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Allergy School on Food Allergy
Trends and Novelties

5 - 7 December 2019
Paris, France

ABSTRACT BOOK

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DHM 2020

2 – 4 April 2020
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Drug Hypersensitivity Meeting

Drug Hypersensitivity Meeting

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GENERAL INFORMATION

CME Accreditation

An application has been made to the UEMS-EACCME® for CME accreditation of this EAACI Allergy School. The CME letter and the Certificate of Attendance can be downloaded after completing the survey which will be sent to you by e-mail after the school. **Please make sure you scan your badge before entering each session room, in order to obtain the CME credits.**

Potential Conflicts of Interest Declaration

Please refer to the relevant event page under the "Meetings" tab on www.eaaci.org for a full conflict of interest declaration, provided by the organising committee and faculty members.

Organising Committee

Rosan Meyer, Co-Organising Chair, EAACI Allied Health & Primary Care
Margitta Worm, Co-Organising Chair, EAACI IG Food Allergy Past Chair 2017-2019
Alexandra F. Santos, Organising Secretary, EAACI IG Food Allergy Chair
Antonella Cianferoni, Organising Secretary, EAACI WG - Eosinophilic Esophagitis Chair

Poster Information

Posters can be mounted on Thursday, 05 December 2019 starting from 11.00 upon your arrival and should be removed after the last poster session on Saturday, 07 December 2019. Please make sure to remove the poster and all poster-mounting material from the board. The organisers will remove posters not taken down on time and will not take any further responsibility for the material.

Meeting & Accommodation Venue

Novotel Paris East Hotel
1 avenue de la République,
93170 Bagnolet, France
Tel: +33 1 49 93 63 00

Contact Details

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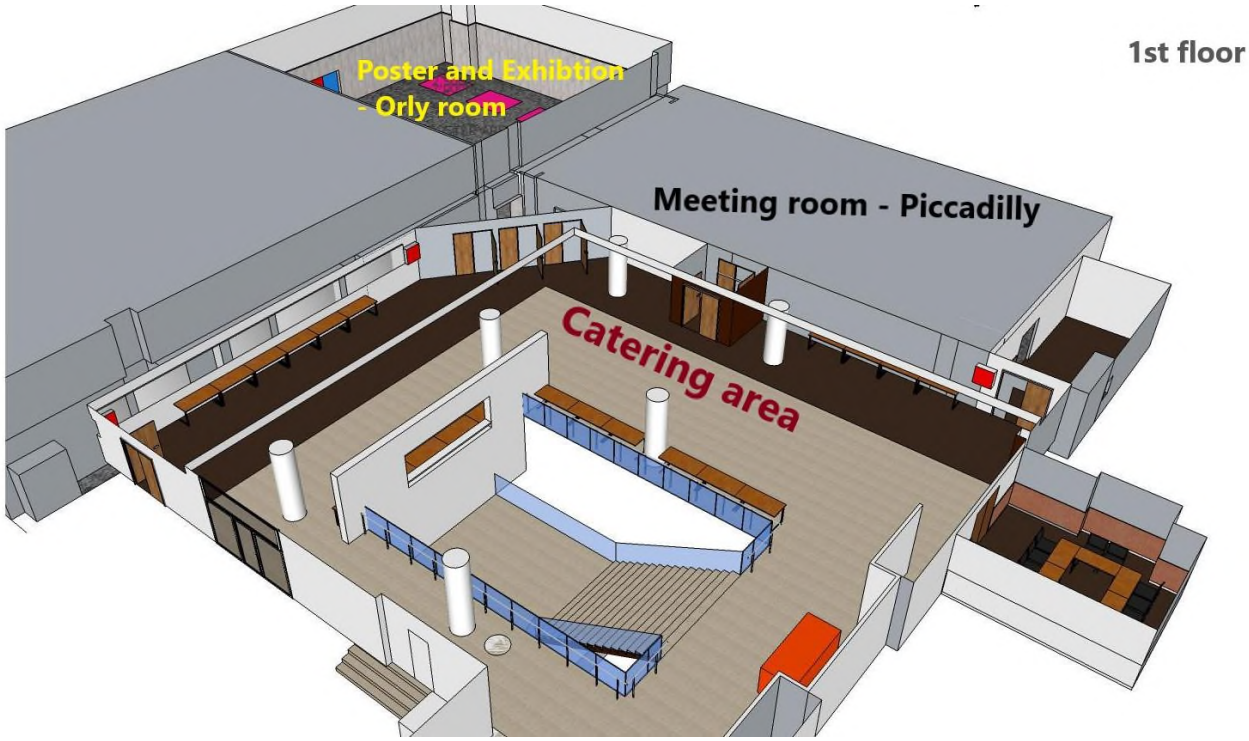
FLOOR PLAN



Workshop Room 1: Plenary Room – Half Piccadilly, 1st floor

Workshop Room 2: Room Kensington – Half Piccadilly, 1st floor

Workshop Room 3: Room Moscou, 1st floor

EAACI Allergy School on Food Allergy
Trends and novelties in food allergy
05-07 December 2019,
Paris, France

Scientific Programme

05 December, Thursday

12:00 - 14:00	Registration
14:00 - 14:15	**Welcome address** *Christoph Dupont, France | Rosan Meyer, France | Margitta Worm, Germany*
14:15 - 15:30	**Session I - Epidemiology and Diagnosis of Food Allergy** *Chairs: Guillaume Lezmi, France| Christoph Dupont, France*
14:15 - 14:45	Epidemiology of Food Allergy (including IgE and non-IgE and Allergic March) *Ronald van Ree, The Netherlands*
14:45 - 15:30	Pathophysiology and Diagnosis of IgE mediated food allergies *Margitta Worm, Germany*
15:30 - 16:00	**Coffee break**
16:00 - 17:30	**Session II - Pathophysiology of Eosinophilic Oesophagitis and non-IgE mediated food allergies** *Chairs: Yvan Vandenplas, Belgium | Rosan Meyer, France*

16:00 - 16:30 Pathophysiology and Diagnosis of Eosinophilic Oesophagitis
Antonella Cianferoni, USA

16:30 - 17:00 Pathophysiology and Diagnosis of Food Protein Induced Proctocolities and Enteropathy and Allergic Dysmotility Disorders
Christoph Dupont, Paris

17:00 - 17:30 Pathophysiology and Diagnosis of FPIES
Jean-Christoph Caubet, Switzerland

17:30 – 18:30 Oral Abstract Presentations
Chairs: Yvan Vandenplas, Belgium | Rosan Meyer, France

17:30 – 17:45 O01 - Discovery Of Novel Fish Allergens And Evaluation Of Immunological Cross-Reactivity – Implications For Improved Diagnostics And Management
Thimo Ruethers, Australia

17:45 – 18:00 O02 - Skin Prick To Prick Tests And Oral Food Challenges: Fishing For A Correlation
Joana Miranda, Portugal

18:00 – 18:15 O03 – Oral Viscous Mometasone is an Effective Treatment for Eosinophilic Esophagitis in Children
Elizabeth Hait, United States

18:15 – 18:30 O04 - Allergenic Food Consumption In Children In The UK
Latifa Rahman, United Kingdom

18:30 – 20:30 Welcome reception in NOVOTEL

06 December, Friday

09:00 - 10:45 Session III - Medical Management of Food Allergies
Chairs: Alberto Alvarez-Perea, Spain | Margitta Worm, Germany

09:00 - 09:30 Acute medical management of IgE mediated Food allergies
Guillaume Lezmi, France

09:30 - 10:00 Medical Management of Eosinophilic Oesophagitis
Antonella Cianferoni, USA

10:00 - 10:30 Medical Management of other Non-IgE mediated conditions
Yvan Vandenplas, Belgium

10:30 -10:45 O05 - Birch Pollen Allergic Patients With Oral Allergic Syndrome To Apple Show Tendency To Increase Basophil Sensitivity To Mal D 1 Exposure After Birch Pollination Season
Alla Litovkina, Russia

10:45 - 11:00	**Coffee break**
11:00 - 12:30	**Session IV – Workshops - Practical Diagnosis and Medical Management (in rotation)**
Plenary Room, Piccadilly	Topic 1: Diagnosis and management of IgE mediated allergies – practical interactive cases *Giovanni Battista Pajno, Italy*
Room Kensington	Topic 2: From diagnosis to medical management of EoE – practical interactive cases *Antonella Cianferoni, USA*
Room Moscou	Topic 3: Diagnosis of FPIES and other non-IgE mediated allergic conditions *Jean-Christoph Caubet, Switzerland* | *Yvan Vandenplas, Belgium*
11:00-11:25	**Workshop round 1**
11:25-11:30	Rotation break
11:30-11:55	**Workshop round 2**
11:55-12:00	Rotation break
12:00-12:25	**Workshop round 3**
12:30 - 14:00	**Lunch & Poster discussion Session**

Poster Walk 1: P01 – P06
Chair: Alberto Alvarez-Perea, Spain | Guillaume Lezmi, France

A16/P01 - Skin Prick Testing Protocol In The First Clinical Trial With VLP Peanut
Pieter-Jan De Kam, United Kingdom
A23/P02 - The Cross-Reactivity Of Monoclonal Antibodies Raised Against Atlantic Cod Allergen Gad M 1 With Other Recombinant Fish Allergens
Aiste Imbrasaite, Lithuania
A32/P03 - Seed Storage Proteins From Flaxseed Are Food Allergens Triggering Severe Symptoms
Cristina Bueno-Díaz, Spain
A34/P04 - Baseline Characteristics And Correlations Between Dysphagia Frequency And Intensity And Disease Activity In Eosinophilic Esophagitis Patients In The Phase 2 Dupilumab Trial
Leda Mannent, France
A35/P05 - CD4+ T-Cell Responses To The Minor Allergen Phl P 12 In Food Allergic Spanish Patients IgE-Sensitized To Profilins
Niels Peter Hell Knudsen, Denmark
A09/P06 - Relation Between Bronchial Asthma And Parasitic Infection In Egyptian Children
Youssef B Habib, Egypt

Poster Walk 2: P07 – P12
Chair: Montserrat Fernandez-Riva, Spain | Imke Reese from Germany

A42/P07 - Peanut and Tree Nut Allergy – Characterization of an Allergology Department Population
Ana Palhinha, Portugal
A13/P08 - Deadly Exercise After A Meal
Jane Chi Yan Wong, China
A21/P09 – Characterization of Patients with Suspected Food Allergy in a high Complex Center of Cali, Colombia
Laura Del Mar Vásquez, Colombia
A24/P10 - Patients With Red Meat Allergy Show In Vitro Allergenicity Towards α-Gal Carrying Glycolipids
Neera Chakrapani, Luxemburg
A48/P11 - 'Squiding Around' Between The Differences Of Cephalopoda Allergy In Adults And Children
Afonso Caires, Portugal
A36/P12 - Patterns Of IgE Mediated Food Allergy Among Patients Attending Allergy And Immunology Unite, Faculty Of Medicine, Zagazig University, Egypt
Reham Mohamed El Mohamed El Shabrawy, Egypt

Poster Walk 3: P13 – P19
Chair: Berber Vlieg Boerstra, The Netherlands | Jean-Christophe Caubet, Switzerland

A18/P13 - The Frequency Of Skin Reactivity To Food Allergens In Different Age Groups Of Children With Asthma
Antonina Buratynska, Ukraine
A30/P14 - Allergen Capture From Allergenic Sources Using Human IgE-Antibodies: Method Showcase For Peanut Allergy
Julia Klueber, Luxemburg
A27/P15 – Sensitisation to Poultry Meat, Fish and Coconut in a multiple Food Allergy Case
Rita Brás, Portugal
A31/P16 - Anaphylaxis After Prick-To-Prick Test With Fish
Burcin Beken, Turkey
A37/P17 - Eosinophilic Esophagitis In A Pediatric Patient. Clínical, Diagnosis And Treatment Features
Paola Castro, Mexico
A19/P18 - Is It Food Allergy?
Fabiana Furci, Italy
A07/P19 - The Clinical Utility Of Basophil Activation Test In Diagnosis Of Hypersensitivity Due To Fermented Soybeans, Natto
Risa Aoki-Fukuda, Japan

14:00 - 15:45	**Session V - Dietary Management of Food Allergies** *Chairs: Yvan Vandenplas, Belgium | Giovanni Battista Pajno, Italy*
14:00 - 14:30	Dietary management of EoE *Berber Vlieg-Boerstra, The Netherlands*
14:30 - 15:00	The controversies in dietary management of non-IgE mediated allergies *Rosan Meyer, France*
15:00 - 15:30	Dietary eliminations in IgE mediated food allergies (including baked egg and milk and selective nut eating) *Imke Reese, Germany*
15:30 – 15:45	O06 - Food Protein-Induced Allergic Proctocolitis May Have Distinct Phenotypes *Ozge Soyer, Turkey*
15:45 - 16:00	**Coffee break**
16:00 - 17:30	**Session VI – Workshops - From paper to practice in food allergy (in rotation)**
Plenary Room	Topic 4: ABC to Food Challenges in IgE and non-IgE mediated Allergies *Berber Vlieg-Boerstra, The Netherlands*
Room	Topic 5: From formula to complementary feeding the food allergic child - practical interactive cases *Imke Reese, Germany*
Room 3	Topic 6: Maternal elimination and complexity of food allergy in the breastfed infant – practical interactive cases *Rosan Meyer, France*
16:00-16:25	**Workshop round 4**
16:25-16:30	Rotation break
16:30-16:55	**Workshop round 5**
16:55-17:00	Rotation break
17:00-17:30	**Workshop round 6**
18:30 - 22:00	**Dinner**

07 December, Saturday

09:00 - 12:30	**Session VII - The Future of Food Allergy** *Chairs: Rosan Meyer, France*
09:00 - 09:30	Prevention of Food Allergies *Kirsten Beyer, Germany*
09:30 - 10:00	Microbiome and Food Allergy- what does the future hold? *Liam O'Mahony, Ireland*
10:00 - 10:30	SCIT, SLIT and other novel treatments for food allergy *Maria Montserrat Fernández-Rivas, Spain*
10:30 - 11:00	**Coffee break**
11:00 - 11:30	When it is not food allergy – the medical perspective *Alberto Alvarez-Perea, Spain*
11:30 - 12:00	Dietary management when it is not food allergy *Imke Reese, Germany*
12:00 – 12:15	O07 - Fecal Calprotectin As A Biomarker Of IgE-Mediated Food Allergy And Disease Severity In Children With Atopic Dermatitis Without Gastrointestinal Symptoms *Marta Navratil, Croatia*
12:15 – 12:30	O08 – Component-Resolved Diagnostics in Food Allergy: a Multicenter Retrospective Study *Enza D'Auria, Italy*
12:30 - 12:45	**Closing remarks** *Christoph Dupont, France | Rosan Meyer, France*

ABSTRACTS

Thursday, 06 December 2019
Oral Abstract Presentations

O01 - Discovery Of Novel Fish Allergens And Evaluation Of Immunological Cross-Reactivity – Implications For Improved Diagnostics And Management

Thimo Ruethers[1,2], Aya C Taki[1,2,3], Roni Nugraha[1,4], Sandip D Kamath[1,2], Shaymaviswanathan Karnaneedi[1,2], Truc T Cao[1], Thu T K Le[1], Martina Koeberl[5], Tanja Kalic[6], Nicholas A Williamson[3], Shuai Nie[3], Michael Leeming[3], Sam S Mehr[7,2,8], Dianne E Campbell[7,2,9], Andreas L Lopata[1,2]

1. James Cook University, Townsville, Australia
2. Centre for Food and Allergy Research, Melbourne, Australia
3. The University of Melbourne, Melbourne, Australia
4. Bogor Agricultural University, Bogor, Indonesia
5. National Measurement Institute, Melbourne, Australia
6. Medical University of Vienna, Vienna, Austria
7. Children's Hospital at Westmead, Sydney, Australia
8. Royal Children's Hospital, Melbourne, Australia
9. University of Sydney, Sydney, Australia

Background
Fish allergy is often a life-long disease with high frequencies of anaphylaxis. A large number of under-investigated fish species and a high variability in commercial fish extracts hamper diagnostics and management as we demonstrated previously. Furthermore, we investigated patient- and fish species-specific reactivity *in vivo* and *in vitro*, as well as the low allergenicity of cartilaginous fish. However, the comprehensive repertoire of fish allergens remains unknown. Salmon parvalbumin (PV), aldolase, and enolase are well investigated fish allergens and registered with the WHO/IUIS, while no *Pangasius*/catfish allergens were described previously. We therefore aimed to identify and quantify all IgE-reactive proteins in the highly farmed freshwater catfish and compare to salmon.

Materials and methods
The presumably world's largest cohort of clinical confirmed paediatric fish-allergic patients was recruited (*n*=77). Patients' *in vivo* reactivity to salmon and catfish was assessed by skin prick testing. Raw and heated protein extracts were evaluated for their comprehensive allergen repertoire and patients' serum IgE reactivity by immunoblotting and advanced mass spectrometric analyses.

Results
Catfish outpaced salmon in both *in vivo* and *in vitro* reactivity. The most IgE-reactive protein was PV (57%), followed by triosephosphate isomerase (TPI; 40%) in raw and tropomyosin (TM; 32%) in heated extracts. In addition to five documented allergens, six yet

unidentified proteins showed reactivity with at least five patients and were registered with the WHO/IUIS including glyceraldehyde-3-phosphate dehydrogenase, creatine kinase, glucose-6-phosphate isomerase, glycogen phosphorylase, pyruvate kinase, and TPI. Importantly, IgE only recognised TM in heated extracts and catfish exhibited two TM isoforms with significantly differing IgE reactivity (32% vs 6%). All extracts contained only small amounts of collagen.

Conclusion
Further research is needed to clarify the clinical relevance and cross-reactivity of the newly identified IgE-reactive proteins. A better understanding of the comprehensive fish allergen repertoire is crucial for the development of species-specific and component-resolved diagnostics (CRD), important for improved clinical management. We demonstrate for the first time IgE reactivity to fish TM and TPI in a large patient cohort. Potential cross-reactivity with the corresponding shellfish allergens should be further investigated. Catfish and salmon PV, TM and TPI should be considered for CRD.

O02 - Skin Prick To Prick Tests And Oral Food Challenges: Fishing For A Correlation

Joana Miranda, Afonso Caires, Ana Margarida Mesquita, José Luís Plácido, Alice Coimbra

Centro Hospitalar Universitário São João, Porto, Portugal

Background
Fish is one of the big 8 food allergens and a major food staple in Portugal. Skin tests are a complementary diagnostic aid but oral food challenges (OFC) are the gold standard.

Materials and methods
A medical records review of adults who underwent OFC with fish who were referred to our department with suspected fish allergy between 2012 and 2019. The outcome of the OFC, skin prick to prick tests (SPPT) results, clinical manifestations and presence of atopy were analysed.
Statistical analysis was performed using IBM® SPSS® Statistics version 19.
SPPTs results were divided as negative to both raw and boiled (-R-B); positive to raw and negative to boiled (+R-B); negative to raw and positive to boiled (-R+B); positive to both raw and boiled (+R+B); negative to boiled (-B) and positive to boiled fish (+B).

Results
A total of 38 patients were included. Four patients were excluded due to incomplete data. The remaining 34 patients had an average age of 42 ±17 years and 74% were women. With respect to atopic diseases, 50% had allergic rhinitis, 24% asthma, 12% dermatitis, 21% allergy to other foods and 3% drug allergy.
The clinical manifestations of the culprit reactions were anaphylaxis in 43%.
A total of 90 OFCs were performed and SPPT with the respective fish was performed in 51. Results of the SPPTS with the respective fish are displayed in Table I. A statistically significant difference between SPPT results and OFC outcome was not found (Table II). Considering the SPPT performed with boiled fish, the negative predictive value (NPV) and

the positive predictive value (PPV) were 47% and 94%, respectively. Specificity was 81% and sensitivity was 78%. Taking into account the SPPTs performed with raw fish, the NPV and the PPV were 57% and 100%, respectively. Specificity was 82% and sensitivity was 100%.

Conclusion

A correlation between SPPT results and OFC outcomes was not found. In this group, PPV, NPV, specificity and sensitivity were slightly higher in the SPPT performed with raw fish. This study reinforces the importance of OFC as the diagnostic gold standard for food allergy.

Table I: Distribution of skin prick to prick tests (SPPTs) results by oral food challenge (OFC) outcome.

OFCs	SPPTs	
POSITIVE	-R-B	11%
	+R-B	0%
	-R+B	0%
	+R+B	78%
(9)	-B	11% (canned tuna)
NEGATIVE	-R-B	64%
	+R-B	5%
	-R+B	2%
	+R+B	10%
	-B	12% (canned tuna)
(42)	+B	7% (canned tuna)

Table II: Chi-square test statistics.

Skin prick to prick tests						
	+R+B	+R-B	-B	-R+B	-R-B	+B
Chi-Square	1.333	0.333	2.667	Chi-Square test cannot be performed	Chi-Square test cannot be performed	Chi-Square test cannot be performed
df	1	1	1			
p-value	0.248	0.564	0.102			

O03 - ORAL VISCOUS MOMETASONE IS AN EFFECTIVE TREATMENT FOR EOSINOPHILIC ESOPHAGITIS IN CHILDREN.

Elizabeth Hait, Erin Syverson, Douglas Mcdonald, **Eitan Rubinstein**, Jeffrey Goldsmith, Peter Ngo, Paul Mitchell, John Lee

Boston Children's Hospital, Harvard Medical School, Boston, United States

Background

Children with eosinophilic esophagitis (EoE) are often treated with chronic oral topical steroids. Mometasone has low systemic bioavailability, yet high binding affinity for the glucocorticoid receptor making it ideal for long term therapy.

Materials and methods
Boston Children's Hospital IRB approved retrospective analysis of histologic and endoscopic findings in children with EoE treated with viscous mometasone compounded to 750mcg/5mL with methylcellulose. Response to therapy was determined histologically by the number of eosinophils per high power field (eos/HPF). Patients were classified as responders (0-15 eos/HPF), partial responders (16-25 eos/HPF), and nonresponders(>25 eos/HPF). The Eosinophilic Esophagitis Endoscopic Reference Score (EREFS) was also used to compare data.

Results
Thirty-four patients were started mometasone for EoE at Boston Children's Hospital between April 2016 and June 2018. Twenty-six (76%) patients experienced histologic response to mometasone and 23 (68%) achieved remission, with median change in peak eos/HPF of −50 (range, −280 to 82; $P < .001$). A decrease in peak eos/HPF was seen in all but 1 patient, who previously had poor response to OVB and also had IgE-mediated food allergies, asthma, and environmental allergies. Eighteen patients had experienced prior steroid failure. Thirteen (72%) demonstrated histologic response, and 10 (56%) achieved remission after mometasone treatment, exhibiting a median change of −46 eos/HPF (range, −280 to 82; $P = .0006$. Sixteen patients were steroid-naive, 13 (81%) of whom achieved histologic response and remission after treatment with mometasone, with median change of −54 eos/HPF (range, −150 to −17; $P < .0001$). Although response and remission rates were higher for steroid-naive patients compared with those with prior steroid failure, these were not statistically significant ($P = .54$ and $P = .11$, respectively; Pearson χ^2 test).

Conclusion
This study is the first to show the effectiveness of swallowed viscous mometasone for treatment of EoE, demonstrating a 76% response rate and 68% remission rate in our population.

O04 - Allergenic Food Consumption In Children In The UK

Latifa Rahman, Kirsty Logan, George Du Toit, Andreina Maria Marques Mejias, Gideon Lack

Paediatric Allergy Research Group, Department of Women and Children's Health, School of Life Course Sciences, King's College London, London, United Kingdom

Background
Successful preventative strategies, demonstrated in the LEAP and EAT Studies, have resulted in changes to public health recommendations on the introduction of allergenic foods in the US, Canada, Australia and UK (1). Although there is a move towards following this advice and a cultural shift towards acceptance of allergenic food consumption in children, there is a lack of information on levels of consumption of these foods in the general population of school-age children in the UK. It is key to know about baseline allergenic food consumption if future public health strategies are to encourage consumption.

Materials and methods

Between 2009-2015, 1303 breastfed infants from a general healthy population across England, Wales and Scotland, were enrolled and followed up within the EAT Study. Infants were randomised to either avoid or consume 6 allergenic foods from 4 months of age (peanut, egg, milk, sesame, cod fish and wheat) to assess the impact of early introduction on development of food allergy (1). The EAT-On Study follows the original EAT cohort at 7-10 years of age. Information about the frequency of consumption of allergenic foods is collected at face-to-face clinical visits. Frequent consumption of a food is defined as the consumption of a 3g protein portion at least three times in the last 6 months.

Results
The EAT-On Study has, to date, enrolled 446 children (52% from the original early introduction group and 48% from the original allergen avoidance group). Many of the common allergenic foods are not being consumed at 7-10 years of age. Proportions of infrequent consumption are 39% for sesame, 35% for peanut, 18% for cooked egg, 10% for cod fish, 5% for fresh milk and 1% for wheat. Some children in the EAT-On Study avoid one or many allergenic foods due to allergy to that food or other foods but many are infrequently consuming despite no allergy concerns. Of those infrequently consuming the allergenic foods, reasons of dislike or family preference not to consume were given by 55%, 36%, 17%, 10% and 2% for sesame, peanut, cooked egg, cod fish and fresh milk respectively.

Conclusion
The EAT-On study presents the opportunity to explore the frequency of consumption of allergenic foods in the UK to inform changes to allergenic food consumption recommendations. Highest rates of infrequent consumption in primary school aged children are for sesame and peanut, 2 of the most common allergens in the US and named on the extended list of common allergens in the European Community legislation (2)

Friday, 06 December 2019
Oral Abstract Presentations

O05 - Birch Pollen Allergic Patients With Oral Allergic Syndrome To Apple Show Tendency To Increase Basophil Sensitivity To Mal D 1 Exposure After Birch Pollination Season

Alla Litovkina[1], Alexandra Nikonova[1], Evgenii Smolnikov[1], Yury Zhernov[1], Olga Elisyutina[1], Elena Fedenko[1], Musa Khaitov[1], Rudolf Valenta[2]

1. NRC Institute of Immunology FMBA of Russia, Moscow, Russia
2. Medical University of Vienna, Department of Pathophysiology, Vienna, Austria

Background
A detailed characterization of human immune cells is needed to better understand mechanisms associated with allergen capture following oral exposure. Our study aimed to evaluate the predictive value of the basophil activation test (BAT) in pollen-associated food allergy.

Materials and methods
27 patients from 12 to 59 years [Me = 30; ±σ=11,12], 17 males and 10 females**,** were involved in the study and formed 2 groups. Group 1: 13 patients sensitized to birch pollen with oral allergic syndrome (OAS) to apple. Group 2: 14 patients sensitized to birch pollen without OAS to apple. BAT was determined in blood samples with BeckmanCoulter Allergenicity Kit with 2 purified recombinant allergens (Bet v 1 and Mal d 1, MERC) in 3 concentrations each (1 ng/ml, 10 ng/ml, 100 ng/ml) before and after birch pollination season. Flow cytometry analysis was performed with BD FACS Canto II.

Results
Patients from group 1 showed higher basophil sensitivity to Bet v 1 and Mal d 1 than patients from group 2 before and after birch pollination season. Before the season basophils were much more sensitive to Bet v 1 than to the cross-reactive Mal d 1. After the season basophils became more sensitive to Mal d 1 in both groups.

Conclusion
Birch pollen allergic patients with OAS showed significantly higher basophil sensitivity to Bet v 1 and the cross-reactive Mal d 1 allergen than patients suffering only from respiratory birch pollen allergy without OAS before and after pollen season. There was no significant difference in sensitivity of basophils to Bet v 1 exposure before and after the season. There is tendency to increased in sensitivity of basophils to Mal d 1 exposure after the pollination season.

This study was supported by a Megagrant of the Government of the Russian Federation, grant number 14.W03.31.0024.

O06 - Food Protein-Induced Allergic Proctocolitis May Have Distinct Phenotypes

Pinar Gur Cetinkaya[1], Melike Kahveci[1], Betul Karaatmaca[1], Saliha Esenboga[1], Umit Murat Sahiner[1], Bulent Enis Sekerel[1], **Ozge Soyer**[2]

1. Hacettepe University Faculty of Medicine, Department of Pediatric Allergy, Ankara, Turkey
2. Hacettepe University Faculty of Medicine Department of Pediatric Allergy, Ankara, Turkey

Background
Food protein-induced allergic proctocolitis (FPIAP) is a non-immunoglobulin E (IgE)-mediated food allergy presents with bloody, mucoid, frothy stool in infants. Although IgE-mediated allergy/sensitization to offending foods have been previously described in other non-IgE-mediated food allergies, it has not been well-defined in FPIAP. **Aim/Objectives:** To identify IgE-mediated allergy/sensitization to offending foods in FPIAP.

Materials and methods
The study population (n=208) were grouped into five according to specific immunoglobulin E (sIgE), skin prick test (SPT) results, and clinical features. Patients who had no IgE-mediated food allergy/sensitization were in *Group I* (n=156), IgE sensitization to offending foods in *Group II* (n=17), IgE sensitization with other than offending foods in *Group III* (n=4), shifted to IgE-mediated allergy to offending foods in *Group IV* (n=7), and mixed type

food allergy in *Group V* (n=24).

Results
The median age at onset of the symptoms and tolerance development was 2 months and 12 months, respectively. The median age at tolerance development of Group IV [16 months (IQR; 15.0-16.0)] was significantly later compared to *Group II* [11.0 months (IQR; 9.5-12.0 months), *p<0.001*] and *Group I* [11 months (IQR; 10-13 months), *p=0.001*]. Of the patients who underwent sIgE/SPT (n=177), 24 (13.5%) had positive IgE to offending foods. Among them, 17 (9.6%) had IgE sensitization, 7 (3.9%) shifted to IgE-mediated phenotype to FPIAP-induced foods. Although sIgE values were similar in *Group IV* and *II* (p=0.899), SPTs were statistically higher in *Group IV* compared to *Group II (p<0.001)*.

Conclusion
To our knowledge, this is the first report demonstrating the transition to IgE-mediated food allergy in FPIAP. These findings emphasize that IgE sensitization and shift to IgE-mediated allergy to culprit foods in non-IgE-mediated food allergies is not very uncommon, and transition to IgE-mediated allergy/sensitization were not only encountered in FPIES

Friday, 06 December 2019
Poster Discussion Session
12:30 – 14:00

P01 - Poster

Skin Prick Testing Protocol In The First Clinical Trial With VLP Peanut

Pieter-Jan De Kam[1], Kemi Oluwayi[1], Chris Jones[1], Murray A Skinner[1], Matthew D Heath[1], Matthias F Kramer[2]

1. Allergy Therapeutics, Worthing, United Kingdom
2. Bencard Allergie, Munich, Germany

Background
Virus-like particles (VLPs) are an innovative and highly effective vaccine platform that has been proven to induce allergen-specific protective immunity. VLP Peanut is a novel VLP coupled to recombinant Ara h2. It is being developed to provide long term protection against allergic reactions provoked by accidental peanut exposure via induction of protective immunity and will be administered subcutaneously. VLP Peanut protects against anaphylaxis in in-vivo studies in mice. The current hypothesis is that administration of the VLP Peanut will demonstrate a reduced level of allergic reactogenicity.

Materials and methods
This first in human study will evaluate skin reactivity in subjects with peanut allergy following administration of VLP Peanut via skin prick test.

Results
Skin testing will be conducted on the same day. Subjects will receive titrated triplicate skin

applications of different concentrations of VLP Peanut (ranging from 1 µg/mL to 1000 µg/mL) applied approximately at the same time, after confirmation that the criteria for negative and positive control are fulfilled based on triplicate tests applied to assigned locations on the arms.

Conclusion
This study will be the "first in human study" of VLP Peanut to provide initial evidence that VLP Peanut is hypo-allergic using skin prick testing in patients with confirmed peanut allergy.

P02 - Poster

The Cross-Reactivity Of Monoclonal Antibodies Raised Against Atlantic Cod Allergen Gad M 1 With Other Recombinant Fish Allergens

Aiste Imbrasaite, Vytautas Rudokas, Gintautas Zvirblis, Aurelija Zvirbliene

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Background
Fish is an excellent source of nutrients, however ingestion or inhalation of fish allergen can trigger life-threatining reactions for atopic individuals. Gad m 1 is the major Atlantic cod allergen, abundant in the white muscle of the fish. Gad m 1 is small (10–12 kDa) and highly stable protein, know as parvalbumin, that shares high sequence similiarity with other fish parvalbumins (salmon, Baltic cod, carp parvalbumins). The generated monoclonal antibodies (MAbs) against a particular fish parvalbumin may represent a useful tool for fish allergy diagnostics. Therefore, it is important to investigate their cross-reactivity pattern with other fish allergens.

Materials and methods
Recombinant salmon parvalbumin (Sal s 1) and Baltic cod parvalbumin (Gad c 1), fused with maltose-binding protein (MBP), were expressed in *E.coli* and purified by affinity chromatography. The MAbs against Atlantic cod parvalbumin (Gad m 1) were generated by hybridoma technology. The cross-reactivity of the MAbs with fish allergens Sal s 1 and Gad c 1 was analyzed by enzyme-linked immunosorbent assay (ELISA) and Western blot.

Results
In total, four MAbs (7B2, 2C1, 18H3 and 16B3) against natural Gad m 1 were generated. Their cross-reactivity with recombinant Sal s 1-MBP and Gad c 1-MBP was analysed. MAbs 18H3 and 16B3 reacted only with Gad m 1 protein. The MAbs 7B2 and 2C1 were reactive with both Gad m 1 and Gad c 1-MBP. None of the MAbs reacted with Sal s 1-MBP protein. All antibodies were shown to recognise linear epitopes of target allergens by Western blot.

Conclusion
This study provides new data on the specificity of MAbs against Atlantic cod parvalbumin (Gad m 1) that may serve as a tool for fish allergen characterization and fish allergy diagnostics. In particular, these MAbs could be applied for the determination of allergenic

components in fish extracts. This study indicates that fish allergens Gad m 1 and Gad c 1 share common epitopes that are recognized by antibodies raised against Gad m 1.

P03 - Poster

Seed Storage Proteins From Flaxseed Are Food Allergens Triggering Severe Symptoms

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Background
Due to its health benefits, flaxseed consumption has become popular in recent years and, consequently, several cases of sensitization to this seed have been reported. Even though seed storage proteins from flaxseed have previously been described, little is known about their role both in allergy and in triggering severe symptoms such as anaphylaxis.
The aim of this study was to evaluate IgE-mediated sensitivity in five patients with a clinical history of severe symptoms, as anaphylaxis or OAS, after eating flaxseed and identify and characterize allergens involved.

Materials and methods
The allergens from flaxseed extract were purified using chromatographic techniques and characterized by electrophoretic mobilities. The peptide sequence was determined by mass spectrometry (MALDI-TOF). Immunoassays were performed using allergic patient' sera.

Results
Four out of five patients recognized a low-molecular-mass protein (around 14 kDa) by immunoblotting of the flaxseed extract, and only two patients recognized a protein of about 50 kDa. The low-molecular-mass protein was isolated using Sephadex G-50 gel filtration and reverse-phase HPLC. This protein was identified as a flaxseed 2S albumin -named *conlinin*- using MALDI-TOF. Conlinin has a molecular mass of 12 kDa and two polypeptide chains of 9 and 3 kDa, linked by a disulfide bounds as revealed by reducing conditions in SDS-PAGE. Purified protein was recognized by IgE from the four allergic patients in immunoblotting and ELISA, but not in vitro cross-reactivity was observed with other foods. On the other hand, inhibition immunoassays revealed cross-reactivity with mustard seed across flaxseed 11S globulin.

Conclusion
Seed storage proteins from flaxseed are involved in food allergy reactions. Isolated 2S albumin showed similar structural characteristics than other proteins described from the

same family. Nevertheless, even though most of the patients presented specific IgE against conlinin, inhibition assays revealed that 11S globulin was the one involved in cross-reactivity with another food sources.

P04 - Poster

Baseline Characteristics And Correlations Between Dysphagia Frequency And Intensity And Disease Activity In Eosinophilic Esophagitis Patients In The Phase 2 Dupilumab Trial

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Background

Eosinophilic esophagitis (EoE) is a chronic type 2 immune-mediated disease. Dupilumab (DPL), a fully human monoclonal antibody, blocks the shared receptor component for IL-4/IL-13, key drivers of type 2 inflammation in multiple diseases. In a double-blind, placebo (PBO)-controlled phase 2 study (NCT02379052), adults with active EoE were randomized (1:1) to receive 12 weeks of subcutaneous DPL 300mg weekly (qw) or PBO. DPL significantly improved dysphagia and histological and endoscopic measures of disease with an acceptable safety profile. The primary endpoint was the Straumann Dysphagia Instrument (SDI) patient-reported outcome score, which assesses dysphagia frequency and intensity. This analysis reports patient baseline (BL) characteristics and assesses correlations between BL dysphagia and objective anatomical and histological outcomes.

Materials and methods

Correlations were assessed using Pearson's correlation coefficient (*r*) of SDI total score (recall period of 7 days), frequency, intensity, and number of episodes (between screening and BL) with objective measures of disease activity (EoE Endoscopic Reference Scoring system [EREFS], peak esophageal intraepithelial eosinophil count, and EoE Collins Histological Score System [HSS] total grade and stage scores [excluding lamina propria fibrosis]) at BL.

Results

The study enrolled 47 patients with BL SDI score 5–8 (total scale 0–9; frequency 0–4; intensity 0–5). BL characteristics were balanced between treatment groups (**Table 1**). The overall population had a mean SDI total score 6.4, frequency score 3, intensity score 3.2, EREFS total score 4.1, peak eosinophil count 101.6 eos/hpf and total HSS stage and grade scores 27.6 and 28.0, respectively. Significant, moderate correlations were observed between dysphagia frequency and EREFS score ($P = 0.04$), and dysphagia intensity and HSS grade score ($P = 0.03$) in the PBO group at BL; no other significant correlations were observed (**Table 2**).

Conclusion

In the phase 2 dupilumab study, EoE patients had high BL severity of dysphagia and eosinophilia, prevalence of atopy, and prior esophageal dilation. Despite small sample size of this study, some correlations were found between dysphagia and objective measures of disease activity at BL, perhaps due to the high severity in this cohort. Further analyses in a larger population with broader disease activity may better identify relationships between clinical symptoms, endoscopic and histological features.

Summary of baseline disease characteristics

Baseline disease characteristics	**Placebo qw (n = 24)**	**Dupilumab 300 mg qw (n = 23)**	**Total (N = 47)**
Age at EoE onset[a], n (%)			
0–18 years old	4 (16.7)	3 (13.0)	7 (14.9)
19–24 years old	5 (20.8)	5 (21.7)	10 (21.3)
25–50 years old	13 (54.2)	15 (65.2)	28 (59.6)
> 50 years old	2 (8.3)	0	2 (4.3)
Duration of EoE (years), mean (SD)	5.0 (3.33)	3.6 (3.74)	4.3 (3.56)
Treated with high-dose PPI's, n (%)	24 (100)	23 (100)	47 (100)
≥1 prior use of a corticosteroid for EoE[b], n (%)	3 (12.5)	7 (30.4)	10 (21.3)
Personal history of allergic disease, n (%)	24 (100)	23 (100)	47 (100)
Weekly SDI PRO score (0−9), mean (SD)	6.4 (1.01)	6.4 (1.04)	6.4 (1.01)
Frequency of Dysphagia (0−4), mean (SD)	3 (0.9)	3 (0.9)	3 (0.9)
Intensity of Dysphagia events (0−5), mean (SD)	3.3 (0.5)	3.2 (0.4)	3.2 (0.4)
Number of Dysphagia Episodes between Screening and Baseline, mean (SD)	40 (56.2)	45 (89.9)	42 (73.9)
Peak Eosinophils Count (eos/hpf), mean (SD)	101.1 (57.12)	102.1 (53.46)	101.6 (54.76)
EREFS Total Score (0−8)[c], mean (SD)	4.3 (1.46)	3.9 (1.87)	4.1 (1.67)
Total Collins Histology Stage Score (0−63)[d], mean (SD)	27.4 (6.46)	27.9 (6.05)	27.6 (6.19)
Total Collins Histology Grade Score (0−63)[d], mean (SD)	27.6 (8.38)	28.5 (7.98)	28.0 (8.10)

Esophageal Distensibility Plateau (mm), mean (SD)	17.60 (2.879)	18.66 (3.799)	18.12 (3.351)
Baseline Blood Peripheral EOS (Giga/L), mean (SD)	0.43 (0.285)	0.31 (0.177)	0.37 (0.242)
Baseline Serum Total Immunoglobulin E (IgE) (IU/mL), mean (SD)	486.21 (900.696)	217.78 (288.804)	358.10 (687.205)
Weekly Reported EEsAI PRO score (0−100)[e], mean (SD)	62.2 (16.45)	62.0 (18.36)	62.1 (17.25)
Any esophageal dilations?, n (%)	10 (41.7)	11 (47.8)	21 (44.7)
Number of Esophageal Dilations, mean (SD)	3.9 (3.31)	5.7 (8.03)	4.9 (6.17)

EOS, eosinophils; qw, once weekly; PRO, patient reported outcome.abased on diagnosis [b]adjudicated. [c]EREFS was used to measure the endoscopically identified EoE esophageal mucosal inflammatory and remodeling features; total score range 0−8; higher scores indicate greater impairment. [d]Collins HSS histology stage and grade scores measure eosinophil density, basal zone hyperplasia, eosinophil abscesses, eosinophil surface layering, surface epithelial alteration, dyskeratotic epithelial cells, and dilated intercellular spaces; total score range 0−63. [e]EEsAI PRO is a 5-item measure of dysphagia; total score range 0−100; higher scores indicate worse symptoms. EEsAI, Eosinophilic Esophagitis Symptom Activity Index; PPI, proton-pump inhibitor; SD, standard deviation.

Correlation analyses between dysphagia and objective anatomical and histological outcomes at baseline in patients with active EoE

	Placebo qw (n = 24)			**Dupilumab 300 mg qw (n = 23)**			**Total (N = 47)**		
Baseline disease characteristics	**N**	***r* (95% CI)**	***P* [a]**	**N**	***r* (95% CI)**	***P* [a]**	**N**	***r* (95% CI)**	***P* [a]**
SDI total score vs EREFS Total Score Inc. Strictures[b]	24	0.3515 (-0.0681, 0.6568)	0.0925	23	-0.1338 (-0.5152, 0.2974)	0.5472	47	0.0767 (-0.2160, 0.3553)	0.6103
Dysphagia frequency vs EREFS Total Score Inc. Strictures[b]	24	0.4263 (0.0183, 0.7033)	0.0369	23	-0.2598 (-0.6032, 0.1764)	0.2345	47	0.0459 (-0.2450, 0.3283)	0.7606
Dysphagia intensity vs EREFS Total Score Inc. Strictures[b]	24	-0.0853 (-0.4710, 0.3311)	0.6953	23	0.2213 (-0.2148, 0.5772)	0.3141	47	0.0860 (-0.2071, 0.3634)	0.5674
Dysphagia episodes vs EREFS Total Score Inc. Strictures[b]	24	0.0915 (-0.3256, 0.4758)	0.6740	23	-0.2116 (-0.5705, 0.2244)	0.3367	47	-0.1123 (-0.3859, 0.1819)	0.4546
SDI total score vs HSS stage (excluding lamina propria)[c]	23	0.1283 (-0.3024, 0.5112)	0.5639	23	-0.0630 (-0.4621, 0.3597)	0.7777	46	0.0336 (-0.2596, 0.3204)	0.8256
Dysphagia frequency vs HSS stage (excluding lamina propria)[c]	23	0.3431 (-0.0883, 0.6573)	0.1098	23	-0.2280 (-0.5818, 0.2083)	0.2993	46	0.0784 (-0.2177, 0.3597)	0.6065
Dysphagia intensity vs HSS stage (excluding lamina propria)[c]	23	-0.4000 (-0.6926, 0.0237)	0.0581	23	0.3398 (-0.0918, 0.6652)	0.1135	46	-0.0827 (-0.3634, 0.2136)	0.5868
Dysphagia episodes vs HSS stage (excluding lamina propria)[c]	23	-0.2698 (-0.6099, 0.1662)	0.2160	23	-0.2444 (-0.5929, 0.1920)	0.2646	46	-0.2450 (-0.4977, 0.0515)	0.1010

SDI total score vs HSS grade (excluding lamina propria)[c]	23	0.1526 (-0.2802, 0.5289)	0.4916	23	-0.0263 (-0.4333, 0.3907)	0.9065	46	0.0632 (-0.2320, 0.3465)	0.6781
Dysphagia frequency vs HSS grade (excluding lamina propria)[c]	23	0.3961 (-0.0282, 0.6902)	0.0609	23	-0.1309 (-0.5131, 0.3000)	0.5560	46	0.1506 (-0.1477, 0.4211)	0.3196
Dysphagia intensity vs HSS grade (excluding lamina propria)[c]	23	-0.4526 (-0.7240, -0.0394)	0.0291	23	0.2217 (-0.2145, 0.5775)	0.3134	46	-0.1620 (-0.4305, 0.1364)	0.2839
Dysphagia episodes vs HSS grade (excluding lamina propria)[c]	23	-0.2541 (-0.5995, 0.1822)	0.2453	23	-0.2192 (-0.5758, 0.2169)	0.3190	46	-0.2240 (-0.4810, 0.0734)	0.1351
SDI total score vs peak eosinophils	24	0.1817 (-0.2430, 0.5423)	0.3999	23	-0.0658 (-0.4642, 0.3573)	0.7681	47	0.0635 (-0.2285, 0.3438)	0.6731
Dysphagia frequency vs peak eosinophils	24	0.2506 (-0.1752, 0.5904)	0.2406	23	-0.0303 (-0.4365, 0.3873)	0.8923	47	0.1232 (-0.1712, 0.3953)	0.4112
Dysphagia intensity vs peak eosinophils	24	-0.1047 (-0.4858, 0.3139)	0.6301	23	-0.1086 (-0.4967, 0.3200)	0.6257	47	-0.1065 (-0.3810, 0.1875)	0.4783
Dysphagia episodes vs peak eosinophils	24	-0.1178 (-0.4956, 0.3022)	0.5877	23	-0.0986 (-0.4892, 0.3289)	0.6581	47	-0.1025 (-0.3775, 0.1914)	0.4952

[a]Inference results are based on Pearson correlation, where both variables as considered as continuous to measure linear relationship. *r* = Pearson's correlation coefficient. . [b]EREFS was used to measure the endoscopically identified EoE esophageal mucosal inflammatory and remodeling features; total score range 0−8; higher scores indicate greater impairment. [c]Collins HSS histology stage and grade scores measure eosinophil density, basal zone hyperplasia, eosinophil abscesses, eosinophil surface layering, surface epithelial alteration, dyskeratotic epithelial cells, and dilated intercellular spaces; total score range 0−63.

P05 - Poster

CD4+ T-Cell Responses To The Minor Allergen Phl P 12 In Food Allergic Spanish Patients IgE-Sensitized To Profilins

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Background
Up to 60% of food allergies are linked with inhalant allergy and cross-reactive inhalant allergen sensitization can result in diverse patterns of allergic reactions. Profilins are mild food and dominant panallergens responsible for many cross-reactions occurring between food and inhalant allergens. Sensitization to plant food profilins is often seen in patients with IgE against pollen profilins and is termed pollen food syndrome (PFS). Sensitization to profilins is usually caused by pollen inhalation, grass pollen being the dominant pollen sensitizer in southern Europe. In areas with higher grass pollen exposure, profilin allergy is linked to a more severe phenotype with patients suffering from severe profilin mediated food reactions. Little is known about the role of minor allergens in overall Tcell reactivity to a sensitizing source. The current study aimed to examine specific Tcell response to Phl p 12 in profilin-sensitized patients with PFS.

Materials and methods
The release of Phl p allergens from pollen was investigated by MS and IHC. Allergen specific CD4 Tcell lines were established through stimulation of PBMC's obtained from 26 Spanish grass allergic donors IgE sensitized to profilin with either recombinant Phl p 12 or natural purified Phl p 1. Tcell responses, epitope mapping and Tcell cross-reactivity to other clinically relevant plant profilins were measured *in-vitro.* Cross-reactivity was addressed *in-vivo* using two different mouse strains.

Results
Phl p 12 and Phl p 1 (a major allergen) are released from pollen simultaneously and in similar amounts. Both T-cell response frequency (17/26 donors) and strength were comparable. Alignment of the investigated profilin sequences from different plants shows that most potential Tcell epitopes had few mismatches to the corresponding Phl p 12 epitope, which explains the observed correlation between sequence homology and Tcell cross reactivity. Data from mice immunized with Phl p 12 showed that cross-reactivity to Bet v 2 was mediated by conserved epitopes, and further influenced by additional genetic factors, likely to be MHC II molecules.

Conclusion
The strength, prevalence and cross-reactivity of Tcell responses towards Phl p 12 is comparable to the major allergen Phl p 1, which supports the hypothesis that Tcells to Phl p 12 can play an important role in development of allergic symptoms, such as those associated with the PFS. Overall, the results support the hypothesis that Tcells play an important role in the development of allergic symptoms.

P06 - Oral

Relation Between Bronchial Asthma And Parasitic Infection In Egyptian Children

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Background
BACKGROUND: Among the many factors influencing the prevalence of asthma in developing countries from the tropics are geo-helminthic infections.

Materials and methods
PATIENTS AND METHODS: A cross-section, analytical study design was chosen to perform this research on 100 school aged children. All children were interviewed and examined clinically and laboratory.

Results
RESULTS: 86%of patients with bronchial asthma lived in urban areas, while 64% of patients with parasitic infestation lived in rural areas.Statistically significantly Negative correlations were found between blood level of IgE and FEV1% of predicted in patients with bronchial asthma as well as patients with parasitic infestation with r=-0.381, -0.325 at p=0.006, 0.021 respectively.Inverse relationship was found between blood level of IgE and FEV1/FVC% in patients with parasitic infestation with r= -0.358 with statistical significant difference at p=0.011.

Conclusion
CONCLUSIONS: Statistically significance higher values of IgE were found in patients with parasitic infestation compared to patients with bronchial asthma .It was noted that patients with combined bronchial asthma and parasitic infestation demonstrated statistically significance higher values of IgE which suggest a possible synergistic effect of two diseases

P07 - Poster

PEANUT AND TREE NUT ALLERGY - CHARACTERIZATION OF AN ALLERGOLOGY DEPARTMENT POPULATION

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Background
Objective: The aim of this study was to characterize the population with IgE-mediated food allergy (FA) to tree nuts and peanuts (TN/P).

Materials and methods
Retrospective analysis of the clinical records of patients of an Allergology Department, who performed TN/P-specific IgE (sIgE) between 2016 and 2018. The TN/A FA diagnosis was assumed in the presence of: a) a suggestive FA clinical history or positive oral provocation test (OPT) and b) positive sIgE and/or skin prick tests (SPT) for the suspected foods.

Statistical analysis was performed using SPSS program, with $p<0.05$ accepted as significant.

Results
We evaluated a total of 148 patients, of whom 36 were excluded (16-eosinophilic esophagitis, 14-incomplete data and 6-FA/sensitization excluded). Sensitization occurred in 112 patients, 13 of whom never ate TN/P and 15 had asymptomatic sensitization without allergy to any TN/P.
The remaining 84 patients were diagnosed with FA (3 with positive OPT), with a total of 129 reactions. Forty-nine patients had a reaction to 1 TN/P, 19 to 2, 10 to 3, 1 to 4, and 1 to 7. In 4 patients the implicated TN/P couldn't be identified.
Of the 129 reactions, 50% had mucocutaneous symptoms, 5% respiratory, 5% gastrointestinal, and 39% anaphylaxis. There was no statistically significant difference between sIgE level and the severity of symptoms (anaphylaxis versus isolated symptoms).
Of the 84 patients with FA, 36 reacted to walnut, 28 to peanuts, 16 to hazelnuts, 11 to almonds, 11 to cashews, 9 to pistachio seeds, 5 to sesame seeds, 5 to sunflower seeds and 4 to pine nuts. Of these, 45 patients tolerate at least 1 TN/P and in 39 tolerance is unknown (do not eat TN/P).
In 49 of 84 patients, sensitization to molecular allergens was evaluated. The sIgE levels of patients with confirmed FA vs those with asymptomatic sensitization to walnuts (4.03 vs 0.18) and peanuts (2.72 vs 1.07) revealed a statistically significant difference. In other TN/P, the number of patients is insufficient to draw conclusions.
There were 31 OPT: 3 positives and 28 negatives. Regarding negatives OPT, in 12 (43%) there was positive sIgE for the tested foods.

Conclusion
In our population, walnut was the most frequently involved TN/P FA, as described in the literature. When assessing TN/P FA it is important to quantify sIgE because higher levels were associated with FA. The positivity of sIgE does not exclude tolerance and therefore the OPT are mandatory in the diagnostic confirmation, especially if the clinical history is not clear.

P08 - Poster

Deadly Exercise After A Meal

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Background
To understand the burden and aetiology of anaphylaxis in Hong Kong, we performed a retrospective review of all anaphylaxis cases referred to our service since its establishment from May 2018 to August 2019.

Materials and methods
Review of almost 200 unique patients showed that "idiopathic" anaphylaxis consisted of 10% of all Immunology & Allergy referrals. Referrals for suspected drug or food allergies prior to consultation were excluded. Fewer than a third of patients had been prescribed an

adrenaline autoinjector prior to consultation.

The baseline demographics, clinical characteristics, investigation results and final diagnosis were analyzed. Cases of cofactor-induced anaphylaxis, especially wheat dependent exercise induced anaphylaxis (WDEIA) were compared with a United Kingdom (UK) cohort from Guy's and St. Thomas' NHS Foundation Trust in London.

Results
After allergological workup, the aetiologies of anaphylaxis were identified in 87% of patients, with the majority being co-factor induced anaphylaxis (67%) with WDEIA consisting of 59%. In comparison to the UK cohort, WDEIA patients in Hong Kong were more likely to present with urticaria (100% vs 77%, p=0.036) and cardiovascular manifestations (100% vs 70%, p=0.015). There was also a lower self-reported compliance to dietary avoidance (50% vs 87%, p=0.007), and nonsteroidal anti-inflammatory drugs were significantly more likely implicated as a co-factor (13% vs 0%, p=0.048).

Conclusion
These findings likely reflect the geographical differences in prescribing and referring practices, as well as patient adherence to avoidance advice. This highlights an alarming deficit in both physician and public education in Hong Kong, which necessitates urgent attention with further interventional and population-based studies in the near future.

P09 - Poster

CHARACTERIZATION OF PATIENTS WITH SUSPECTED FOOD ALLERGY IN A HIGH COMPLEX CENTER OF CALI, COLOMBIA

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Background
Food allergy affects between 2 and 10% of the population. Its diagnosis is made by clinical history and specific tests, being the oral provocation (OP) the confirmatory test. The objective of this study was to describe the clinical and epidemiological characteristics of patients with suspected food allergy treated at a high complexity center in Cali, Colombia

Materials and methods
Retrospective descriptive study. We included patients with suspected food allergy evaluated in the Allergology Service of Valle del Lili Foundation between January 2011 and December 2018, who were had performed one or more oral provocation as a confirmatory test. Demographic data, allergic history, clinical manifestations and studies before the provocation were analyzed, information that was obtained from the clinical history.

Results

176 patients were included. 122 (69.3%) were children. 89 (50.6%) were men. 112 (63.6%) had a personal history of allergic diseases, rhinoconjunctivitis being the most frequent in 72 patients (64.3 %). The clinical manifestations were cutaneous in 140 (66.4%), gastrointestinal in 56 (26.5%) and respiratory in 46 (21.8%). 51 (24.2%) presented anaphylaxis. A 126 (71.6%) were performed skin tests, of all 14 (11.1%) were positive to aeroallergens, 33 (26.2%) to foods and 63 (50%) to both. 98 (55.7%) underwent specific IgE, being positive in 63 of them (54.3%). A total of 211 OP, 72 (34.1%) with cow's milk, 57 (27%) with seafood, 33 (15.6%) with egg , 25 (11.8%) with fish , 8 (3.8%) with leg umes . All of them, only 12 (5.7%) were positive

Conclusion
The suspicion of food allergy was higher in children. The principal clinical manifestations were mostly skin. The food most frequently involved was cow's milk. The final demonstration of allergy was low.

P10 - Poster

Patients With Red Meat Allergy Show In Vitro Allergenicity Towards α-Gal Carrying Glycolipids

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Background
Red meat allergy is associated with the presence of IgE directed to the carbohydrate galactose-α-1,3-galactose. The sensitization is caused via tick bites and clinically reactive patients present a delayed onset of reaction upon consumption of mammalian meat. Glycolipids in general have a slower digestion and processing kinetics than glycoproteins, and therefore α-Gal carrying lipids might play a role in the delayed onset of reaction.

Materials and methods
Glycolipids were extracted from rabbit erythrocytes via chloroform/methanol extraction. Aqueous phase was collected (Folch partition) and vacuum dried. The presence of α-Gal epitope was confirmed on HPTLC plates by orcinol detection and immunostaining. Patients with a history of α-Gal allergy were recruited (n=16; sIgE a-Gal = 0,9 – 69 kU/L) to assess IgE-reactivity towards glycolipids. An optimized ELISA assay was used to determine IgE-reactivity of the extracted glycolipids and a commercially available α-Gal carrying protein (Human Serum Albumin; α-Gal HSA). In addition, the *in vitro* allergenicity of both

molecules was analysed in a basophil activation test.

Results
TLC immunostaining confirmed the presence of α-Gal bearing long and short chain carbohydrates in the extracted glycolipids. Both α-Gal carrying glycolipids as well as glycoproteins were recognized by IgE antibodies in the sera of red meat allergic patients. In addition, glycolipids were able to activate basophils from sensitized patients, although at a lower sensitivity than for α-Gal HSA. Maximal basophil reactivity was reached upon stimulation with 1 µg/ml glycolipids whereas maximal reactivity for α-Gal HSA was reached with 10 fold less glycoprotein.

Conclusion
Red meat allergic patients with IgE antibodies directed to α-Gal recognised glycolipids carrying the carbohydrate. Moreover, the molecules were able to activate basophils, thereby demonstrating the allergenic potential of glycolipids in the context of α-Gal allergy.

P11 - Poster

‘Squiding Around’ Between The Differences Of Cephalopoda Allergy In Adults And Children.

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Background
Food allergy to Cephalopoda has been reported both in adults and children and Portugal is one of the major consumers of seafood in Europe

Materials and methods
This study aimed to assess the differences between adults and children with suspected allergy to Cephalopoda. Medical records of patients who underwent an oral food challenge (OFC) with cooked Cephalopoda between 2012 and 2019 were reviewed. Data collected included clinical manifestations, presence of atopy, skin prick tests (SPT) to cephalopods, skin prick-prick tests (SPPT) to octopus and/or squid (raw and boiled), total and specific IgE (sIgE), and OFC outcome.

Results
Thirty patients were included, 17 (57%) children (<18 years) and 13 adults (43%), with a female predominance in both groups.
All underwent an OFC with at least one culprit: octopus and/or two different species of squid. Due to fear of patient/parent perceived reactivity to fish allergy, 7 (41%) of children and 3 (23%) of adults were avoiding cephalopod ingestion.
Majority were atopic; 16 (94%) of the children and 7 (54%) of the adults had at least one atopic disease, allergic rhinitis, atopic dermatitis and asthma. Anaphylaxis was the clinical manifestation in 20% of the suspected cases in both children and adults.

The median total IgE was approximately 3 times higher in children than in adults. Octopus sIgE was positive (>0.35 KU/L) in 18% of the children and in 66% of the adults.
SPT with commercial extracts for octopus and squid were negative in all the children and positive in 56% of the adults that had performed SPT.
The SPPT were positive in 23% of the children (67% for both octopus and squid and 33% only for squid) and in 56% of the adults (60% for both squid and octopus, 20% only for squid and 20% only octopus).
Only 1 child and 2 adults had positive OFC; details are in table 1. The OFC were negative in 16 children (94%) and 11 adults (85%). In group with negative OFC, sIgE was positive in 30% of the children and in 62% of the adults, SPT were positive in 62% of the adults and none of the children; and SPPT were positive in 25% of the children and 50% of the adults.

Conclusion
Almost all children were atopic while only half of the adults were. SPPT were positive in one quarter of the children and in half of the adults who had a negative oral challenge with the respective cooked cephalopod. Cephalapod sIgE was positive in 30% of the children and 62% of the adults with a negative oral challenge highlighting the diagnostic importance of oral food challenges.

Table 1: Positive oral food challenge patient characteristics

Suspected culprit	**Sex**	**Age (years)**	**Total IgE (KU/L)**	**Octopus sIgE (KU/L)**	**SPT (positive): commercial extracts**	**SPPT**	**Tested cephalapod (Positive OFC)**
N/A (fish allergy)	Male	11	232	0	Not performed	Negative to both octopus and squid	Octopus + Squid
Squid	Female	35	126	1.64	Octopus + Squid	Not performed	Octopus
Squid	Male	22	168	Not performed	Not performed	Positive to squid	Squid

P12 - Poster

Patterns Of IgE Mediated Food Allergy Among Patients Attending Allergy And Immunology Unite, Faculty Of Medicine, Zagazig University, Egypt.

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Background
Food allergy (FA) is a global health problem with significant personal and social impacts. Unfortunately, data regarding FA is deficient worldwide and even more scarce when it comes to developing countries. This work aimed to detect how FA contributes to the manifestations of immediate allergic reactions and the most common food allergens among Egyptian patients.

Materials and methods

This study included 1373 allergic patients. Investigations included thorough history taking, prick to prick test, serum specific IgE (sIgE) level, food elimination test, and oral food challenge test.

Results

419 patients (30.5%), 78 children, and 341 adults were sensitized against food allergens. Among children patients, 41(52.5%) had Urticaria, 31(39.7%) allergic rhino-conjunctivitis, 13(16.6%) oral food pollen syndrome, 16(20.5%) asthmatics, 9(11.5%) eczema and 7(9%) had GIT symptoms. Only one child experienced wheat anaphylaxis. Among adults, 152(44.5) had allergic rhino-conjunctivitis, 149(43.6) Urticaria, 57(16.7) had GIT symptoms. No statistically significant difference was found in FA presentation patterns in both children and adults.(Table 1) The most common allergens among children were: peanut [31(39.7%)], fish [29(37%)], egg [18(23%)], and strawberry [17(21.79%)]. In adult, they were: pepper 123(36%), Egg [122(35.7%)], Tomato [120(35.1%)], Peanut [110(32.2%)], and fish [109(31.9%)] (Table 2). Statistically significant associations between different types of food allergen were found (Table 3).

Conclusion

FA is an essential contributor to immediate allergic reactions affecting about one-third of allergic patients. Pepper, peanut, egg, fish, tomato, strawberry are the most common food to which Egyptian patients are allergic.

Clinical presentations of food allergy among children and adults.

	Children	Adults		
	No (%)	No (%)	χ^2	P
Urticaria	31(39.7)	149(43.6)	0.084	0.77
Rhino-conjunctivitis	41(52.5)	152(44.5)	0.426	0.51
Oral-pollen syndrome	13(16.6)	57(16.7)	0.024	0.87
Asthma	16(20.5)	58(17)	0.199	0.65
Eczema	9(11.5)	37(10.8)	0.001	0.96
GIT	7(9)	31(9)	0.035	0.85
Total	78	341		

Food allergen to which patients were sensitized

	Children	Adults		
	No (%)	No (%)	χ^2	p
Peanut	31(39.7)	110(32.2)	0.564	0.452
Egg	18(23)	122(35.7)	2.058	0.151
Fish	29(37)	109(31.9)	0.245	0.620
Tomato	16(20.5)	120(35.1)	2.955	0.085
Pepper	11(14.1)	123(36)	7.39	0.006*
Cocao	13(16.6)	107(31.3)	3.49	0.06
Strawberry	17(21.79)	94(27.5)	0.44	0.504
Banana	16(20.5)	89(26)	0.44	0.506
Milk	10(12.8)	74(21.7)	1.74	0.186
Citrus mix	11(14.1)	72(21.1)	1.02	0.311
Mango	16(20.5)	65(19)	0.007	0.932
Maize	6(7.6)	56(16.4)	2.40	0.120

Peach	7(9)	52(15.2)	1.1830.276
Wheat	6 (7.7)	46 (13.5)	1.135.208
Beans	4(5.1)	44(12.9)	2.47 0.115
Meat	---	31(9)	--- ---
Chicken	3(3.8)	18(5.2)	0.0440.832
Sesame	1(1.2)	29(11.4)	3.51 0.060
Shrimps	3(3.8)	26(7.6)	0.7560.384
Lentils	2(2.5)	26(7.6)	1.6350.200
Crab	1(1.2)	20(5.8)	1.7490.185
Total	78	341	

The association between sensitization of different food allergens

		Number of cases sensitized against both allergens	
Allergens (no)			χ^2 P
Cocoa (120)	Wheat (54)	23	5.91 0.02*
Cocoa (120)	Peanut (141)	60	20.13<0.001**
Peanut (141)	Tomato (136)	34	6.75 0.009**
Peanut (141)	Wheat (54)	33	20.94<0.001**
Peanut (141)	Maize (62)	12	6.66 0.01*
Tomato (136)	Pepper (134)	70	35.16<0.001**
Tomato (136)	Mango (81)	44	21.89<0.001**
Tomato (136)	Beans (48)	22	4.42 0.04*
Tomato (136)	Lentil (28)	17	10.930.001**
Citrus (83)	Mango (81)	33	27.70<0.001**
Citrus (83)	Maize (62)	22	11.260.001**
Citrus (83)	Lentil (28)	13	13.39<0.001**
Mango (81)	Maize (62)	19	5.97 0.02*
Mango (81)	Beans (48)	11	5.60 0.02*
Mango (81)	Lentil (28)	13	14.13<0.001**
Strawberry (111)	Banana (105)	46	21.58<0.001**
Strawberry (111)	Peanut (141)	21	8.29 0.004**
Peach (59)	Banana (105)	22	5.47 0.02*
Peach (59)	Maize (62)	19	16.5 <0.001**
Peach (59)	Lentil (28)	8	5.21 0.02*
Banana (105)	Beans (48)	19	6.09 0.01*
Maize (62)	Lentil (28)	10	10.410.001**
Beans (48)	Lentil (28)	8	8.67 0.003**
Shrimp (29)	Crab (21)	11	70.92<0.001**

P13 - Poster

The Frequency Of Skin Reactivity To Food Allergens In Different Age Groups Of Children With Asthma.

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Background

The clinical presentation of asthma may worsen after food allergen ingestion in sensitized individuals. However, the prevalence of food sensitization in children with asthma remains unknown.

Materials and methods
One hundred four asthmatic patients, ages 3-17 and 89 age and gender-matched controls were enrolled in this study. Each patient completed a questionnaire and underwent a skin prick test with commercial food allergens.

Results
Positive skin prick tests occurred in 49 patients (47.12%) and 12 controls (13.5%). Boys with asthma had food sensitization four times more often than girls with asthma. Sensitization to one food allergen was detected in 19 (38.8%) children with asthma. Most children with asthma (61.2%) had food sensitization for two or more food allergens. Positive skin reactivity frequency distribution was: grapes (26.5%), beets (24.5%), bananas (22.5%), cow's milk (20.4%), tomatoes (20.4%), chicken protein (18.4%), fish and apples (18.4%), soy beans (16.3%), pork (16.3%). Only boys were sensitized to egg whites, chicken and fish. In patients ages 3-6 with asthma the most common sensitized food was bananas (45.5%) while beet sensitization (31.6%) was found only in patients ages 7-17 with asthma. In controls ages 3-6 years the most common sensitized foods were cow's milk and egg whites. In controls 7-17 years the most common food sensitization was oranges.

Conclusion
Food sensitization was frequent in Ukrainian children with asthma. Sensitization to grapes, beets, bananas, cow's milk and tomatoes, chicken protein, fish and apples, soy and pork were the most common sensitized foods. However, sensitization to each specific allergen varied for each age group. Sensitization to plant food allergens is much more common than to other allergens

P14 - Poster

Allergen Capture From Allergenic Sources Using Human IgE-Antibodies: Method Showcase For Peanut Allergy

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Background
Specific serum IgE are important biomarkers in the clinical diagnosis and management of allergic patients. Component-resolved approaches based on single allergen components

increase the sensitivity and the specificity of in-vitro testing. However, available allergen panels are limited to known allergen components.
We thought to develop a new immunoassay for the capture of novel allergens from allergenic sources using IgE-antibodies from allergic patients.

Materials and methods
A chimeric construct called IgE-Aviquant, composed of the FcεRI ectodomain and an avian IgY constant domain, was produced in HEK293 cells and purified by column chromatography. The purified antibody was bound to epoxy Dynabeads, followed by coating of variable amounts of IgE-antibodies from sera of food-allergic patients (peanut). Purified allergens were bound to IgE ligated to the IgE-Aviquant/bead-construct. Quantification of eluted allergens was performed by allergen-specific ELISA and identified by mass spectrometric (MS) analysis.

Results
Depending of the nature of individual patient sera, the IgE-binding capacity of IgE-Aviquant, as determined using an anti-chicken IgY ELISA, was shown to be variable. Bound IgE-antibodies varied in a range from 2,000-5,000 ng per co-immunoprecipitation assay. Allergens (peanut) were bound in a range between 3.8-6.0 nmol per assay, depending on the allergen-specific IgE-sensitization profile of the index patient serum used. Eluted allergens were quantified by ELISA, recovering expected amounts as calculated for antibody/antigen-binding rates. The presence and identity of peanut allergens was confirmed by MS analysis of allergen eluates.

Conclusion
A co-immunoprecipitation assay was established, based on a chimeric construct binding IgE from allergic patients, which allows specific binding and elution of allergens. This assay provides the basis for capturing new allergens from any allergen source for their future characterization and application in diagnostic settings.

P15 - Poster

SENSITISATION TO POULTRY MEAT, FISH AND COCONUT IN A MULTIPLE FOOD ALLERGY CASE

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Background
Poultry meat(PM) allergy is rare and may present as primary or secondary, in the context of bird-egg-syndrome. Chicken(CM) and turkey(TM) meat are responsible for most reactions. Cross-reactive allergens (parvalbumins, enolases, aldolases) between fish and CM have been described (fish-chicken syndrome). Coconut(Co) allergy is also rare. Coc n2 (7S globulin) and Coc n4 (11S globulin) have been implicated. Cross reactivity between Co, walnuts, hazelnuts, sesame seeds and lentils have been reported.

Case report
We present the case of a 16-year-old boy, referred to our consultation for multiple food allergy. The symptoms started at the age of 8 with fish: first with salmon (vomiting, oropharyngeal pruritus, lip angioedema), then codfish, horse mackerel, sea bass and canned tuna. At the age of 15, he started multiple other food reactions: PM (anaphylaxis with CM, TM and duck meat), although he tolerated chicken eggs; cashew and pistachio (tongue angioedema, oropharyngeal pruritus), tolerating hazelnut, almonds and peanut; *rosaceae* fruits peel (oral allergy syndrome, mostly peach); Co (lip angioedema and facial pruritus after Co cake). Interestingly, he used body cream/shampoo with Co oil for the last 4-5 years, without reaction. He had a mild persistent rhinitis, but no history of atopic eczema.
Skin-prick test(SPT) and prick-prick test(PPT) were all positive for fishes except for tuna and monkfish (fresh and baked), with sIgE (ImmunoCAP) for parvalbumin of 0.64kU/L. PM allergy was confirmed (CM, TM and duck meat), with sIgE for CM of 4.28kU/L. Curiously, he had PPT positive for fresh and baked egg yolk/white. SPT and sIgE were positive for cashew, pistachio and hazelnut, although he tolerates the last one. PPT was positive for peach peel (negative for pulp) with sIgE for peach 0.39kU/L and sIgE for rPru p3 negative. Co allergy was also confirmed through PPT and sIgE (3.5kU/L). ISAC showed very high levels of rDer p2 and rDer f2, moderate/high levels of rDer p1, rDer f1, rDer p10, rAni s3, nBla g7, nPen m1, and low levels of rGad c1, rCor a8 and Fel d1. SDS-PAGE Immunoblotting assay detected IgEs in the patient's serum that recognized Co liquid endosperm (Co water) and Co solid endosperm (Co pulp) proteins that allow us to assume that the patient may be sensitized to 7S Co globulin. The study for PM proteins is ongoing at this time.

Conclusion
The present case illustrates the complexity of multiple food allergy. Cross-reactive allergens and routes of sensitization should always be considered.

P16 - Poster

Anaphylaxis After Prick-To-Prick Test With Fish

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Background
Skin prick testing is a widely used, safe, cheap, and easily performed method for diagnosing IgE-mediated sensitization. Commercial food extracts are commonly used, while the "prick-to- prick" method is performed when extracts of specific foods are not available or differences in the allergenicity of different subspecies exist. Previous studies showed a very low risk of systemic reactions with prick tests and prick-to-prick tests. Here, we report a case of anaphylaxis following prick-to-prick test with eleven different types of fishes.

Case report
A 5-year-old male patient was admitted to our department with the complaint of swelling of the eyelids and lips immediately after consuming fish for a total of 5 times since the age of 2.5. The resposible fishes were salmon, anchovies, sea bream and sea bass. He was eating shellfish and canned tuna without any problem. Prick testing with commercial cod fish extract revealed positivity (Cod fish wheal 11 mm, histamine wheal 6 mm). Specific IgE studies for fish allergens were not available in the hospital, therefore prick-to-prick test was planned with all different types of fish available in the local market (sardine, sea bass, sea bream, horse mackerel, stripped seabream, gilt-head bream, mackerel, spicara, boops, red mullet, solea). Prick-to-prick skin testing was performed according to the practice guidelines with single-use prick lancets after obtaining written informed consent from the parents. Five minutes after the test, he developed urticarial rash on his face, neck, upper trunk,and extemities, angioedema over his lips ,cough, and wheeze. Intramuscular epinephrine 0.01 m/kg was administered. He was also given a nebulized salbutamol, oxygen, cetirizine, and methylprednisolone while being observed closely. The patient recovered uneventfully within 30 minutes. No biphasic reaction was observed. He was discharged after a 6 h follow-up.

Conclusion
Although allergic reactions during skin prick tests are considered to be extremely rare (estimated prevalence of 0.008% in food allergic patients), physicians who perform skin prick tests and/or prick-to-prick tests should be aware, well trained, and equipped to treat these reactions especially systemic ones.

P17 - Poster

Eosinophilic Esophagitis In A Pediatric Patient. Clínical, Diagnosis And Treatment Features.

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Background
Eosinophilic esophagitis (EoE) is a chronic immune and antigen mediated disease that can result in permanent fibrosis and stricture formation. During the last 2 decades, the incidence in children have increased significantly. EoE is pathogenically related to a TH2 inflammation characterized by a mixed IgE and non IgE mediated reaction to food and/or environmental agents.

EoE presents with a diverse range of gastrointestinal symptoms. The diagnostic is based on esophageal eosinophilia. In the mayority of children with EoE not responsive to proton-pump inhibitor, we must suspect sensitivity to foods and treatment with an elimination diet can be effective associated with topical esteroids.

Case report
A 15 year old man, with chronic symtoms of dysphagia, nausea and substernal discomfort for more than a year, treated with proton-pump inhibitor without any response. He has past respiratory allergic histories and any allergic evaluation. physical examination was unremarkable, and any skin lesions were not observed. The laboratory testing showed a white bood cell with peripheric eosinophilia, total IgE level elevated.
Esophagogastroduodenoscopy showed some linear furrows and multiple mucosal nodularities on the lower and mid esophagus, multiple biopsies at the stomach and duodenum were perform with normal reported, heavy esosinophilic infiltrarion was observed on the esophageal mucosa. The patient was diagnosed as EoE. Skin prick test was perfomed positive for respiratory allergens and milk.
We first started treatment with propon pump inhibitors, Six food elimination diet and oral budesonide for 6 weeks. The patient´s symtoms were improved gradually.
3 months later, follow up endoscopy revealed a disapperance of the mucosal irregularities, and the biopsia the decrease in eosinophil counts. The food was gradually reintroduced one at a time except for milk, and subcutaneus AIT for asthma showed adecuate clinical response. The patient was stable.

Conclusion
Distinct clinical EoE phenotypes, including cases with atopy, coonective tissue disorders, or responsiveness to PPI was observed. The understanding of the clinical manifestations, the inidications and efficacy of PPI therapy and topical steroid therapy will aid in the diagnostic and management of these deiseases. Avoiding iatrogenic drug effects and nutrional defiencies, as well as maintaining an adequate quality of life, is also essential. Future studies focused on immunologic analyses of larger patient cohort are needed in mexico to assist in identifying EoE. The objetive of the clinic is improve outcomes in pediatric patients with food allergy.

P18 - Poster

Is It Food Allergy?

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Background
The most common clinical manifestation of food allergy in adults occurs at the

oropharyngeal mucosa and at the lips. Other triggers, such as venom hymenoptera, drugs (in particular non-steroid anti-inflammatory drugs, aspirin, antibiotics, and ACE-inhibitors) may cause angioedema.
Here we describe the clinical case of a patient, in therapy with ACE-inhibitors for 7 years, who presented with 2 episodes of angioedema 30 minutes after ingestion of hazelnut.

Materials and methods
A 65-year old man came to our observation with a positive history for angioedema (in particular lip and tongue swelling) which occurred after ingestion of hazelnut in 2 episodes: in particular in the first after ingestion of 6 hazelnuts and a glass of beer, in the second event after ingestion of hazelnut ice cream.
Both reactions were immediate.
The patient had a negative history for drug allergy, or respiratory allergy and he referred not to have taken any drug in those episodes other than antihypertensive therapy that he had been taking daily for 7 years.
The reactions were treated with antihistamine and cortisone therapy with resolution in 24 hours.

Results
Peripheral blood count, liver function tests, renal function tests, thyroid hormones, thyroid autoantibodies, C3/C4 complement, C1 inhibitor level and function, basal serum tryptase were normal.
We advise patients to replace his antihypertensive therapy with a non-ACE inhibitor molecule.
We performed a prick test, and prick by prick test for the most common food allergens, in particular hazelnut, walnut, peach, apple, maize, plum with negative results. Specific IgE antibodies to selected hazelnut components, in particular to Cor a 8, Cor a 1, Cor a 9, Cor a 14 and ISAC test were negative.
Therefore, a double-blind placebo-controlled food challenge (DBPCFC) for hazelnut was performed without the appearance of adverse reactions.
We advised the patient that he could take any food.

Conclusion
On the basis of our observation, a patient in therapy with ACE inhibitors may present angioedema in some conditions, during which other allergens may be considered a possible cause of the reaction.
Therefore, a complete investigation (anamnesis and physical examination, in vivo and in vitro tests, oral food challenge) is necessary to exclude or confirm food allergy, as in this clinical case, in which the appearance of adverse reaction may be related to the ingestion of food.

P19 - Poster

The Clinical Utility Of Basophil Activation Test In Diagnosis Of Hypersensitivity Due To Fermented Soybeans, Natto

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Background
Several cases of late-onset anaphylaxis due to fermented soybeans, natto, have been reported recently, and we also recently found that natto can cause chronic allergic urticaria and worsen chronic idiopathic urticaria. Poly-γ-glutamic acid (PGA), a polymer in which D- and L- glutamic acids unite, is the causative allergen contained in natto mucilage. The characteristic delay of symptom development hampers appropriate diagnosis, but skin tests or provocation tests can be burdensome for patients. The objective of our study is to clarify the clinical utility of a basophil activation test (BAT) in diagnosis of hypersensitivity for natto.

Materials and methods
Three patients with hypersensitivity history including anaphylaxis, chronic allergic urticaria and chronic idiopathic urticaria were assessed as a patient group, who were suspected to have hypersensitivity to natto. Seven patients with chronic idiopathic urticaria, who have no suspicion of those to natto, were enrolled as a control group. Patients underwent laboratory tests, scratch tests and BAT. BAT was performed with two different incubation time with allergen, 15 minutes and 1 hour.

Results
The results of specific IgE antibodies for soybeans were negative except for 2 control patients. Two of patient group were positive for natto in scratch tests and residual 1 patient had the late phase reaction. Control group were negative for natto in scratch test. Scratch tests for soybeans were negative in all patients who underwent it. In BAT, natto increased CD203c expression of basophils after 1-hour incubation in both patient and control groups, while boiled soybeans did not. On the other hand, after 15-minute incubation, natto increased CD203c levels of basophils only in patient group but not in control group, showing clinical correlation of BAT results. Frozen natto, PGA, D- and L-glutamic acid did not increase CD203c levels after 15-minute incubation.

Conclusion
We found that BAT with 15-minute method can be useful to identify patients with natto hypersensitivity. Furthermore, these results indicated that freeze-and-thaw procedure may affect the antigenicity of PGA. Recently, natto has been increasingly consumed all over the world. And PGA is used in a variety of applications, including foods. Although patients with hypersensitivity to natto may not be rare, useful *in vitro* diagnostic tool has not been available. BAT would be an useful tool to make the diagnosis of natto hypersensitivity

O07 – Fecal Calprotectin As A Biomarker Of IgE-Mediated Food Allergy And Disease Severity In Children With Atopic Dermatitis Without Gastrointestinal Symptoms

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Background

Recents studies suggest fecal calprotectin (FCP) as a biomarker of intestinal inflammation in children with food allergy. The aim of this study is to compare FCP level in infants and children under 4 years of age suffering from atopic dermatitis (AD) with and without IgE-mediated food allergy (FA) and without gastrointestinal sympthoms, with FCP level healthy controls.

Materials and methods

In total, 35 infants and children (age, mean 13.7 months ± 12) newly diagnosed with AD were devided in two groups: G1, children with AD and FA without gastrointestinal symptoms (N=25), G2, children with AD and without FA and gastrointestinal symptoms (N=10). Control group (G3) consisted of healthy children of the same age (N=18). In all subjects, a complete blood count, total IgE, specific IgE to nutritive allergens, immunoglobulins, FCP and SCORAD score were assessed.

Results

The median FCP was 68 (IQR 148.4) μg/g in the 35 infants and children with AD and 77.75 (IQR 155) μg/g in the control group (p=0.5597). There was no difference between G1 and G3 in FCP level (G1: median 70, IQR 317.3 μg/g μg/g vs G3: median 77.75, IQR 155 μg/g; p=0.2835). There was no difference between G2 and G3 in FCP level (G2: median 41, IQR 60.4 μg/g vs G3: median 77.75, IQR 155 μg/g; p=0.5619). Median FCP level was signifficantly increased in G1 compare to G2 (G1: median 70, IQR 317.3 μg/g vs G2: median 41, IQR 60.4 μg/g; p= 0.0408). The FCP level significantly correlated with immunoglobulin (Ig) G level (r=-0.4977, p=0.0255) and SCORAD score (r=0.3421, p=0.0443). SCORAD score significantly correlated with IgG (r=-0.5021, p=0.0241), and IgM (r=-0.4691, p=0.0369).

Conclusion

FCP level in patients with AD without FA is decreased in comparasion to patients having both, AD and FA. Significant association of FCP level and SCORAD score suggests FCP as a potential biomarker of AD severity. Our results provide the evidence supporting the potential utility of a FCP as biomarker of IgE mediated FA in children. However, new studies are required in order to estimate the role of FCP as a biomarker of IgE-mediated FA in infants and children with AD and FA.

O08 - COMPONENT-RESOLVED DIAGNOSTICS IN FOOD ALLERGY: A MULTICENTER RETROSPECTIVE STUDY

Enza D'Auria1, Amelia Licari2, Samuele Palazzo3, Simone Pilloni1, Giovanni Casazza4, Giacomo Colella1, Marco Ugo Andrea Sartorio1, Gian Luigi Marseglia2, Gian Vincenzo Zuccotti1

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Background

Cow's milk allergy (CMA), hen's egg allergy (HEA) and hazelnut allergy (HA) are among the most frequent food allergies (FA) in children. Our study aimed to investigate the diagnostic performance of component-resolved diagnostics (CRD) to cow's milk, hen's egg and hazelnut proteins, by correlating the level of CRD with the outcome of the oral food challenge (OFC) and with the severity of symptoms during OFC for CMA.

Materials and methods

230 patients with suspicious of FA were considered: 97 were evaluated for CMA, 87 for HEA and 46 for HA. All the patients underwent the following diagnostic tests: Skin Prick Test (SPT), food-specific IgE, CRD for the major components of the suspect food and OFC. We evaluated the diagnostic accuracy of CRD by correlating its results with the outcome of the OFC. We also evaluated the correlation between milk CRD and the severity of symptoms during milk OFC (based on the Sampson Score). The performance of CRD was assessed by calculating ROC curves, selecting optimal negative and positive cutoffs for the diagnosis of CMA, HEA and HA.

Results

Casein-specific IgE resulted as the best predictor of CMA among the CRD tests with area under the curve (AUC) of 0.85. With a positive cutoff of 2.70 kUA/L, the Sp and PPV were 99% and 94% respectively. If this positive cutoff was considered 17 OFC could have been spared, 16 of these were positive OFC (59% of all positive milk OFC), one would have been a false positive result.

The milk CRD test which showed the highest correlation with the severity of the reactions during milk OFC was casein, with 0.74 AUC in the identification of subjects with Sampson Score ≥ 3.

Ovomucoid-specific IgE and Ovalbumin-specific IgE resulted as the best predictors of HEA, with 0.70 and 0.71 AUC respectively. With a negative cutoff of 0.13 kUA/L, ovalbumin-specific IgE had 95% Sn and 94% NPV. If this negative cutoff was considered 18 OFC (21% of the total OFC) could have been spared, however one of the 18 OFC would have been a false negative result.

Cor a 9 and Cor a 14 resulted the best predictors of the OFC outcome (AUC was 0.78 for both tests). Hazelnut SPT had a better performance than all the CRD tests, with 0.84 AUC.

Conclusion

CRD may allow to reduce the amount of OFCs to diagnose FA, considering both negative and positive cutoffs. Further studies are warranted to confirm the diagnostic performance of CRD in other populations. Indeed, the OFC should be still considered the gold standard for the diagnosis of FA.

SPEAKERS' DOCUMENTS

Only to be used for individual study purposes

Session IV- Workshops.

Persistent Cow's Milk Allergy treated with Oral Immunotherapy.

Giovanni B. Pajno . Department of Pediatric- Allergy Unit, University of Messina- Messina- Italy. **Fernanda Chiera.** Pediatric Unit – "San Giovanni di Dio" Hospital- Crotone- Italy

Background

Cow's milk allergy (CMA) is one of the most common food allergy in children.

Two main mechanisms, IgE and non-IgE mediated, are responsible of immune mediated reaction to cow's milk (CM), as well as to other food.

IgE-mediated reactions account for 60% of CMA and are characterized by immediate onset of symptoms after CM assumption. Adverse reactions range from mild symptoms to life-threatening anaphylaxis. Symptoms involve skin, gastrointestinal tract, respiratory system and cardiovascular system. (Figure 1)

Case Report

Chiara, was followed at our outpatients clinic for CMA from the age of 7 months when she experienced her first allergic reaction to formula milk (150 ml), few minutes after ingestion, with urticaria, cough and sneezing. Her mother reported that Chiara, in the past, drank some formula milk in her first days of life without adverse reactions. We performed skin prick test (SPT) resulted positive for CM whey fractions (casein 7 mm, α-lactalbumine 5 mm and β-lactoglobulin 7 mm): these results were confirmed by high level of CM specific IgE 18.6 kU/L, so we suggest a cow's milk protein-free diet. At the age of 18 months she performed an oral food challenge (OFC) for CM developing urticaria, angioedema, sneezing and cough. At the age of 2 and 3 years, after she had ingested, accidentally, small amounts of CM products she experienced anaphylaxis (urticaria, facial erythema, angioedema, bronchospasm and drowsiness), she was admitted in hospital after epinephrine injection. At the age of 4 years, she was initially tested for sIgE against casein, α-lactalbumine and β-lactoglobulin using the ImmunoCAP assay system (Thermo Fisher Scientific, Uppsala, Sweden), resulted 68, 15.4, and 94.6 kUA/L, respectively. She also underwent SPT and OFC for CM stopped at 5 ml of milk due to the appearance of anaphylaxis.

We decide to start an oral immunotherapy (OIT) protocol to CM, starting from 1 ml of whole milk diluted 1:100 with water, corresponding approximately to 0.3 mg of CM proteins, after placement of an intravenous catheter. The dose was increased every hour for two days (in the second day milk was diluted 1:10) during the escalation phase reaching the final dose of 2.5 ml of undiluted milk (82,5 mg of CM proteins), then once a week until reaching the maintenance dose of 200 ml. (Table 1) The previous tolerated dose was taken at home twice a week. Before discharge, she remained under observation for 2 hours after the final dose each day, or more if required.

Chiara experienced three adverse reaction during desensitization protocol: the first one at the end of rush phase (itchy mouth and flushing) treated with cetirizine; the second and third adverse reaction characterized by diffuse urticaria and cough occurred during maintenance phase at home in conjunction with a viral intercurrent illness (common cold). In that case the dose was not increased in the next week, but the previous tolerated dose was repeated.

When she reached the maintenance dose of 200 ml, she was asked to drink 200 ml of milk daily for 1 month. After that, an OFC was performed with the maximum dose of 300 ml without any adverse reaction. She was discharged with the recommendation to continue follow-up every six months, avoid dairy during acute illness or in the setting of sport , and consume milk at least twice a week plus other foods containing milk proteins in order to maintain desensitization.

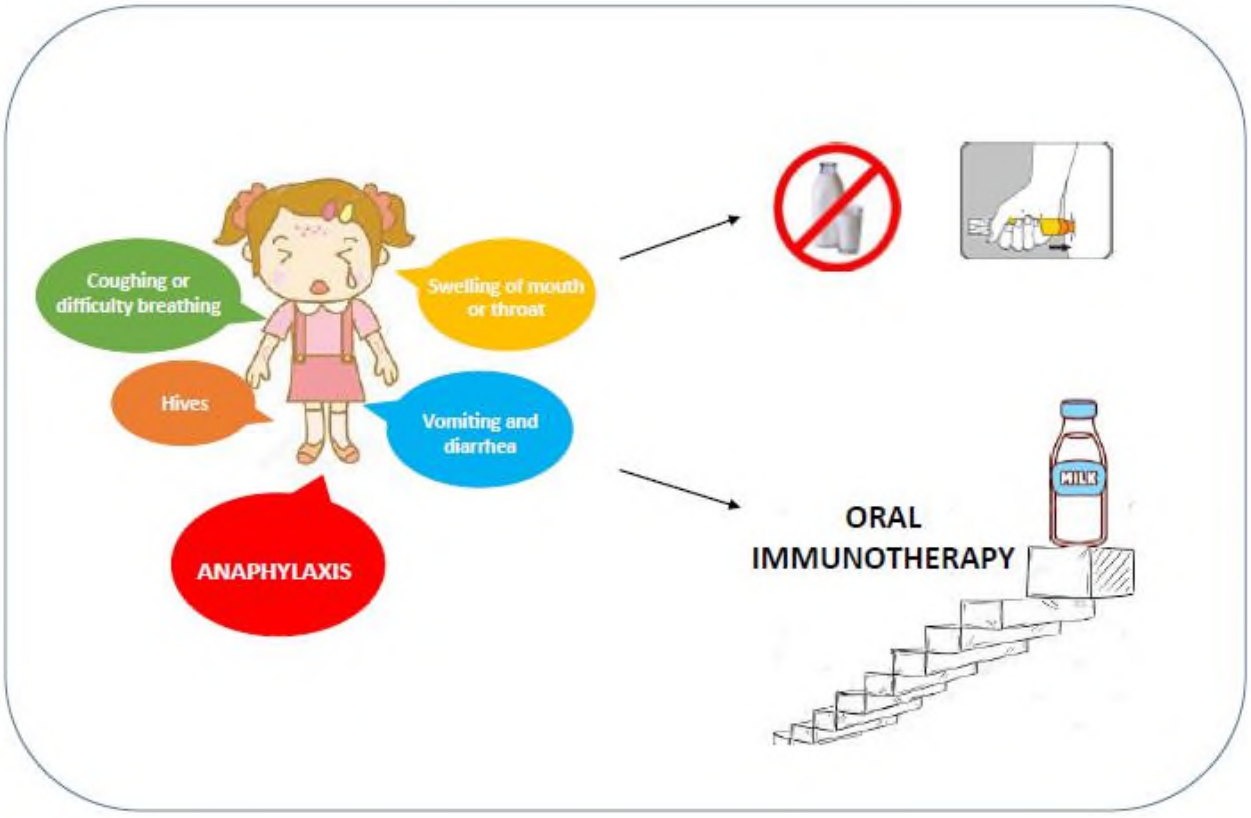

Figure 1. IgE-mediated milk allergy is associated with a high frequency of adverse reactions. The standard treatment include management of anaphylaxis and food avoidance. In case of persistent milk allergy, oral immunotherapy represents the only active treatment able to modify the natural history of food allergy.

Table 1. Desensitization protocol for OIT

Day/week	Milk diluition	Volume (ml)	Proteins
Day 1	1/100	1	0.3 mg
"	1/100	2	0.7 mg
"	1/100	4	1.3 mg
"	1/100	8	2.7 mg
"	1/10	1,6	5 mg
Day 2	1/10	1,6	5 mg
"	1/10	3,2	10,6 mg
"	1/10	6,4	21,1 mg
"	1/10	12	39,6 mg
"	Undiluted	2.5	82,5 mg

Week 2	**Undiluted**	**4**	**132 mg**
Week 3	**Undiluted**	**6**	**198 mg**
Week 4	**Undiluted**	**8**	**264 mg**
Week 5	**Undiluted**	**10**	**330 mg**
Week 6	**Undiluted**	**12**	**396 mg**
Week 7	**Undiluted**	**15**	**495 mg**
Week 8	**Undiluted**	**20**	**660 mg**
Week 9	**Undiluted**	**25**	**825 mg**
Week 10	**Undiluted**	**30**	**990 mg**
Week 11	**Undiluted**	**40**	**1.320 mg**
Week 12	**Undiluted**	**50**	**1.650 mg**
Week 13	**Undiluted**	**75**	**2.475 mg**
Week 14	**Undiluted**	**100**	**3.300 mg**
Week 15	**Undiluted**	**150**	**4.950 mg**
Week 16	**Undiluted**	**200**	**6.600 mg**

From formula to complementary feeding in the food allergic child

Dr. Imke Reese PhD
Private Practice for Dietary Counselling and Nutrition Therapy with Focus on Adverse Reactions to Food
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www.ernaehrung-allergologie.de

Complementary Feeding: A Position Paper by the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) Committee on Nutrition

- ✓Infants should be offered foods with a variety of flavours and textures including bitter tasting green vegetables.
- ✓Whole cows' milk should not be used as the main drink before 12 months of age.
- ✓Allergenic foods may be introduced when complementary feeding (CF) is commenced any time after 4 months.
- ✓ Infants at high risk of peanut allergy should have peanut introduced between 4 and 11 months, following evaluation by an appropriately trained specialist.
- ✓Gluten may be introduced between 4 and 12 months, but consumption of large quantities should be avoided during the first weeks after gluten introduction and later during infancy.
- ✓All infants should receive iron-rich CF including meat products and/or iron-fortified foods.
- ✓No sugar or salt should be added to CF and fruit juices or sugar-sweetened beverages should be avoided.

Case 1 - Anna

- 5 months of age
- with 2 months parents tried to feed cow's milk formula
- immediate swelling of lips and eye, generalized urticaria, itching
- hospitalization for 1 night
- change to extensively hydrolysed formula
- no further reaction

- How to proceed with introduction of complementary feeding?

Case 2 - Bill

- 3 months of age
- Atopic dermatitis since early infancy
- Extensively hydrolysed formula recommended by pediatrian
- Skin status better but still flares from time to time

- How to proceed with introduction of complementary feeding?

Case 3 - Jenny

- 6 months of age
- atopic dermatitis since early infancy
- Mother not able to breastfeed
- When introducing the second meal → vomiting, swelling of eye, exacerbation of skin
- RAST in hospital:

Egg	[illegible]
Milk	[illegible]
Fish	<0.10 kU/l
Wheat	[illegible]
Peanut	<0.10 kU/l
Soy	0.28 kU/l

Case 4 - Richard

- 4 months of age
- Severe atopic dermatitis since early infancy
- Change of breast feeding to extensively hydrolysed formula recommended by pediatrian
- RAST to common food allergens in childhood shows low peanut sensitization

- How to proced with introduction of complementary feeding?

References

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Shaker M, Verma K, Greenhawt M. The Health and Economic Outcomes of Early Egg Introduction Strategies. Allergy 2018:

Eigenmann PA, Beyer K, Lack G, Muraro A, Ong PY, Sicherer SH, et al. Are avoidance diets still warranted in children with atopic dermatitis? Pediatric Allergy and Immunology 2019:

Togias A, Cooper SF, Acebal ML, Assa'ad A, Baker JR, Jr., Beck LA, et al. Addendum guidelines for the prevention of peanut allergy in the United States: Report of the National Institute of Allergy and Infectious Diseases-sponsored expert panel. J Allergy Clin Immunol 2017; 139: 29-44

Dietary elimination in IgE-mediated food allergy

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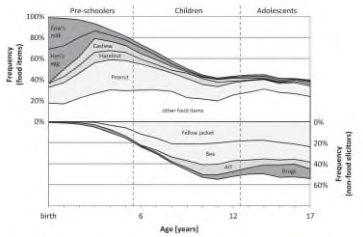


FIG 1. Elicitor of anaphylaxis by age only for known elicitors (n = 1565). Rare elicitors were omitted (eg, other insects and latex). *AIT*, Allergen immunotherapy.

Grabenhenrich JACI 2016

Peanut Allergen Threshold Study (PATS): Novel single-dose oral food challenge study to validate eliciting doses in children with peanut allergy

Jonathan O'B. Hourihane, MD, DM,* Katrina J. Allen, MD, PhD,[b,c] Wayne G. Shreffler, MD, PhD,[d] Gillian Dunngalvin, PhD,[b,e] Julie A. Nordlee, MS,[f] Giovanni A. Zurzolo, PhD,[b,e] Audrey Dunngalvin, PhD,[b,e] Lyle C. Gurrin, PhD,[b] Joseph L. Baumert, PhD,[f] and Steve L. Taylor, PhD[f]

Conclusion: A single administration of 1.5 mg of peanut protein elicited objective reactions in fewer than the predicted 5% of patients with peanut allergy. The novel single-dose oral food challenge appears clinically safe and patient acceptable, regardless of the outcome. It identifies the most highly dose-sensitive population with food allergy not otherwise identifiable by using routinely available peanut skin prick test responses or specific IgE levels, but this single-dose approach has not yet been validated for risk assessment of individual patients. (J Allergy Clin Immunol 2017;139:1583-90.)

Outcome of oral food challenges in children in relation to symptom-eliciting allergen dose and allergen-specific IgE

C. Rolinck-Werninghaus[1], B. Niggemann[1,2], L. Grabenhenrich[3], U. Wahn[1] & K. Beyer[1]

Allergy 2012

Number of oral food challenges		Cow's milk n = 633		Hen's egg n = 496		Wheat n = 265		Soy n = 317	
Age (years)	median (min–max)	1.0	(0.2–16.2)	1.6	(0.3–14.9)	1.4	(0.1–16.0)	1.1	(0.3–16.1)
Specific IgE (kU/l)	% sIgE <0.35 kU/l	31.3		17.2		27.4		41.7	
	% sIgE 0.35–0.60 kU/l	11.6		8.0		7.5		8.3	
	% sIgE 0.70–3.48 kU/l	22.8		27.0		23.9		24.6	
	% sIgE 3.5–17.40 kU/l	18.4		33.7		21.7		15.5	
	% sIgE 17.5–49.00 kU/l	9.0		9.8		10.6		6.1	
	% sIgE 50–100 kU/l	4.2		3.3		7.5		2.3	
	% sIgE >100 kU/l	2.6		1.0		1.3		1.5	
History of atopic dermatitis	n (%)	557	(88)	410	(91)	229	(87)	296	(94)
History of wheeze	n (%)	94	(15)	91	(20)	48	(18)	58	(18)
History of allergic rhino-conjunctivitis	n (%)	48	(8)	47	(10)	18	(7)	24	(8)
DBPCFC	n (%)	458	(73)	310	(66)	212	(80)	213	(68)
Positive food challenge	n (%)	305	(48)	313	(69)	88	(33)	51	(16)

Positive DBPCFC 48% 69% 33% 16%

ORIGINAL ARTICLES www.jpeds.com • THE JOURNAL OF PEDIATRICS

Oral Food Challenges in Children with a Diagnosis of Food Allergy

David M. Fleischer, MD, S. Allan Bock, MD, Gayle C. Spears, PA-C, Carla G. Wilson, MS, Naomi K. Miyazawa, PA-C, Melanie C. Ellenson, PA-C, Elizabeth A. Rynkiewicz, PA-C, James R. Murphy, PhD, Dan Atkins, MD, and Donald Y. M. Leung, MD

J Pediatr 2011;158:578-83

Table II. OFC results on foods avoided due to immunoassay or PST

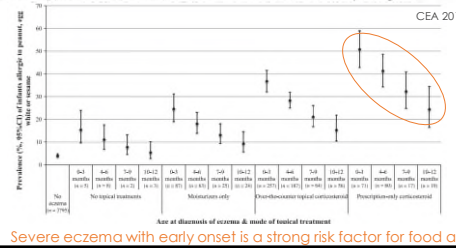
Food group	Avoiding on admission	OFC positive result	OFC negative result	Avoiding on discharge	% Negative
Egg	10	1	9	1	90%
Fruits	10	2*	8	2	80%
Meats	13	0	13	0	100%
Milk	9	0	9	0	100%
Oats	4	0	4	0	100%
Peanut	7	1	6	1	86%
Shellfish	2	0	2	0	100%
Soy	19	1	18	1	95%
Vegetables	6	0	6	0	100%
Wheat	13	3	10	3	77%
Other	18	0	18	0	100%
Totals	111	8	103	8	93%

*Two positive tests to banana.

Which infants with eczema are at risk of food allergy? Results from a population-based cohort

E. E. Martin[1,2,3], J. K. Eckert[1,2], J. J. Koplin[1,2], A. J. Lowe[3], L. C. Gurrin[3], S. C. Dharmage[3], P. Vuillermin[1,2,4,5], M. L. K. Tang[1,2,6], A.-L. Ponsonby[1], M. Matheson[1], D. J. Hill[1], K. J. Allen[1,2,3,7] and for the HealthNuts Study Investigators

CEA 2014; 45: 255-64



Severe eczema with early onset is a strong risk factor for food allergy

Are avoidance diets still warranted in children with atopic dermatitis?

Philippe A. Eigenmann[1] | Kirsten Beyer[2] | Gideon Lack[3] | Antonella Muraro[4] | Peck Y. Ong[5] | Scott H. Sicherer[6] | Hugh A. Sampson[6]

- Foods may exacerbate AD in some children
- 40% with moderate-severe AD have food allergies, some of them only flares
- Recent studies encourage ingestion of allergens (prevention/ tolerance)
- Dietary elimination impacts on quality of life and may lead to nutritional risks
- Allergy testing for foods has liminted utility in terms of eczema and should only be performed after optimal skin care treatment
- A rationale to reduce rather to eliminate possible food triggers can be considered

PAI 2019

Patient's history is mandatory before any dietary intervention

Egg
Milk
Fish
Wheat
Peanut
Soy

- Have egg, milk and wheat been eaten before allergy testing?
- What about fish, peanut and soy?
- If yes, were they tolerated or what were the symptoms? If exacerbation of AD, to what extend?
- If milk/ egg are eaten, are they tolerated in any form (baked, cooked, raw)?
- Have you already started ED?
- If yes, since when?

Rapid publication

Immunologic changes in children with egg allergy ingesting extensively heated egg

Heather Lemon-Mulé, MD, Hugh A. Sampson, MD, Scott H. Sicherer, MD, Wayne G. Shreffler, MD, PhD, Sally Noone, RN, and Anna Nowak-Wegrzyn, MD *New York, NY*

Tolerance to extensively heated milk in children with cow's milk allergy

Anna Nowak-Wegrzyn, MD, Katherine A. Bloom, MD, Scott. H. Sicherer, MD, Wayne G. Shreffler, MD, PhD, Sally Noone, RN, Niya Wanich, MD, and Hugh A. Sampson, MD *New York, NY*

JACI 2008

Matrix effect on baked egg tolerance in children with IgE-mediated hen's egg allergy

Stefania Micali Sopo[1], Monica Greco[1], Barbara Cuomo[2], Annamaria Bianchi[3], Lucia Liotti[4], Silvana Monaco[1] & Iride Delle Iacono[5]

Safety of food challenges to extensively heated egg in egg-allergic children: a prospective cohort study

Paul J. Turner[1,2], Sam Mehr[3], Preeti Joshi[4], John Tan[5], Melanie Wong[6], Alyson Kakakios[2,3] & Dianne E. Campbell[1,2]

PAI 2013

The natural history and clinical predictors of egg allergy in the first 2 years of life: A prospective, population-based cohort study

Rachel L. Peters, MPH,[a,b] Shyamali C. Dharmage, MBBS, MSc, MD, PhD,[a,c] Lyle C. Gurrin, PhD,[a,c] Jennifer J. Koplin, PhD,[a,b] Anne-Louise Ponsonby, BMedSci, MBBS, PhD, FAFPHM, FRACP,[a,d] Adrian J. Lowe, PhD,[a,c] Mimi L. K. Tang, MBBS, FRACP, FRCPA, FAAAAI, PhD,[a,b,e] Dawn Tey, MBBS, FRACP,[a,b,e] Marnie Robinson, MBBS, FRACP,[f] David Hill, MBBS, FRACP,[g] Helen Crouch, BNurs, RN,[g] Leone Thiele, BA, RN, MMSc,[g] Nicholas J. Osborne, PhD,[a,c,h] and Katrina J. Allen, BMedSci, MBBS, FRACP, FAAAAI, PhD[a,b,e,i] for the HealthNuts study

JACI 2013

ORIGINAL ARTICLE

Matrix effect on baked milk tolerance in children with IgE cow milk allergy

S. Micali Sopo[a,*], M. Greco[a], S. Monaco[a], A. Bianchi[b], B. Cuomo[c], L. Liotti[d], I.D. Iacono[a]

Table 2 Sensitisation patterns of main CM proteins compared to OFC outcomes (passed/failed).

Processed cow's milk OFC (no. pts)		Positive to casein (%)	Positive to beta-lactoglobulin (%)	Positive to alfa-lactoalbumin (%)
Clombellone				
Failed OFC (9)	81%	9/9 (100%)	7/9 (78%)	9/9 (100%)
Passed OFC (39)		28/39 (72%)	30/39 (77%)	33/39 (85%)
Baked liquid cow's milk				
Failed OFC (14)	56%	12/14 (86%)	11/14 (79%)	13/14 (93%)
Passed OFC (18)		12/18 (67%)	15/18 (83%)	17/18 (94%)
Parmigiano reggiano				
Failed OFC (8)	78%	8/8 (100%)	7/8 (88%)	8/8 (100%)
Passed OFC (28)		18/28 (64%)	21/28 (75%)	24/28 (86%)
Partially hydrolysed formula				
Failed OFC (5)	82%	4/5 (80%)	4/5 (80%)	5/5 (100%)
Passed OFC (23)		17/23 (74%)	19/23 (83%)	20/23 (87%)

OFC, oral food challenge.

BRIEF COMMUNICATION

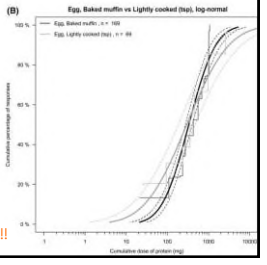
WILEY Allergy

Minimal impact of extensive heating of hen's egg and cow's milk in a food matrix on threshold dose-distribution

B. C. Remington[1] | J. Westerhout[1] | D. E. Campbell[2,3] | P. J. Turner[3,4]

TABLE 1 Combined ED50 range estimated by the log-normal, log-logistic, and Weibull distributions for oral food challenges using egg and cow's milk (CM; both in native form and "baked" into a muffin)

Allergen	Form	Number of individuals (left censored, right censored)	Predicted ED50 range
Egg	Lightly cooked	69 (15, 11)	296-360 mg protein (95% CI: 185-570 mg protein)
	Baked	169 (23, 37)	232-384 mg protein (95% CI: 274-453 mg protein)



Baked-food is not equal to less allergenic!!

Cow's milk and hen's egg allergy: what do molecular-based allergy diagnostics have to offer?

Part 20 of the series Molecular allergology

Conclusions for clinical practice

"Determining IgE to single allergens confers no benefit in the diagnostic work-up of cow's milk and hen's egg allergy in clinical routine compared with the determination of cow's milk- and hen's egg-specific IgE using extracts."

"Single allergen determination is not able to answer the question of whether cow's milk or hen's egg are tolerated in baked form."

Managing Nut Allergy: A Remaining Clinical Challenge

Philippe A. Eigenmann, MD, Gideon Lack, FRCPCH, Angel Mazon, MD, Antonio Nieto, MD, Diab Haddad, MRCPH, Helen A. Brough, FRCPCH, and Jean-Christoph Caubet, MD

JACI 2017

TABLE I. Current options in the management of nut allergy

Options	Pro	Con
Avoid index nut	No other safe option	
Avoid all nuts, including clinically tolerated nuts	• Decreases the risk of accidental reactions due to cross-contamination • Easier avoidance of all nuts than specific ones	• Extensive dietary restriction possibly decreasing the quality of life • Possibly increased risk of becoming allergic to nuts previously tolerated
Continue eating nuts previously tolerated, and introduce nuts likely to be tolerated after OFC	• Tailored avoidance diet may increase quality of life • Possibly decreases the risk of also becoming allergic to these nuts	• Increases the risk of accidental reactions due to cross-contamination, or confusion in identifying nuts • Possibly increases the risk of becoming allergic to these nuts

NUT Co Reactivity - ACquiring Knowledge for Elimination Recommendations (NUT CRACKER) study

Allergy 2018

TABLE 1 Rate of sensitization vs clinical allergy for each tree-nut

Tree-nuts (n = All)	Sensitization (SPT ≥ 3 mm)	Clinical allergy: Total[a]	Clinical allergy: Reaction in last 2 y[b]	Clinical allergy: OFC (+)[c]	Clinical tolerance: Total[a]	Clinical tolerance: Consumption[c]	Clinical tolerance: OFC (−)[c]
Walnut	71	33 (74.6%)	22 (41.5%)	31 (58.5%)	38 (25.4%)	6 (33.3%)	12 (66.7%)
Pecan	37	24 (39.6%)	8 (23.5%)	26 (76.5%)	22 (60.4%)	2 (8.7%)	21 (91.3%)
Cashew	65	40 (61.6%)	13 (32.5%)	27 (67.5%)	21 (34.4%)	9 (42.9%)	12 (57.1%)
Pistachio	63	26 (48%)	8 (30.7%)	18 (69.3%)	39 (60%)	6 (38.5%)	33 (84.6%)
Hazelnut	68	54 (23%)	4 (28.6%)	50 (71.4%)	67 (77%)	34 (72.3%)	13 (27.7%)
Almond	49	1 (2%)	0	1 (100%)	48 (98%)	20 (41.7%)	28 (58.3%)

TABLE 2 Rate of co-allergy between tree-nuts

Tree-nut	Other tree-nut allergies: Walnut	Pecan	Cashew	Pistachio	Hazelnut	Almond
Walnut (n = 53)	-	34 (64.2%)	20 (37.7%)	11 (20.8%)	11 (20.8%)	0
Pecan (n = 34)	34 (100%)	-	19 (41.2%)	6 (17.6%)	10 (29.4%)	0
Cashew (n = 40)	20 (50%)	14 (35%)	-	26 (65%)	6 (15%)	0
Pistachio (n = 26)	11 (42.3%)	6 (23.1%)	25 (100%)	-	3 (11.5%)	0
Hazelnut (n = 54)	11 (78.6%)	11 (78.6%)	6 (42.9%)	3 (21.4%)	-	0
Almond (n = 1)	0	0	0	0	0	-

The impact of oral food challenges for food allergy on quality of life: A systematic review

Hannah M. Kansen | Thuy-My Le | Yolanda Meijer | Bertine M. J. Flokstra-de Blok | Paco M. J. Welsing | Cornelis K. van der Ent | André C. Knulst | Francine C. van Erp

"Food allergy-specific parent-reported HRQL improved significantly after an OFC irrespective of the outcome in children with a suspected food allergy in two publications.... In addition, parent-reported HRQL improved after an OFC to assess the eliciting dose in children with a confirmed food allergy. The parental burden was significantly reduced after an OFC to assess resolution of food allergy. A meta-analysis could not be performed due to the limited numbers of, and considerable heterogeneity between, eligible publications.

Conclusion: An OFC is associated with an improved food allergy-specific HRQL and a reduced parental burden of food allergy."

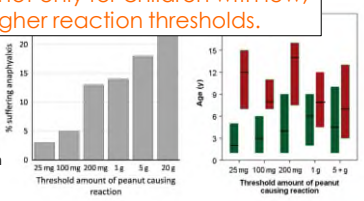
Severity and threshold of peanut reactivity during hospital-based open oral food challenges: An international multicenter survey

Pediatr Allergy Immunol. 2018;29:754–761

Peter D. Arkwright | Jayne MacMahon | Jennifer Koplin

Tailored immunotherapy programs might be considered not only for children with low, but also higher reaction thresholds.

- OF
- 525 (32%) reacted:
  - 28% to 25 mg
  - 38% after ingestion ≥ 1g
  - 10% (n=55) with anaphylaxis
- Anaphylaxis 3 times more common in teenagers than in younger children



Conclusions

- Food allergies to basic foods, such as milk and egg, predominantly occur in early childhood.
- Allergic reactions can vary from flares to anaphylaxis.
- Severe atopic eczema is a risk factor for food allergy.
- A patient's history must be taken before dietary interventions start as sensitizations can be without clinical relevance.
- Strict allergen avoidance only where necessary.
- Tolerated foods or food preparations should be consumed regularly.
- No precautionary elimination of whole food groups.
- Oral food challenge improves quality of life.
- Tailored management of food allergy should be targeted.

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Dietary management when it is not food allergy

Dr. Imke Reese PhD
Private Practice for Dietary Counselling and Nutrition Therapy with Focus on Adverse Reactions to Food
Munich, Germany
www.ernaehrung-allergologie.de

Fructose malabsorption

Lactose intolerance

Adverse reations after consuming lactose or fructose are NO food allergies and should not be treated as such!

In lactose intolerance, only lactose-containing milk products need to be reduced.

Dietary management

- Not the amount of lactose/ fructose eaten is relevant, but how fast these sugars reach the enterocytes → tolerable daily amounts are useless!
- Gastric emptying and gastrointestinal transit time differ dependent on meal composition.
  - Soluble fibre, protein and/ or fat delay gastric emptying and are released slowly into the small intestine.
  - Carbohydrates (starch and sugars) and/ or fluid components tend to be released earlier and may „flood" the small intestine.

⇒ Mixed meals made of freshly prepared foods should be preferred.
⇒ Not only lactose content, but also fat content should be considered.
⇒ Fruits should be eaten with or after a meal, ideally combined with yoghurt.

Histamine intolerance

REVIEW ARTICLE
Histamine and gut mucosal immune regulation
E. Smolinska[1,2], M. Jutel[1,3], R. Crameri[4] & L. O'Mahony[5]

Allergy 2013

"Histamine can have both pro-inflammatory and anti-inflammatory effects on immunoregulatory processes, depending on which histamine receptor is activated."

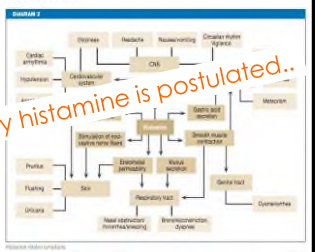
⇨Histamine has many physiological functions as a hormone and neurotransmitter and can also have immune-regulatory effects.

REVIEW ARTICLE

Histamine Intolerance in Clinical Practice

Laura Maintz, Thomas Bieber, Natalija Novak

- „In patients with typical symptoms, histamine int… should be …
- …, patients improve … histamine-free diet plus antihistamines or substitution with DAO"

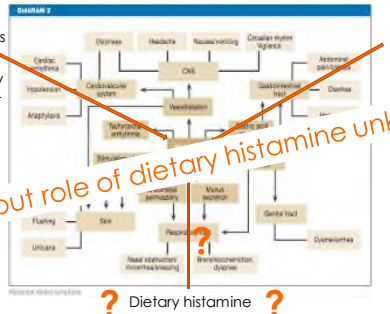


Intolerance to dietary histamine is postulated..

Dtsch Arztebl 2006; 103(51–52): A 3477–83.

increased endogenous release of histamine by mast cells or intestinal bacteria

impaired histamine degrading capacity



.. but role of dietary histamine unknown

? Dietary histamine ?

Histamine intolerance: lack of reproducibility of single symptoms by oral provocation with histamine: A randomised, double-blind, placebo-controlled cross-over study

Wien Klin Wochenschr 2010

Multicentre double-blind, placebo-controlled crossover study in order to:

- objectify and quantify histamine-associated symptoms
- analyse whether oral administration of the histamine-degrading enzyme diamine oxidase (DAO) caused a reduction of symptoms

39/ 56 patients were included after positive open challenge with 75 mg histamine in peppermint tea

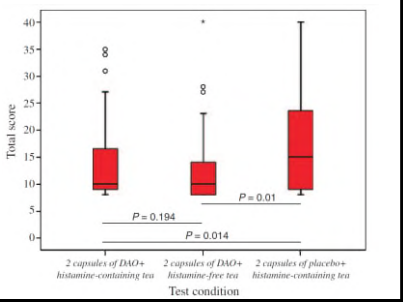
DBPCFC in randomized order

a. placebo capsules and histamine-containing tea
b. DAO-capsules and histamine-containing tea
c. DAO-capsules and histamine-free tea

⇒ „both the main and secondary symptoms were not reproducible. Subjects reacted sometimes unexpectedly and randomly."

"Due to the random reactions and thus the lack of reproducibility, primary and secondary objectives could not be evaluated."

"Regarding the *total* symptom scores, the differences between the three treatment groups...were statistically significant."



German guideline for the management of adverse reactions to ingested histamine

Guideline of the German Society for Allergology and Clinical Immunology (DGAKI), the German Society for Pediatric Allergology and Environmental Medicine (GPA), the German Association of Allergologists (AeDA), and the Swiss Society for Allergology and Immunology (SGAI)

"The scientific evidence to support the postulated link between ingestion of histamine and adverse reactions is limited, and a reliable laboratory test for objective diagnosis is lacking. This position paper reviews the data on the clinical picture of adverse reactions to ingested histamine, summarizes important aspects and their consequences, and proposes a practical diagnostic and therapeutic approach."

Allergo J Int 2017

Dietary management

1) Diagnostic work-up to indentify possible underlying disease
2) 3-step dietary adjustment
3) An individualized nutritional therapy focussing on optimized meal composition (no restrictive histamine-free diet!).

Table 2 Phases of the three-step dietary adjustment

Phase	Aim	Recommendation	Duration
Phase 1: avoidance	To reduce symptoms to the greatest possible extent	– Mixed diet with emphasis on vegetables and reduced biogenic amine intake, in particular histamine intake – Nutrient optimization – Changes in meal composition – Principles of a balanced diet	10–14 Days
Phase 2: test phase	To expand the choice of food while taking individual risk factors (stress, menstruation, medication use, etc.) into account	– Targeted re-introduction of suspected foods while taking the patient's individual dietary preferences into consideration – Determination of individual histamine tolerance	Up to 6 weeks
Phase 3: long-term diet	Continuous, balanced supply of nutrients High quality of life	– Individual nutritional recommendations guided by the individual histamine tolerance, taking exogenous risk factors into consideration	–

Allergo J Int 2017

Gluten sensitivity

Exploring the Strange New World of Non-Celiac Gluten Sensitivity

In critical moments, men sometimes see exactly what they wish to see.

Spock: Star Trek, the Original Series

Lebwohl & Leffler Clinical Gastroenterology and Hepatology 2015;13:1613–1615

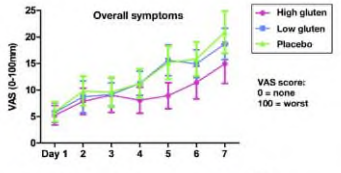
Going Against the Grains: Gluten-Free Diets in Patients Without Celiac Disease—Worthwhile or Not?

Benjamin A. Lerner[1] · Peter H. R. Green[1] · Benjamin Lebwohl[1,2]

Digestive Diseases and Sciences (2019) 64:1740–1747
https://doi.org/10.1007/s10620-019-05663-x

No Effects of Gluten in Patients With Self-Reported Non-Celiac Gluten Sensitivity After Dietary Reduction of Fermentable, Poorly Absorbed, Short-Chain Carbohydrates

Gastroenterol 2013;145:320-8

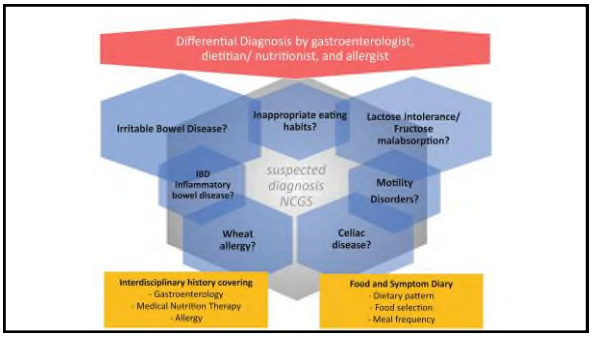


- ✓ worsening of symptoms to a similar extent after each challenge
- ✓ only 3 subjects (8%) had gluten specific symptoms
- ✓ worst at first challenge - regardless of wether gluten or placebo was given
  ⇨**high nocebo-response**

Non-celiac gluten/wheat sensitivity (NCGS)—a currently undefined disorder without validated diagnostic criteria and of unknown prevalence

Position statement of the task force on food allergy of the German Society of Allergology and Clinical Immunology (DGAKI)

1) No validated diagnostic criteria, frequent self-diagnosis
2) No reliable identification of gluten as trigger
3) Improvement on gluten-free can be due to many factors.
4) Potential disadvantages and risks are often disregarded.
5) Exclusion of celiac disease prior to introduction of GFD is imperative!
6) Patients on GFD should be encouraged to seek dietary counselling.



Tasks and aims of nutritional therapy in non-allergic adverse reactions

- Take a detailed patient's history ideally supported by a food and symptom diary!
- Make sure that important other causes/ underlying diseases have been excluded!
- Differenciate between claimed and real triggers by a 2-week food and symptom diary!
- Name the risks and disadvantages of a non-individualized diet!
- Establish an individualized dietary concept with each patient!

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REVIEW ARTICLE

WILEY Allergy

Recent developments and highlights in mechanisms of allergic diseases: Microbiome

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Abstract

All body surfaces are exposed to a wide variety of microbes, which significantly influence immune reactivity within the host. This review provides an update on some of the critical novel findings that have been published on the influence of the microbiome on atopic dermatitis, food allergy and asthma. Microbial dysbiosis has consistently been observed in the skin, gut and lungs of patients with atopic dermatitis, food allergy and asthma, respectively, and the role of specific microbes in allergic disorders is being intensively investigated. However, many of these discoveries have yet to be translated into routine clinical practice.

KEYWORDS

asthma, atopic dermatitis, food allergy, immune tolerance, microbiome

1 | INTRODUCTION

An enormous variety of microbes colonize the skin and mucosal body surfaces. These microbes are organized within complex community structures, utilizing nutrients from other microbes, host secretions and the diet. The microbiome is defined as the sum of these microbes, their genomic elements and interactions in a given ecological niche. In addition to bacteria, viruses are also considered to be an important component of the microbiome (virome). The composition of the microbiome is dependent on the specific body site examined, resulting in a series of unique habitats within and between individuals that can change substantially over time.[1] This presents significant challenges to the local immune system, which should tolerate the presence of these microbes to avoid damaging host tissue while retaining the ability to respond appropriately to pathogens. The mechanisms that mediate host-microbe communication are highly sophisticated and need to be constantly coordinated.[2] Indeed, disrupted communication between the microbiome and the host due to altered microbiome composition and/or metabolism is thought to negatively influence immune homeostatic networks and may play a role in immune hypersensitivity to environmental exposures, such as allergens.[3-5]

For several years, epidemiological studies have suggested associations between the migration from traditional farming to urban environments, increase in processed food intake, lack of contact with animals and excessive hygiene practices with the increased incidence

Abbreviations: AAI, allergic airway inflammation; AD, atopic dermatitis; AHR, airway hyper-responsiveness; AMP, antimicrobial peptides; COPD, chronic obstructive pulmonary disease; CRS, chronic rhinosinusitis; GCS, glucocorticoids; HDM, house dust mite; HMOs, human milk oligosaccharides; ICSs, inhaled corticosteroids; LABAs, long-acting β2 adrenergic receptor agonists; OIT, oral immunotherapy; PARs, protease-activated receptors; PSMs, phenol-soluble modulins; RSV, respiratory syncytial virus; SCFAs, short-chain fatty acids; TLR, Toll-like receptor.

of asthma, atopic dermatitis and food allergy. However, it is only relatively recently that the importance of the gut, lung and skin microbiomes in regulation of immune tolerance and its aberrations in a variety of human diseases including allergy and asthma has been recognized.[6,7] In particular, early-life events such as mode of delivery, breastfeeding, mother's diet and health status, antibiotics and other drug usage in pregnancy and early childhood, early-life environment (ie, siblings, pets at home, proximity to farm animals and green areas) significantly influence the timing of bacterial colonization and establishment, which modify the risk of developing allergies and asthma, as summarized in Figure 1.[8-17] In this review, we will highlight some of the recent advances in our knowledge regarding the influence of the microbiome on immune reactivity in the skin, gut and lungs of patients with atopic dermatitis, food allergy and asthma. In addition, we will discuss the potential translation and challenges associated with microbial-based therapies in patients with these allergic disorders.

2 | MICROBIOME IN ATOPIC DERMATITIS

The skin microbiome is comprised of bacteria, fungi, viruses and archaeal communities, with bacteria being the most widely studied.[18] The skin microbiome is influenced by age, gender, ethnicity, climate, UV exposure and lifestyle factors.[19] 16S ribosomal RNA (rRNA) sequencing has demonstrated that significantly diverse bacterial phyla exist on healthy skin with site-specific differences in composition. This is primarily driven by the physiology of a skin niche. *Propionibacterium* species are predominantly found in sebaceous sites, with *Corynebacterium* and *Staphylococcus* species occurring in moist microenvironments. *Malassezia* represents the predominant fungal flora on human skin.[20] Figure 2 illustrates the interactions between the skin microbiome and host cells.

Atopic dermatitis (AD) is characterized by epidermal barrier dysfunction resulting from a synergistic decrease in epidermal barrier structural proteins, alteration in lipid composition and skin pH, activation of local and systemic inflammatory responses and decrease in skin microbiome diversity.[19] *Staphylococcus aureus* overgrowth is consistently linked with AD pathogenesis and correlates with disease severity and eczematous flares.[1,21] High IL-4 and IL-13 levels within AD skin can deplete keratinocyte-produced antimicrobial peptides (AMPs), cathelicidin LL-37, human beta defensin hBD-2 and hBD-3, necessary for controlling pathogenic organisms.[22] Defective TLR-2 expression in Langerhans cells of AD skin has also been observed, which may contribute to the impairment in effective immune recognition and clearance of pathogenic bacteria such as *S. aureus*.[23] Epidermal lipid composition strongly correlates with bacterial diversity and composition at typical sites for AD lesions. For example, *S. aureus* dominance was associated with elevated levels of ceramide AS.[21]

Staphylococcus aureus overgrowth with concomitant decline in *Staphylococcus epidermidis* is a general feature of AD and is not restricted to eczematous lesions.[19,21] *Staphylococcus aureus* colonization is evident in 90% of AD cases,[24] associates with AD severity and increased allergen sensitization.[25] Intervention studies with antimicrobials targeting *S. aureus* can reduce AD severity. Restoration of the epithelial barrier with anti-inflammatory and emollient use is able to increase microbial diversity of lesional skin.[1,24] Patients with severe AD can be colonized with a single *S. aureus* strain, which persists even post-eczematous flare albeit at a lower relative abundance. In contrast, *S. epidermidis* strains were more heterogeneous. Interestingly, patients with more severe AD were colonized with

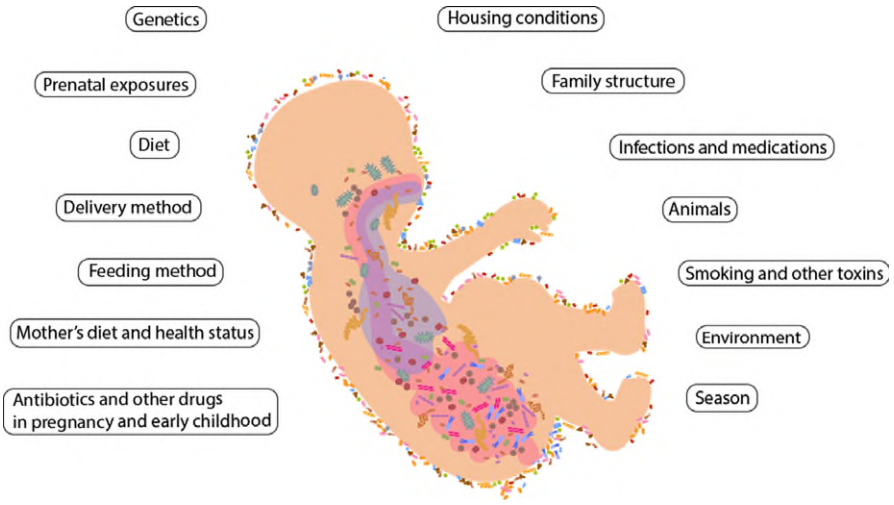

FIGURE 1 Early infancy is a critical window for microbiome establishment and immune development. The microbiome shapes innate and adaptive immune responses, and timely colonization with niche-specific taxa is crucial for immune tolerance evolution. While reports on in utero colonization are still controversial, there is no doubt that the mother's health status, diet and prenatal exposures influence the neonate's immune system. Maternal antibodies and microbial-derived molecules are transferred through the placenta and with breastmilk. Colonization with beneficial microorganisms, impacted by birth delivery method and breastfeeding, is associated with lower risk of asthma and allergy. Further environmental exposures that influence the microbiome composition include diet, housing conditions, siblings and pets

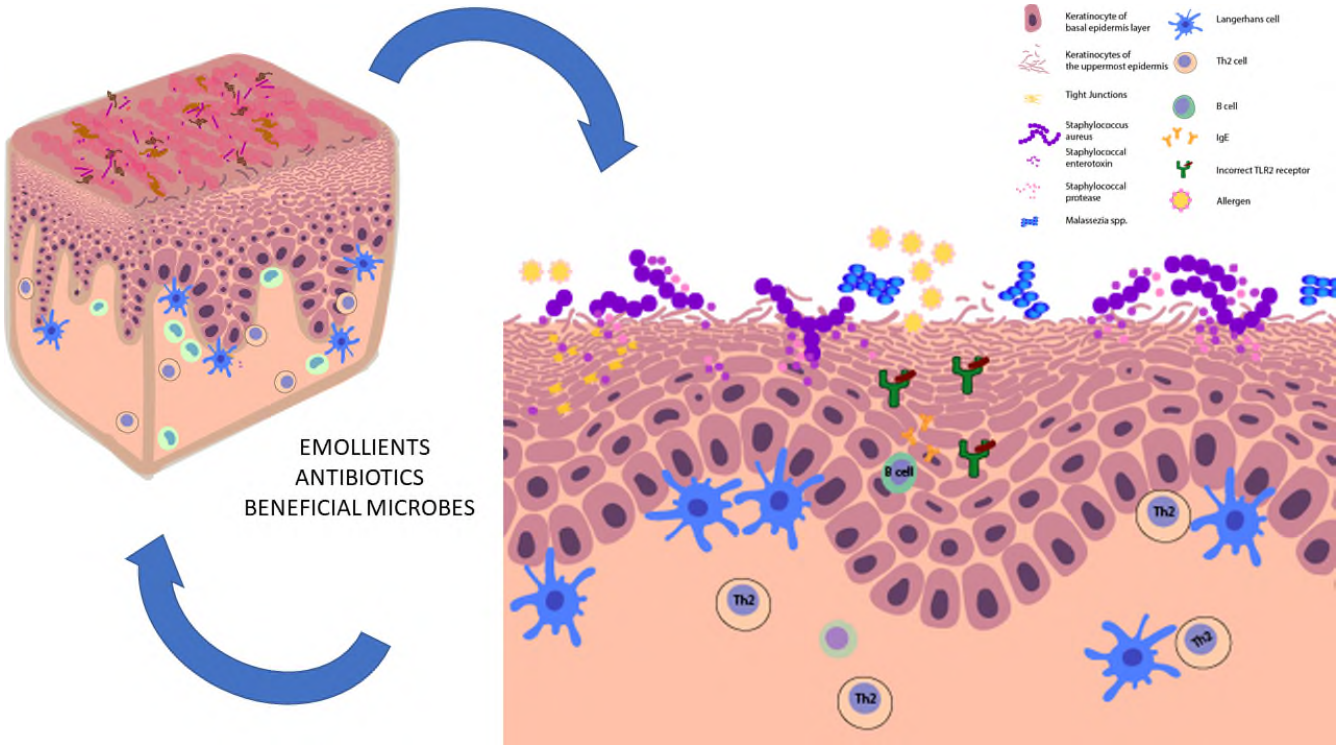

FIGURE 2 Microbiome of the skin. The human skin microbiome is abundant in bacteria, fungi and other microbes, and certain communities preferentially colonize specific niches. Atopic dermatitis skin creates such a specific niche itself. Key pathophysiological features of atopic dermatitis skin are as follows: altered composition of lipid barrier and epidermal barrier dysfunction, downregulation of keratinocyte differentiation markers (eg, filaggrin), defective Toll-like receptor 2 (TLR2) expression on Langerhans cells, increased uptake of potentially allergenic antigens, subsequent lymphocyte priming and infiltration with immune cells characteristic for Th2 type of inflammation. These features associated with atopic dermatitis skin are conducive to colonization by *Staphylococcus aureus*. Atopic dermatitis skin is also more abundant in *Malassezia* species. Colonization by *S. aureus* and *Malassezia* species is associated with disease severity; however, it is not limited only to lesional skin. Staphylococcal proteases directly and indirectly (through activation of protease-activated receptors (PARs) on epidermal cells) contribute to the disruption of epidermal barrier. Staphylococcal enterotoxins further disrupt epidermal integrity and act as allergens. Staphylococcal exotoxins damage keratinocytes and activate mast cells. Mast cell products further contribute to cutaneous inflammation. This pathogenic positive feedback loop can be interrupted by the use of emollients, topical antibiotics or topical beneficial microbes

methicillin-sensitive *staphylococci*, whereas less severe AD was more frequently associated with methicillin-resistant strains. This observation may have significant treatment implications, particularly when methicillin-sensitive *S. aureus* and methicillin-resistant *S. epidermidis* strains are present.[26] In a recent study, the skin microbiome of infants with AD showed a consistent absence of *S. aureus* sequences at multiple time points on lesional skin contrary to reported finding in patients with established AD. The most prevalent species were *S. epidermidis* and *S. cohnii*. However, those who developed AD at 12 months had significantly lower levels of these commensal *staphylococci* detectable at 2 months of age.[27] This study suggests that *S. aureus* colonization may not always predate clinical AD and highlights the need for longitudinal studies to investigate the transition to microbial dysbiosis in AD.

Commensal *S. epidermidis* strains can also increase during disease flares.[24] Coagulase-negative *staphylococci* (CoNS), which include *S. epidermidis*, *S. hominis* and *S. lugdunensis*, can secrete antimicrobials that limit *S. aureus* overgrowth and biofilm formation.[1,28] In addition, *S. epidermidis* activates TLR2, thereby promoting tight junction protein expression and inducing keratinocyte-derived antimicrobial peptide secretion. Early occupation of the neonatal human skin by *S. epidermidis* is associated with induction of *S. epidermidis*-specific FOXP3+ Treg cells that regulate local activation of host immune responses.[29] Other members of the healthy skin microbiota, such as *Propionibacterium*, *Streptococcus*, *Acinetobacter*, *Corynebacterium*, *Prevotella* and *Proteobacteria*, are frequently reduced in AD patients.[28,30]

Staphylococcus aureus can contribute to epidermal barrier disruption in a number of ways. *Staphylococcus aureus* downregulates terminal differentiation proteins such as filaggrin and loricrin, while secretion of proteases contributes to the disruption of the epidermal integrity via direct proteolytic activity or activation of protease-activated receptors (PARs). Superantigens such as staphylococcal enterotoxins A and B or toxic shock syndrome toxin-1 trigger a cytokine response that further disrupts the epidermal barrier. These enterotoxins also act as allergens, and toxin-specific IgE contributes to cutaneous inflammation.[28,31] *Staphylococcus aureus* expresses exotoxins such as cytolytic α-toxin, which damage keratinocytes, while β-, γ- and δ-toxins stimulate mast cell degranulation.[28,32] Phenol-soluble modulins (PSMs) induce keratinocyte damage and secretion of the alarmins IL-1α and IL-36α, which further exaggerate skin

inflammation.[33] An impaired skin barrier results in increased exposure of the immune system to microbial components, resulting in a progressive cycle of inflammatory responses and tissue damage. It was recently suggested that reactivity to *S. aureus* can be facilitated via allergen co-exposure and vice versa since patients with sensitization to house dust mite also show significantly more IgE reactivity to *S. aureus* and *Escherichia coli*, two abundant species in the house dust mite microbiome.[34] A subset of AD patients is susceptible to eczema herpeticum (EH), and *S. aureus* may contribute to EH susceptibility as it has been shown to secrete products that enhance viral replication.[1]

Despite *Malassezia* species having a commensal role in healthy skin, in AD *Malassezia* may contribute to disease pathogenesis. *Malassezia* DNA has been detected in 90% of AD skin lesions, and colonization increases with disease severity.[35] In addition, different *Malassezia* strains were found in AD and healthy individuals suggesting the existence of key pathogenic strains in AD.[36] Higher levels of IgE sensitization to *Malassezia* have been detected in adult AD compared to healthy individuals and childhood AD.[22,36] *Malassezia* could contribute to AD pathogenesis by secreting immunogenic proteins that induce proinflammatory cytokines, expression of TLR2 and TLR4 on keratinocytes and induction of auto-reactive T cells.[22]

Atopic dermatitis is considered a first step in the atopic diathesis, facilitated in part by the defective epidermal barrier of AD. The IL-4/IL-13 axis in AD is also thought to upregulate the pore-forming claudin-2 expression in the gut leading to barrier defects.[19] In addition to the skin microbiota, AD has been associated with changes in the gut microbiota. Patients with AD have lower levels of *Bifidobacterium* in the gut compared to healthy controls, and *Bifidobacterium* levels were inversely correlated with AD disease severity.[37] Several studies have shown that alterations in gut microbiota composition can precede the development of AD. Early gut colonization with *C. difficile* was associated with AD development,[38] and low gut microbiota diversity and specifically low *Bacteroidetes* diversity at 1 month were associated with AD development at 2 years of age.[35,39] A recent whole-metagenome analysis demonstrated a lower abundance of key metabolic pathways in AD children associated with depletion of mucin-degrading bacteria such as *Akkermansia muciniphila*, *Ruminococcus gnavus* and *Lachnospiraceae*.[40] These bacteria not only are able to influence immune development through directly influencing signalling pathways and antigen processing but also can lead to a reduced microbial diversity as these bacteria are able to degrade complex polysaccharides into short-chain fatty acids (SCFAs)—nutrient sources that allow for gut colonization by other microbes.[40] Dog exposure at birth was associated with a dose-related reduced risk of AD in early life, suggesting that exposure to an environment rich in microbial components may be protective.[41] In contrast, antibiotic exposure during the first 2 years of life is associated with an increased risk of AD.[42] Infants with high faecal calprotectin levels (an antimicrobial protein used as a biomarker of

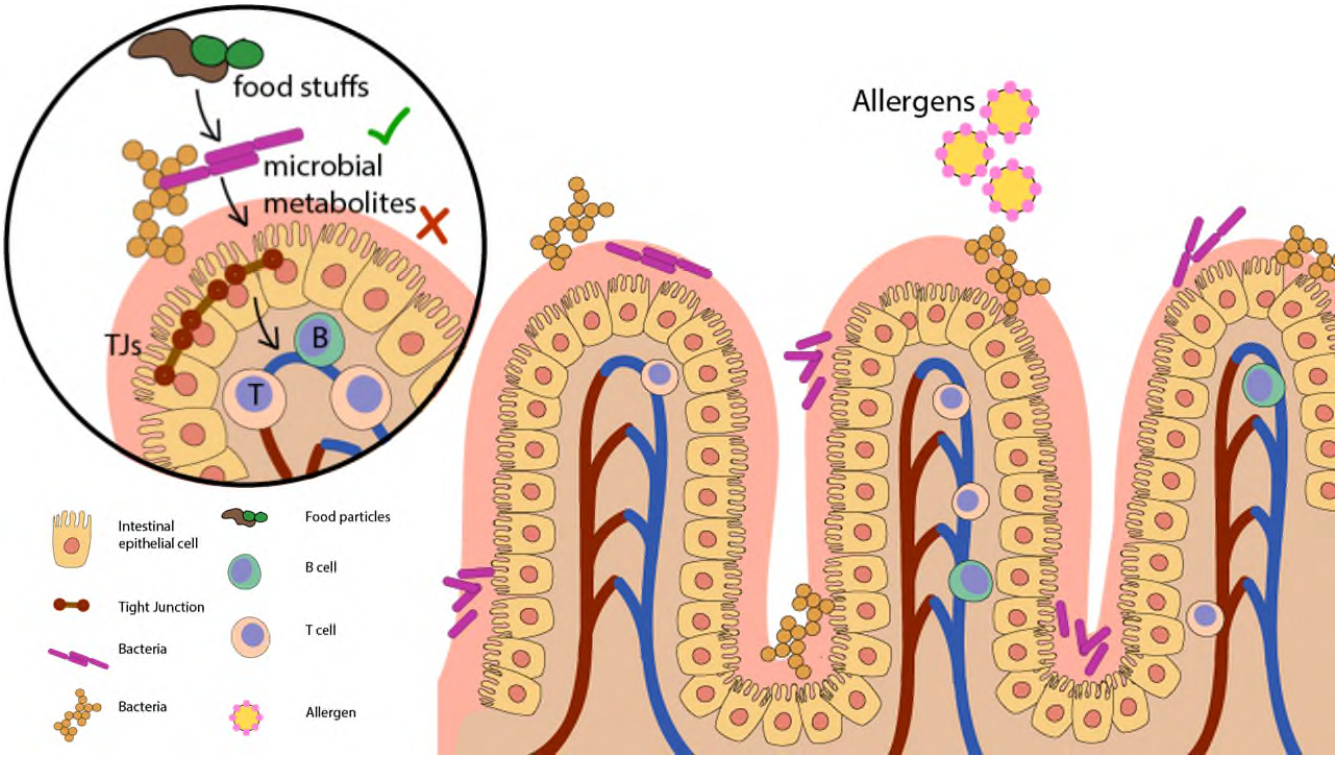

FIGURE 3 Microbiome of the gut. The gastrointestinal tract is densely colonized by bacteria, and resident microbes directly interact with consumed food, resulting in production of metabolites, such as short-chain fatty acids that promote tolerance responses. Intestinal epithelial cells interact with the microbiome, and the epithelial barrier is heavily influenced by microbiome composition and activities. In the absence of appropriate microbial signals, type 2 immunity is strongly enhanced within the gut mucosa

intestinal inflammation) measured at 2 months of age had an increased risk of AD and asthma by 6 years of age. High faecal calprotectin was also shown to be inversely correlated with levels of *E. coli*. Reduced early colonization with *E. coli* was shown to impair IL-10 regulation.[43]

3 | MICROBIOME IN FOOD ALLERGY

The human gut microbiome is increasingly being considered as a crucial factor in the development of food allergy, with a strong interrelation between the human gut microbiota, environmental factors, human genetics and gastrointestinal atopy.[4,44] In particular, the composition and metabolic activity of the gut microbiota are intimately linked with the development of oral tolerance.[45,46] Therefore, disturbed microbial homeostasis, especially early in life, appears to significantly influence allergic disease susceptibility. Figure 3 illustrates some of the known interactions between the gut microbiome and host mucosal cells.

Recently, the oral bacterial composition in saliva samples from healthy and allergic children up to 7 years of age was described. The result confirmed that early changes in oral microbial composition seem to associate with immune maturation and allergy development.[47] Milk-allergic infants have higher total bacteria and anaerobic bacterial counts compared with healthy control children after 6 months of differential formula intake. In addition, higher proportions of *Lactobacilli* and lower proportions of *Enterobacteria* and *Bifidobacteria* were observed in 46 milk-allergic infants.[48] The spontaneous resolution of milk allergy in infants was associated with a specific gut microbiota composition.[49] Bunyavanich et al showed that *Clostridia* and *Firmicutes* were enriched in the infant gut microbiome of subjects whose milk allergy spontaneously resolved. This result suggested that early infant gut microbiota may shape food allergy outcomes in childhood and bacterial taxa within *Clostridia* and *Firmicutes* species could be further investigated as probiotic candidates for milk allergy therapy.[49] An additional study examining the gut microbiome of 141 children with egg allergy and healthy controls found that genera from *Lachnospiraceae* and *Ruminococcaceae* were associated with egg sensitization; however, there was no association between early-life gut microbiota and egg allergy resolution by age 8 years.[50] A prospective microbiome association study in 14 children with food allergy and 87 children with food sensitization showed that the genera *Haemophilus*, *Dialister*, *Dorea* and *Clostridium* were underrepresented among subjects with food sensitization, whereas the genera *Citrobacter*, *Oscillospira*, *Lactococcus* and *Dorea* were underrepresented among subjects with food allergy.[51] An additional prospective study identified both temporal variation and long-term variation in the differential abundance of specific bacterial genera in children developing IgE-associated allergic disease, with *Faecalibacterium* correlating with IL-10 and Foxp3 mRNA levels.[52] Human milk oligosaccharides (HMOs) have been shown to be important in supporting the establishment of the infant gut microbiome as they are selective substrates for protective microbes such as Bifidobacteria.[53] Two recent studies have described differences in HMO composition that are associated with cow's milk allergy or food sensitization.[54,55] One potential mechanism for this association is that different HMO profiles may support the establishment of different microbes early in life, thereby indirectly influencing immune maturation and education. In conclusion, a number of human studies now suggest that food allergy could be associated with changes in microbial exposures in early life, which modifies the development of host immunity and results in pathologic immune responses to food allergens.

4 | MICROBIOME IN ASTHMA

Composition of the microbiome at all mucosal sites changes dynamically in the first days, months and years of life. If the process of "healthy" and timely colonization is disrupted, the early-life dysbiosis of the gut and lung becomes an important risk factor for atopy, allergy and asthma. In the Canadian Healthy Infant Longitudinal Development (CHILD) study, the lower relative abundance of the bacterial genera *Lachnospira*, *Veillonella*, *Faecalibacterium* and *Rothia* in the gut was associated with the development of asthma later in life and mechanistically linked with the reduced levels of faecal SCFAs.[56] Another recent study also showed that high levels of SCFAs early in life were protective against later life sensitization and asthma.[57] In a US birth cohort, lower relative abundance of *Bifidobacterium*, *Akkermansia* and *Faecalibacterium*, with higher relative abundance of *Candida* and *Rhodotorula*, in the gut of neonates significantly increased the risk of developing multisensitized atopy and asthma later in life.[58] Interestingly, the faecal metabolome of those children at increased risk contained increased levels of pro-inflammatory metabolites, among which 12, 13-DiHOME was able to induce IL-4 production in CD4+ T cells and decreased the abundance of Tregs.[58] Increased abundance of nasopharyngeal *Lactobacillus* species during acute respiratory infection with respiratory syncytial virus (RSV) in infancy was associated with reduced risk of wheezing at 2 years of age.[59] Colonization of the airways with *Streptococcus*, *Moraxella* or *Haemophilus* within the first 2 months of life was associated with virus-induced acute respiratory infections in the first 60 weeks of life as well as increased risk of asthma later in life.[60] Colonization of the hypopharynx within the first month of life with *Moraxella catarrhalis*, *Haemophilus influenzae* or *Streptococcus pneumoniae* was associated with low-grade systemic inflammation as assessed by serum CRP, TNF-alpha and IL-6 levels.[61] In addition, a positive association was observed between RSV infection and hospitalization in children with nasopharyngeal colonization with *H. influenzae* and *Streptococcus*.[62,63] Importantly, the relative nasopharyngeal abundance of *Streptococcus* and *Staphylococcus* negatively correlated with FEV1 and PC20 in children.[64] Children who were breastfed and those who had low rates of respiratory infections in the first 2 years of life were colonized early within the upper respiratory tract with *Staphylococcus* species, followed by *Corynebacterium*, *Dolosigranulum* and *Moraxella*.[65-67] However, the most impressive data regarding asthma protection have been observed in

relation to traditional farming environments, associated with a high endotoxin and bacterial-containing dust within the home.[5,15,17,68-71]

Adult asthma patients treated with inhaled corticosteroids (ICSs) have greater upper and lower airway microbiota diversity compared to control subjects, especially enriched in the phylum *Proteobacteria*, which include *Haemophilus*, *Comamonadaceae*, *Sphingomonadaceae*, *Nitrosomonadaceae*, *Oxalobacteraceae* and *Pseudomonadaceae* families.[72-76] The phylum *Proteobacteria* is also associated with worse asthma control, whereas *Actinobacteria* correlates with improvement or no change in asthma control.[77] Interestingly, neutrophilic exacerbations of asthma and chronic obstructive pulmonary disease (COPD) correlated with the presence of *Proteobacteria* in the sputum, whereas eosinophilic exacerbations correlated with the presence of *Bacteroidetes*.[78] *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* are also often found in the airways of the severe asthmatic.[79] Macrolide antibiotic treatment may be useful in this subgroup of patients, but patients should be carefully selected.[80] Both clarithromycin and azithromycin have been shown to reduce airway hyper-responsiveness and decrease the abundance of *Pseudomonas*, *Haemophilus* and *Staphylococcus*,[73,81] while increasing the relative abundance of *Streptococci*.[82] However, it is currently not clear how significant a role asthma medications play in directly influencing the composition of the airway microbiota. It has been reported that combination of ICS and oral glucocorticoids (GCS) correlates positively with the increased abundance of *Proteobacteria*, specifically *Pseudomonas*, and with a decreased abundance of *Bacteroidetes*, *Fusobacteria* and *Prevotella*.[83] In corticosteroid-resistant patients, *Neisseria-Haemophilus*, *Campylobacter* and *Leptotrichia* species are present in the lower airways.[75] Interestingly, treatment of COPD patients with ICS and long-acting β2 adrenergic receptor agonists (LABAs), compared to LABA alone, significantly increased the bacterial load, increased bacterial diversity and changed composition of the microbiome in the airways.[84] However, prospective longitudinal studies involving corticosteroid-naïve asthma patients are still needed to address the issue of medication effects on the airway microbiome. The mechanisms responsible for changes in the airway microbiome are also not well understood, and in addition to medications, it is possible that the type of inflammatory response (ie, eosinophil vs neutrophil), changes in host secretions (eg, lipids[85,86]) and cellular metabolism might influence microbial colonization and growth within the airways. Figure 4 illustrates the immune responses in the airways that can be influenced by the respiratory microbiome.

In addition to asthma, the potential for microbes to play a role in the initial aetiology of rhinitis, or in exacerbations and progression to more severe inflammatory sequelae (such as asthma) is currently being examined. The phylum *Proteobacteria* is enriched in children with rhinitis, which may be clinically important given the *Proteobacteria*-related asthma associations described above.[69] Dysbiosis of the inferior turbinate mucosa microbiota, particularly an increase in *S. aureus* and a decrease in *P. acnes*, was associated with high total

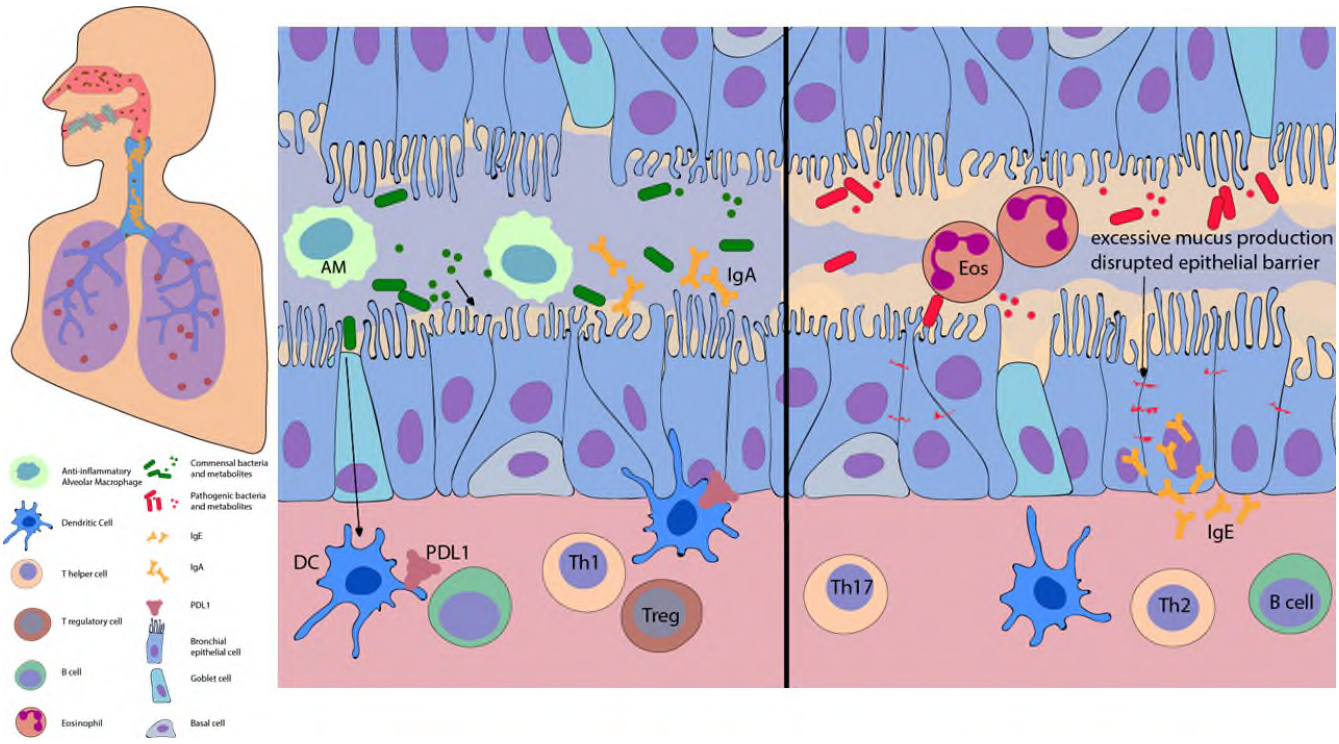

FIGURE 4 Microbiome of the airway. Recently, it has been accepted that the airways are not sterile and are inhabited with niche-specific bacteria and fungi. Timely exposure and colonization by commensal microbes attenuate airway allergic inflammation via enhanced expression of programmed death ligand 1 (PDL1) on dendritic cells, and promote regulatory lymphocytes and IgA secretion (left panel). Exposure to pathogenic bacteria can drive excessive host inflammatory responses, enhances Th2/Th17 cell polarization, IgE secretion, disrupts the epithelial barrier and promotes excessive mucus secretion (right panel)

IgE levels in adults with allergic rhinitis.[87] In adults with chronic rhinosinusitis (CRS), the genus *Corynebacterium* was depleted, accompanied by increased relative abundance of genera from the phyla *Firmicutes* (including *Staphylococcus* and *Streptococcus*), *Proteobacteria* (including *Haemophilus*, *Pseudomonas* and *Moraxella*) or *Fusobacteria*. This trend was particularly evident in subjects with comorbidities such as asthma and cystic fibrosis.[88] Similarly, another study reported that middle meatus samples from CRS patients without nasal polyps were enriched in *Streptococcus*, *Haemophilus* and *Fusobacterium* but exhibited loss of diversity compared to healthy, CRS with nasal polyps and allergic rhinitis subject samples.[89]

5 | LEARNING FROM ANIMAL MODELS

Despite the compelling observations and associations in humans that link changes in the microbiota with allergic diseases, very often the causal relationship is not clear. Microbial dysbiosis can be the reason for the disease but can also be the consequence of inappropriate immune reactivity. Animal models have been used to better understand the role of microbes in directly influencing allergic diseases and to elucidate the molecular mechanisms underpinning host-microbe crosstalk.

5.1 | Atopic dermatitis

Similar to humans, dogs naturally develop AD and associated allergen sensitization. Canine AD is associated with reduced bacterial diversity, with increased abundance of *Staphylococcus pseudintermedius* and *Corynebacterium* species.[90] Canine AD lesions improve with antimicrobial treatment and a reduction in *Staphylococcus* species coincided with restoration of bacterial diversity.[30]

Filaggrin-deficient flaky tail mice carry a loss-of-function *filaggrin* mutation, which is associated with a defective epidermal barrier, epidermal hydration and flexibility. *Staphylococcus aureus* abundance on the skin of these mice correlates with Th2 cytokine levels.[91] Inbred DS-Ng mice develop spontaneous dermatitis, and the skin lesions have been shown to be heavily colonized by *S. aureus*.[29] *Staphylococcus aureus* triggered cutaneous inflammation involve the accessory gene regulatory (Agr) virulence systems of *S. aureus* and induced δ-toxin molecules, which initiate Th2 type skin inflammation. Targeted *S. aureus* and *Corynebacterium bovis* antimicrobial therapy improved eczematous lesions and increased bacterial diversity in Adam 17 (a transmembrane metalloproteinase)-deficient mice. Withdrawal of targeted antimicrobials resulted in a recurrence of eczema and microbial dysbiosis.[30] In a mouse itch model, IL-17A and IL-22 drive neutrophils to limit the overgrowth of *S. aureus* on injured skin.[25] C5aR-deficient mice develop reduced microbial diversity, suggesting that the complement system may also regulate the skin microbiota.[29] A mouse model of AD showed that application of a *Vitreoscilla filiformis* bacterial lysate reduced the inflammatory manifestations following allergen application.[24] Studies in mice during the neonatal period suggest that tolerance to skin commensals such as *S. epidermidis* is preferentially established early in life. This supports the hypothesis that exposure to certain microbes at a critical window early in life is required for normal development of the immune system.[30]

5.2 | Food allergy

The potential role of the gut microbiome in food allergy has been studied in multiple murine models. Rodriguez et al[92] demonstrated that intestinal colonization with *Staphylococcus* protects against oral sensitization and allergic responses. The microbiota of allergen-sensitized IL-4raF709 mice differentially promoted OVA-specific IgE responses and anaphylaxis when reconstituted in wild-type germ-free mice, which could play a role in food allergy.[93] The disease-susceptible IL-4raF709 mice display enhanced signalling through the interleukin-4 receptor (IL-4R) and exhibit STAT6-dependent impaired generation and function of mucosal allergen-specific Treg cells, which failed to suppress mast cell activation and expansion.[94] Interestingly, STAT6 gene variants are also implicated in the pathophysiology of food allergy in humans.[95] The gut microbiota can also regulate Th2 responses through the induction of RORγt Treg cells and Th17 cells.[96] Certain bacterial strains such as *Bifidobacterium longum* 35624, *Lactobacillus rhamnosus* JB-1, *Clostridia* species and *Bacteroides fragilis* can induce intestinal Treg cells that are able to suppress food allergy and colitis.[97,98] Pattern-recognition receptor activation on DCs is a potential mechanism by which intestinal microbes may promote Treg cell differentiation.[99]

5.3 | Asthma

Important insights regarding the role of the microbiota in the pathogenesis of airway inflammation have come from mouse models. Neonatal mice are more susceptible to develop house dust mite (HDM)-induced allergic airway inflammation (AAI) and airway hyperresponsiveness (AHR) than mature mice.[100] This phenomenon was associated with a shift from *Gammaproteobacteria* and *Firmicutes* towards a *Bacteroidetes*-dominated microbiota and the development of PDL-1–dependent Helios- Treg cells.[100] Mice housed under germ-free conditions display significantly more pronounced type 2 inflammation and AHR as compared to conventionally colonized mice. Recolonization, especially early in life, can reverse many of these immunological defects.[101] Similarly, antibiotic-driven dysbiosis in neonatal mice leads to impaired maturation of Tregs and enhanced Th2 responses and promotes proinflammatory colonic iNKT cells.[80,102-105] Conversely, specific bacterial strains, their components or metabolites can successfully induce a variety of anti-inflammatory responses in the gut and in the lung. *L. rhamnosus* decreased AAI and AHR induced by Bet v 1 in mice.[106] Bacterial strains isolated from neonatal mouse lungs and then administered intranasally very early in life (starting at day 2 after birth) can protect or worsen HDM-induced airway inflammation, depending which cytokine profile they induced in vitro on precision-cut lung slices.[107] Intramuscular treatment with a DNA plasmid encoding a *M. leprae* 65 kDa heat-shock protein (DNA-HSP65) or subcutaneous injections with

TABLE 1 Microbiota summary

Location	Phyll (Genus)	Effect	Reference
Oral cavity	↑ *Gemella haemolysans* ↓ *Lactobacillus gasseri*, *Lactobacillus crispatus*	Increased risk of allergic diseases	47
Intestine	↑ *Staphylococcus* species	Protection against oral sensitization and allergic responses	92
Intestine	↑ *Clostridia*, *Firmicutes*	Milk allergy resolution	49
Intestine	↑ *Lachnospiraceae*, *Ruminococcaceae*	Associated with egg allergy	50
Intestine	↓ *Haemophilus*, *Dialister*, *Dorea*, *Clostridium*	Associated with food sensitization	51
Intestine	↓ *Citrobacter*, *Oscillospira*, *Lactococcus*, *Dorea*	Associated with food allergy	51
Intestine	↓ *Escherichia coli*	High faecal calprotectin, impaired IL-10 activation, increased risk of AD and asthma	43
Intestine	↓ *Bifidobacterium*	Correlates with AD severity	37
Intestine	Early colonization with *C. difficile*	Associated with AD development	38
Intestine	↓ *Bacteroidetes* diversity	Associated with AD development	39
Intestine	↓ *Akkermansia muciniphila*, *Ruminococcus gnavus* and *Lachnospiraceae*	Associated with AD development	40
Intestine	↓ *Lachnospira*, *Veillonella*, *Faecalibacterium*, *Rothia*	Reduced levels of faecal SCFAs, increased risk of asthma	56
Intestine	↓ *Bifidobacterium*, *Akkermansia*, *Faecalibacterium* ↑ *Candida*, *Rhodotorula*	Increased risk of developing multisensitized atopy, increased circulating proinflammatory metabolites	58
Upper airways	Early colonization with *Staphylococcus* species, *Corynebacterium*, *Dolosigranulum*, *Moraxella*	Associated with lower rate of respiratory infections in the first 2 years of life	65-67
Upper airways	Early colonization with *Streptococcus*, *Moraxella*, *Haemophilus*	Increased risk of virus-induced acute respiratory infections and increased risk of asthma	60
Upper airways	↑ *Proteobacteria*	Associated with rhinitis in children	69
Nasopharynx	↑ *Haemophilus influenzae*, *Streptococcus* species	Increased risk of hospitalization during RSV infection	62
Nasopharynx	Colonization with *Staphylococcus aureus*	Decreased risk of hospitalization during RSV infection	63
Nasopharynx	↑ *Streptococcus*, *Staphylococcus*	Abnormalities in functional tests of the respiratory system	64
Nasopharynx	↑ *Staphylococcus aureus* ↓ *P. acnes*	Associated with high IgE levels	87
Nasopharynx	↑ *Firmicutes (Staphylococcus & Streptococcus)*, *Proteobacteria (Haemophilus*, *Pseudomonas & Moraxella)*, *Fusobacteria* ↓ *Corynebacterium*	Associated with CRS in adults	88
Nasopharynx	↑ *Streptococcus*, *Haemophilus*, *Fusobacteria* ↓ Diversity	Associated with CRS without nasal polyps in adults	89
Nasopharynx	↑ *Lactobacillus* during acute respiratory infection with RSV	Reduced risk of wheezing	59
Hypopharynx	Colonization with *Moraxella catarrhalis*, *Haemophilus influenzae*, *Streptococcus pneumoniae*	Low-grade systemic inflammation	61
Lower airways	↑ *Proteobacterium* (*Klebsiella* species) (*Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*)	Associated with severe asthma	77,79
Lower airways	↑ *Actinobacteria*	Improvement in asthma control	77
Lower airways	↑ *Neisseria*, *Haemophilus*, *Campylobacter*, *Leptotrichia*	Associated with resistance to corticosteroids in asthma	75
Sputum	↑ *Proteobacteria*	Associated with neutrophilic asthma exacerbations	78
Sputum	↑ Bacteroidetes	Associated with eosinophilic asthma exacerbations	78
Skin	↑ *Staphylococcus aureus*	Epidermal barrier dysfunction, cutaneous inflammation, formation of AD skin lesions, associated with AD severity and allergen sensitization, associated with susceptibility to eczema herpeticum among AD patients	19,21,23
Skin	Colonization with single clonal *Staphylococcus aureus* strains	Associated with AD severity	26
Skin	↑ *Malassezia* species.	Associated with AD severity	35

(Continues)

TABLE 1 (Continued)

Location	Phyll (Genus)	Effect	Reference
Skin	↑ *Corynebacterium, Proteobacterium*	Associated with AD severity	21
Skin	↑ coagulase-negative staphylococci: (*Staphylococcus epidermidis*, *S. hominis*, *S. lugdunensis*)	Limits *Staphylococcus aureus* overgrowth	28
Skin	Colonization with *S. epidermidis*	TLR2 activation, epidermal barrier maintenance	1
Skin	↓ *Proteobacteria* (*Propionibacterium*, *Streptococcus*, *Acinetobacter*, *Corynebacterium*, *Prevotella*)	Associated with AD	28,30
Skin	Early colonization with *S. epidermidis*	Local activation of the host immune response through induction of *S. epidermidis*-specific FOXP3 Treg cells	29
Skin	↑ in resident skin bacteria	Associated with AD flares	24

This table summarizes the bacterial changes that have been associated with atopic dermatitis, food allergy or asthma.

proteins from *M. tuberculosis* delivered in the presence of the TLR9 agonist CpG were able to significantly inhibit development of Der p 1-induced AAI and AHR in MyD88- or Fas-dependent manner.[108] In addition, an exopolysaccharide from *B. longum* subsp. *longum* 35624 was shown to protect against colitis and AAI in murine models, which was dependent on TLR2-induced IL-10 secretion.[109,110] SCFAs or dietary fibres that are metabolized to SCFAs potently reduced experimental asthma, as well as increased the levels of colonic *Bacteroidetes* and *Actinobacteria* species, while decreasing the levels of *Firmicutes* and *Proteobacteria*.[111,112] Importantly, the beneficial effects of SCFAs or a high-fibre diet were transferred to the offspring after treatment of pregnant mice via epigenetic mechanisms.[112,113] Mechanistically, SCFAs have been repeatedly shown to increase Treg numbers and effectiveness.[114,115] In addition, SCFAs influence bone marrow haematopoiesis,[111] reduce effector T-cell activity,[116] improve epithelial barrier[117,118] and inhibit mast cell and ILC2 activation.[119,120] Other bacterial metabolites, such as histamine, can induce a wide and complex spectrum of regulatory mechanisms.[121,122] Increased numbers of histamine-secreting bacteria were observed in adult patients with asthma and correlated with asthma severity.[123] Histamine signalling through the H2R is involved in AAI,[124] while the use of H2R antagonists in children during their first 6 months of life is associated with significantly increased risk of allergic diseases and asthma.[10]

6 | THERAPEUTIC TARGETING OF THE MICROBIOME

Despite the growing number of studies that associate changes in the microbiota with allergic and immune-related outcomes, only a relatively small number of studies have shown clinical benefits and there are no microbe-based therapies that are currently universally accepted for the prevention or treatment of allergies or asthma. A number of reasons can be suggested for this, which may include the poor choice of therapeutic microbes to begin with. It is likely that many confounding factors do influence the success of a microbiome therapeutic, such as diet, age, obesity, ethnicity and other environmental exposures. These need to be taken into account and controlled for. In addition, given the explosion in knowledge regarding disease endotypes, it is possible that specific microbes will need to be carefully selected to mechanistically fit with specific disease endotypes and it is likely that one intervention will not work for everyone. Certain interventions such as faecal transplantation may be too crude an approach, and until critical safety concerns are resolved, this type of intervention should not be considered outside the setting of carefully monitored clinical trials.

6.1 | Atopic dermatitis

Early intervention aimed at protecting the skin barrier may ameliorate progression of the atopic march in a subset of patients.[19] Skin microbiome manipulation may offer novel therapeutic opportunities, as has been seen with the emollients supplemented with a *Vitreoscilla filiformis* lysate.[125] Similarly, topically administration of *Roseomonas mucosa* improved clinical severity scores in adults and children with AD.[125] Autologous microbiome transplant (AMT) of *S. hominis* and *S. epidermidis* showed efficacy in controlling *S. aureus* overgrowth.[126]

In addition to topical bacterial treatments, oral administration of probiotics has also been examined. Prenatal and post-natal treatment with *Lactobacillus* and *Bifidobacterium* strains can reduce risk of AD development in infants,[35,127,128] which may associate with changes in T cell–mediated responses.[129] A mixture of probiotic strains was recently shown to reduce SCORAD index and topical steroid use in children with AD.[130] Little has been reported on probiotic treatment of adults with AD, but administration of *B. longum* 35624 to adults with psoriasis resulted in reduced circulating CRP, TNF and IL-17 levels, possibly due to increased numbers of Tregs, which suggests that bacteria in the gut can influence skin inflammatory activity in adults.[131,132] Taken together, supplementation with specific probiotic strains may modulate the gut bacteria in a way that influences inflammation within the skin and may protect some children against AD development.[35]

6.2 | Food allergy

The use of probiotics in food allergy treatment and prevention has been examined. Supplementation of cow's milk-allergic children with *Lactobacillus casei* and *Bifidobacterium lactis* did not accelerate cow's milk allergy resolution.[133] However, the combination of *L. rhamnosus*

GG and extensively hydrolysed casein formula did accelerate milk allergy resolution after 6 and 12 months when compared to the formula-only control group.[134] The combination of *L. rhamnosus* supplementation and peanut oral immunotherapy (OIT) was evaluated in peanut-allergic children for 18 months. The combination was effective in inducing possible sustained unresponsiveness and immune changes that suggested modulation of the peanut-specific immune response.[135] In addition, a sustained beneficial effect on psychosocial impact of food allergy at 3 and 12 months after end of treatment was recently reported.[136] However, the major limitation of this study is that further work is required to determine the relative contributions of the probiotic vs OIT due to the lack of an OIT and *L. rhamnosus* supplementation control groups in this trial.

6.3 | Asthma

A significant number of studies have examined the effect of probiotic supplementation on asthma-related outcomes. A recent systematic review of probiotic studies in children with asthma identified eleven studies eligible with a total of 910 children. The proportion of children with fewer episodes of asthma was significantly higher in the probiotic group than in the control group, but no statistical significance was observed in childhood asthma control test, asthmatic symptom in the day and night, the number of symptom-free days, forced expiratory volume in the first second predicted and peak expiratory flow.[137] In the future, it will be interesting to evaluate microbial administration directly to the airways, in addition to the gut.[138]

7 | CONCLUSIONS

Significant advances have been made in recent years in describing the composition of the microbiome in the gut, airways and skin. The changes in bacterial communities that associate with, or sometimes precede, atopic dermatitis, food allergy and asthma are being identified (summarized in Table 1). Accumulating evidence suggests that microbial exposures might be most effective at preventing atopic disorders during the first 1-2 years of life. However, substantial gaps in our knowledge on the microbiome still exist. In particular, the field has been slow to translate potentially effective microbiome-associated therapies into the clinic via appropriate clinical trials performed to high standards and showing meaningful clinical responses that are superior to current avoidance approaches. While the critical role of the microbiota in cancer immunotherapy has been established, there are currently no published data on the potential role of the microbiota in influencing the success of immunotherapy or biologics in allergy or asthma.[139] In addition, novel probiotics and not just the traditional probiotic strains need to be clinically tested. Furthermore, microbial components or their metabolites should also be examined; in particular, the application of these novel microbial drugs to the diseased site (eg, the airways) must be explored. Lastly, there are no microbial therapeutics currently approved for routine clinical practice, and significant effort and investment are still required to identify the optimal microbial interventions for allergy and asthma.

CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

NL, PS, ZL, MS, TE and LOM contributed to drafting the manuscript. All authors read, reviewed and agreed the final version of this manuscript.

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The Controversies in Dietary Management of Non-IgE mediated Allergies

By Rosan Meyer (RD PhD)

Unlike Immunoglobulin E (IgE)-mediated food allergies, there is paucity of data in many areas of dietary management of non-IgE mediated allergies, outside of eosinophilic oesophagitis (EoE) and food protein induced enterocolitis syndrome. Clinical features of this delayed allergy, includes growth faltering, symptoms of dysmotility (e.g. diarrhoea, constipation and/or vomiting) and inflammation.(1) Nutritional support therefore may play a role in the management of all aforementioned symptoms, but data on nutritional components, including amino acid versus peptides, whey hydrolysates, content of lactose, pre and probiotics and level of avoidance remains controversial.

The mainstay of management for cow's milk protein (CMA) related non-IgE mediated allergies in the young remains the elimination of cow's milk.(2) When breastmilk is insufficient or not available, a hypoallergenic formula is recommended, comprising both amino acid (AAF) and extensively hydrolysed formulas.(3) In non-IgE mediated allergies, the use of an AAF as first line treatment, outside of EoE remains a debated topic.(4) Meyer et al.(5) found in a recent review, that in children with non-IgE mediated allergies, with multiple system involvement, in particular in the presence of faltering growth an AAF is warranted as first line formula. For all other presentations, an EHF should be used as first line treatment.

Due to diarrhoea (with/without gut inflammation) being a common feature of non-IgE mediated allergies, the appropriateness of hypoallergenic formulas with medical grade lactose has been questioned; the concern being a secondary lactose intolerance. Already in 2012, the European Society of Paediatric Gastroenterology, Hepatology and Nutrition guidelines on CMA found no concern for use in children with non-IgE mediated allergies.(6) The addition of lactose has been shown to have a positive impact on the gut microbiome and bioavailability of certain micronutrients.(7, 8) Furthermore, Meyer et al.(9) found in a prospectively recruited non-IgE mediated cohort, that lactose intolerance was not present.

Gastric emptying is commonly affected in non-IgE mediated allergies.(10) Breastmilk is rich in whey protein, which is known to have different (faster) gastric emptying kinetics than casein.(11) The routine use of whey-based EHF has therefore been questioned in children with food protein induced gastro-oesophageal reflux disorder. Emptying kinetics change when milk protein is hydrolysed and to date no convincing data has been published in cow's milk allergic children that a whey EHF is superior to a casein EHF.(12)

The addition of medium chain triglycerides (MCT) at varying amounts is common place in EHF. MCT as fat source have a different small bowel absorption pattern to long chain fatty acids, in that they are hydrolysed faster by digestive juices and pancreatic lipase, which optimises absorption in fat malabsorption disorders.(13) To date, not study has been published to substantiate the co-existence of fat malabsorption in children with CMA. There is therefore no current indications for its routine use in non-IgE mediated allergies and clinicians need to note that MCT may impact thermoregulation and growth in the young.(14)

It has been shown that children with a non-IgE mediated CMA have dysbiosis,(15) which leads to the question of pre and probiotics as part of nutritional management in non-IgE mediated allergies. To date the majority of research in regards to pre and probiotic use in food allergy

has been on IgE-mediated allergies.(16) Guidelines therefore, do not explicitly provide information on the routine use in delayed food allergy. There is some data pointing towards early tolerance development to CMA with the addition of Lactobacillus GG to an EHF in non-IgE mediated allergies.(17) In addition, a recent study has been published, trialling synbiotics in an AAF in non-IgE mediated allergies; whilst the results related to the stool microbiota looks promising, no clinical differences were seen in patients.(18)

Many aspects of the management of non-IgE mediated food allergy remain controversial. Research is being conducted in numerous areas and therefore healthcare professionals should stay abreast with newly published data that may change practice.

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Maternal elimination and complexity of food allergy in breastfed infants – practical interactive cases

By Rosan Meyer (RD, PHD)

The presence of food allergy in breastfed infants is often disputed, because limited evidence has been published in non-IgE mediated allergies. This is in part due to the randomisation of breastmilk against formula being unethical and symptoms of non-IgE mediated allergies often overlapping with commonly reported colic, regurgitation and loose stools in early infancy.(1) However, it is known that ß-lactoglobulin, soya isoflavones and ovalbumin transfer through breastmilk in varying amounts, which have the potential to cause reactions.(2-4)
It has been documented that 0.5% of 2.2% of children with CMA, reacted whilst breastfed and since then several observational studies have been published, where children presented with non-IgE mediated symptoms affecting the skin and the gastrointestinal tract, whilst being breastfed.(5, 6) There is limited data on elimination diets in breastfed children, but it is thought that cow's milk is the most commonly reported allergen with some data on egg, soya and wheat.(7, 8)
When a non-IgE mediated allergy is suspected in a breastfed infant, a maternal elimination diet needs to be considered. An allergy focused history should guide the maternal elimination diet and care needs to be taken to avoid unwarranted eliminations of food, as maternal health may be affected.(8, 9) In addition, it is essential that after an elimination diet, the reintroduction of the allergen should take place to confirm the diagnosis. Whilst the elimination diet occurs, breastfeeding mothers' micronutrient requirements need to be considered not only to support breastfeeding but to account for eliminating the food allergen (e.g. cow's milk).
All current guidelines support exclusive breastfeeding until around 6 months of age also for children with non-IgE mediated allergies.(8) This is in line with current World Health Organisation guidelines for exclusive breastfeeding until 6 months of age.(10) In addition, the recent World Health Assembly has highlighted concern in regards to inappropriate marketing of breastmilk substitutes and include hypoallergenic formulas (previously seen as a Food for Special Medical Purpose) under this guidance document.(11) Healthcare professionals working in food allergy have recently been criticised for inappropriately promoting hypoallergenic formulas and according to the author, impacting breastfeeding rates.(12) Whilst, there is no data to substantiate this claim, healthcare professionals practicing in food allergy need to understand the importance of breastmilk and support required by breastfeeding mothers of a food allergic infant. As such the following guidelines should be adhered to:

1. Support breastfeeding where possible and provide parents with local support (lactation specialist and support associations) where possible
2. Ensure that the elimination diet is done in a way that does not negatively impact on breastfeeding and the health of the mother
3. Provide optimal vitamin and mineral supplementation information to the mother and infant
4. Do not recommend a hypoallergenic formula in a breastfed baby, unless this is requested by the parents or clinically required
5. Consider the impact on quality of life on the breastfeeding mother (13)

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Medical management of Non-IgE mediated conditions (except Eosinophilic Oesophagitis and FPIES).

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Non–IgE mediated allergy, outside of food protein-induced allergic enterocolitis / proctocolitis and eosinophilic oesophagitis, is not well understood, leading to variations in the diagnosis and management thereof.

The diagnosis of non–IgE-mediated gastrointestinal (GI) allergic disease is a clinical challenge. Whilst each disease has unique symptoms and signs, these may overlap and vary in severity for several conditions or diseases. It is also not uncommon for more than one organ system to be involved or several symptoms in one organ system, as well in allergic disease as in functional GI disorders. The majority of infants diagnosed as suffering a functional GI disorder also present with more than one symptom. Non–IgE-mediated food protein-related GI conditions usually present at a young age, or are insufficiently recognized in older children and adults. Further complicating the diagnosis of non–IgE-mediated food allergy is that symptoms such as altered bowel habit, reflux, constipation and colic may occur in about or even more than half of otherwise healthy infants. Cow's milk is the most common allergen, but evidence shows that other allergenic food proteins including egg, soya and wheat. Clinicians who adopt a single organ approach may therefore risk missing the possibility of a unifying cause such as non–IgE-mediated food allergies. The Cow's Milk related Symptom Sore (CoMiSS^{TM}) may help to increase awareness resulting in a more appropriate detection of these infants. The following paragraph focusses on cow's milk protein allergy. The situation is more straight forward for infants presenting with eosinophilic oesophagitis, food protein induced enterocolitis (FPIES) and food protein induced allergic procto-colitis (FPIAP). The diagnosis of these conditions necessitates endoscopy and histologic confirmation of the diagnosis. In infants, symptoms of eosinophilic oesophagitis and gastro-oesophageal reflux

disease (GORD) with over regurgitation/vomiting are overlapping. Therefore, endoscopy and biopsies are recommended, not to confirm the diagnosis of GORD but to diagnose or exclude other conditions with similar symptomatology. If atopic dermatitis disappears under elimination diet and reappears when the suspected food is reintroduced, the pathophysiological mechanism would be hard to understand if the immune system would not be involved. However, the proof of involvement of the immune system in infant presenting with reflux, constipation and colic is less straight-forward, even if the symptoms disappear during elimination and reappear during reintroduction. Hydrolysates empty the stomach more rapid than intact protein and are also associated with softer stools in all infants. Both may have an impact on infant distress and crying, and infant colic. Moreover, many extensively hydrolysed formulas have a different carbohydrate content (no lactose) and different lipid content (no palm oil). Therefore "improvement during elimination diet" is not a proof of involvement of the immune system. Last but not least, these functional GI disorders are recognized to occur frequently in infants as troublesome regurgitation and infantile colic occur both in ~20 % of infants and constipation in 10 %.

Then, the question arises is the elimination needs to be with extensive hydrolysates, or if there is a role for soy or even partial hydrolysates. Obviously, extensive hydrolysates are "the best" from the immunological point of view. But, they have a poor taste and are expensive. Soy has a better taste, and is much cheaper. In most of the European countries, this issue has been regulated by industry, as there is no soy infant formula available on the market. The safety of soy under the age of six months is heavily debated, but hard evidence for soy being harmful is weak. However, soy protein is also reported to be as allergenic as cow's milk protein in young infants. Although also the following is contradicted, there is some evidence that soy is less tolerated in infant with non-IgE mediated cow milk allergy than in IgE mediated allergy. Since both non-IgE mediated allergy as functional disorders disappear around the age of one year or earlier, the evidence-based indications for soy infant formula in these conditions are limited.

There is consensus that partially hydrolysed formulas should not be used in allergic infants because of the remaining relatively high degree of antigenicity and allergenicity, what can be associated with adverse reactions. However, all formulas on the market for the management of functional GI disorders are partially hydrolysed, because of better digestion and tolerance than intact protein. But the question can be raised: is this situation not comparable to the patients with established cow milk allergy tolerating baked or processed milk or small amounts of milk because the structure of the protein has changed as a consequence of the

production process? There are data showing that a partial hydrolysate in tolerated in up to 60 % of infants with a positive double blind challenge test. The debate is: is tolerance of a partial hydrolysate a proof that the immune system is not involved?

Probably because of the confusion and difficulties that health care professionals have in distinguishing non-IgE allergy from functional GI disorders, thickened extensive and partial hydrolysates are commercially quite successful. The question is: what is best: a symptomfree infant without having established a clear diagnosis, or a diagnosis after having prolonged the period of symptoms?

The debate on non-IgE allergy versus functional GI disorders mainly focusses on cow milk. Other foods involved with non-IgE allergy (egg, wheat,..) do not cause functional GI symptoms in infants and young children, or are less well recognised. The guidelines and reviews on the management of infant GOR(-disease) and constipation and colic all include a trial of an extensive hydrolysate because of the overlap of symptoms. On the other side, an infant presenting with only regurgitation or only constipation is unlikely to be allergic. Therefore, thickened formula and laxantia such as lactulose are proposed as first line options. However, infants presenting with a combination of symptoms are more likely to benefit from hydrolysates. Whether that is a proof of involvement of the immune system in non-IgE mediated allergy is open for debate.

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Session IV- Workshops.

Persistent Cow's Milk Allergy treated with Oral Immunotherapy.

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Background

Cow's milk allergy (CMA) is one of the most common food allergy in children.

Two main mechanisms, IgE and non-IgE mediated, are responsible of immune mediated reaction to cow's milk (CM), as well as to other food.

IgE-mediated reactions account for 60% of CMA and are characterized by immediate onset of symptoms after CM assumption. Adverse reactions range from mild symptoms to life-threatening anaphylaxis. Symptoms involve skin, gastrointestinal tract, respiratory system and cardiovascular system. (Figure 1)

Case Report

Chiara, was followed at our outpatients clinic for CMA from the age of 7 months when she experienced her first allergic reaction to formula milk (150 ml), few minutes after ingestion, with urticaria, cough and sneezing. Her mother reported that Chiara, in the past, drank some formula milk in her first days of life without adverse reactions. We performed skin prick test (SPT) resulted positive for CM whey fractions (casein 7 mm, α-lactalbumine 5 mm and β-lactoglobulin 7 mm): these results were confirmed by high level of CM specific IgE 18.6 kU/L, so we suggest a cow's milk protein-free diet. At the age of 18 months she performed an oral food challenge (OFC) for CM developing urticaria, angioedema, sneezing and cough. At the age of 2 and 3 years, after she had ingested, accidentally, small amounts of CM products she experienced anaphylaxis (urticaria, facial erythema, angioedema, bronchospasm and drowsiness), she was admitted in hospital after epinephrine injection. At the age of 4 years, she was initially tested for sIgE against casein, α-lactalbumine and β-lactoglobulin using the ImmunoCAP assay system (Thermo Fisher Scientific, Uppsala, Sweden), resulted 68, 15.4, and 94.6 kUA/L, respectively. She also underwent SPT and OFC for CM stopped at 5 ml of milk due to the appearance of anaphylaxis.

We decide to start an oral immunotherapy (OIT) protocol to CM, starting from 1 ml of whole milk diluted 1:100 with water, corresponding approximately to 0.3 mg of CM proteins, after placement of an intravenous catheter. The dose was increased every hour for two days (in the second day milk was diluted 1:10) during the escalation phase reaching the final dose of 2.5 ml of undiluted milk (82,5 mg of CM proteins), then once a week until reaching the maintenance dose of 200 ml. (Table 1) The previous tolerated dose was taken at home twice a week. Before discharge, she remained under observation for 2 hours after the final dose each day, or more if required.

Chiara experienced three adverse reaction during desensitization protocol: the first one at the end of rush phase (itchy mouth and flushing) treated with cetirizine; the second and third adverse reaction characterized by diffuse urticaria and cough occurred during maintenance phase at home in conjunction with a viral intercurrent illness (common cold). In that case the dose was not increased in the next week, but the previous tolerated dose was repeated.

When she reached the maintenance dose of 200 ml, she was asked to drink 200 ml of milk daily for 1 month. After that, an OFC was performed with the maximum dose of 300 ml without any adverse reaction. She was discharged with the recommendation to continue follow-up every six months, avoid dairy during acute illness or in the setting of sport , and consume milk at least twice a week plus other foods containing milk proteins in order to maintain desensitization.

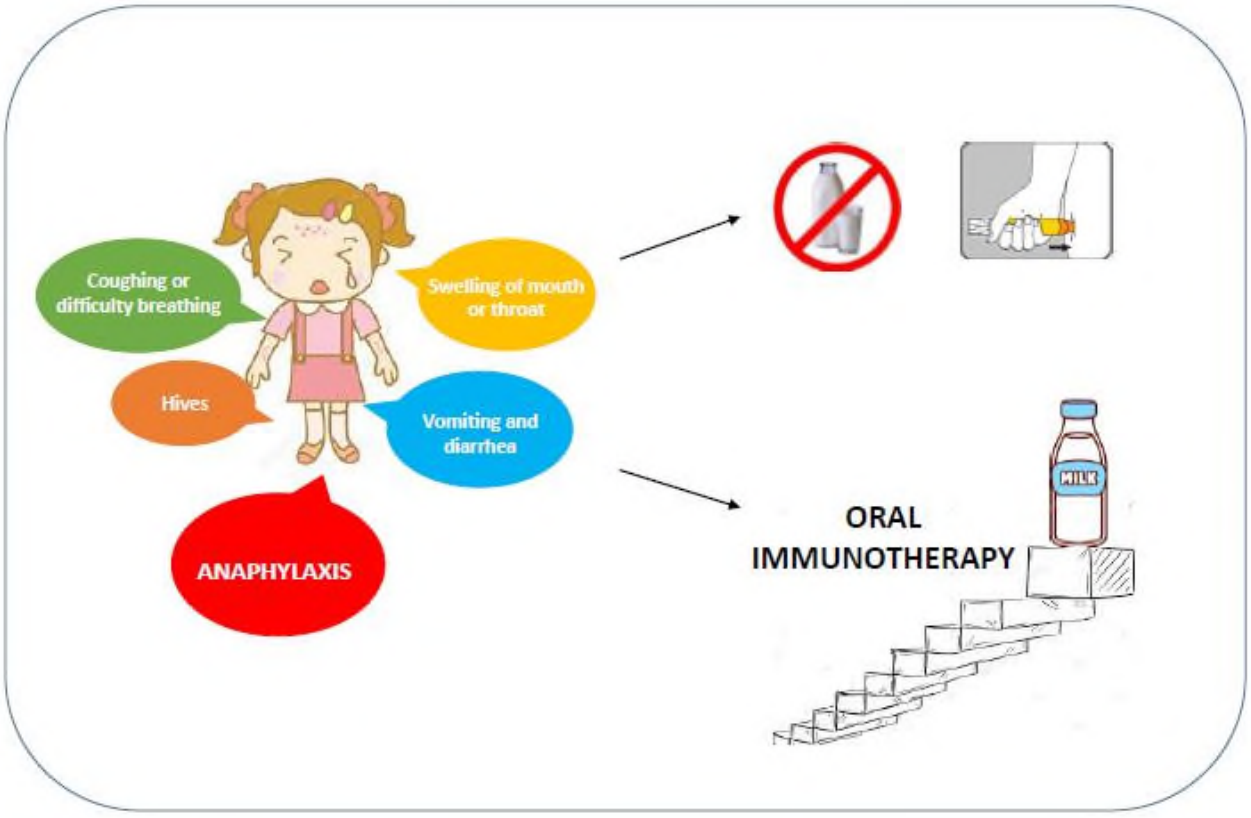

Figure 1. IgE-mediated milk allergy is associated with a high frequency of adverse reactions. The standard treatment include management of anaphylaxis and food avoidance. In case of persistent milk allergy, oral immunotherapy represents the only active treatment able to modify the natural history of food allergy.

Table 1. Desensitization protocol for OIT

Day/week	Milk diluition	Volume (ml)	Proteins
Day 1	1/100	1	0.3 mg
"	1/100	2	0.7 mg
"	1/100	4	1.3 mg
"	1/100	8	2.7 mg
"	1/10	1,6	5 mg
Day 2	1/10	1,6	5 mg
"	1/10	3,2	10,6 mg
"	1/10	6,4	21,1 mg
"	1/10	12	39,6 mg
"	Undiluted	2.5	82,5 mg

Week 2	**Undiluted**	**4**	**132 mg**
Week 3	**Undiluted**	**6**	**198 mg**
Week 4	**Undiluted**	**8**	**264 mg**
Week 5	**Undiluted**	**10**	**330 mg**
Week 6	**Undiluted**	**12**	**396 mg**
Week 7	**Undiluted**	**15**	**495 mg**
Week 8	**Undiluted**	**20**	**660 mg**
Week 9	**Undiluted**	**25**	**825 mg**
Week 10	**Undiluted**	**30**	**990 mg**
Week 11	**Undiluted**	**40**	**1.320 mg**
Week 12	**Undiluted**	**50**	**1.650 mg**
Week 13	**Undiluted**	**75**	**2.475 mg**
Week 14	**Undiluted**	**100**	**3.300 mg**
Week 15	**Undiluted**	**150**	**4.950 mg**
Week 16	**Undiluted**	**200**	**6.600 mg**

NOTES

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