reactions such as allergic alveolitis and bronchopulmonary aspergillosis.[19]

Fungal Fragments

An important component of bioaerosols is the aero allergic filamentous fungi and their metabolites. Among the filamentous fungi, *Cladosporium*, *Alternaria*, *Botrytis*, *Epicoccum*, *Fusarium*, *Aspergillus*, and *Penicillium* genera are generally found outdoors.[18] Among these genera, *Penicillium*, *Aspergillus*, *Alternaria*, and *Cladosporium* are aeroallergens that can be transported in enclosed areas via air, humans, or animals. Indoor areas also include species such as *Mucor* and *Rhizopus*.[21] Spores are the reproductive cells of moulds, which when germinated transform into micelles. Micelles are branched as hyphae. Gorny et al.[22] showed that fragments or intact spores of the fungi and hyphae are also potential allergens. The spores increase in number in the open air especially at the end of summer and the first months of autumn, and can be transported thousands of kilometres away via organic dusts.[18] In enclosed spaces that are not well ventilated and humid, the number can reach ≤250,000 per cubic metre and the spores remain in the environment all year round.[23] In particular, food, waste, wood industry, laboratory, agricultural, and museum workers are at risk of allergic diseases due to fungi.[24-26]

β-1, 3-glucan is an immunologically active glucose polymer present in the cell wall of fungi. It plays a role in the pathogenesis of bioaerosol-mediated inflammatory and allergic respiratory diseases by stimulating both Th1 and Th2 cells. Animal experiments have shown that the synergistic effect of β-1, 3-glucan with bacterial endotoxin causes airway inflammation and, moreover, β-1, 3-glucan alone can increase IgE levels.[27,28] In another study about the pro-inflammatory properties of β-1, 3-glucan, garbage men showed a significant inflammatory response in their nasal mucosa following β-1, 3-glucan exposure, but a significant increase could only be observed in *in vitro* experiments with high concentrations.[29]

Secondary Metabolites

Mycotoxins are allergenic, carcinogenic, teratogenic, and neurotoxic products of fungal metabolism. Mycotoxins are considered to be occupational risk factors for agricultural workers. They contaminate many nutrients and seeds, such as hazelnut, peanut,

corn, oat, wheat, milk, coffee, pistachio, almond, bean, and rice. Drought, high temperature, insect infestation, and high humidity increase fungus reproduction and mycotoxin production. Primer and secondary amines, hydroxyl and phenolic groups, lactams, carboxylic acids, and amides have been identified in many mycotoxins.[30] In a study on corn silos, 10 different fungal genera (especially *Penicillium* and *Paecilomyces*) and 6 different mycotoxins (zearalenone, T-2 toxin, aflatoxins, fumonisins, ochratoxins, and deoxynivalenol) produced by these fungi were detected.[31] Supronienе et al.[32] found five *Fusarium* species and three mycotoxins (zearalenone, T-2 toxin, and deoxynivalenol) at low concentration in cereals produced by organic agriculture. These mycotoxins that are found in foods are harmful not only for the workers but also for the consumers. This remains a serious problem for developing countries not paying attention to contamination during food production and storage.[30]

Apart from mycotoxins, fungi also produce chemicals that have low molecular weight and high volatility, such as mixtures of alcohols, aldehydes, acids, ethers, esters, ketones, terpenes, thiols, and their derivatives. These chemicals are the volatile compounds (VOC) produced by fungi. Very little is known about the biosynthetic origins or molecular structures of these molecules. About 300 fungal VOC have been defined up to now. In places with fungus reproduction, the heavy smell that people easily perceive is caused by these chemicals.[33] It is said that the VOC may be the cause of the syndrome known as 'sick building syndrome', which is seen in individuals working in closed areas for long hours and is accompanied by symptoms, such as headache, nasal discharge, sore throat, and chronic fatigue. According to data from the World Health Organization (WHO), 30% of the individuals with these complaints are living in such buildings with mould and poor ventilation.[18] Although there is insufficient information about the effects on humans, fungal VOC showed neurodegenerative effects on *Drosophila melanogaster*.[34] Therefore, further studies are urgently needed.

BIOHAZARDS ORIGINATING FROM PARASITES

Arthropods

Allergy to arthropods arises from inhaled body particles, accidental contact, sting, or bite and venom injection of bees, ants, and wasps.[35] Although these types of allergies are observed in atopic individuals, non-sensitised workers are also affected. Outdoor workers, construction personnel, farmers, foresters, wildlife workers, food processors, beekeepers, laboratory and field biologists, and silk producers are especially at risk. The first line of defence should be avoidance or exclusion of the offending agent. However, the majority of the medically important arthropods are unknown and misdiagnosed, as many workers never report minor contacts and the lesions are very similar.[36] Recently Uzunoğlu et al.[4] observed a blister dermatitis due to contact with *Paederus* type insects among nut farm workers. Although many different *Paederus* species have been identified during entomology studies in various European countries, no clinical case report has been reported from the European countries, except Italy.[37] *Paederus* dermatitis is an acute irritant contact dermatitis caused by pederin, a haemolymph fluid released when *Paederus* beetles are crushed against the skin.[38,39] Pederin is a caustic and toxic amide that contains two tetrahvdropyran/furan rings.[40] It causes inflammation, vesicles, and pustules. This dermatitis can heal itself in a week or can lead to various complications. These complications are post-inflammatory hyperpigmentation, secondary infections, extensive peeling of the skin, and ulcerous dermatitis requiring hospitalisation.[41] Fever, arthralgia, nausea, vomiting, and neuralgia can be seen in severe cases.[42] It can be confused with viral and bacterial skin diseases such as bullous impetigo, herpes simplex, and herpes zoster. Other diseases that must be considered in the differential diagnosis are bullous or allergic contact dermatitis, liquid burns, and phytodermatitis.[43] General medicine, ophthalmology, dermatology, or entomology books do not include enough information about this clinical phenomenon.[44] Questioning the patient's occupation or whether they have undertaken a farmland visit and carrying out a physical examination of the patient has paramount importance in diagnosis.[45]

Although some allergen exposures are a result of direct contact with arthropods, the majority of the cases are because of inhalation of bioaerosols. Cockroach, mite, and silkworm moth allergies are the best studied of all the arthropod induced sensitivities.[35] During silk production, potent allergens of silkworm moth (*Bombyx mori*) such as sericin, fibroin, pupal fragments, and also *Anthrenus* beetle larvae that feed on silk waste cause asthma, allergic rhinitis, conjunctivitis, and

dermatitis in workers.[45] Cockroach infestations are a great challenge for seagoing ships and their crew.[46] Steroid therapy dependence and IgE levels are higher in cockroach asthmatics than the other asthmatics.[47] Kang et al.[48] analysed the allergens of crude whole body extract of American, German, and Oriental cockroaches. They compared the results with the sera of 16 cockroach-allergic patients with asthma. Up to 12 allergenic bands were identified from 13 of 16 individual sera. Another arthropod group that is well documented is mites. Mites are microscopic organisms that cause inflammatory reactions in those who are atopic and exposed to a high concentration of mites in the early stages of their life.[49] The secretion and faecal matter of the mites have a strong antigenic character.[50] They can induce both clinically unimportant and life threatening allergic reactions. It is known that the mites in cereal storage are the reasons for occupational disease in the employees, including farmers, and they can cause dermatitis, allergic rhinitis, asthma, and conjunctivitis.[51] Storage from the families *Acaridae* and *Glycyphagidae* are usually predominant. They are in a wide range of food including grain, fishmeal, hay, and substances containing sugars like dried fruit and cereals.[52] In 1997, Armentia et al.[53] examined the sensitivity of various mite species on 4,000 people living near cereal facilities. The prevalence of mite sensitisation among 50 grain workers was nearly 19%. The six highest prevalences of sensitisation were to the four Pyroglyphid dust mites: *Dermatophagoides pteronyssinus* (Trouessart) (58%) and *Dermatophagoides farinae* (Hughes) (48%), *Tenebrio molitor L*. (50%) and cockroach *Blatta orientalis L*. (36%), and to two of the storage mites, *Lepidoglyphus destructor* (Schrank) and *Tyrophagus putrescentiae* (Schrank) (both 38%). Additionally, 11 grain workers who were sensitised to storage mites gave negative Radio Allergosorbent Test (RAST) results with the dust mites.[53] Numerous mites (including *Pyemotes ventricosus*) causing occupational dermatitis were observed due to exposure to infested foods since the 1980s. Symptoms vary from skin eruption to chills, fever, malaise, diarrhoea, and anorexia. Although clinical diagnosis is often simple and based only on the patient's history, the identification of these causative mites is still troublesome.[54]

Inhalent allergies to the other arthropods such as insects, spiders, and beetles are also possible. Liebers et al.[55] determined occupational asthma against an insect allergen (*Chit*I) in a fish food factory workforce. A new respiratory allergy to cellar spider body parts due to arginine kinase was presented by Bobolea et al.[56] Increased frequency of beetle allergies are a huge problem, especially in endemic areas. Albright et al.[57] presented a case series about the multicoloured Asian lady beetle, which is a biological control agent against crop-destroying aphids in the USA. A great deal of arthropods like honeybees, flies, or even a nematode (*Anisakis simplex*), are also determined to be aerosol allergens.[58-60] It seems that the list will continue to grow due to climate change and/or poor working conditions.

CONCLUSION AND RECOMMENDATIONS

The main goals of occupational health programmes are to protect workers from occupational disease, provide safe environments, generate physically and mentally healthy employees, and enhance nations socially and economically. The prevention and treatment of occupational disease requires a multidisciplinary approach. National ministries of health, education, environment, industry, social security, and agriculture should be well-informed about occupational health practice.

Early diagnosis and prevention are the cornerstones for prevention of mortality and morbidity. Workers with inflammatory complaints usually tend to consult occupational health specialists, chest disease specialists, or dermatologists, as their main symptoms are related to the respiratory system or the skin. However, medical professionals from all disciplines should be aware of these issues. The co-operation of medical microbiologists, entomologists, epidemiologists, biomedical engineers, and immunologists is important, especially for the microbial allergens. Finally, well-organised surveillance programmes for warning of outbreaks and identification of exposure breakpoints are urgently required.

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THE USE OF EMERGING TECHNOLOGIES IN ALLERGEN IMMUNOTHERAPY MANAGEMENT

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ABSTRACT

Emerging technologies are profoundly changing the landscape of allergy diagnoses and future allergy treatments. At the single patient level, the introduction of single components and allergen microarrays for allergy diagnoses has significantly modified treatment strategies. In epidemiological terms, the availability of information from large dataset analyses has allowed and, more importantly, will allow for changes in prophylaxis and treatment strategies in many patients. In this report, we describe the different fields where new technologies have had a significant effect on allergy management and identify new scenarios where the combination of data from basic, clinical, and epidemiological research will improve our knowledge of allergy diagnosis and treatment.

Keywords: Allergy, immunotherapy, single-plexed test, multi-plexed test, computer assisted diagnosis, big data.

INTRODUCTION

Allergen immunotherapy (AIT) was empirically described more than 100 years ago and immediately showed its clinical efficacy in controlling allergic respiratory diseases.[1,2] Its efficacy is, however, strictly related to a correct aetiological diagnosis. Fifteen years ago, the introduction of molecular components as reagents in blood tests for the identification of specific immunoglobulin (Ig)E radically changed the strategies used to identify the proper treatment of allergy. Along this line, Valenta et al.[3] suggested selecting patients for AIT based on their reactivity to genuine molecules. More recently, Schmid-Grendelmeier[4] showed that the best results obtained with AIT were achieved in patients sensitised to genuine components, while the worst were obtained in patients sensitised to cross-reacting components. Then, studies by Sastre et al.[5,6] and Passalacqua et al.[7] showed that AIT prescriptions were improved significantly by the availability of molecular allergy diagnosis (MAD) results. In particular, the list of allergens to be included in an AIT treatment was modified by the identification of sensitisation to a genuine allergen or of sensitisation to one or more cross-reacting components. As a result of these studies, Douladiris et al.[8] described an algorithm that indicated the best AIT approach, which considered sensitisations to genuine and cross-reacting components. Notably, this procedure also considered the possibility of false positives due to the presence of cross-reactive carbohydrate determinants (CCD) in the 'natural highly purified' component used in the assay. Along this line, a list of components to be re-evaluated following a direct test with CCD was given. Other important information was provided by Sastre et al.,[9] who demonstrated that adverse reactions to AIT could be expected in patients characterised by a given IgE profile. Currently, in addition to molecular-based diagnoses, other novel approaches are being considered due to the support of artificial intelligence (AI), as well as the use of 'big data' analysis in the identification of specific IgE profiles in allergic patients. In this review, we describe these three approaches and consider both the pros and cons of an optimal and personalised diagnosis and AIT prescription.

Table 1: Examples of reflex tests implemented in clinical pathology laboratories.

Positive extractive allergen	Controlled molecular components	To verify whether
Mite allergens	Der p 1, Der p 2, Der f 1, Der f 2, Der p 10 (tropomyosin)	The immune-response versus mites is specific (before starting a long-lasting AIT)
Phleum pratense	Phl p 1, Phl p 5, Phl p 7 (CBP), Phl p 12 (profilin)	The sensitisation is genuine and/or cross-reacting
Betula verrucosa	Bet v 1, Bet v 2 (profilin), Bet v 4 (CBP)	The sensitisation is genuine and/or cross-reacting
Latex	Hev b 8 (profilin)	The sensitisation is genuine and/or cross-reacting
Peanut	Ara h 8 (profilin), Ara h 9 (LTP)	The sensitisation is against dangerous or non-dangerous components

CBP: calcium-binding protein; LTP: lipid transfer protein; AIT: allergen immunotherapy.

THE USE OF MOLECULAR ALLERGY RESOURCES

Single-Plexed Diagnostics

Single-plexed diagnostic (SPD) tools have been implemented in a few different platforms (Phadia Immunosystem [Thermo Fisher Scientific Inc., Waltham, Massachusetts, USA], Immulite [Siemens, Munich, Germany], and Euroline [Euroimmun UK Ltd., London, UK]). Even though their methods are slightly different, the results are comparable overall.[10] The SPD approach is highly dependent on each physician's habits and culture. Indeed, SPD is largely based on a physician's specific requests; therefore, different strategies are possible. The simplest (which is also used in laboratory medicine) is the so-called 'reflex test', which is based on a list of recombinant molecules to be tested when a certain extractive agent is positive. According to this strategy, different choices can be made (Table 1) based on the depth of the investigation, costs, and reagent availability. Certainly, in the hands of a skilled allergist, the largest resource is the component selection and the deepest is the information. A different strategy is based on the doctor's choice of components to be tested. This is based on an allergist's experience and the complexity of the patient's situation. Finally, a third approach provides the combined use of extractive allergens and components in the same panel. This is a more sophisticated approach that is based on the fact that a sensitisation can be defined as 'genuine' when the IgE recognises a genuine sensitiser molecular component. In this context, for instance, the use of birch raw extract should be avoided, and the Bet v 1 component should be used. Similarly, *Parietaria* spp. extractive allergens can be substituted by Par j 2, which is a genuine sensitising allergen. SPD can be used after exhaustive skin prick tests (SPT) and specific IgE (sIgE) testing when the clinical picture remains unclear and when AIT has to be prescribed. More recently, documented preparations for AIT have described that, in addition to short-term clinical improvements, the treatment can also have long-lasting effects.[11] It is therefore crucial, when prescribing a long-lasting and expensive treatment, that the relevant molecular targets are clearly identified. However, when using this approach, one can only obtain what is sought. This can be seen as a real advantage or an embarrassing disadvantage.[12]

Multiplexed Diagnostics

Multiplexed diagnostics (MPD) in allergy treatment are based on allergens (both highly purified molecules or recombinant components) inserted in a pre-defined diagnostic panel. For this reason, the list of molecules is based on different reasons, ranging from the real value in the diagnostic process, to the patent coverage, to the capacity of that given molecule to be linked to a solid phase.

The first platform available was ImmunoCAP ISAC (Thermo Fisher Scientific Inc.), which is now characterised by 112 different allergens (either purified or recombinant). The majority of the experience acquired in the multiplex diagnostic assay field came from the use of this tool.[7,13]

More recently, the MEDALL group, in strict co-operation with industries, developed a novel microarray by adding more than 70 new components to the standard ImmunoCAP Immuno-Solid Phase Allergy Chip (ISAC) 112 panel.[14] The clinical features of the MEDALL microarray were

further evaluated during the so-called 'allergen-march' from childhood to adolescence.[15]

A different approach has been developed by an English/Swedish company that designed a microarray involving both single-allergen components and whole extracts.[16] This Microtest system was tested with three other allergy test methods (SPT, ImmunoCAP, and ImmunoCAP ISAC 112), and the results produced agreed with the currently used diagnostic tests.

Finally, another platform, which uses natural extracts and molecular components (ALEX® [Macro Array Diagnostics GmbH, Vienna, Austria]), seems to be a promising technological approach.

Allergen MPD offer both advantages and disadvantages. The advantages are represented by the large number of both natural purified and recombinant molecules on the same platform. For this reason, a small amount of blood is used, and the incubation and washing procedures are simple and rapid. More interestingly, sIgE MPD can also identify not only genuine and cross-reacting components but also harmless and potentially dangerous pan-allergens. Finally, the presence of more than one component of the same family (for example, profilins in ISAC are represented by four reagents, while in the Euroimmun, they are represented by two reagents) allows for clear specificity of the IgE repertoire. In this context, it is evident that if SPD obtains just what is sought, then MPD, which is based on a predefined allergen list, also gives unrequested results.[10] This possibility has been considered a disadvantage by allergists; indeed, the occurrence of unexpected results may, in certain cases, embarrass the allergist. Other disadvantages are represented by the cost (SPD, which measures up to 10 molecules, is cheaper) and complexity of interpretation (see below).

Patients Obtaining Beneficial Effects From Molecular Allergy Diagnosis

Poly-sensitised patients can obtain beneficial effects from MAD for many reasons. Indeed, a patient is defined as poly-sensitised when more than two allergens belonging to different families are positive in SPT or sIgE testing. Therefore, a patient positive for mites, birch, and grasses is considered poly-sensitised. However, sensitisation to pan-allergens or cross-reacting components may influence the SPT and sIgE test results. For example, a patient who is sensitised to both Phl p 1 (a genuine grass component) and Phl p 12 (a profilin) may have positive results to many other allergens belonging to trees, grasses, and weeds.

Table 2: Food pollen syndromes or associations.[17]

Syndrome or association	Relevant allergen components involved	
Alternaria-spinach syndrome	Alt a 1	-
Mite-shrimp syndrome	Der p 10	tropomyosin
Cat-pork syndrome	Fel d 2	cat serum albumin
Bird-egg syndrome	Gal d 5 alpha-livetin	chicken serum albumin
Birch apple syndrome	Mal d 1	Bet v 1 homologue
Celery mugwort spice syndrome	Pru p 3	nsLTP
Cypress peach syndrome	Art v 4 Art v 60 kDa	profilin, Api g 5 homologue
Goosefoot melon association	Art v 4 Art v 3	profilin, nsLTP
Mugwort chamomile association	Art v 1	defensin
Mugwort mustard syndrome	Art v 3 Art v 4 Art v 60 kDa Amb a 6 Amb a 8	nsLTP profilin nsLTP - profilin
Mugwort peach association	Che a 2	profilin
Ragweed-melon banana association	Mal d 1	Bet v 1 homologue

nsLTP: non-specific lipid transfer protein.

MAD, when used in such a patient, may not only indicate positivity to genuine components but also indicate that genuine components are negative and that profilin sensitisation is the cause of other positive results.

Food pollen syndromes are listed in Table 2. Pollen-food syndromes (as well as food-food and other complex food allergies) are caused by sensitisation to an inhalant component that cross-reacts with a very similar food component. The classic example is birch-apple syndrome, where sensitisation to Bet v 1 (a PR-10, the main component of birch sensitisation) is highly homologous to another PR-10 contained in apples, Mal d 1. Therefore, patients that eat apples have an oral allergy syndrome.[17] Notably, for PR-10 sensitivity, heated, cooked, or industrially manipulated apples do not cause oral allergy syndrome. MAD allows for the identification of not only the principal sensitiser (the Bet v 1), but also for Mal d 1 sensitisation, which explains the observed syndrome. In contrast, other methods (such as SPT or sIgE with allergen extracts) do not allow for such a diagnosis. In this context, MAD is also useful in identifying foods that should be avoided if the allergist is planning to suggest a special diet for the patient.

In a series of pivotal studies on grass sensitisation, Tripodi et al.[18] showed that in a small percentage of cases, the IgE profile to *Phleum* components were represented in grass extracts for AIT. In particular, very few patients obtain an optimal vaccine according to their IgE repertoire. Additionally, the effects from the AIT can be foreseen on the basis of the IgE profile;[19] however, an accurate IgE profile may suggest specific strategies in the AIT prescription.[20] Another interesting and innovative use of allergen microarrays is allergen immunotherapy monitoring. Indeed, it was recently observed[21] that allergen microarrays are useful in monitoring the development of allergen-specific IgG responses during specific immunotherapy, both against the allergen present in the specific immunotherapy vaccine as well as against cross-reactive allergens. The application of this technique may finally offer a general-purpose tool for monitoring the immunological effects of AIT, resulting in better treatment control and an even better understanding of therapeutically positive and negative results. These data were further supported by an article by Schmid et al.[22] that demonstrated that pretreatment allergen component-specific IgE appears to determine IgG4 induction in the updosing phase. Induced IgG4 seems to suppress IgE levels in an ISAC, resulting in a marked decrease in ISAC-measured specific IgE levels after subcutaneous immunotherapy updosing. The authors concluded that decreased ISAC IgE levels can be used to monitor the blocking effect of allergen-specific immunotherapy-induced non-IgE antibodies.

MPD assays have been suggested as a helpful tool to predict the onset of adverse reactions, as shown by Sastre et al.,[9] who documented that the adverse reaction rate, either local or systemic, is related to the number of sensitising grass pollen allergens.

COMPUTER ASSISTED DIAGNOSIS OF ALLERGY SENSITISATION

The introduction of expert system technology to support MAD introduced new diagnostic approach concepts. Indeed, the possible combinations of 112 allergens together with the difficulty of determining different component characteristics (and the reciprocal relationships) indicated that an AI tool could offer some advantages. In practice, relevant information can be obtained from AI elaborated allergen microarray results. Allergenius®, an expert system developed for ISAC result interpretation, by a team co-ordinated by Dr Melioli, can be considered a prototype because, by mixing different approaches, it offers a comprehensive view of the microarray results.[23] ISAC seems to be redundant to some extent. For example, the number of profilins and lipid transfer proteins could be considered excessive. However, it was observed that a hierarchy of cross-reacting components can be identified using large-scale MAD assays.[24] They showed that IgE reactivity to PR-10 proteins is characterised by a hierarchical intrarelationship: Bet v 1 > Mal d 1 > Cor a 1.04 > Ara h 8 > Pru p 1 > Aln g 1 > Api g 1 > Act d 8 > Gly m 4. For this reason, it is evident that many cross-reacting components are much more indicative than few. Along this line, Allergenius uses the rule that if the number of positive components is >40% of the total number of components of a given family, then the patient can be considered sensitised to the whole family of cross-reacting molecules. Additionally, Allergenius always identifies the first sensitiser of the cross-reacting component family as the member identified by the highest IgE score. Other added values can be derived from these rules. For example, if a discrepancy is identified between the SPT (or sIgE) results for a certain extractive allergen and the ISAC results (namely,

a positive SPT result with negative specific components derived from that allergen), then Allergenius evaluates whether other cross-reacting components (belonging to other allergen sources but cross-reacting with components well known to be detectable in the whole allergen) are also positive. Therefore, for example, if *Ambrosia artemisiifolia* is positive in the SPT but Amb a 1 is negative, other cross-reacting components are evaluated, such as profilins, PR-10, and CBP, which are all well represented in *Ambrosia* but not present in ISAC. If at least one of these cross-reacting components is positive, then there is no discrepancy. In contrast, if all the possible cross-reacting components are negative, then a clear discrepancy is declared. By using this approach, the number of apparent discrepancies is reduced significantly. Another added value described in Allergenius is related to the capacity of the expert system to evaluate the sums of the genuine inhalant and inhalant component scores that belong to cross-reacting families. As mentioned in the introduction, patients with genuine allergies seem to be more responsive to AIT, and Allergenius helps in the identification of these patients. Additionally, other issues can be managed by AI, including the identification of potentially dangerous sensitisations, the interpretation of sensitisations in certain geographic areas (such as lipid transfer proteins or peanut allergens in southern Europe), and the evaluation of the role of CCD in the interpretation of certain positivities (such as Phl p 4 and Jug r 2).

THE MANAGEMENT OF BIG DATASETS IN MOLECULAR ALLERGY

Big data are represented by statistical evaluation of a very large number of events. For example, traffic on the streets is measured in real time by aggregating data from cellular phones in that area. Certain tendencies on social behaviour are extracted from the very large number of data present in social networks. Therefore, extraction of relevant information from these large databases seems to be a frontier of laboratory epidemiology in the future. For example, the comparison of sensitisations with different components allows for better identifying areas where certain prophylactic activities (for example, tree cultivations or implants) may impact the quality of the life of patients. At present, big data are used to evaluate conditions in the supply chain of pharmacies for drugs and other medical devices. Alternatively, big data that are available on the internet allow for the identification of regions where certain pollens are present or where certain wind conditions may provide environments that are potentially harmful for an allergic patient. Data from microarrays, as well as data from large scale diagnostics laboratories, may occupy terabytes of memory. Furthermore, an accurate analysis of the sensitisation profile of large populations allows for molecular diagnostic management in a more convenient manner. From a clinical point of view, by using cluster analysis techniques to analyse data from thousands of ISAC sets,[25] the presence of five different clusters of patients has been clearly shown. However, only Groups I and II (characterised by sensitisation to a large fraction of genuine components) are optimal targets for AIT, while Groups III and IV have worse expectations for success. Group V is constituted by food allergies. Such an analysis would have been impossible without techniques, such as cluster analysis, that allow for big data processing. Other approaches have been used in recent years. For example, in a specific environment represented by hymenoptera hypersensitisation of horses, Marti et al.[26] described the use of advanced statistical methods to identify relevant sensitisations and validate their experimental approach. These techniques, which are particularly efficient when the variables are more frequent than the samples, allow for description of microarray features in a trustable manner. Prosperi et al.[27] followed up on this approach and used machine learning to interpret allergen microarray results in relation to clinical symptoms. The results of these machine learning experiments will not only be extremely useful to allergists, but also to laboratory scientists who utilise single and multi-plexed diagnostics. Indeed, after validation, the mathematics used demonstrated reasonable discrimination between asthma, rhino-conjunctivitis, and wheezing, but not eczema (where it is well known that ISAC is largely negative). Therefore, the identification of certain patterns of specific IgE positivity allows for automatic assay result validation just by knowing some clinical aspects of the patient.

CONCLUSIONS

Allergists will face new challenges in the near future; these will include the availability of new analytical technologies that offer many more results to accurately describe the IgE repertoire of allergic patients. These new technologies, such as microarrays, produce a very large number of

results that cannot be easily managed by allergists and are difficult to interpret for general practitioners. In these cases, AI can help in identifying the most relevant sensitisations, cross-reactions, and allergen lists that may have advantages for AIT. In the same context, many microarrays, which contain hundreds of results, will offer the possibility of studying sensitisation epidemiology with great accuracy. This will have an important impact not only on the management of single patients but also in large scale prophylaxis and allergy treatment strategies.

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NEOFORMED COMPOUNDS FROM THE MAILLARD REACTION IN INFANT FORMULAS: A NEW RISK FACTOR FOR ALLERGY?

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ABSTRACT

Food allergies, which are T helper cell Type 2 aberrant responses of the immune system to food proteins, are increasing. Environmental factors, including food contaminants, are often mentioned to explain this increase. Heat treatment of food induces the Maillard reaction, a non-enzymatic reaction between reducing sugars and free amino groups of proteins or free amino acids. This leads to the genesis of neoformed compounds, including advanced Maillard reaction products (also called dietary advanced glycation end-products [AGEs]). Infant formulas are very sensitive to the Maillard reaction because of their high content of lactose and proteins and their long shelf life. The dietary AGEs content is particularly high in hydrolysed infant milk. Among dietary AGEs, Nε-carboxymethyllysine is the main form in milk. An increasing number of studies show potentially deleterious effects of dietary AGEs, including inflammation genesis. These effects seem to be in a great part dependent on the receptor of AGEs (RAGE). RAGE is present on immune cells and studies have shown that RAGE is involved in T helper cell priming, proliferation, and differentiation. Moreover, there is increasing evidence that the Maillard reaction enhances the allergenicity of proteins. All these data indicate a potential role of dietary AGEs in allergies. Nevertheless, the impact of dietary AGEs on the immune system favouring the T helper cell Type 2 profile and consequently predisposition to develop allergy is poorly documented and needs further investigation.

Keywords: Maillard reaction, dietary advanced glycation end-products (AGEs), infant formula, neoformed compounds, Nε-carboxymethyllysine (CML), allergy.

INTRODUCTION

The incidence and prevalence of food allergies have dramatically increased in recent decades, especially in children. The prevalence varies from one country to another but is particularly high in countries with Western lifestyles.[1-4]

Allergy is a hypersensitivity reaction with specific immunologic mechanisms inducing objectively reproducible symptoms initiated by exposure to a substance, the so-called allergen, at a dose tolerated by a healthy person.[5] There are two distinct phases. The first phase, without clinical manifestations, is the allergen sensitisation phase. This leads to the activation and proliferation of a particular population of lymphocytes, the T helper Type 2 (Th2) cells. Th2-cytokines (interleukin [IL]-4, IL-5, etc.), will promote the production of allergen-specific immunoglobulin (Ig)Es and the recruitment of inflammatory cells (eosinophils, mast cells, or basophils).[6] The second phase is the effector phase. Upon further contact with the allergen, the interaction between the allergen and IgEs on target cells, such as mast cells, results in the release of mediators, such as histamine. Induced symptoms vary from moderate reactions, such as eczema, to severe reactions, such as oedema or anaphylactic shock. Atopy is an individual and/or familial genetic predisposition to develop allergies with enhanced IgE-mediated responses to common allergens.[5]

Breastfeeding is often recommended up to the age of 6 months to reduce the risk of developing an allergy. However, beyond the child's sixth month, the majority of parents use infant formulas made

from cow's milk. As a consequence, one of the first allergies in children is cow's milk allergy (CMA). Thus, many parents use hypoallergenic infant formulas with partially hydrolysed proteins or extensively hydrolysed proteins, especially in atopic families, in order to limit the risk of developing CMA.[7,8] However, their preventive action on the development of other allergies is not clearly demonstrated since the literature presents contradictory evidence.[9-13]

CMA is often only the first step in the 'atopic march' (or allergic career). If CMA is often relieved before the age of 10 years, the atopic child may become sensitised to other allergens and may develop new allergies, which will, most often, persist into adulthood. For example, 50% of children who have had CMA will develop another food allergy and 50–80% of them will develop allergy against inhalants.[10,14]

While the predisposition to develop an allergy is partly determined genetically, environmental factors (including diet) seem to play a very important role in the onset and development of allergies, especially in young children whose biological functions are immature.[15] Several hypotheses have been proposed to explain the increased incidence of allergies, including the reduction of viral or bacterial exposure (hygiene hypothesis), changes in the composition of the gastrointestinal flora, or the presence in the food matrix of compounds that could modify susceptibility to develop an allergy.[16] Since the industrial preparation of infant formula can generate neoformed compounds by glycation of milk proteins, formula-fed babies could be exposed to them, and in particular to advanced Maillard reaction products (advanced glycation end-products [AGEs]).

DIETARY ADVANCED GLYCATION END-PRODUCTS IN INFANT FORMULAS

Heat treatment of food ensures its safety and extended shelf life. However, due to this treatment, several reactions occur and give rise to neoformed compounds genesis. In dairy products, the Maillard reaction is predominant among these reactions. This non-enzymatic reaction occurs between reducing sugars and free amino groups of protein or free amino acids. This reaction takes place in three steps (Figure 1). The initial step (Early) leads to the formation of Amadori products.

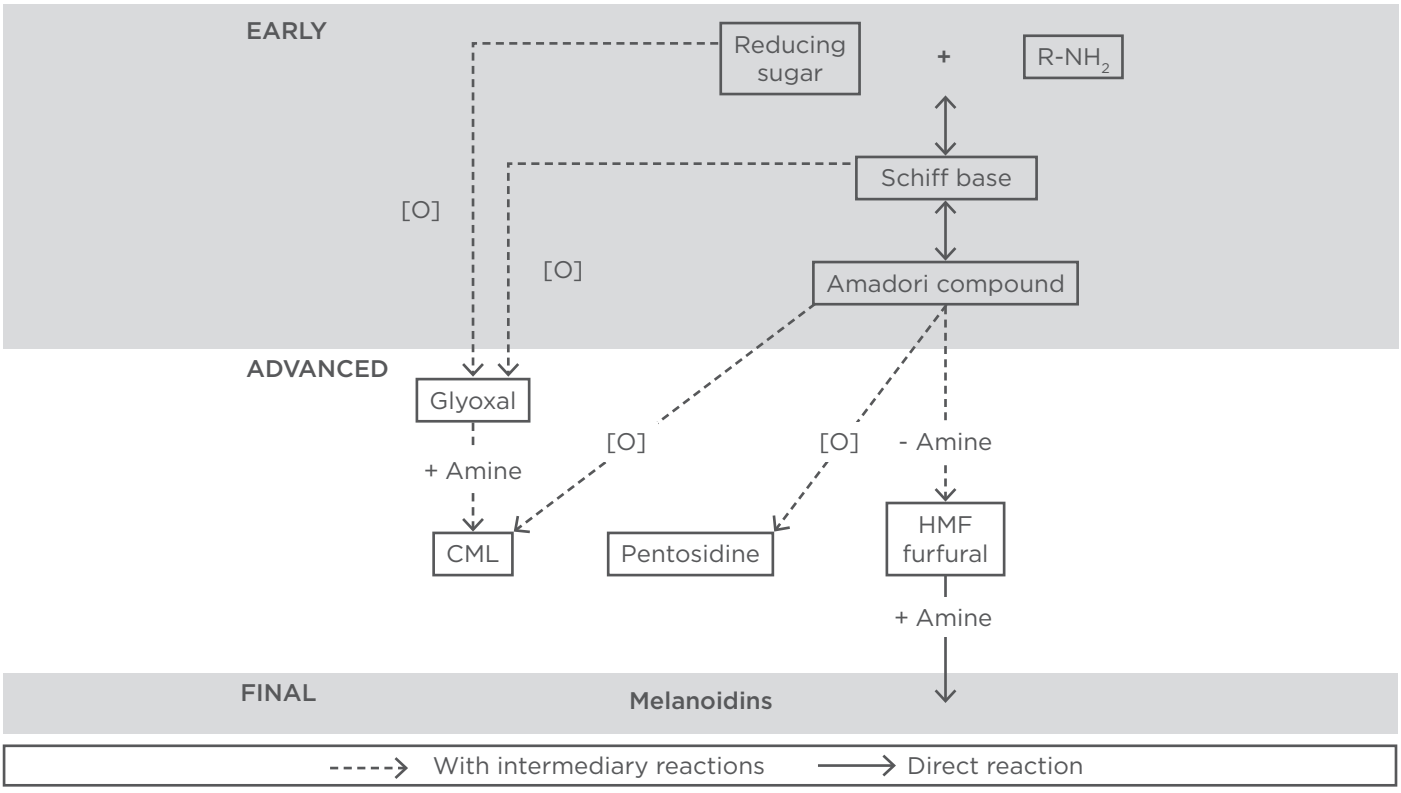

Figure 1: Main steps and pathways of the Maillard reaction.
CML: Nε-carboxymethyllysine; HMF: 5-hydroxymethylfurfural.
Adapted from Hodge.[17]

This intermediate product (Advanced) can be then transformed into advanced Maillard reaction products (MRPs), also called AGEs, which are chemically more stable. The final step of the Maillard reaction (Final) can lead to the formation of brown polymers, called melanoidins.[17]

Dairy products contain very few free amino acids,[18] with the exception of hydrolysed infant formulas. The Maillard reaction is favoured in milk because of its high content of lactose and proteins, such as caseins or serum proteins, that are rich in lysine. They carry amine functions that are involved in the Maillard reaction. The most predominant form of Amadori products is lactulosyllysine, which results from reactions between lactose and lysine.[19] During prolonged heating, these Amadori products are transformed to several types of MRPs, whose main form is Nε-carboxymethyllysine (CML).[19]

Among the different forms of milk, infant formulas are those with the highest levels of CML (Table 1).[20-22] CML levels of infant formula are ≤45-times higher than in highly sterilised (ultra high temperature) milks and ≤83-times higher than breast milk.[23] The amount of CML in breast milk is dependent on the diet of the breastfeeding mothers, since CML does pass through breast milk, but is usually low.[23] By contrast, the long shelf life of infant milk, and the often high iron and lactose content, makes it particularly sensitive to the Maillard reactin.[24] Moreover, the highest CML content is measured in hydrolysed infant milk.[21] This partial or total hydrolysis of these milk proteins leads to an increased proportion of free lysines and other amino acids, which will then actively participate in the Maillard reaction during heat treatment.

DIETARY ADVANCED GLYCATION END-PRODUCTS AND HEALTH

AGEs were first described as endogenous compounds whose concentration increases with age. They form through an *in vivo* process, referred to as 'non-enzymatic glycosylation' or 'glycation'. Their presence in excess has been described in age-related diseases, such as metabolic disorders, atherosclerosis, and Alzheimer's disease.[25] It has been shown that dietary AGEs, also called MRPs, contribute significantly to the systemic burden of AGEs.[26] These compounds are chemically the same and mainly come from glycation. Furthermore, an increasing number of studies show potentially deleterious effects of dietary AGEs, although the results may be divergent due to the great variability of the forms and contents of AGEs depending on the food.[27,28]

Table 1: Comparison of measurements of CML in different milks.

		Fenaille et al.[20]		Delatour et al.[21]		Assar et al.[22]	
		n	ng/mg protein	n	ng/mg protein	n	ng/mg protein
Liquid							
	Human		--	27	6.32±4.22		--
	Raw		--	2	1.76±0.61	--	9.3
	Pasteurised	1	16.3±3.3	2	1.30±0.72	--	10.4
	UHT	3	38.2±8.6	2	8.88±7.04		--
	IF	2	62.9±13	3	153±40		--
	Hydrolysed		--	3	405±195		--
	Hydrolysed lactose free		--	5	58.6±70.6		--
Powder							
	HA	5	225±68	9	184±131		--
	Hydrolysed lactose free		--	2	50.9±52.1		--
	IF	8	71±40	7	76±48		--

n=number of samples tested. CML levels are expressed in ng/mg protein.
UHT: ultra high temperature (highly sterilised); IF: infant formula; HA: hypoallergenic; CML: Nε-carboxymethyllysine.

Dietary Advanced Glycation End-Products and Gut Homeostasis

The host microbiota is a key component of gut homeostasis since it contributes to its physical protection, metabolism of food (e.g. short chain fatty acids production), and synthesis of new compounds (e.g. vitamins, neurotransmitters) but also exerts strong interactions with the mucosal and immune cells.[29] This interaction with the host is a long process that starts mainly at birth and necessitates some training from either side to reach an almost perfect regulation. However, under some conditions, by modifying the Th balance, this cross communication is altered and the microbiota profile becomes altered. One of the conditions at the origin of such modifications is the food matrix. The composition of the food matrix conditions the gut microbiota profile, which adapts to it. This changes the type of interaction between the host and microbiota, which has two main consequences: the production of potentially antigenic substances and/or facilitation of increased numbers of potentially pathogen micro-organisms, including gammaproteobacteria, which are detrimental for *lactobacilli* and *bifidobacteria*.[30]

As stated above, the Maillard reaction results in increasingly complex compounds whose effects on health are equivocal. This also applies for their interaction with the intestinal microbiota. From the literature, it has been indicated that Amadori products (e.g. fructoselysine) are poorly absorbed but metabolised by some bacteria.[31] As they are generally ingested in high quantities, we may then suggest that they influence the composition (density and diversity) of the gut microbiota. By contrast, as CML is known to be rapidly absorbed and transported into the blood circulation, it will not be used by the intestinal microbiota. At last, due to their chemical composition, most of high molecular weight MRPs (e.g. melanoidins) are likely to escape the upper gastrointestinal tract and may be more susceptible to be metabolised by the microbiota[32] as they behave as prebiotic fibres.

Formula-fed infants present 46% higher plasma CML levels and higher CML (60-fold) urinary excretion than breast-fed infants.[33] This is as CML absorption and urinary excretion are mostly linked to the level of CML in the food matrix (dietary intake), which is higher in formula than in breast milk, in which low levels of CML are detected.[23]

Free MRPs are not substrates for the intestinal lysine transporters.[34] However, when bound to small peptides, some MRPs may translocate into epithelial cells via di and tri-peptides transporters (PEPT1). In general, the longer MRPs are peptide-bound during intestinal digestion, the more hydrophobic they are and there is a higher chance of their appearance in the circulation. Then, once they have translocated into the epithelial intestinal cell, they are submitted to intracellular proteolysis. While glycated amino acids with polar or charged chains (e.g. CML) remain trapped inside the cell, glycated amino acids with unipolar side chains (e.g. maltosine, pyrraline) can pass through the membrane.[34-36] Their outcome is not clearly established and needs further investigation.

However, it is well understood that biologically formed AGEs bind to a plasma membrane receptor of AGEs (RAGE). This receptor is highly expressed by several types of cells, including immune, neuron, lung, and heart cells. Because it belongs to the immunoglobulin superfamily, once activated, it may initiate intracellular pro-inflammatory pathways, such as Ras/MAPK and JAK/STAT. These pathways often converge to nuclear factor-kappa B (NF-κB) activation and correlate to tissue damage by activating pro-inflammatory cytokines secretion.[37-39] It is not clear whether these pro-inflammatory pathways are also involved in intestinal epithelial cells. From our preliminary *in vitro* data, we observed that, in physiologic doses (amount possibly found in food) CML seems not to alter the Caco-2 epithelial monolayer, since the trans-epithelial electric resistance (an indicator of intestinal permeability) is maintained after 24 hours of exposure. Moreover, from these data we did not measure any expression of RAGE in the absence, as well as in the presence, of CML at the dose used. However, we have not measured the amount of intracellular CML in the Caco-2 cells after their exposure to MRPs (unpublished data).

Dietary Advanced Glycation End-Products and Inflammation

Dietary AGEs may predispose individuals to inflammation, which plays a major role in the development of chronic diseases (for review[40]). Thus, dietary AGEs such as CML are suggested to participate in metabolic disorders[41] and cardiovascular dysfunctions.[42] As mentioned above, consumption of dietary CML is correlated with circulating CML levels but also with an increased release of biomarkers of the inflammatory reaction and/or oxidative stress in both humans and animals.[43-45] By contrast, it has been shown that

acute exposure to dietary CML may not influence inflammation[46] and that some forms of CML are unable to activate an inflammatory response.[47] As mentioned previously, arguments in favour of its participation in the inflammatory reaction are that RAGEs are present on immune cells (mononuclear phagocytes, dendritic cells, T cells) and that cells expressing high levels of RAGE are often close to areas in which AGEs are abundant.[48-50] Their role in the regulation of the immune response has been studied in several *in vitro* and *in vivo* models.

Activation of immune cells, such as dendritic and TCD4+/TCD8+ cells, induce increased RAGE expression and this increase is more sustained in the presence of a RAGE ligand.[51] Furthermore, Dumitriu et al.[52]pointed out that, in both human and mice *in vitro* models, neutralisation of RAGE reduces the maturation of dendritic cells. This in turn present a lower secretion of IL-12 and a lower activation of the intermediate signalling pathways: MAPK and NF-κB. They also showed that TCD4+ cells cultured in the presence of anti-RAGE antibodies presented a decreased proliferation.[52] Other studies using RAGE$^{-/-}$ mice murine models have shown that the presence of RAGE on T cells is necessary for T cell priming and activation by CD28.[53,54] Furthermore, RAGE is involved in Th cell differentiation, since RAGE-deficient T cells released higher amounts of IL-10, IL-4, and IL-5, but lower amounts of interferon (IFN)-γ, which suggested an impaired Th1 differentiation and an increased Th2 differentiation in response to TCR activation.[53,54] The impact of RAGE on TCD4+ cell differentiation seems to be dependent on polarisation conditions. Indeed, in an allergic asthma murine model, the deficiency of RAGE reduces allergic airway inflammation and inhibits Th2 cell response i.e. Th2 cytokines IgE production and eosinophil recruitment.[55,56]

Dietary Advanced Glycation End-Products and Allergy

The Maillard reaction generated by heat treatment of food is responsible for conformational changes of proteins and consequently of allergens. Allergens altered by the Maillard reaction are often efficiently uptaken and presented by dendritic cells leading to better CD4+ T cell priming and differentiation toward the Th2 profile. This is associated with an increased proliferation of CD4+ T cells, a marked production of IL-2, IL-4, and IL-5 and a decreased production of IFN-γ and might enhance the allergic response.[57,58] Depending on the structure of allergens and the modifications induced by the Maillard reaction, a marked or reduced IgE binding to allergen proteins was observed.[59]

Consequently, there is now evidence that the Maillard reaction enhances the allergenicity of proteins. Nevertheless, the impact of dietary AGEs on the immune system favouring the Th2 profile and consequently on the predisposition to develop an allergy has not been studied so far. Our preliminary results showed that CML, the main dietary AGE present in infant formula, increases differentiation and proliferation of naïve T cells into the Th2 profile (unpublished data). Furthermore, mice exposed to CML during the sensitisation phase had higher levels of antigen-specific IgE and exhibited more severe allergic reactions.[60]

CONCLUSION

All together, these studies indicate a potential role of dietary AGEs in allergies. This needs further investigation because of the high levels of AGEs, notably CML, in infant formula and the specific vulnerability of the immune system to early environmental changes. Indeed, there is growing evidence that exposures in the early post-natal period can modify gene expression and disease susceptibility and that these dietary changes play a central role in this epigenetic paradigm. While hydrolysed formulas are often used for primary prevention of allergy, clinical studies show contradictory results on the rates of allergic infants from the breast-fed versus formula-fed populations.[13] Since CML levels are particularly high in hydrolysed formula, determining the role of dietary AGEs in allergy susceptibility is crucial for atopic babies who are fed with these types of milk and who are at high risk of allergy. If their role is proved, it would require food industries to modify the infant formula process in order to limit the occurrence of AGEs.

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ORAL IMMUNOTHERAPY FOR FOOD ALLERGY: WHAT HAVE WE ACHIEVED SO FAR?

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ABSTRACT

The burden of food allergy is significant, multi-faceted, and well documented. In an effort to improve food-allergic patients' quality of life, there is a continuous effort to provide novel treatment options for food allergy. Food immunotherapy is an exciting area of research that has seen tremendous progress over the last decade. This review examines the current literature and provides insights into key oral immunotherapy studies published so far. Areas requiring further study, the role of food oral immunotherapy, and its potential future applications for patient care are also discussed.

Keywords: Food allergy, immunotherapy, desensitisation, sustained unresponsiveness, tolerance, immunomodulators.

INTRODUCTION

Food allergy affects 6–8% of children and its prevalence is increasing. Milk allergy affects ~2% of infants, whereas egg allergy is the most common food allergy in childhood, with rates of up to 8.9% reported in a recent Australian study.[1] Peanut allergies were once rare, but now are the leading cause of fatal food-allergic reactions.[2] Their prevalence has doubled over the past two decades, mostly in the Western world, with the disease currently affecting 0.4–3% of children.[1,3-5]

Strict food avoidance, emergency medication, and education on how to promptly recognise and treat reactions currently represent the mainstream approach of managing food allergy. Unfortunately, accidental reactions are common, with cross-contamination and the ingestion of unlabelled foods being responsible for the vast proportion of all inadvertent reactions. In addition, food labelling is often inadequate, but this can vary between countries.[6-8] Food-allergic individuals can experience a low quality of life due to high levels of anxiety and increased awareness that their condition can be fatal.[9] Parents of food-allergic children also present with high levels of stress, due to the perceived risk of death of their child and constant dietary and social restrictions.[10] The burden of food allergy is such that there is a clear need for a form of treatment that has the potential to be disease-modifying.

FOOD ORAL IMMUNOTHERAPY

Over the last decade, food oral immunotherapy (OIT) has become an area of intense research and has shown significant promise as a form of active treatment for common food allergies encountered in childhood. Immunotherapy consists of the administration of small, gradually increasing doses of the specific food that patients are allergic to, with the aim to desensitise them and ultimately enable them to eat varying amounts of the allergenic food without reactions. Desensitisation refers to a rise in the allergenic threshold of reactivity and implies ongoing, usually daily, dose ingestion. Sustained unresponsiveness refers to the ability of subjects who have completed an immunotherapy protocol to take breaks from treatment, usually a few weeks or months, and then return to daily allergen consumption at their previous dose, without suffering any allergic reactions. Long-term tolerance is defined as the ability to eat the previously allergenic food ad lib, in

any amount and with any period of food abstinence, however prolonged, without any problems or the need for ongoing daily treatment. In addition to OIT, alternative routes of immunotherapy such as sublingual and epicutaneous are being pursued.

Food OIT studies have examined various food allergens, but mostly milk, egg, and peanut. Studies on food immunotherapy for milk and egg have shown promise in desensitising allergic children.[11,12] A systematic review on milk immunotherapy reported that OIT, when compared to a milk elimination diet alone, increased the likelihood of achieving full tolerance to cow's milk. Five randomised control trials (RCTs) fulfilled the criteria of this systematic review and it is recommended by the authors that larger RCTs measuring all patient-important outcomes are still needed.[13] Skripak et al.[14] reported on a double-blind placebo-controlled study of OIT for cow's milk allergy in children. After OIT, the median cumulative dose inducing a reaction in the active treatment group was 5,140 mg compared with 40 mg pre-OIT. There was no change in the median threshold in the placebo group. Although reactions were common during the study, nearly 90% were transient and did not require treatment. Reactions involving some combination of gastrointestinal, lower respiratory tract, and skin symptoms were rare, occurring with a median frequency of 1% of active doses.[14]

Baked milk immunotherapy for baked milk-reactive patients showed less encouraging results compared to fresh cow's milk studies. In fact, a small study reported that only 21% of participants were successfully desensitised to baked milk. Only a limited increase in the challenge threshold to unheated milk was observed for those who succeeded in baked milk desensitisation, and the risk of anaphylaxis and adverse reactions was significant during the intervention.[15] This study raises the important question of whether baked milk-reactive patients are amenable to OIT in the first place, as they appear to have a severe allergic phenotype, although the data provided on extensively heated versus unheated milk is currently limited. In addition, children who are unable to tolerate baked milk are still selected to participate in OIT studies. Generally, children who could tolerate baked milk and subsequently progress to less modified forms of dairy have a good prognosis.[16,17]

For egg allergies, a double-blind placebo-controlled, randomised OIT study of 55 children with egg allergy resulted in a 55% rate of desensitisation in the active group after 10 months of therapy. In the placebo group the desensitisation rate was 0%. After another year of OIT, the desensitisation rate rose to 75%, suggesting that longer treatment duration results in more successful desensitisation.[12] A 4-year follow up of these subjects reiterated this conclusion, reporting that sustained unresponsiveness after egg OIT is enhanced with longer duration of therapy and increases the likelihood of tolerating unbaked egg in the diet.[18] It is important to mention that the longer OIT continues, the greater the chance of natural acquisition of tolerance for foods such as egg and milk, and, as such, the data require careful interpretation. Important consideration should be given to the participating subjects, as certain studies may include subjects more or less likely to outgrow their milk/egg allergy in the upcoming 1–2 years.

For peanut OIT, USA investigators reported that, in a RCT, 84% of active subjects passed a final challenge of 20 peanuts (~5,000 mg peanut protein) compared with only 1 peanut (280 mg peanut protein) tolerated by the placebo subjects in the final challenge, after completing a year of OIT. The study regimen was well tolerated with clinically relevant symptoms seen after only 1.2% of build-up doses and no peanut OIT subject requiring adrenaline administration.[19] The largest Phase II, randomised controlled, crossover trial of peanut OIT, which originated in the UK, investigated the role of peanut OIT in desensitising 99 children, aged 7–16 years, inclusive of all severities of peanut allergy. Following completion of the intervention, in the active group, 84% were desensitised to 5 peanuts, whereas 62% of OIT participants successfully passed a 10-peanut challenge. Participants who successfully completed the study protocol had a significant 25-fold increase in their peanut threshold; therefore, the treatment allowed them to eat large quantities of peanuts, well above the levels present in contaminated snacks and meals. Adverse effects, seen in most participants, were mild and easily treatable, with oral itching being the most common side effect, occurring after 6.3% of all doses. Approximately 20% of patients reported respiratory symptoms during up-dosing; these symptoms responded to the administration of inhaled bronchodilators.[20] Quality of life of subjects participating in food OIT studies is significantly improved following successful desensitisation. It has also been reported that immunotherapy improves caregivers' health-related quality of life.[20,21]

SAFETY AND ADVERSE REACTIONS DURING FOOD ORAL IMMUNOTHERAPY

It appears from the above studies, and other published data, that food OIT presents an interesting and promising novel form of intervention for food-allergic children, showing good efficacy for desensitisation. The safety profile is acceptable, with most subjects experiencing mild or moderate reactions during treatment. As severe reactions can occur, it is of utmost importance that children have both an action plan and adrenaline autoinjectors readily available to treat any allergic reactions. Families should also be educated on the fact that viral illnesses and other factors (exercise, tiredness, and menstruation) may lower the threshold of reactivity in patients undergoing OIT.

For milk OIT, a Cochrane systematic review by Yeung et al.,[22] which included 16 records representing five different trials, reported adverse reactions in 97/106 milk-OIT patients, experienced at least one symptom, although most were local and mild. For every 11 patients receiving milk OIT, 1 required intramuscular epinephrine. One patient required it on two occasions.[22]

A different systematic review, investigating efficacy and safety of egg OIT, included four RCTs and a total of 167 individuals (100 OIT participants and 67 controls), all of whom were children aged 4–15 years. Sixty-nine per cent of the participants presented with mild-to-severe adverse effects during OIT treatment and 5 of the 100 participants receiving OIT required epinephrine.[23]

Concerns have been raised about the onset of eosinophilic oesophagitis (EoE) after OIT and there is debate on whether OIT incites EoE or unmasks a pre-existing condition. Such cases have been described and a meta-analysis showed that up to 2.7% of patients with immunoglobulin (Ig)E-mediated food allergies undergoing food OIT could develop this complication, with EoE often resolving following discontinuation of OIT treatment. However, the available data are limited, often of low quality, and a causal relationship between food OIT and EoE remains controversial.[24,25] Future studies will need to concentrate on further improving the safety of this form of treatment. The group of patients who are likely to benefit most from OIT will need to be identified and targeted for this intervention, keeping in mind that certain patient groups may not be suitable for immunotherapy at all.

MULTIPLE FOOD ALLERGENS

For children with multiple food allergies, the simultaneous administration of a combination of food allergens compared with the administration of a single allergen has been studied. Fifteen participants who were only allergic to peanut were compared with 25 who had additional food allergies. The primary aim of the trial was to assess safety and achieve a 10-fold increase from the initial challenge threshold. The dosing protocol was designed to continue dose increases up to a daily maintenance dose of 4,000 mg protein of each allergen, up to a 20,000 mg cumulative dose for those on five allergens, which was achieved by the majority of study participants. Most reactions during multi-food OIT were mild, and there was no statistical difference in adverse event rate or severity when comparing single with multi-OIT regimens. This approach has the potential to minimise the number of hospital patient visits and the overall cost of treatment, as OIT to more than one food allergen can be time-consuming and expensive if the allergens are to be administered sequentially, one at a time.[26,27] Future developments of this approach could include the concept of personalised patient treatment. A combination of different food allergens, depending on the patient's unique food-allergic profile, may be used to match the intervention to individual requirements and preferences.

ROLE OF IMMUNE-MODULATORS

The use of immune-modulators in combination with OIT has been suggested as a potential treatment for food allergy, with the aim to facilitate the OIT process. For peanut-allergic children, a double-blind, placebo-controlled, randomised trial of the probiotic *Lactobacillus rhamnosus* together with concurrent administration of peanut OIT was examined. This combined intervention was effective in inducing desensitisation in the majority (89.7%) of the active subjects; however, there was no direct comparison group that received peanut OIT without probiotics and not all patients had entry food challenges prior to participating.[28] As a result, data should be interpreted with caution and further studies are required comparing peanut OIT with probiotics directly. Currently, there is a lot of interest in the role of probiotics in inducing tolerance in food-allergic patients.

The use of anti-IgE (omalizumab) as an adjuvant in milk immunotherapy was examined in a randomised, double-blind, placebo-controlled trial that included 57 subjects with severe, persistent milk allergy. Significant improvements were shown in terms of safety, but not in outcomes of efficacy for the omalizumab and OIT-treated group compared with the group that received placebo and OIT.[29] Omalizumab, in combination with peanut OIT, was also investigated in 13 peanut allergic children with high peanut specific IgE levels. Omalizumab was shown to be effective in facilitating rapid oral desensitisation, but allergic reactions recurred once it was discontinued.[30]

When omalizumab was evaluated in 25 OIT paediatric patients with multiple food allergens, results were encouraging. Omalizumab was administered for 8 weeks prior to, and 8 weeks following, the initiation of a rush multi-OIT schedule. Doses were determined based on weight and total IgE levels as per omalizumab global dosing schedule. After pre-treatment with omalizumab, 19/25 participants tolerated the initial rapid escalation day with minimal or no rescue therapy and the majority of reactions experienced by participants were mild. Only one severe reaction was reported, which was treated successfully with adrenaline. Interestingly, participants could reach the top maintenance dose (4 g) for each allergen by at a median time of just 18 weeks. In a previous, similar study, without administration of omalizumab, participants required a median of 85 weeks to reach the same top dose, for up to five foods administered simultaneously with oral OIT.[26,27]

TRANSIENT AND LONG-TERM EFFECTS

The acquisition of long-term tolerance appears to be the goal for most individuals. Interestingly though, for many families, desensitisation to a level protective of accidental ingestion reactions is also actively pursued and accepted as a satisfactory outcome of OIT. Various studies have looked at transient discontinuation of daily OIT doses, usually for a few weeks, to assess whether food immunotherapy can be considered a cure. Approximately 25–50% of patients maintain their desensitisation after these breaks of OIT treatment.[12,31-33] Results appear to be much more encouraging for younger children.[34] Generally, the effect on successful, long-term, tolerance to foods after completion of OIT is much smaller compared with successful desensitisation, which, in most studies, is achieved by the majority. More data are needed and we are still missing a systematic, universally applied, approach to this important issue with well-designed and much larger studies.

THE ROLE OF FOOD ORAL IMMUNOTHERAPY IN EVERYDAY CLINICAL PRACTICE

There is currently some controversy on whether food OIT is ready to be implemented in daily clinical practice.[35-37] Food-allergic children are subject to significant dietary and social restrictions and a successful treatment is very much desired by patients and caregivers.

Despite various concerns that have been raised, food OIT is already offered as a clinical treatment in many parts of the world, especially in private practice. Wasserman et al.[37] described their experience of treating >300 patients with peanut OIT, in both the private and hospital sector, and reported that 85% of their patients managed to reach the target maintenance dose. Adverse reactions occurred in 11.9% of patients, but only 1/5 of these required adrenaline administration. The investigators reported 0.7 of 1,000 doses during dose escalation, and 0.2 of 1,000 doses during maintenance, needed treatment with adrenaline.[38] To understand the existing practices of allergists who perform OIT in the USA, Greenhawt et al.[38] published the results of an online survey of members of the American Academy of Allergy Asthma and Immunology (AAAAI). A total of 442 clinicians responded to the survey, with a minority (13.8%) providing OIT as a service or studying OIT under a research protocol. Some important differences in the practice of OIT between academic and non-academic providers were highlighted, with academics obtaining institutional review board and investigational new drug approval more often than non-academic clinicians.[39]

CONCLUSION

Published studies on food OIT have shown encouraging results regarding its efficacy in desensitising food-allergic patients, with an acceptable safety profile and a documented improvement in quality of life. Adverse reactions occurring during treatment are mostly mild to moderate, although episodes of anaphylaxis have also been recorded and the risk should be considered prior to a decision being made to participate in food OIT.

Current protocols vary widely in their dosing schedules and duration of treatment, as the optimal escalation, maintenance dose, and duration of immunotherapy is still unknown. It is reasonable to speculate that severity of the disease at study entry may affect individual patient results, although the exact interplay between the two requires further investigation. Currently, patient selection also varies between studies, with some trials including food-allergic patients of all severities and others choosing to enrol only subjects that the investigators consider to be at the high-risk end of the spectrum for food allergy. Our ability to identify this group is limited.

It is still unclear what the long-term effects of food OIT are and for how long the treatment should be continued. Cessation of maintenance dosing and its effect on previously treated patients, as well as long-term tolerance, constitute important issues that have not yet been fully addressed. The question of whether food immunotherapy is better than strict allergen avoidance is still a controversial issue and the health economics of this novel treatment are also largely unknown.

In summary, food OIT presents an exciting, potentially disease-modifying, treatment approach for food allergy, but is still facing challenges that require further work to optimise this intervention and unveil its full potential. Food OIT is not yet recommended for use outside the research setting and the realm of specialist allergy centres. Currently, Phase III trials on food immunotherapy are underway and approval by the US Food and Drug Administration (FDA) is actively being pursued by pharmaceutical companies. It appears that the future management of food allergy is likely to become a balancing act between avoiding allergens and actively promoting acquisition of tolerance through food immunotherapy.

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MACROPHAGE ACTIVATION SYNDROME IN SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS

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ABSTRACT

One of the complications of systemic juvenile idiopathic arthritis (SJIA) is macrophage activation syndrome (MAS), which may be considered as a form of secondary haemophagocytic lymphohistiocytosis. Trigger factors are drugs (aspirin, nonsteroidal anti-inflammatory drugs, gold preparations, methotrexate, and tumour necrosis factor blocking agents), drug change, drug side effects, or initiation of biological drugs and infections. The pathogenesis of MAS is still unclear and it may be explained by uncontrolled activities of macrophages. A lot of proinflammatory cytokines such as tumour necrosis factor-α, interleukin (IL)-1, IL-6, and interferon gamma play important roles in the pathogenesis of MAS. The diagnosis of MAS is often challenging. In 2016, the European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) approved classification criteria for MAS complicating SJIA. Corticosteroid and cyclosporin A treatment have been used in the treatment of MAS. Intravenous immunoglobulin treatment has been used in some cases of MAS. Biologic agents have been used, such as anakinra (IL-1 alpha and beta inhibition), canakinumab (IL-1 beta inhibition), and tocilizumab (IL-6 inhibition). Early detection and early intervention are vital to avoid poor outcomes in MAS. SJIA is a subtype of juvenile idiopathic arthritis, and MAS is a serious, potentially fatal, complication of SJIA that occurs most commonly in children.

Keywords: Macrophage activation syndrome (MAS), systemic juvenile idiopathic arthritis (SJIA), pathogenesis, diagnosis, treatment.

SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS, MACROPHAGE ACTIVATION SYNDROME, AND HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Systemic juvenile idiopathic arthritis (SJIA) is a subtype of juvenile idiopathic arthritis (JIA), which is characterised by arthritis of unknown origin and extra-articular symptoms like spiking fever, often accompanied with a macular rash, serositis, hepatosplenomegaly, and generalised lymphadenopathy due to reticuloendothelial involvement.[1] The prevalence rate of the disease varies widely in different series (3.5–5 cases/100,000) and the yearly incidence varies from 0.4–0.9 cases per 100,000 children.[2] According to the JIA criteria of Edmonton made by the International League of Associations for Rheumatology (ILAR) in 2001, SJIA is defined as arthritis affecting one or more joints, usually in the juvenile age group (<16 years of age), with, or preceded by, fever of ≥2 weeks duration that is documented to be daily (quotidian) for ≥3 days, which may be associated with evanescent (non-fixed) erythematous rash or generalised lymph node enlargement or hepatomegaly, splenomegaly, both, or serositis.[2]

Macrophage activation syndrome (MAS) is most common in SJIA, and it has been reported that the frequency of marked MAS is ˜10%, but it is known that the frequency of MAS, which is not reflected in clinical practice, reaches up to 30–40%.[3] It also can occur in patients with other rheumatic disorders such as Kawasaki disease, adult-onset Still's disease, Behçet's disease, systemic lupus erythematosus, and juvenile dermatomyositis.[2,4,5]

Additionally, in the case of an adolescent boy with human leukocyte antigen, B27-positive ankylosing spondylitis has been reported,[6] and it is typically characterised by high fever, lymphadenopathy, and hepatosplenomegaly and is variably associated with haemorrhage as well as signs of liver, central nervous system, and kidney involvement, and may lead to multiple organ failure.[7,8] This can be characterised by hyperferritinaemia, transaminitis, hypofibrinogenaemia, and hypertriglyceridaemia.

MAS is also a form of secondary haemophagocytic lymphohistiocytosis (HLH) associated with rheumatologic conditions.[9] HLH has two forms: primary, or familial HLH, which is autosomal recessive,[9] and secondary HLH, which may occur in patients with infections such as Epstein–Barr virus, haematological malignancies, metabolic conditions, and a range of autoimmune and other inflammatory conditions.[10] MAS is classified among the secondary forms of HLH. The diagnostic criteria of HLH was based on the HLH 2004 diagnostic guideline. It follows the presence of a molecular diagnosis with specific gene mutations (*PRF*, *UNC13D*, *STX11*) that are associated with HLH or meet five out of eight clinical and laboratory diagnostic criteria including fever, hepatosplenomegaly, cytopenia, hypertriglyceridaemia/hypofibrinogenaemia, haemophagocytosis, low or absent natural killer (NK) cell activity, ferritin >500 ng/mL, and soluble CD25 >2,400.[11] The diagnosis requires five out of the eight criteria to be fulfilled, but patients with a molecular diagnosis consistent with HLH do not necessarily need to fulfil the diagnostic criteria.[9]

Macrophage Activation Syndrome and Genes

Mutations in the perforin (*PRF1*) gene can be linked to MAS. *PRF1* mutations play a role in the development of MAS in SJIA patients. PRF1 is a protein that mediates cytotoxic activity of NK and T cells, and its mutations can lead to NK dysfunction. It is therefore tempting to assume that (heterozygous) mutations in other genes involved in the pathogenesis of HLH, such as genes encoding Syntaxin[11] and MUNC13-4, could also be involved in the development of MAS in SJIA patients. Heterozygous protein-altering rare variants in the known genes (*LYST*, *MUNC13-4*, and *STXBP2*) were found in some patients.[12,13,14]

MACROPHAGE ACTIVATION SYNDROME CAUSE AND PATHOGENESIS

MAS may be triggered as a complication of an underlying disease without any triggering factor or in relation to any infection, or drug side effect.[3,15] In MAS, acute infections show that an additional contribution must be provided by the inflammatory status of the patient; indeed, the majority of MAS episodes occur during active disease phases or at disease onset.[7] Minoia et al.[15] reported that MAS was believed to be related to a treatment side effect (8 of the 11 instances involved a biologic agent).

The pathogenesis of MAS is still unclear. The development of MAS is characterised by a cytokine 'storm', with the elaboration of numerous proinflammatory cytokines.[16] It has been explained that the over-activated T lymphocytes and macrophages are found in various organs, and perforin deficiency and some cytokines, such as tumour necrosis factor-α (TNF-α), interleukin (IL)-1, IL-6, and interferon gamma (IFN-γ), play roles in the pathogenesis of MAS. Perforin is a cytotoxic protein that lymphocytes secrete to kill virus-infected cells and has the function of controlling lymphocyte proliferation. Therefore, perforin deficiency may lead to persistent lymphocyte activation.[2]

IL-1β is a proinflammatory cytokine produced primarily by monocytes and macrophages, and it is believed to be central to the pathogenesis of SJIA. IL-1β signals through its receptor and causes lymphocyte and endothelial activation as well as production of other inflammatory cytokines, including IL-6.[16]

IL-6 is a pleotropic cytokine produced in the early stages of inflammation and is central in driving the acute-phase response.[12] It plays a role in the amplification of inflammatory responses induced by TLR ligands.[17] The role of IL-6 has recently been confirmed by the therapeutic effects of tocilizumab (TCZ), a neutralising antibody to the IL-6 receptor (IL-6R).[18] However, some research shows that serum IL-6 levels in patients with MAS did not differ from IL-6 levels during active SJIA in the absence of MAS.[1]

IL-18 is a unique cytokine in the IL-1 family and is constitutively present in keratinocytes, epithelial cells, and blood monocytes. It induces production of IFN-γ by NK cells and T cells as well as TNF-α and chemokine secretion by macrophages.[16]

Table 1: Preliminary diagnostic guidelines for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis in 2005.[21]

Laboratory criteria	Decreased platelet count (<262 × 1/L) Elevated aspartate aminotransferase levels (>59 U/L) Decreased WBC count (<4 × 1/L) Hypofibrinogenaemia (≤2.5 g/L)
Clinical criteria	CNS dysfunction (e.g. irritability, disorientation, lethargy, headache, seizures, coma) Haemorrhages (e.g. purpura, easy bruising, mucosal bleeding) Hepatomegaly (≥3 cm below the costal margin)
Histopathologic criterion	Evidence of macrophage haemophagocytosis is found in the bone marrow aspirate sample (The demonstration of haemophagocytosis in bone marrow samples may be required in doubtful cases)

WBC: white blood cell count; CNS: central nervous system.

Some reports showed that an imbalance between IL-18 and its natural inhibitor, IL-18-binding protein, resulted in Th-1 lymphocyte and macrophage activation, which escaped the control by NK-cell-mediated cytotoxicity and may have allowed for secondary hemophagocytic syndrome.[19]

IFN-γ is a proinflammatory cytokine produced by T lymphocytes and NK cells when activated by antigen-presenting cells via IL-12 and IL-18. The primary function is to profoundly activate monocytes and macrophages.[16] The high levels of IFN-γ and chemokine (C-X-C motif), ligand 9 (CXCL9), CXL10, and CXCL11 and their correlation with the severity of laboratory abnormalities of MAS suggest a pivotal role of IFN-γ in MAS.[20]

TNF-α is produced largely by monocytes and macrophages that are activated by TLR ligands, such as endotoxin, and cytokines, such as IL-18, stimulating local endothelial cells as well as lymphocytes. TNF-α similarly does not appear to be central to the pathogenesis of MAS in patients with SJIA. Serum levels of TNF-α are only modestly elevated and are not significantly higher than those seen in active SJIA.[16]

DIAGNOSTIC CRITERIA OF MACROPHAGE ACTIVATION SYNDROME

MAS associated with JIA was first described by Hadchouel et al.[2] The diagnosis of MAS is often challenging, since the disease can mimic infections and malignancies, and presents as a life-threatening complication with SJIA. Ravelli et al.[21] made a preliminary diagnostic guideline for MAS complicating SJIA in 2005 (Table 1). The diagnosis of MAS requires the presence of ≥2 of the following laboratory criteria, or ≥2 of the following clinical criteria:

- Ravelli et al's.[21] criteria have been applied over many years, and some clinicians hold the view that the criteria are of value only in patients with active SJIA. The thresholds of laboratory criteria are provided only as an example. The clinical criteria are probably more useful as classification criteria rather than as diagnostic criteria because they often occur late in the course of MAS; therefore, they may hold limited value in the early diagnosis of the syndrome.[2]
- In 2013, the American College of Rheumatology (ACR) updated the 2011 recommendations for the treatment of juvenile idiopathic arthritis, focussing especially on the addition of SJIA recommendations. They focussed on SJIA with features that are concerning for MAS. The features concerning for MAS were defined as any combination of the following disease manifestations: persistent (rather than quotidian) fever, cytopenias or falling cell line counts (particularly platelets), falling erythrocyte sedimentation rate, hypertriglyceridaemia, hypofibrinogenaemia, haemophagocytosis, transaminitis, coagulopathy, organomegaly, low or absent NK cell activity, hyperferritinaemia, or central nervous system dysfunction. This definition was left intentionally broad given the lack of validated classification criteria for MAS. The scenarios specifically excluded critically ill patients requiring intensive care unit admission.[22]
- In 2016, the European League Against Rheumatism (EULAR)/ACR approved classification criteria

for MAS complicating SJIA, after quantitatively validating the criteria in patient datasets. Experts identified the laboratory tests (platelet count, and serum ferritin and aspartate aminotransferase levels) in which changes over time are most valuable for the timely diagnosis of MAS occurring in the context of SJIA.[23] They found that ferritin levels (≥500 ng/mL) could discriminate between MAS and systemic infections. Hyperferritinaemia did not increase the sensitivity and specificity of the guidelines for MAS in SJIA, but it did enhance their capacity to differentiate MAS from systemic infections.[24] According to the criteria, a febrile patient with known or suspected SJIA is classified as having MAS if several criteria are met (Table 2).[25]

Differential Diagnosis

Many conditions can lead to the clinical picture of MAS, including malignancies (leukaemia, lymphoma, other solid tumours), infections (viral, bacterial, or parasitic), and rheumatoid disorders (systemic lupus erythematosus/Kawasaki disease). MAS, a serious complication of systemic inflammatory disorders, is thought to be caused by excessive activation and proliferation of T lymphocytes and macrophages; moreover, in the same way as in HLH, it has been shown that in addition to corticosteroids, cyclosporin A (CsA) is also effective in patients with MAS.[11]

TREATMENT

In the treatment of MAS, extensive, high dose corticosteroid treatment is used in the beginning to control the findings. In addition, CsA treatment is used as immunosupressive treatment.

Table 2: EULAR/ACR criteria for MAS complicating SJIA in 2016.[25]

Ferritin >684 ng/mL and any two of the following:
Platelet count ≤181 × 1/L
Aspartate aminotransferase >48 U/L
Triglycerides >156 mg/dL
Fibrinogen ≤360 mg/dL

EULAR: European League Against Rheumatism; ACR: American College of Rheumatology; MAS: macrophage activation syndrome; SJIA: systemic juvenile idiopathic arthritis.

Etoposide treatment is used in primary HLH. It is rarely used in cases of MAS related with SJIA. Intravenous immunoglobulin treatment is currently applied in some cases.[15] In maintenance treatment, or in rare cases where activity findings cannot be suppressed with classical treatment, anti-IL-1 or IL-6 treatment is used. Anakinra (IL-1 alpha and beta inhibition), canakinumab (IL-1 beta inhibition), and TCZ (IL-6 inhibition) are biological drugs used for this purpose.[3,26]

Non-Biologic Treatments

In treatment, corticosteroids and cyclosporin are used.[22] Most clinicians start with intravenous methylprednisolone pulse therapy (e.g. 30 mg/kg for 3 consecutive days) followed by 2–3 mg/kg/day in 2–4 divided doses. If response to steroids is not immediately evident, parenteral administration of CsA (2–7 mg/kg/day) is usually initiated. Addition of CsA not only provides rapid control of the symptoms, but also avoids excessive use of steroids.[16] Etoposide was reported to be used in MAS because it is a central medication in HLH therapeutic protocols and it was able to induce rapid recovery in cases of steroid and CsA resistant MAS without serious adverse events.[15,23] The potential toxicity of the drug etoposide is a major concern, particularly in patients with hepatic impairment.[16] It has been argued that the HLH protocol is too aggressive for use as first-line therapy in SJIA–associated MAS.[15]

Biologic Agents

Anti-IL-1 drugs are used in some resistant cases.[23] For severely ill children, IL-1 blockade has been remarkably effective in a relatively brief time frame, such as anakinra (IL-1 alpha and beta inhibition), canakinumab (IL-1 beta inhibition). Rituximab, an anti-CD20 antibody that depletes B lymphocytes, has been successfully used in Epstein–Barr virus-induced lymphoproliferative disease and could be considered in Epstein–Barr virus-driven MAS.[16]

IL-6 blockade, via the anti-IL-6 receptor monoclonal antibody TCZ, has proven highly efficacious in treating SJIA.[16] The role of IL-6 has recently been confirmed by the therapeutic effects of TCZ,[18] but the additional caution in TCZ use for children with a history of MAS is warranted to avoid serious adverse events related to cytopenias.[27] Given that infections remained the most prevalent trigger for MAS in canakinumab-treated patients with SJIA, increased vigilance and prompt initiation of aggressive therapy appear warranted in all

suspected cases.[28] Intravenous immunoglobulin was administered to a sizeable proportion of the patients, probably owing to both its immunoregulatory properties and its potential to aid in preventing septic complications.[15]

CONCLUSION

MAS is a complication of SJIA which increases morbidity and mortality and can be rapidly fatal if left untreated. It requires prompt recognition to initiate appropriate treatment and prevent deleterious outcomes.[23] Early detection and early intervention are vital to avoiding poor consequences.

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Contact With Farm Animals Protects From Asthma

MICROBES on farms have long been known to help protect children from allergies, including asthma. However, a new study from immunologists at the University of Zürich, Zürich, Switzerland has demonstrated that even a non-microbial molecule, a sialic acid, is effective against inflammation of lung tissue.

The number of people with allergies and asthma has continued to increase over recent decades. This is particularly pronounced in industrialised countries, and globally, ~30% of children have been diagnosed with allergies; however, farm children are the notable exception. Even when these children are compared to other local children who do not live on a farm, the incidences of allergy and asthma cases are still vastly different.

Dr Remo Frei's team from the Swiss Institute of Allergy and Asthma, University of Zürich in co-operation with the Center for Allergy Research and Education (CK-CARE), Children's Hospital of Eastern Switzerland, St. Gallen, Switzerland have shown that petting farm animals and eating food from farm animal sources, including milk, can prevent asthma. Dr Frei commented: "Early childhood contact with animals and the consumption of food of animal origin seems to regulate the inflammatory reactions of the immune system."

A sialic acid, N-glycolylneuraminic acid (Neu5Gc), is common in vertebrates, but is absent in humans due to a genetic mutation. Humans can, however, absorb Neu5Gc through interaction with animals or by eating animal products, whereby it is integrated into glycoproteins. Neu5Gc triggers an antibody reaction, this reaction can therefore be used as a measure of contact with farm animals and thus the exposure to Neu5Gc. Therefore, the researchers measured Neu5Gc antibody serum concentrations of >1,000 children from two epidemiological studies. Dr Frei commented: "Farm children have many more antibodies against Neu5Gc in their blood, and children with more antibodies suffered considerably less from asthma." The influence of Neu5Gc was further confirmed by a mouse model study.

> "Our research results open up opportunities for transferring the protective effect of farms to all children. In this way, we can possibly lay an important foundation stone for effective allergy prevention."

The mechanism behind the association was, surprisingly, not a reduction in immunoglobulin E but the initiation of an anti-inflammatory reaction of the immune system via regulatory T-cells. Dr Frei summarised: "These T-cells dampen incorrect responses of the immune system and have a strong anti-inflammatory effect. Our research results open up opportunities for transferring the protective effect of farms to all children. In this way, we can possibly lay an important foundation stone for effective allergy prevention."

Gene Therapy to 'Turn Off' Severe Allergies

THE MANAGEMENT of asthma and other allergies is problematic in Australia. Discussing the statistics, Dr Peter Anderson, Chief Executive Officer, Asthma Foundation of Queensland and New South Wales, Australia, commented: "Even though there are effective treatments available for the vast majority, patients face a number of obstacles and challenges in their self-management practices."

Research carried out at the University of Queensland, Queensland, Australia now presents a novel single treatment, potentially giving lifelong protection from severe allergies, including asthma. Associate Prof Ray Steptoe, University of Queensland Diamantina Institute, and his researchers have demonstrated the ability to 'turn-off' the immune response causing an allergic response in animals. Once an allergic response has been triggered, T-cells build a 'memory' to specific allergens and can become very resistant to treatments. This memory has been 'wiped' by Steptoe's team, allowing animals to become desensitised to previous allergy-inducing allergens, and thus being able to tolerate the allergen. This has been made possible through the use of blood stem cells with an inserted gene that regulates the allergen protein. Once the cells are introduced to the patient, the newly engineered cells produce new blood cells expressing the protein, which are then able to target specific immune cells, 'turning off' any allergic response.

Currently, this novel therapy is primarily targeted at severe asthma sufferers or those with potentially lethal food allergies. However, the treatment could be extended in the future. The therapy is currently subject to further preclinical investigation, involving human cells, with the aim to make it simpler and safer, with a primary goal of producing a single injection therapy replacing short-term treatments.

Dr Anderson concluded: "The Foundation welcomes the findings of this research and looks forward to a day in the future when a safe one-off treatment may be available that has the potential to eliminate any experience of asthma in vulnerable patients."

"The Foundation welcomes the findings of this research and looks forward to a day in the future when a safe one-off treatment may be available that has the potential to eliminate any experience of asthma in vulnerable patients."

Phthalates Increase the Risk of Allergic Asthma Among Children

> "...epigenetic modifications are apparently responsible for the fact that children of mothers who had a high exposure to phthalates during pregnancy and breast feeding have an increased risk of developing allergic asthma."

PHTHALATES, which are used to make plastics more flexible, have been shown to considerably increase the risk of allergic asthma among children born to mothers who have been heavily exposed to them during pregnancy and breastfeeding. During everyday life, we often come into contact with plastics containing phthalates. Phthalates can enter the body through the skin, food, and respiration, which can subsequently affect metabolism and fertility. However, Dr Tobias Polte, Helmholtz Centre for Environmental Research (UFZ), Leipzig, Germany, explained: "The results of our current study demonstrate that phthalates also interfere with the immune system and can significantly increase the risk of developing allergies."

Firstly, urine from pregnant women from the LINA mother-child cohort was studied for the presence of phthalate metabolites. Dr Irina Lehmann, head of the LINA study, explained: "There was a clearly discernible relationship between higher concentrations of the metabolite of benzyl butyl phthalate (BBP) in the mother's urine and the presence of allergic asthma in their children."

The results were confirmed by means of a mouse-model study at the University of Leipzig. Mice were exposed to certain phthalate concentrations during pregnancy and lactation, leading to comparable urine concentrations of BBP metabolite to the LINA mothers. Their offspring had a high tendency to develop allergic asthma and even the third generation continued to be affected, but the adult mice exposed did not express allergic symptoms, indicating that it is the prenatal development process that is altered by phthalates exposure.

A genetic analysis of the mice born to exposed mothers was conducted. It was found that epigenetic modifications of the DNA caused the alterations. Methyl groups covered an area of DNA associated with regulation of T-helper cells and thus immune responses, preventing the associated proteins being translated. This blockage of repressor genes prevented the suppression of T-helper 2 cells, allowing an allergy to develop. It was also shown that when substances designed to release the methyl 'locks' were used, the mice then demonstrated fewer signs of allergic asthma. Following this, the genetic make-up of children with allergic asthma were studied, and it was found that methyl groups were blocking the corresponding gene in these children. Dr Polte concluded: "We have been able to demonstrate that epigenetic modifications are apparently responsible for the fact that children of mothers who had a high exposure to phthalates during pregnancy and breast feeding have an increased risk of developing allergic asthma." Future research will have to be carried out to fully understand how phthalates cause methylation.

High Sugar Intake During Pregnancy Associated With Allergy Development

MOTHERS who consume large levels of sugar during pregnancy could increase the risk of their children developing allergies and allergic asthma. Researchers, led by those from Queen Mary University of London, London, UK, carried out an observational study on data collected from a world leading birth cohort study ALSPAC, also known as the 'Children of the 90s'.

Almost 9,000 mother-child pairs were analysed and associations between maternal intake of free sugars and the allergies and asthma of offspring at 7 years of age were assessed. Results for the association of sugar intake and asthma were weak, whereas there was a strong association with the onset of allergies and allergic asthmas. Indeed, when the 20% of mothers with the highest sugar intake were compared with the lowest 20%, the risk for children developing allergies was increased by 38% and by 101% for allergic asthma. No association was found between maternal sugar intake and the onset of eczema or hay fever.

> "However, given the extremely high consumption of sugar in the West, we will certainly be investigating this hypothesis further with some urgency."

How high sugar intake during pregnancy may cause allergies and allergic asthma is still speculative. The Queen Mary University of London researchers explained that it may be due to high fructose intake causing a persistent postnatal allergic immune response that resulted in to allergic inflammation in the offspring's developing lungs. Of note, the offspring's early childhood free sugar intake was not found to affect the onset of allergies or allergic asthma.

Prof Seif Shaheen, lead researcher, Queen Mary University of London, noted that whilst the results do not allow scientists to conclude a definite causal link between a mother's pregnancy sugar intake and allergy and allergic asthma onset in their offspring, they are striking nonetheless. "However, given the extremely high consumption of sugar in the West, we will certainly be investigating this hypothesis further with some urgency," Prof Shaheen commented. The next step in verifying the results is to assess whether the findings can be replicated in a different cohort of mother-child pairs. If similar results are found, future research would then be able to assess if reducing sugar consumption during pregnancy could prevent the onset of allergies and allergic asthma. At present, Prof Shaheen recommends that pregnant women should follow current guidelines, which recommend avoiding excessive sugar consumption.

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UPCOMING EVENTS

2017 Meeting of the European Society for Immunodeficiencies (ESID)

11th–14th September 2017

Edinburgh, UK

Offering access to the latest research in the field of immunodeficiencies, this year's ESID meeting will focus on the theme of autoimmunity and inflammation in pelvic inflammatory disease. Participants can look forward to a spectacular opening ceremony providing an overview of the autoinflammatory genes, followed by 3 more days of educational sessions, industry-sponsored symposiums, debates, and workshops in the fascinating city of Edinburgh, UK.

The British Society for Allergy and Clinical Immunology (BSACI) Annual Meeting

1st–3rd October 2017

Telford, UK

This conference will include expert clinicians and nurses amongst the speaker programme, focussing particularly on the incidence, thresholds, and pathophysiology of anaphylaxis. Other hot topics being discussed include the interaction between sleep and allergy, and the effects of pollution on allergic disease. With a range of expert physicians, basic scientists, primary care physicians, dieticians, and nurses as the speakers, this conference is not to be missed!

XI World Congress on COPD, Asthma and Immunopathology 2017

5th–8th October 2017

Moscow, Russia

Taking place in the beautiful city of Moscow, Russia, this world-renowned congress will cover various faces of immunopathology, including asthma, allergic inflammation, and food allergy. The conference will be supported by representatives from many leading allergy organisations across the world, such as the World Immunopathology Organization (WIPO) and the World Allergy Organization (WAO), who have crafted an exciting programme which promises to create a memorable event.

Pediatric Allergy and Asthma Meeting (PAAM) 2017

26th–28th October 2017

London, UK

The 5th PAAM meeting, held by the European Academy of Allergy and Clinical Immunology (EAACI), promises to be an insightful event. Held in the vibrant city of London, UK, this conference will facilitate scientific discussion between paediatricians and primary care physicians who are passionate about paediatric allergy and asthma. An example of the research presented includes the immunological mechanism that underpins successful childhood tolerance to foods.

3rd International Primary Immunodeficiencies Congress (IPIC 2017)

8th–10th November 2017

Dubai, United Arab Emirates

Building on previous IPIC meetings, this year's congress, held in the cosmopolitan city of Dubai, will focus on clinical developments in the field of managing pelvic inflammatory diseases. By including a clinically orientated programme designed by doctors, nurses, and patients, the 2017 IPIC meeting will be a unique event, covering topics such as transplant advances, novel treatments, and ethical care issues.

World Immunology Congress 2017

14th–15th December 2017

Dubai, United Arab Emirates

This prestigious conference will include a range of keynote speeches, networking sessions, and poster presentations, all centred around this year's theme of 'Trends in Traditional and Novel Immunological Approaches'. Touching on highlights including immunity and host defences, autoimmunity, and transplantation, this congress promises an exciting programme packed with invaluable insights into immunology.

American Academy of Allergy, Asthma and Immunology (AAAAI) and World Allergy Organization (WAO) Joint Meeting 2018

2nd–5th March 2018

Orlando, Florida, USA

In line with the congress theme of 'Expanding Practice: Diagnosis and Treatment of Drug Hypersensitivity', the 2018 meeting will include the most recent developments in new diagnostic tools for drug hypersensitivity. Attendees can look forward to popular plenary sessions and keynotes speeches on topics such as re-emerging infectious diseases. Lastly, participants can take part in workshops and courses where advances in allergy prevention and cure will be discussed.

European Academy of Allergy and Clinical Immunology (EAACI) Congress 2018

26th–30th May 2018

Munich, Germany

This congress provides an opportunity for leading healthcare professionals and key opinion leaders to come together from around the world to exchange knowledge and learning. Following the jam-packed programme of the EACCI 2017 congress, next year's event promises to be another spectacular occasion that is not to be missed by anyone, especially those interested in the fast-paced field of allergy and immunology.

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