World Allergy Forum Symposium: “Novel Approaches to Food Allergy”
Thursday, June 30, 2005 – 1:30pm - 3:00pm
International Congress Center (ICM) Auditorium
XIX World Allergy Congress
Munich, Germany
You Are Invited To Attend

WAF Symposium:  “The Management of Severe Asthma”
Sunday, November 6, 2005
American College of Allergy, Asthma and Immunology Annual Meeting
November 4-9, 2005
Anaheim, California, USA

Chairs:
G. Walter Canonica, University of Genova DIMI
Genova, Italy
Constance H. Katelaris, Westmead Medical Centre
Westmead, Australia

Topics/Speakers:
The Natural History of Severe Asthma
Michael Kaliner

Treatment Options for Severe Asthma
Carlos E. Baena-Cagnani

Economic Analysis of the Cost of Treatments for Severe Asthma
Michael Blaiss

Supported through an unrestricted educational grant from

Novartis
Genentech
“Novel Approaches to Food Allergy”

Program

Chairs:
Carlos E. Baena-Cagnani, Catholic University of Cordoba
Cordoba, Argentina

Ulrich Wahn, University Children’s Hospital
Berlin, Germany

1. Welcome to the World Allergy Forum Symposium and Introduction to “Novel Approaches to Food Allergy”
   Carlos E. Baena-Cagnani, Catholic University of Cordoba
   Cordoba, Argentina
   Ulrich Wahn, University Children’s Hospital
   Berlin, Germany

2. Epidemiological Risk Factors and Prevention of Food Allergy
   Gideon Lack, St Mary’s Hospital
   London, England

3. Diagnosis of Food Allergy
   Bodo Niggemann, University Children’s Hospital
   Berlin, Germany

4. Treatment of Food Allergy
   Hugh Sampson, Mount Sinai School of Medicine
   New York, New York, USA

2003-2005 World Allergy Forum Advisory Board

Chair
Carlos E. Baena-Cagnani, Argentina

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About the World Allergy Organization

World Allergy Organization (WAO)
The World Allergy Organization (WAO) is an international umbrella organization of over 70 regional and national allergy and clinical immunology societies. By collaborating with member societies, WAO provides direct educational outreach programs, symposia and lectureships to almost 40,000 WAO individual members around the globe.

The World Allergy Organization Mission
The World Allergy Organization (WAO) exists to build a global alliance of allergy societies to advance excellence in clinical care, research, education and training.

Programs of the World Allergy Organization

GLORIA Global Resources in Allergy™
The GLORIA program promotes good practice in the management of allergic diseases through programs developed by panels of world experts. GLORIA educates medical professionals worldwide through regional and national presentations and local training initiatives. GLORIA educational modules promote the World Allergy Organization’s (WAO) mission – to optimize allergy care worldwide.

GLORIA Modules
Module 1: Allergic Rhinitis and Allergic Conjunctivitis
Module 2: Allergic Conjunctivitis (Expanded Version)
Module 3: Allergic Emergencies
Module 4: Immunotherapy
Module 5: Symptoms and Treatment of Asthma
Module 6: Food Allergy

World Allergy Forum (WAF) symposia are held at major international allergy meetings. Developed by international expert advisory panels, the symposia provide up-to-the-minute presentations on scientific and clinical developments in the field of allergic disease.

PAAA: Prevention of Allergy and Allergic Asthma
Prevention of Allergy and Allergic Asthma (PAAA) is a collaborative project with the World Health Organization providing guidelines and recommendations for prevention of the allergen-specific immunological sensitization necessary for disease.

Emerging Societies Meetings
WAO offers advice on initiating and developing allergy societies throughout the world. This proactive initiative aims to expand and improve the specialty of allergy by supporting colleagues working in the field of allergy worldwide. Through sharing practical experiences and alerting new societies to the criteria required for WAO membership, ESM creates relationships with future World Allergy Organization member societies, and educates WAO’s leadership about the challenges and opportunities faced by colleagues in developing countries.

WAO Journals
ACI International – Journal of the World Allergy Organization (ACII - JWAO) and International Archives of Allergy and Immunology
Read the latest in global allergy and asthma news and research through subscriptions to WAO’s journal partners: ACI International - Journal of the World Allergy Organization (ACII - JWAO) and International Archives of Allergy and Immunology.

World Allergy Day – July 8, 2005
WAO, in conjunction with EAACI, will announce World Allergy Day to the media at the World Allergy Congress in Munich, Germany, June 26 - July 1, 2005. Increased public awareness of allergy as a major worldwide health issue, as well as the prevention of allergy, will be emphasized during worldwide celebrations on World Allergy Day.

WAO Seminars and Conferences
The Seminars and Conferences program invites member societies to apply to host a WAO Invited Lecturer. Complementing WAO’s existing programs, Seminars and Conferences gives Member Societies the opportunity to bid for an international speaker to give a plenary lecture in the scientific program of the Society’s annual meeting, on a topic of the Society’s choice.
WAO Member Societies

National Member Societies*

Albanian Society of Allergology and Clinical Immunology
American Academy of Allergy, Asthma and Immunology
American College of Allergy, Asthma and Immunology
Argentine Association of Allergy and Immunology
Argentine Society of Allergy and Immunopathology
Australasian Society of Clinical Immunology and Allergy
Austrian Society of Allergology and Immunology
Brazilian Society of Allergy and Immunopathology
British Society for Allergy and Clinical Immunology
Bulgarian National Society of Allergology
Canadian Society of Allergy and Clinical Immunology
Chilean Society of Allergy and Immunology
Chinese Allergology Society and Chinese Allergists
Croatian Society of Allergology and Clinical Immunology
Cuban Society of Allergology
Danish Society of Allergology
Ecuadorian Society of Allergology and Allied Sciences
Egyptian Society of Allergy and Clinical Immunology
Finnish Society of Allergology and Clinical Immunology
French Society of Allergology and Clinical Immunology
German Society for Allergology and Clinical Immunology
Hellenic Society of Allergology and Clinical Immunology
Hungarian Society of Allergology and Clinical Immunology
Indian College of Allergy, Asthma and Applied Immunology
Indonesian Society for Allergy and Immunology
Israeli Society of Allergy and Clinical Immunology
Italian Society for Allergology and Clinical Immunology
Japanese Society of Allergology
Korean Society of Allergology
Malaysian Society of Allergy and Immunology
Mexican College of Pediatricians Specialized in Allergy and Clinical Immunology
Mexican College of Allergy, Asthma and Clinical Immunology
Netherlands Society of Allergology
Norwegian Society of Allergology and Immunopathology
Paraguayan Society of Immunology and Allergy
Peruvian Society of Allergy and Immunology
Philippine Society of Allergy, Asthma and Immunology
Polish Society of Allergology
Portuguese Society of Allergology and Clinical Immunology
Russian Association of Allergology and Clinical Immunology
Allergy Society of South Africa
Spanish Society of Allergology and Clinical Immunology
Swedish Association for Allergology
Swiss Society for Allergology and Immunology
Allergy and Immunology Society of Thailand
Turkish National Society of Allergy and Clinical Immunology
Uruguayan Society of Allergology
Venezuelan Society of Allergy and Immunology
Vietnam Association of Allergy, Asthma and Clinical Immunology

Regional Organizations

The Asian Pacific Association of Allergology and Clinical Immunology
Commonwealth of Independent States (CIS Society)
European Academy of Allergology and Clinical Immunology
Latin American Society of Allergy and Immunology

Affiliate Organizations

International Association of Asthmology

Associate Member Societies

Azerbaijan Society for Asthma, Allergy and Clinical Immunology
Bangladesh Society of Allergy and Immunology
Belgian Society of Allergology and Immunology
(Chinese) Hong Kong Institute of Allergy
Colombian Allergy, Asthma and Immunology Association
Czech Society of Allergology and Clinical Immunology
Georgian Association of Allergology and Clinical Immunology
Icelandic Society of Allergy and Clinical Immunology
Iranian Society of Immunology and Allergy
Lebanese Society of Allergy and Immunology
Mongolian Society of Allergology
Romanian Society of Allergology and Clinical Immunology
Singapore Society of Immunology, Allergy & Rheumatology
Ukrainian Association of Allergologists and Immunology
Zimbabwe Allergy Society

For WAO membership information please contact the Secretariat
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Tel: +1 414 276 1791 • Fax: +1 414 276 3349
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Web site: www.worldallergy.org

*As of April 2005
June 30th, 2005

Dear Colleagues,

It is my pleasure to welcome you to Munich for the World Allergy Congress, the XIXth Congress of the World Allergy Organization, and to the 26th World Allergy Forum symposium, Novel Approaches to Food Allergy. The World Allergy Forum is the longest-running educational program of World Allergy Organization (WAO), and we are proud to bring you an excellent international faculty for today’s symposium. WAO sincerely recognizes the unrestricted educational grant provided by Novartis which supports the World Allergy Forum program.

WAO is an alliance of allergy and clinical immunology societies, and currently represents over 70 Allergy and Clinical Immunology Societies around the world. Partnership with our member organizations is essential for the success of WAO and the worldwide development of Allergy as a specialty. I would like to thank warmly my co-chair Prof. Ulrich Wahn for his untiring work, both as a member of the World Allergy Forum Advisory Board, and as President of EAACI. I would also like to extend my thanks to the entite European Academy of Allergology and Clinical Immunology and the German Society for Allergology and Clinical Immunology for their collaboration in planning this Congress.

In addition to World Allergy Forum and the well-established GLORIA™ program, WAO is proud to announce the WAO Seminars and Conferences Program. This program will offer member societies the opportunity to apply for WAO Lecture-ships at member society meetings, to provide an international speaker to speak on a topic of the society’s choice. The flexibility of WAO Seminars and Conferences is a perfect complement to the GLORIA program, which offers a selection of established educational modules on major topics in clinical allergy. Given the selection of WAO programs, I hope that your national society will wish to apply for a WAO program at your next meeting.

Lastly, I would like to note the publication of Prevention of Allergy and Allergic Asthma. This work resulted from over 5 years’ collaboration with the WHO, and is a tremendous WAO accomplishment. Prevention of Allergy and Asthma has been chosen as the theme of the first World Allergy Day, which was launched during this Congress and will be celebrated on 8th July 2005. World Allergy Day is an important initiative to increase the visibility of allergy amongst the public, medical professionals, and health care authorities, and I encourage you to show your support by arranging activities within your country.

To receive updates on WAO activities and membership benefits, register for WAO News and Notes, our monthly e-letter. Each e-letter offers a review of the latest allergy papers published in the major journals, news from our member societies, information about our Congresses and educational programs, and other items such as new allergy book reviews and synopses. To subscribe to our e-letter, please visit our Web site www.worldallergy.org.

Thank you for attending this World Allergy Forum symposium today and for your valuable contribution to the specialty of allergy.

With my best regards,

Prof. Carlos E. Baena-Cagnani
President
World Allergy Organization
Dear colleagues,

The area of food allergy has always been considered as one of the most complex and sometimes highly controversial areas of allergic disease. On one hand early diagnosis is of the highest importance, since infantile sensitization to food, and the subsequent development of adverse reactions, often represent the first clinical manifestation of the “atopic march”. On the other hand, the precision of our diagnostic tools was often limited, which led to frustration in a large number of young and old patients reporting food allergies, that frequently could not be confirmed by the specialist.

Recent developments have led to very encouraging results. In some food allergy models the “decision points” predicting a 95% or 99% probability of anaphylactic reaction have been evaluated. Clinical procedures including the atopy patch test, as well as oral challenge tests, are currently performed following widely accepted guidelines. Remarkable progress has been made in the provision of recombinant allergens, which are obviously promising tools for the future and have the potential to lead to better sensitivity, specificity and reproducibility of in-vivo and in-vitro tests.

This year’s World Allergy Forum includes some of the leading experts, who have contributed significantly during the last years to the complex field of food allergy diagnosis and treatment. It is our wish to present the most recent achievements and stimulate discussions with our experts upon challenges and the new developments we can anticipate in the near future.

Carlos Baena-Cagnani
Ulrich Wahn
Dr Gideon Lack is a Consultant in Paediatric Allergy & Immunology at St Mary’s Hospital Medical School, and Senior Lecturer at Imperial College, London. Having completed his medical degree and senior house officer appointments at the John Radcliffe Hospital in Oxford, he spent four years training as a Paediatrician in New York, and then a further four years specialising in Paediatric Allergy & Immunology in Denver, Colorado.

During the past 10 years, Dr Lack has worked at St Mary’s Hospital, where he runs the Department of Paediatric Allergy and Immunology. His research has focused on the prevalence of food allergies in children, and the relationship between food allergies and asthma. He is currently working on novel immunomodulatory treatments for food allergies, and on developing new strategies to prevent food allergies in childhood. His current funding is from the Food Standards Agency (UK), the Immune Tolerance Network, and the National Peanut Board (US).

Abstract

IgE mediated food allergy occurs in 5-8% of children under the age of 5. The rate of peanut allergy has doubled in the past 10 years. Strategies to date have focused on food allergen avoidance. Numerous studies have taken place over the past few decades (1). All studies which attempted to remove food allergens from the infant’s diet or from maternal diet during pregnancy and lactation, have failed to significantly impact on food allergies.

It is unclear whether these methods have failed because of insufficient allergen reduction or simply because oral tolerance to food does not depend on allergen avoidance. More recent work (2) suggests that sensitisation to peanut occurs in children with moderate to severe eczema who are exposed to topical arachis oil in preparation of creams and ointments used in the treatment of eczema and skin rashes. This data suggests that sensitisation may occur to environmental peanut allergens through a disrupted skin barrier.

Peanut allergy is seen only rarely in countries where peanuts are consumed in very significant amounts during infancy, such as in South East Asia and southern Africa. In these countries, infants are typically exposed to large amounts of peanut in the first year of life. Thus, there is a real question as to how peanut allergy arises, and what is the best strategy to prevent the development of peanut and other food allergies? There are 3 possible strategies to consider:

1. Early aggressive treatment of eczema to prevent cutaneous sensitisation.
2. Complete removal of environmental peanut exposure (topical preparations and foods). This may be difficult to achieve.
3. Early high dose introduction to induce oral tolerance.

Randomised controlled interventional studies using these approaches must be carried out if we are to have a basis for future recommendations.

References:

Epidemiological Risk Factors and Prevention of Food Allergy

Dr Gideon Lack
Imperial College Faculty of Medicine
at
St Mary’s Hospital
London, UK

Rates of Peanut Allergy in past decade

  Reported peanut allergy doubled 0.5-1%
  Peanut sensitization trebled 1.1%-3.3%* p=.001

• **USA: Questionnaire study 1997-2002 Sicherer SH et al. JACI 2003;112:1203-7**
  Reported peanut allergy doubled 0.4%-0.8% p=.05

UK Department of Health

**In those families with a history of allergic diseases**

• Pregnant and lactating women and infants “may wish” to avoid peanuts and peanut products

• Those infants with a parent or sibling with an atopic disease should, if possible, be breast-fed exclusively for four to six months & during weaning of such infants, and until they are at least three years of age, they should not be exposed to peanuts and peanut products.
### Peanut Avoidance Guidelines for ‘at risk’ children

<table>
<thead>
<tr>
<th>Country</th>
<th>Date</th>
<th>Pregnancy</th>
<th>Breast-Feed</th>
<th>Infancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.K.</td>
<td>D.O.H. 1998</td>
<td>Avoid</td>
<td>Avoid</td>
<td>Until 3 years</td>
</tr>
<tr>
<td>USA</td>
<td>AAP Consensus, 2008</td>
<td>Avoid</td>
<td>Avoid</td>
<td>Until 3 years</td>
</tr>
<tr>
<td>AUS</td>
<td>References UK guidelines</td>
<td>Avoid</td>
<td>Avoid</td>
<td>Until 3 years</td>
</tr>
<tr>
<td>N.Z.</td>
<td>References UK guidelines</td>
<td>Avoid</td>
<td>Avoid</td>
<td>Until 3 years</td>
</tr>
<tr>
<td>Europe</td>
<td>EAAC/EFSPPHAN 1999</td>
<td>NO</td>
<td>NO</td>
<td>Introduce all solids at 5/12.</td>
</tr>
</tbody>
</table>

### Intervventional Studies – Prevention of Food Allergies I

<table>
<thead>
<tr>
<th>Studies</th>
<th>No. of subjects, types of studies</th>
<th>Dietary Intervention</th>
<th>Follow up period years</th>
<th>Definition of food allergy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kalliomaki 1997</td>
<td>Early introduction of solids</td>
<td></td>
<td>0-2 age, infants born at term, randomized</td>
<td>No egg and cow’s milk in 3rd trimester as no restriction</td>
<td>1-5-6</td>
</tr>
<tr>
<td>Hittinger 1996</td>
<td>115-125 age, infants born at term, randomized</td>
<td></td>
<td>0-2 age, infants born at term, randomized</td>
<td>No egg, cow’s milk and fish during lactation vs no restriction</td>
<td>1-5-6</td>
</tr>
<tr>
<td>Ulj 1997</td>
<td>115-125 age, infants born at term, randomized</td>
<td></td>
<td>0-2 age, infants born at term, randomized</td>
<td>No egg, cow’s milk and fish during lactation vs no restriction</td>
<td>1-5-6</td>
</tr>
<tr>
<td>Looi 1996</td>
<td>75-153, 1 prematurity and term infants, randomized, 2 infants randomized only 1 study fully randomized</td>
<td></td>
<td>0-2 age, infants born at term, randomized</td>
<td>Breast milk versus cow’s milk protein; Feeding cow’s milk for 4-6 months vs cow’s milk</td>
<td>1-5-6</td>
</tr>
</tbody>
</table>

### Intervventional Studies – Prevention of Food Allergies II

<table>
<thead>
<tr>
<th>Studies</th>
<th>No. of subjects, types of studies</th>
<th>Dietary Intervention</th>
<th>Follow up period years</th>
<th>Definition of food allergy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghoneini 1991</td>
<td>Breast both versus cow’s milk and egg, randomized</td>
<td></td>
<td>0-2 age, infants born at term, randomized</td>
<td>Food challenge Eosinopenia</td>
<td>1-5-6</td>
</tr>
<tr>
<td>Ghoneini 1991</td>
<td>Cow’s milk versus both: cow’s milk and egg, randomized</td>
<td></td>
<td>0-2 age, infants born at term, randomized</td>
<td>Food challenge Eosinopenia</td>
<td>1-5-6</td>
</tr>
<tr>
<td>Zeeho 1999</td>
<td>Breast milk and soy milk in controls, breast milk and soy milk, randomized</td>
<td></td>
<td>0-2 age, infants born at term, randomized</td>
<td>Food challenge Eosinopenia</td>
<td>1-5-6</td>
</tr>
</tbody>
</table>

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* EAAC/EFSPPHAN: European Academy of Allergy and Clinical Immunology and European Federation of Societies for Pediatric Immunology and Allergy

* AAP: American Academy of Pediatrics

* D.O.H.: Department of Health, England

* IgE: Immunoglobulin E

* Eosinopenia: Reduction in the number of eosinophils, a type of white blood cell.
Allergic sensitisation is not the same as an allergic reaction

- Normal
- Sensitisation
- Allergic reaction

---

**Figure 1:** Prevalence of sensitisation to cat allergens and IgG antibody to Fel d1 >125 units/mL for six equal-exposure groups for cat allergen.

The range of exposure to Fel d1 in μg Fel d1/μg and the number of children in each group is shown. The number of atopic children in each group starting with the lowest exposure group was 17, 22, 23, 18, 22, and 20.

Platts-Mills et al., The Lancet 2001; 357:752-756

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**Table 3. Atopic sensitisation assessed by skin prick testing and specific serum IgE**

<table>
<thead>
<tr>
<th></th>
<th>Active</th>
<th>Control</th>
<th>Relative risk and p value (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Skin prick tests</td>
<td>25 (29)</td>
<td>12 (12)</td>
<td>1.0 (0.86-1.13) p = 0.91</td>
</tr>
<tr>
<td>Cat 1</td>
<td>11 (14)</td>
<td>7 (7)</td>
<td>1.62 (0.92-2.88) p = 0.10</td>
</tr>
<tr>
<td>Cat 2</td>
<td>14 (17)</td>
<td>6 (6)</td>
<td>1.24 (0.74-2.06) p = 0.40</td>
</tr>
<tr>
<td>MPR</td>
<td>20 (25)</td>
<td>12 (12)</td>
<td>1.33 (0.89-2.01) p = 0.13</td>
</tr>
<tr>
<td>75%</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>NA</td>
</tr>
<tr>
<td>100%</td>
<td>3 (3)</td>
<td>0 (0)</td>
<td>2.51 (0.34-20.93) p = 0.09</td>
</tr>
<tr>
<td>Sensitized</td>
<td>42 (52)</td>
<td>17 (17)</td>
<td>1.03 (0.52-2.00) p = 0.94</td>
</tr>
<tr>
<td>T 1</td>
<td>8 (10)</td>
<td>3 (3)</td>
<td>2.88 (0.62-14.85) p = 0.10</td>
</tr>
<tr>
<td>T 2</td>
<td>9 (11)</td>
<td>6 (6)</td>
<td>1.07 (0.58-2.00) p = 0.91</td>
</tr>
<tr>
<td>MPR</td>
<td>8/70</td>
<td>11/4</td>
<td>2.22 (0.60-8.26) p = 0.19</td>
</tr>
<tr>
<td>75%</td>
<td>8/71</td>
<td>11/3</td>
<td>1.25 (0.43-4.20) p = 0.68</td>
</tr>
<tr>
<td>Sensitized</td>
<td>26 (35)</td>
<td>15 (20)</td>
<td>1.34 (0.27-2.70) p = 0.51</td>
</tr>
</tbody>
</table>

Definition of abbreviations: NA = not applicable.

Woodcock et al., Am J Resp Crit Care Med 2004; 170 : 436
**Logical Error I**

\[
\text{Allergic Reaction} = \text{Allergic Sensitisation}
\]

\[
\text{Causes of Allergic Reaction} = \text{Causes of Allergic Sensitisation}
\]

**Logical Error II**

\[
\text{Peanut consumption causes allergic reactions}
\]

\[
\therefore \text{Peanut consumption causes allergic sensitisation}
\]
LOGICAL ERROR III

Peanut Consumption has Increased

Peanut Allergy has Increased

Therefore Increased Peanut Consumption is the Cause of Peanut Allergy

LOGICAL ERROR IV

Greater consumption of peanut causes a more severe reaction

.: Exposure to large amounts of peanut increases the risk of sensitisation

LOGICAL ERROR V

Breast feeding decreases allergic reactions

.: Breast feeding prevents allergic sensitisation
NEGATIVE FINDINGS

Sensitisation is not present at birth.

Maternal consumption of peanuts does not cause peanut allergy.

Infant consumption of peanut does not cause peanut allergy.

Breast feeding does not protect against peanut allergy.

Lack et al, NEJM 2003; 348:977-985
Use of Arachis oil-based creams is increased in infants who develop peanut allergy

Peanut allergy is associated with:

- Eczema: OR=2.6 (1.4 - 5.0)
- Oozing crusted rash: OR=5.2 (2.7 - 10.2)
- Topical Arachis oil: OR=6.8 (1.4-32.9)

G. Lack et al., NEJM 2003; 348: 977-985
Distribution of peanut in the environment

Purpose: Detection of peanut allergen in the environment
Efficacy of cleansing methods

Methods: Elisa to Ara h 1 on samples from cafeteria tables, other surfaces in schools, hands — before and after washing

Perry et al 2004 JACI:113:973-976

### TABLE II. Results of hand wipe samples*

<table>
<thead>
<tr>
<th>Cleaner</th>
<th>No. detectable</th>
<th>Detectable range (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None (n = 9)</td>
<td>9/9</td>
<td>480-5.6 × 10^6</td>
</tr>
<tr>
<td>Water (n = 12)</td>
<td>3/12</td>
<td>164-8274</td>
</tr>
<tr>
<td>Antibacterial hand sanitizer (n = 12)</td>
<td>6/12</td>
<td>136-1711</td>
</tr>
<tr>
<td>Commercial wipes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wet Ones (n = 12)</td>
<td>0/12</td>
<td>BD</td>
</tr>
<tr>
<td>Tidy Tykes (n = 10)</td>
<td>0/10</td>
<td>BD</td>
</tr>
<tr>
<td>Liquid soap (n = 12)</td>
<td>0/12</td>
<td>BD</td>
</tr>
<tr>
<td>Bar soap (n = 10)</td>
<td>0/10</td>
<td>BD</td>
</tr>
</tbody>
</table>

*BD: Below detection.
*Participants cleaned 5 mL peanut butter off hands using various cleaning agents or plain water. One milliliter was applied to hands before cleaning with hand sanitizer.

Perry et al 2004 JACI:113:973-976
Routes of Exposure in Peanut Allergy

Measures of Peanut Exposure

- Maternal consumption during pregnancy
- Maternal consumption during lactation
- Environmental exposure = Total household consumption in first year of life

<table>
<thead>
<tr>
<th>Type of food</th>
<th>Times eaten in a week</th>
<th>Amount eaten each time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peanut butter</td>
<td>slices</td>
<td></td>
</tr>
<tr>
<td>Crackers</td>
<td>bars</td>
<td></td>
</tr>
<tr>
<td>Peanut M&amp;M's</td>
<td>pack(s)</td>
<td></td>
</tr>
<tr>
<td>Whole peanuts</td>
<td>handfuls</td>
<td></td>
</tr>
<tr>
<td>Creamy Nut Cerealis</td>
<td>bonds</td>
<td></td>
</tr>
<tr>
<td>Creamy Nut Cerealis Red</td>
<td>bonds</td>
<td></td>
</tr>
</tbody>
</table>
**Interim Data Analysis – Average weekly household peanut consumption**

![Graph showing average weekly household peanut consumption](image)

- Mann-Whitney test:
  - Peanut vs Egg: p=0.0001
  - Peanut vs Non Allergic: p=0.0001
  - Egg vs Non Allergic: p=0.0001

Strong evidence of a difference (p<0.0001) between the three groups of infants (peanut allergic, egg allergic controls and normal children) using the Kruskal-Wallis test.

---

**Immune response to peanut – dose of peanut exposure**

- High dose
- Low dose → Sensitisation
- Tolerance

---

**Immune response to peanut – route of peanut exposure**

- Oral
- Cutaneous
- Inhaled → Sensitisation
- Tolerance
### Food Allergies among Allergy Clinic patients

<table>
<thead>
<tr>
<th>Country</th>
<th>% Peanut Allergy</th>
<th>Dietary practice recommendations (Infant peanut consumption)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK (n=191)</td>
<td>25%</td>
<td>Avoidance</td>
</tr>
<tr>
<td>USA (n=300)</td>
<td>69%</td>
<td>Avoidance</td>
</tr>
<tr>
<td>Israel (n=992)</td>
<td>2.1%</td>
<td>High Infant Exposure</td>
</tr>
<tr>
<td>Philippines (n=184)</td>
<td>0%</td>
<td>High Infant Exposure</td>
</tr>
</tbody>
</table>

---

### Strategies to Prevent Sensitisation

- Early treatment of eczema?
- Complete environmental avoidance?
- Early high dose oral tolerance induction?
Acknowledgments

Jean Golding and ALSPAC          Kevin Babb
Kate Northstone                 Adam Fox
Deborah Marriage                Victor Turcanu

Yitzhak Katz
Tom Blyth
George Du Toit
Helen Fisher
Graham Roberts

National Peanut Board
Food Standards Agency
Bodo Niggemann works at the Department of Paediatric Pneumology and Immunology of the Humboldt University in Berlin. Based mainly in Germany, his career began as a Post-doctoral Fellow in the Department of Pharmacology and Toxicology at the Medical University in Hanover. In 1983 he started his paediatric education at the University Children’s Hospital in Hamburg. In 1990 he joined the Department of Paediatric Pneumology and Immunology at the Humboldt University as the Assistant Head. In 1995 he became member of the faculty and in 2001 he was appointed Associate Professor of the Humboldt University. Bodo Niggemann’s research experience spans the spectrum of paediatric allergy and pneumology, with a focus on food allergy. He has performed multiple clinical trials in the field of paediatric allergy and pulmonology, resulting in more than 100 publications in peer-reviewed journals. In 2001 he won the Albrecht-von-Graefe Prize for excellent teaching at the Humboldt University. In addition, he is currently an Associate Editor of Allergy and for many years he has been an active member of the Board of the Paediatric Section of the European Academy of Allergy and Clinical Immunology (EAACI).

Abstract
The most common foods leading to IgE-mediated allergic reactions are cow’s milk, hen’s egg, wheat, soy, and peanut and tree nuts. The diagnostic work-up of food allergy includes a thorough medical history, in vitro tests [e.g. specific serum IgE], in vivo tests [e.g. skin prick test, atopy patch test], and oral challenges (preferably performed as double-blind, placebo-controlled food challenges).

Decision points have been established by some groups for a couple of allergens, allowing us to make oral food challenges superfluous in cases where the cut-off value exceeds the 95% or 99% predicted probability. However, these values vary considerably among populations studied and have to be established for each allergen separately. Our data indicate that specific IgE decision points can be calculated for hen’s egg (95% = 12.6 kU/l, 99% = 59.2 kU/l), but not for cow’s milk, wheat or soy.

Skin prick test decision points can be calculated in the same way. Our study resulted in values of 13.0 mm (95%) and 17.8 mm (99%) for hen’s egg, and 12.5 mm (95%) and 17.3 mm (99%) for cow’s milk. Infants tend to have slightly lower levels compared to older children.

The atopy patch test, an epicutaneous test performed with native foods, provides the best specificity and positive predictive values as a single test. The combination of the atopy patch test together with the skin prick test or specific serum IgE enhances the efficiency of each single test.

Around 10% of positive oral food challenges are not IgE-mediated. Therefore, the suspicion of food-related symptoms, rather than proof of specific IgE, should be the indication to perform oral challenges.

The time point of the diagnostic work-up seems to determine, which parameter may be helpful: while all mentioned parameters add information to determine which patient should receive an elimination diet, only oral food challenges are currently meaningful to decide whether a patient has become tolerant after a time of avoidance.

In the daily practice, no oral food challenge is required in the case of a suggestive history of an anaphylactic reaction, if specific serum IgE or the skin prick test value is above the decision point, or if the patient suffers from a clear oral allergy syndrome induced by pollen associated food allergens. Open challenges may be justified in cases of questionable anaphylaxis or immediate type clinical reactions. Double-blind, placebo-controlled food challenges are recommended if late phase clinical reactions are suspected or the patient complains of subjective symptoms.
Bodo Niggemann

„Diagnosis of Food Allergy“

WAF-Symposium, Munich, 30.06.2005

### Food allergy/ -intolerance:

<table>
<thead>
<tr>
<th>OCCUPATION</th>
<th>DISEASE</th>
<th>FOODS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatologist</td>
<td>- Urticaria</td>
<td>- Additives</td>
</tr>
<tr>
<td></td>
<td>- Atopic Dermatitis</td>
<td>- Aeroallergens</td>
</tr>
<tr>
<td>Gastroenterologist</td>
<td>- Eosinophil Gastroenteropathies</td>
<td>- Wheat, soy</td>
</tr>
<tr>
<td>Pediatrician</td>
<td>- IgE-mediated Allergy</td>
<td>- Cow’s milk, hen’s egg</td>
</tr>
<tr>
<td>Pneumologist</td>
<td>- Oral Allergy Syndrome</td>
<td>- Pollen associated foods</td>
</tr>
<tr>
<td>Neurologist</td>
<td>- Hyperkinetic Syndrome, Migraine</td>
<td>- Sugar, phosphate</td>
</tr>
<tr>
<td>Psychologist</td>
<td>- Multiple Chemical Sensitivity</td>
<td>- „Odors of everything“</td>
</tr>
</tbody>
</table>
Food allergy

Most common food allergens
Food allergy

Over-assessed foods
Food allergy

Diagnostic work-up
Food allergy
Diagnostic procedures:
- Medical history
- Symptom-Food-Diary
- In vitro tests
  (Specific IgE)
- In vivo tests
  (Skin Prick Test, Atopy Patch Test)
- Oral food challenges
  (DBPCFC)

Food allergy

Specific serum IgE

Specific IgE decision points (95%) in food allergy

Sampson HA J Allergy Clin Immunol 2001; 107: 891-89
Specific IgE and food allergy

- Patients: n = 501 (boys 60%, girls 40%)
- Challenges: n = 992
- Age: 1 mo to 16.1 years (median 13 mo)
- Atopic dermatitis: 440 / 501 (88%)
- SCORAD:
  - 0 - 25 (n = 204)
  - 25 - 50 (n = 116)
  - > 50 (n = 56)
- Allergens: cow’s milk, hen’s egg, wheat, soy

Hypotheses for differences between populations?

- Pattern of clinical reactions? (e.g. early versus late clinical reactions)
- Study population? (e.g. atopic eczema as underlying disease)
- Age of patients? (e.g. infants versus children)
- Proof of clinical relevance? (e.g. convincing history versus DBPCFC)
- Criteria for positive challenge? (e.g. vomiting once versus recurrent vomiting)
- Time-point of diagnostics? (e.g. in the beginning of the “career” vs later on)

### Early versus late clinical reactions during DBPCFC
**Hen’s egg**

<table>
<thead>
<tr>
<th>IgE early</th>
<th>IgE all</th>
</tr>
</thead>
<tbody>
<tr>
<td>90%</td>
<td>6.0 kU/l</td>
</tr>
<tr>
<td>95%</td>
<td>11.2 kU/l</td>
</tr>
<tr>
<td>99%</td>
<td>44.3 kU/l</td>
</tr>
</tbody>
</table>

* = 90%, 95% and/or 99% predictive values could not be calculated.

---

### Total and specific IgE in serum
**Ratio:**

- **Ratio = 200**
  - 10,000 kU/l
  - 50 kU/l

- **Ratio = 2**
  - 100 kU/l
  - 50 kU/l
Skin Prick Test

SPT and food allergy

- Patients: n = 385 (boys 58%, girls 42%)
- Challenges: n = 735
- Age: 3 mo to 14.5 years (median 22 mo)
- Atopic dermatitis: 335 / 385 (87%)
- SCORAD:
  - 0 - 25 (n = 168)
  - 25 - 50 (n = 87)
  - > 50 (n = 41)
- Allergens: cow’s milk, hen’s egg, wheat, soy
### SPT (mm absolute) and food allergy

<table>
<thead>
<tr>
<th>Cut-off</th>
<th>&lt;1 year</th>
<th>≥ 1 year</th>
<th>All children</th>
</tr>
</thead>
<tbody>
<tr>
<td>HE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90%</td>
<td>9.3</td>
<td>11.1</td>
<td>10.8</td>
</tr>
<tr>
<td>95%</td>
<td>11.2</td>
<td>13.3</td>
<td>13.0</td>
</tr>
<tr>
<td>99%</td>
<td>15.4</td>
<td>18.3</td>
<td>17.8</td>
</tr>
<tr>
<td>(n = 26)</td>
<td>(n = 134)</td>
<td>(n = 160)</td>
<td></td>
</tr>
<tr>
<td>CM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90%</td>
<td>7.9</td>
<td>13.2</td>
<td>10.4</td>
</tr>
<tr>
<td>95%</td>
<td>9.7</td>
<td>15.7</td>
<td>12.5</td>
</tr>
<tr>
<td>99%</td>
<td>13.5</td>
<td>*</td>
<td>17.3</td>
</tr>
<tr>
<td>(n = 154)</td>
<td>(n = 149)</td>
<td>(n = 303)</td>
<td></td>
</tr>
</tbody>
</table>

Legend: * = 90%, 95% and/or 99% predictive values could not be calculated

---

### Early versus late clinical reactions during DBPCFC

**Hen’s egg**

<table>
<thead>
<tr>
<th>Cut-off</th>
<th>SPT early</th>
<th>SPT all</th>
</tr>
</thead>
<tbody>
<tr>
<td>90%</td>
<td>10.5 mm</td>
<td>10.8 mm</td>
</tr>
<tr>
<td>95%</td>
<td>12.4 mm</td>
<td>13.0 mm</td>
</tr>
<tr>
<td>99%</td>
<td>16.5 mm</td>
<td>17.8 mm</td>
</tr>
</tbody>
</table>

* = 90%, 95% and/or 99% predictive values could not be calculated
IgE and SPT

Specific IgE and SPT in food allergy

<table>
<thead>
<tr>
<th></th>
<th>HE IgE</th>
<th>HE SPT</th>
<th>CM IgE</th>
<th>CM SPT</th>
<th>Wheat IgE</th>
<th>Wheat SPT</th>
<th>Soy IgE</th>
<th>Soy SPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>83%</td>
<td>93%</td>
<td>97%</td>
<td>85%</td>
<td>79%</td>
<td>65%</td>
<td>69%</td>
<td>21%</td>
</tr>
<tr>
<td>Specificity</td>
<td>53%</td>
<td>59%</td>
<td>51%</td>
<td>75%</td>
<td>38%</td>
<td>77%</td>
<td>50%</td>
<td>88%</td>
</tr>
<tr>
<td>PPV</td>
<td>63%</td>
<td>80%</td>
<td>80%</td>
<td>76%</td>
<td>41%</td>
<td>52%</td>
<td>22%</td>
<td>29%</td>
</tr>
<tr>
<td>NPV</td>
<td>76%</td>
<td>83%</td>
<td>89%</td>
<td>83%</td>
<td>77%</td>
<td>85%</td>
<td>88%</td>
<td>83%</td>
</tr>
<tr>
<td>Efficiency</td>
<td>68%</td>
<td>83%</td>
<td>81%</td>
<td>78%</td>
<td>53%</td>
<td>74%</td>
<td>53%</td>
<td>81%</td>
</tr>
</tbody>
</table>

„Decision points“ for hen’s egg

<table>
<thead>
<tr>
<th></th>
<th>Specific IgE</th>
<th>Skin Prick Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>95 %</td>
<td>12.6 kU/l</td>
<td>13.0 mm</td>
</tr>
<tr>
<td>99 %</td>
<td>59.2 kU/l</td>
<td>17.8 mm</td>
</tr>
</tbody>
</table>
### Number and percentage of children above decision point

<table>
<thead>
<tr>
<th></th>
<th>HE IgE</th>
<th>HE SPT</th>
<th>CM IgE</th>
<th>CM SPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>90%</td>
<td>80/227 (35.2%)</td>
<td>36/160 (22.5%)</td>
<td>13/398 (3.3%)</td>
<td>27/303 (7.9%)</td>
</tr>
<tr>
<td>95%</td>
<td>49/227 (21.6%)</td>
<td>11/160 (6.9%)</td>
<td>0/398 (0%)</td>
<td>7/303 (2.3%)</td>
</tr>
<tr>
<td>99%</td>
<td>7/227 (3.1%)</td>
<td>5/160 (3.1%)</td>
<td>0/398 (0%)</td>
<td>0/303 (0%)</td>
</tr>
</tbody>
</table>

### Atopy Patch Test
### Single tests:

<table>
<thead>
<tr>
<th></th>
<th>CM (n = 71)</th>
<th>HE (n = 42)</th>
<th>Wheat (n = 39)</th>
<th>Soy (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sens.</td>
<td>84% IgE SPT APT 89%</td>
<td>90% IgE SPT APT 95%</td>
<td>67% IgE SPT APT 67%</td>
<td>75% IgE SPT APT 75%</td>
</tr>
<tr>
<td>Spec.</td>
<td>38% IgE SPT APT 36%</td>
<td>57% IgE SPT APT 57%</td>
<td>47% IgE SPT APT 47%</td>
<td>52% IgE SPT APT 52%</td>
</tr>
<tr>
<td>PPV</td>
<td>70% 81% 95%</td>
<td>75% 81% 94%</td>
<td>57% 60% 94%</td>
<td>23% 56% 50%</td>
</tr>
<tr>
<td>NPV</td>
<td>59% 64% 51%</td>
<td>83% 73% 52%</td>
<td>57% 60% 89%</td>
<td>92% 90% 95%</td>
</tr>
</tbody>
</table>

Roehr CC et al. JACI 2001; 107: 548-553

### Combined tests:

<table>
<thead>
<tr>
<th></th>
<th>CM (n = 71)</th>
<th>HE (n = 42)</th>
<th>Wheat (n = 39)</th>
<th>Soy (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sens.</td>
<td>85% A 79% B 74% C 81% D</td>
<td>96% A 94% B 84% C 94% D</td>
<td>71% A 92% B 86% C 91% D</td>
<td>100% A 100% B 100% C 100% D</td>
</tr>
<tr>
<td>Spec.</td>
<td>56% A 100% B 100% C 100% D</td>
<td>43% A 83% B 89% C 75% D</td>
<td>50% A 89% B 90% C 86% D</td>
<td>91% A 83% B 100% C 100% D</td>
</tr>
<tr>
<td>PPV</td>
<td>83% A 100% B 100% C 100% D</td>
<td>86% A 94% B 94% C 94% D</td>
<td>63% A 92% B 92% C 91% D</td>
<td>50% A 50% B 100% C 100% D</td>
</tr>
<tr>
<td>NPV</td>
<td>60% A 64% B 74% C 67% D</td>
<td>75% A 83% B 73% C 75% D</td>
<td>60% A 89% B 82% C 86% D</td>
<td>100% A 100% B 94% C 100% D</td>
</tr>
</tbody>
</table>

A = IgE plus SPT  B = APT plus IgE  C = APT plus SP T  D = APT plus IgE plus SPT

Roehr CC et al. JACI 2001; 107: 548-553

### Non-IgE mediated reactions
Positive oral food challenges (DBPCFC)
\( n = 111 \)

IgE-mediated reactions
(SPT and/or specific IgE positive)
\( n = 99 \) (89%)
- CM \( n = 46 \)
- HE \( n = 37 \)
- Wheat \( n = 16 \)

Non-IgE-mediated reactions
(SPT plus specific IgE negative)
\( n = 12 \) (11%)
- CM \( n = 6 \)
- HE \( n = 1 \)
- Wheat \( n = 5 \)

JACI 2001; 108: 1053-1058

Atopy patch test (APT)
Results: group A vs. group B

- APT n.s. (p = 0.208)
- Early/late reactions n.s. (p = 0.398)
- Age of children n.s. (p = 0.576)
- Total IgE trend (p = 0.078)
- Allergens \( p = 0.042 \)
Time point of diagnosis

Food allergy and time point of diagnostic work-up

First Challenge
74 children (median age 11 mo)
121 challenges
median time interval 16 mo

Second challenge
74 children (median age 32 mo)
99 challenges
median time interval 15 mo

Third challenge
15/74 children (median age 51.5 mo)
22 challenges

Characteristics of children with three challenges (n = 22)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>First challenge</th>
<th>Second challenge</th>
<th>Third challenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)</td>
<td>9 (2; 87)</td>
<td>30 (11; 165)</td>
<td>52 (22; 132)</td>
</tr>
<tr>
<td>SCORAD (points)</td>
<td>33 (9; 86)</td>
<td>10 (9; 50)</td>
<td>0 (0; 55)</td>
</tr>
<tr>
<td>Total IgE (kU/L)</td>
<td>25 (19; 348)</td>
<td>189 (12; 1,109)</td>
<td>199 (10; 1,100)</td>
</tr>
<tr>
<td>Specific IgE (kU/L)</td>
<td>8 (&lt;0.35; &gt;100)</td>
<td>15 (&lt;0.35; &gt;100)</td>
<td>3 (&lt;0.35; &gt;100)</td>
</tr>
</tbody>
</table>


Peptide-specific IgE in Peanut Allergy

Beyer K et al. J Allergy Clin Immunol 2003; 112: 202-207

Food allergy and time point of diagnostic work-up

Diagnostic work-up at early signs + Diagnostic work-up during time-course

0 2 4 6 years

IgE, SPT, APT, Challenge Peptides, Challenge
### Conclusions

#### Suspicion of food related clinical symptoms (suggestive history)

<table>
<thead>
<tr>
<th>specific IgE and/or SPT</th>
<th>decision points for specific IgE and/or SPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>negative</td>
<td>below</td>
</tr>
<tr>
<td>positive</td>
<td>above</td>
</tr>
</tbody>
</table>

- **oral food challenge**
  - negative
  - positive
  - APT
    - negative
    - positive
    - oral food challenge
      - negative
      - positive
      - IgE/SPT above threshold
        - specific elimination

- **no specific diet**
  - specific elimination

*Allergy 2005; in press*

---

<table>
<thead>
<tr>
<th>No challenge</th>
<th>Open challenge</th>
<th>DBPCFC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highly suggestive history of an anaphylactic reaction (with specific IgE)</td>
<td>Introduction of new foods in highly sensitized infants (before exposure)</td>
<td>Introduction of new foods in highly sensitized infants (before exposure)</td>
</tr>
<tr>
<td>Specific serum IgE and/or SPT above decision point</td>
<td>Re-challenge after (long-term) avoidance of a food</td>
<td>Re-challenge after (long-term) avoidance of a food</td>
</tr>
<tr>
<td>Special Case: APT and specific IgE (defined level?) positive</td>
<td>Questionable anaphylactic reaction (with or without IgE)</td>
<td>Expected late phase clinical reaction (e.g. AD)</td>
</tr>
<tr>
<td>Typical oral allergy-syndrome plus corresponding sensitization</td>
<td></td>
<td>Subjective symptoms (e.g. abdominal discomfort)</td>
</tr>
<tr>
<td>No improvement with elimination (or oligo-allergenic) diet</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Novel Approaches to Food Allergy: Treatment of Food Allergy

Hugh A. Sampson, M.D.
Mount Sinai School of Medicine, New York, USA

Dr. Sampson is a Professor of Pediatrics and Immunobiology at the Mount Sinai School of Medicine in New York. He is Chief of the Division of Allergy & Immunology in the Department of Pediatrics, Director of the Jaffe Food Allergy Institute, and Director of the General Clinical Research Center at the Mount Sinai Medical Center. Dr. Sampson did his Allergy/Immunology Fellowship at Duke University and then served on the Duke faculty before going to Johns Hopkins University where he was promoted to Professor of Pediatrics and Director of the Pediatric Clinical Research Center.

Dr. Sampson’s research interests have focused on food allergic disorders including work on the immunopathogenetic role of food hypersensitivity in atopic dermatitis, the pathogenesis of food-induced anaphylaxis, characterization of food-induced gastrointestinal hypersensitivities, and immunotherapeutic strategies for treating food allergies. His research has been funded by a number of grants from the National Institutes of Health, and private foundations. He has published over 250 articles and 60 book chapters on these topics and co-authored 3 books on food allergic disorders. Dr. Sampson serves on the editorial boards of several journals, is a member of the Institute of Medicine of the National Academies, and was recently elected Secretary/Treasurer of the American Academy of Allergy, Asthma and Immunology.

Abstract

Food allergy is a major problem in westernized countries, e.g., it affects about 3.5% of the U.S. population, and is the leading single cause of anaphylaxis treated in hospital emergency departments in many “westernized” countries. The “standard of care” for food allergy consists of educating patients and caregivers how to avoid food allergens and arming them with medications to treat accidental ingestions. Food allergic patients with asthma or a history of a previous severe reaction or a reaction to peanuts, nuts, seeds or seafood should be given self-injectable epinephrine in addition to a written emergency plan for treatment of an accidental ingestion. However, given the continued high rate of severe food allergic reactions, it is clear that the current “standard of care” is inadequate. An attempt to “desensitize” peanut-allergic patients utilizing a traditional “desensitization” protocol demonstrated a limited rate of response and a high rate of adverse reactions, leading most investigators to conclude that alternative immunotherapeutic approaches are necessary for this potentially fatal allergy.

Three of seven novel immunotherapeutic approaches being investigated as treatment modalities for food allergy will be reviewed: (1) humanized anti-IgE monoclonal antibody therapy, (2) “engineered” [mutated] allergen protein immunotherapy, (3) a Chinese herbal medication, (4) plasmid DNA-based immunotherapy, (5) antigen-immunostimulatory sequence (ISS)-modulated immunotherapy, (6) peptide immunotherapy, and (7) an Fc-engineered chimeric fusion protein vaccine.

1) Anti-IgE Therapy: Two humanized, recombinant monoclonal anti-IgE antibody preparations were available for clinical trials in food allergic patients, HU-901 [Tanox Inc, Houston, TX] and omalizumab [Genentech/Novartis/Tanox]. Both bind to the third domain of the Fc region of IgE molecules, thus preventing the molecule from binding to FceRIa. A phase I/II double-blind placebo-controlled trial of HU-901 in 82 peanut allergic patients, compared monthly injections of placebo, 150, 300, and 450 mg of HU-901. The median sensitivity threshold obtained in the 450 mg HU-901 dose group, 2,805 mg, is equivalent to approximately 8 peanuts and is likely to provide protection from accidental ingestions in most patients. Currently a similar Phase II multicenter clinical trial is underway to evaluate the efficacy of omalizumab in treating peanut-allergic patients.

2) “Engineered” [mutated] Allergen Protein Immunotherapy: The immunodominant epitopes of the three major peanut proteins, Ara h 1-3, were altered by a single amino acid substitution, which dramatically reduced IgE binding to individual epitopes and left T cell epitopes intact. In vivo efficacy of the engineered recombinant proteins were tested in the murine model of peanut anaphylaxis, which demonstrated suppressed synthesis of Ara h2-IgE and significantly decreased symptoms following oral peanut challenge compared to a sham-treated group. In order to potentiate the immuno-modulatory effect and increase efficacy of modified peanut vaccines, heat-killed E coli (HKE) producing mutated proteins Ara h1, 2 and 3 [HKE-MP123] were administered rectally (pr) in a murine model of peanut anaphylaxis. HKE-MP123-treated mice remained protected for up to 10 weeks posttherapy. IgE levels were significantly lower in all HKE-MP123-treated groups (P <0.001), and in vitro IL-4, IL-13, IL-5 and IL-10 production by peanut-stimulated splenocytes of high-dose HKE-MP123-treated mice were significantly decreased and IFN-γ and TGF-β production were significantly increased compared with sham-treated mice at the time of the last challenge. An IND is being filed with the FDA to begin clinical trials.

3) Traditional Chinese Medicine: Traditional Chinese Medicine (TCM) is based on herbal remedies, which have been used successfully in Asia for centuries for treatment of diverse diseases, including asthma and environmental allergies. A 9-herb formulation, FAHF-2, was developed and tested in peanut-allergic mice. It prevented allergic reactions following peanut challenge and induced significantly reduced peanut-specific IgE for up to 24 weeks posttherapy. Splenocytes from FAHF-2-treated mice showed significantly reduced IL-4, IL-5 and IL-13 production and enhanced IFN-γ production to recall peanut-stimulation in vitro. An IND is being submitted to investigate FAHF-2 in a Phase I/II clinical trial to determine whether it will be effective and safe for treating peanut-allergic patients.
Novel Approaches to Food Allergy:

Treatment of Food Allergy

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Mount Sinai School of Medicine
Division of Pediatric Allergy & Immunology
Jaffe Institute of Food Allergy

WAO 8/30/05

Food Allergy:
International Problem

Food Allergy & Anaphylaxis

- Food Allergy – 3.5% of U.S. population
- Anaphylaxis in the United States:
  Food 33% Insect sting 14% Medications 13%
- Anaphylaxis in Australia:
  Food 61% Insect sting 20% Medications 8%
  Mullins RJ. Clin Exp Allergy 2003; 33:1933-44.
- U.S. experience [Population - 280 Million]:
  - Olmstead County, MN [Yocum et al JACI 1998; 104:452-456]
    - 30 cases/100,000 persons/yr (Food - 36%)
    - ~ 30,000 cases of food-induced anaphylaxis / yr
Current Methods for Managing Food Allergies

- Education:
  - early signs of a reaction
  - learn to read food labels & recognize high risks
  - Food Allergy & Anaphylaxis Network (FAAN)
- Emergency treatment plans in writing
  - FAAN website: www.foodallergy.org
- Access to self-Injectable epinephrine
- Antihistamines: liquid
cetirazine or diphenhydramine
- Go to medical facility
- Medic Alert tag or bracelet

Future Immunotherapies

- Anti-IgE immunotherapy
- “Engineered” recombinant protein
- Chinese Herbal medications
- Plasmid DNA vaccine
- ISS [CpG]-Allergen vaccine
- Peptide-based vaccine
- Fcγ-antigen chimeric conjugate

Anti-IgE Therapy: α-IgE Complexes with Free IgE

Trial of Humanized Anti-IgE Antibodies [TNX-901]

- Double-blind placebo-controlled, randomized, dose escalation of TNX-901
- 84 subjects: 12 – 60 yrs
- IgE ≤ 1,000 IU/L
- 3 dose cohorts = 150, 300 & 450 mg/mo s.c.
  - drug:placebo = 3:1
- Challenge: quantity of peanut flour necessary to elicit symptoms
- Endpoint: change in dose of antigen that elicits symptoms

---

Mean Threshold Dose (±95% CI) to Peanut

![Threshold Dose Graph]

- 450 mg dose group vs. placebo, p<0.001 (log10-transformed data)

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Clinical Implications

- No systemic adverse events
- Average accidental peanut exposure ~1-2 peanuts or fewer (~325-650 mg of peanut)
- Thresholds achieved with 450 mg dose = 2.8 gm, (~9 peanuts), should protect most patients
  ~ 25% could ingest 8 gm or > 20 peanuts
  ~25% had no change in threshold dose
- Should raise threshold for other (any) foods
- Omalizumab [Xolair®] approved for treating moderate – severe asthma, is NOT the same drug
  - clinical trial of Xolair® now under way
Peptide Microarray Technology

- 210 overlapping peptides covering Ara h1, Ara h2 and Ara h3 were spotted on glass slides
- Immunolabeled with sera from 90 patients

Shreffler et al. JACI 2004; 113:776-782

Epitope Diversity & Reactivity

Greater epitope diversity => more severe reactions
Greater epitope diversity => more peanut-specific IgE molecules present on mast cells => greater reactivity
- with anti-IgE therapy, need to get peanut-specific IgE lower in patients with greater diversity

Shreffler et al. JACI 2004; 113:776-782

“Engineered” Recombinant Proteins

- Identified Ara h1 - 3 as major allergenic proteins, isolated, sequenced & cloned full-length cDNAs
- Identified IgE-binding epitopes on Ara h1 - 3
- Substituted single amino acid within epitope using PCR mutagenesis;
  - e.g. Ara h2 – a.a. 27-36 - DRRCQSQLER
  - eliminates or markedly reduced IgE binding
  - T cell proliferative response unchanged
  - recombinant protein produced in E. coli
“Engineered” Recombinant Protein

Single amino acid substitution
Ara h1

“Engineered” HKE-mAra h1-3

E coli
L monocytogenes
(Li et al JI 2003)
(Frick et al
Allergy 2005)


Desensitization with Rectal
HKE-mAra h1-3

<table>
<thead>
<tr>
<th>Sensitization</th>
<th>Desensitization</th>
<th>Challenge</th>
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<tr>
<td>I.g.</td>
<td>p.r.</td>
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<tr>
<td>W0</td>
<td>W6</td>
<td>W10</td>
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<td>W11</td>
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<td>W16</td>
<td>W22</td>
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Sensitization:
7 groups
N=12/group

Desensitization:
Sham
HKE-mAra h1-3, 6.3 µg
HKE-mAra h1-3, 3 µg
HKE-mAra h1-3, 30 µg
HKE-vector
HKE-mAra h1-3, 30 µg, - saline
Naive

Challenge:
1st
n=12
m=4
Sac. 4
gp culture
---
2nd
n=8
m=4
Sac. 4
---
Murine Model of Anaphylaxis: Scoring System

0: No sign of reaction.
1: Scratching and rubbing around the nose and head.
2: Decreased activity with an increasing respiratory rate, pilo errect and/or swelling around the snout and eyes.
3: Labored respiration and cyanosis around the mouth and tail.
4: Slight or no activity after prodding, or tremors and convulsion.
5: Death

Assessment of Allergic Response in Mice: Anaphylactic Symptom Scores

Anaphylactic reaction

Desensitization with Rectal HKE-mAra h1-3: Symptom Scores: W22 Challenge

** p<0.01 vs Sham

Methyl Cellulose
Desensitization with p.r. HKE-mAra h1-3: Cytokine Production by Spleen Cells

Traditional Chinese Medicine

- Herbal remedies used in Asia for centuries
- Favorable safety profile
- Low cost
- FAHF-1 shown to abrogate peanut-induced anaphylaxis in mice
  (Li et al. JACI. 2001; 108:639)

Persistent Protection by FAHF-2

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<th>Week</th>
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Sensitization
5 wk old female C3H/HeJ mice were orally sensitized with 10mg Peanut + cholera toxin at wk 0-6 and boosted at wk 1, 2, 3, 4, 5, 6 & 8

Treatment (p.o.)
- Sham
- FAHF-2 (9 herbs)
- FAHF-5 (3 herbs)
- FAHF-5 2X
- Naive

Analyses
- Antibody responses
- Anaphylactic symptoms
- Histamine release

Srivastava K et al. JACI 2005; 115:171-179
Blocking Anaphylaxis and Histamine Release: W-22

Blocking Anaphylaxis and Histamine Release: W-40

Mean Symptom Scores

Serivastava K et al. JACI 2005; 115:171-178
Mean Peanut Specific IgE Levels

![Graph showing mean peanut specific IgE levels over time.](image)

***, P<0.001 vs Sham

TCM: Effect on Cytokine Production by Splenocytes

![Graphs showing cytokine production by splenocytes.](image)

Srivastava K et al. JACI 2003; 113:171-176

Treatment of Food Allergy: CONCLUSIONS

- Food allergy is a major health problem in "westernized" countries; affects 3.5% of U.S. population
- Few foods account for ~90% of food allergic reactions: milk, egg, peanuts, nuts, shellfish & fish
- Attempts at primary prevention have not been effective
- New therapies are on the horizon
  - Anti-IgE – increase threshold of food allergic reactions
  - Modified allergenic proteins - “reverse” food allergy
  - Herbal meds may provide prolonged protection