World Allergy Forum Symposium:
Food Allergy: Pathogenesis and Prevention

2012 AAAAI Annual Meeting
Sunday, 4 March 2012
10:45 – 12:00
Orlando, FL, USA

Moderators:
Ruby Pawankar (Japan)
Dennis K. Ledford (USA)

Prenatal Events and Development of Food Allergies
Susan Prescott (Australia)

Early Dietary Exposures and Feeding Practices
Scott H. Sicherer (USA)

Food Allergy and Atopic Eczema
Gideon Lack (UK)

www.worldallergy.org

The World Allergy Organization (WAO) is an international organization of 89 regional and national allergy and clinical immunology societies. WAO’s mission is to be a global resource and advocate in the field of allergy, advancing excellence in clinical care, education, research and training through a world-wide alliance of allergy and clinical immunology societies. WAF is an educational program of the World Allergy Organization.
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WISC 2012
2012 WAO International Scientific Conference

Severe Allergies, Severe Asthma:
New Strategies for Optimal Treatment & Prevention

Online Registration and Abstract Submission Now Open!

Hyderabad, India
6-9 December 2012

www.worldallergy.org/wisc2012
“Food Allergy: Pathogenesis and Prevention”

Program

Moderators:
Ruby Pawankar
Nippon Medical School
Tokyo, Japan

Dennis K. Ledford
University of South Florida College of Medicine
Tampa, FL, USA

1. Welcome to the World Allergy Forum Symposium and Introduction to “Food Allergy: Pathogenesis and Prevention”
   Ruby Pawankar and Dennis Ledford

2. Prenatal Events and Development of Food Allergies
   Susan Prescott
   University of Western Australia School of Paediatrics and Child Health
   Perth, Australia

3. Early Dietary Exposures and Feeding Practices
   Scott H. Sicherer
   Mount Sinai School of Medicine
   New York, NY, USA

4. Food Allergy and Atopic Eczema
   Gideon Lack
   St. Thomas Hospital
   London, UK

Upon completion of this session, participants should be able to:
- Describe the genetic and environmental events which predispose individuals to food allergy;
- Identify the possible dietary and environmental interventions to prevent food sensitization;
- Recognize when food allergy is implicated in the patient with atopic eczema.
The World Allergy Organization (WAO) is an international alliance of 89 regional and national allergy, asthma and clinical immunology societies. Through collaboration with the Member Societies, WAO provides a wide range of educational and outreach programs, symposia and lectureships to allergists/immunologists around the globe and conducts initiatives relating to clinical practice, service provision, and physician training in order to better understand and address the challenges facing allergists/immunologists worldwide. WAO helps expand the knowledge, expertise and skills of young physicians establishing careers in allergy through Research Fellowships with international placements at renowned allergy centers.

**Mission of the World Allergy Organization**

WAO’s mission is to be a global resource and advocate in the field of allergy, advancing excellence in clinical care through education, research and training as a world-wide alliance of allergy and clinical immunology societies.

**WAO Meetings**

**World Allergy Congress™ (WAC)**

WAO hosts the World Allergy Congress™ (WAC) — its main scientific meeting — biennially in different regions of the world. Please join us in Milan, Italy in 2013 and Seoul, South Korea in 2015.

**WAO International Scientific Conference (WISC)**

In 2010, WAO launched its theme-based scientific conferences alternating with and complementing WAO’s biennial World Allergy Congresses. The 2nd WAO International Scientific Conference on Severe Allergies, Severe Asthma: New Strategies for Optimal Treatment and Prevention will be held in Hyderabad, India — 6-9 December 2012. The 2012 Conference will provide a forum for the most useful combination of the latest research, review of current theory and practice, and hands-on, problem-based learning. For more information, visit www.worldallergy.org/wisc2012.

**World Allergy Organization Journal**

The World Allergy Organization Journal (WAO Journal) provides a global forum for the exchange of research and information on allergy, asthma, and clinical immunology. The journal supports this scientific interaction among members of the World Allergy Organization, an alliance of 89 societies worldwide, through publication of original research, clinical reviews, position papers, and epidemiological studies that contribute to current knowledge in patient care. Articles cover diagnosis, therapeutic options, crisis management, and treatment efficacy. Authors and reviewers represent all geographic regions, providing a truly global perspective. Published monthly online, with access on computers and mobile devices, the journal ensures the widest availability of practice-relevant science at the point of care. In 2010, the WAO Journal launched a new feature, Chief Editor Podcasts, consisting of audio downloads of interviews with authors of recently published articles on the latest research. www.waojournal.org

**WAO Online Resources**

As a leading global online destination for allergy, asthma and clinical immunology the WAO website supports and enhances WAO educational activities and provides materials specifically designed for continued medical training.

Popular resources include:

- Specially commissioned educational synopses on major topics posted in the Allergic Diseases Resource Center
- Interactive case studies that challenge allergists to diagnose unusual cases
- Online learning programs including the Immunology Online Lecture Series, Asthma and Allergic Rhinitis Online Lecture Series, and the interactive learning modules with CME on Food Allergy and Drug Allergy
- An archive of webinars recorded at major meetings, and audio recordings of interviews with key opinion leaders around the world
- A special section, Defining the Specialty, which provides easy access to WAO publications and other resources that help to define the specialty of allergy and immunology including the WAO White Book on Allergy
- Disease-specific sections of the website including the Allergic Rhinitis Working Group, Small Airways Working Group, and HAE Alliance.

The WAO website is HONcode certified. www.worldallergy.org

**WAO Programs for Education, Research and Patient Care**

**Global Resources in Allergy™ (GLORIA)**

GLORIA promotes best practices in the management of allergic disease through programs developed by international advisory expert panels. Modules are created from established guidelines and recommendations to address different aspects of allergy-related patient care. GLORIA is presented at national and regional allergy society meetings throughout the world and also at regional, state and local society meetings within the United States. All current GLORIA modules are available for free download at www.worldallergy.org/gloria.

**World Allergy Forum ® (WAF)**

The World Allergy Forum ® (WAF) program brings cutting edge symposia to major allergy meetings throughout the world. 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. WAF is the longest running educational program series sponsored by WAO and currently provides two or three placements a year with up to 1,000 attendees at each program. WAF is supported by an unrestricted educational grant from Novartis. View presentations for free at www.worldallergy.org/waf.
WAO Programs for Education, Research and Patient Care (continued)

Emerging Societies Program (ESP)
In order to advance the WAO mission of supporting developments that will enable allergists to better serve patients now and in the future, the Emerging Societies Program (ESP) aims to disseminate information on and share experiences about new treatments for allergic disease and about new indications for available therapies. As a response to an area of need identified by ESP Delegates, the ESP has also started to offer World Allergy Training Schools (WATS) in various regions of the world. All ESP meetings and training schools are conducted with the help and support of WAO Member Societies and held in conjunction with a Member Society’s annual meeting and in partnership with the American College of Allergy, Asthma and Immunology (ACAAI). View all ESP activities at www.worldallergy.org/.

WAO Publications
WAO papers support and promote the specialty of allergy and help set standards for clinical practice and training. A full bibliography is available at www.worldallergy.org/publications/.

World Allergy Week
In 2011, based on feedback from WAO Member Societies over recent years, WAO inaugurated the first annual World Allergy Week as a way for WAO Member Societies to collaborate in a global effort to disseminate information of worldwide importance about allergic and immunologic diseases and asthma. Participation covered a wide spectrum of activities including promotions through websites and social media avenues, patient information sessions, and interviews for radio and television programs. The next World Allergy Week will be held from 16 to 22 April 2011. Watch for updates and view last year’s activities at www.worldallergy.org/worldallergyweek/.

WAO Junior Members Group
www.worldallergy.org/juniormembers/
The WAO Junior Members Group aims to support and encourage young scientists and clinicians by providing the opportunity for them to contribute to the ongoing work of the WAO and become future WAO leaders! Applicants must be working in the field of allergy/clinical immunology, be 35 years of age or under and/or within 5-years of their latest degree, and a current member of a WAO Member Society. Visit www.worldallergy.org/juniormembers/ for further information or to apply.
WAO Member Societies

The World Allergy Organization (WAO), a world federation of allergy, asthma, and clinical immunology societies, consists of 89 Member Societies. All active members of dues-paying Member Societies are Individual Members of WAO.

Albanian Society of Allergology and Clinical Immunology
National Association for Private Algerian Allergists
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
Azerbaijan Society for Asthma, Allergy and Clinical Immunology
Belarus Association of Allergology & Clinical Immunology
Bangladesh Society of Allergy and Immunology
Belgian Society for Allergy and Clinical Immunology
Brazilian Society of Allergy and Immunopathology
British Society for Allergy and Clinical Immunology
Bulgarian Society of Allergology
Canadian Society of Allergy and Clinical Immunology
Chilean Society of Allergy and Immunology
Chinese Society of Allergy and Immunology
Colombian Allergy, Asthma, and Immunology Association
Croatian Society of Allergology and Clinical Immunology
Cuban Society of Allergology
Czech Society of Allergology and Clinical Immunology
Danish Society of Allergology
Egyptian Society of Allergy and Clinical Immunology
Egyptian Society of Pediatric Allergy and Immunology
Finnish Society of Allergology and Clinical Immunology
French Society of Allergology
Georgian Association of Allergology and Clinical Immunology
German Society for Allergology and Clinical Immunology
Hellenic Society of Allergology and Clinical Immunology
Honduran Society of Allergy and Clinical Immunology
Hong Kong Institute of Allergy
Hungarian Society of Allergology and Clinical Immunology
Icelandic Society of Allergy and Immunology
Indian College of Allergy, Asthma and Applied Immunology (ICAAI)
Indonesian Society for Allergy and Immunology
Israel Association of Allergy and Clinical Immunology
Italian Association of Territorial and Hospital Allergists
Italian Society of Allergy and Clinical Immunology
Japanese Society of Allergology
Jordanian Society for Allergy and Clinical Immunology
Korean Academy of Allergy, Asthma and Clinical Immunology
Kuwait Society of Allergy and Clinical Immunology
Latvian Association of Allergists
Lebanese Society of Allergy and Immunology
Malaysian Society of Allergy and Immunology
Mexican College of Clinical Immunology and Allergy
Mexican College of Pediatricians in Allergy and Clinical Immunology
Mongolian Society of Allergology
Moroccan Society of Allergology and Clinical Immunology
Netherlands Society of Allergology
Norwegian Society of Allergy and Immunopathology
Panamanian Association of Allergology and Clinical Immunology
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
Romanian Society of Allergology and Clinical Immunology
Russian Association of Allergology and Clinical Immunology
Serbian Association of Allergologists and Clinical Immunologists
Allergy and Clinical Immunology Society (Singapore)
Slovenian Association for Allergology and Clinical Immunology
Allergy Society of South Africa
Spanish Society of Allergology and Clinical Immunology
Swiss Society for Allergology and Immunology
Allergy, Asthma and Immunology Society of Thailand
Ukrainian Association of Allergologists and Clinical Immunologists
Uruguayan Society of Allergology
Venezuelan Society of Allergy and Immunology
Vietnam Association of Allergy, Asthma and Clinical Immunology
Zimbabwe Allergy Society

Associate Member Societies

Belarus Association of Allergology & Clinical Immunology
Canadian Society of Allergy and Clinical Immunology
Ecuadorian Society of Allergology and Affiliated Sciences
Egyptian Society of Pediatric Allergy and Immunology
Moldavian Society of Allergology and Immunology
Swedish Association for Allergology
Tunisian Society of Respiratory Diseases and Allergology

Regional Organizations

Asian Pacific Association of Allergy, Asthma and Clinical Immunology
Commonwealth of Independent States Society of Immunology and Allergology
European Academy of Allergology and Clinical Immunology
Latin American Society of Allergy and Immunology

Affiliate Organizations

British Society for Immunology
GA\LE\EN (Global Allergy and Asthma European Network)
International Association of Asthma

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Web site: www.worldallergy.org

Apply for your National Allergy Society to become a WAO Member Society at www.worldallergy.org/wao_societies/apply.php.
For WAO membership information please contact the Secretariat.
March 4, 2012

Dear Colleagues,

A warm welcome to the forty-first symposium in the World Allergy Forum (WAF) series: Food Allergy: Pathogenesis and Prevention. Recognizing the importance of food allergy, the World Allergy Organization (WAO) is delighted to bring this symposium to the 2012 Annual Meeting of the American Academy of Allergy, Asthma and Immunology (AAAAI).

WAO is proud to announce that the year 2012 marks the 15th anniversary of the World Allergy Forum. The first WAF was presented at the AAAAI Annual Meeting in San Francisco in 1997 and WAO is appreciative that this symposium is an annual event at the AAAAI Annual Meeting. Since 1997, WAF has flourished and become the longest continuing educational program of World Allergy Organization (WAO).

The area of food allergy has always been considered one of the most important and complex areas of allergic disease and its escalating prevalence in recent years makes it a growing public health concern. This WAF Symposium will examine the pathogenesis and prevention of food allergy. Prof. Susan Prescott will begin the symposium by examining the events responsible for this dramatic increase in food allergy and explore earlier preventive strategies. Dr. Scott H. Sicherer will focus on the role of early dietary exposures (infant feeding) and feeding practices (timing and types of foods chosen) on food allergy. Prof. Gideon Lack will conclude today’s symposium by examining the relationship between food allergy and atopic eczema. There will be an open discussion following the formal lectures.

The WAO Board hopes that you enjoy today’s program with its wealth of information and if you would like to access the faculty materials after the session they will be available at: www.worldallergy.org/waf.

WAO gratefully acknowledges the unrestricted educational grant from Novartis that supports educational programs such as this conjoint program at the AAAAI meeting.

With best regards,

Ruby Pawankar, MD, PhD, AAAAI
President
World Allergy Organization

Dennis Ledford, MD, AAAAI
President
American Academy of Allergy, Asthma and Immunology
Prenatal Events and the Development of Food Allergies

Professor Susan Prescott, PhD, MD
Paediatric Immunologist, Princess Margaret Hospital for Children, and
Winthrop Professor, School of Paediatrics and Child Health
University of Western Australia
Perth, Australia

Abstract:
Food allergy is now a substantial and evolving public health issue, recently emerging as a poorly understood “second wave” of the allergy epidemic. In regions like Australia, there has been a 5-fold increase in food anaphylaxis in preschool children over the last decade and challenge-proven IgE-mediated food allergy now affects up to 10% of infants. The greatest burden of this new epidemic is in young children, who are not only experiencing the most dramatic increase in food allergy, but also earlier presentations and increasing persistence of disease. As these younger generations reach adulthood, the burden of allergic diseases is expected to increase even more.

This dramatic and unprecedented rise in food allergy reinforces the pressing need to better define the events responsible in order to instigate earlier preventive strategies. There is no doubt that modern environmental changes must be disrupting the natural processes of oral tolerance in very early infancy. New data generated from our randomised controlled trials aimed at earlier introduction of allergenic foods have revealed worrying new evidence that a significant proportion of 4-6 month old infants already have established egg-sensitisation and clinical reactivity prior to the randomisation process. In some cases, the “first” introduction of egg at <5 months induced anaphylaxis. This clearly indicates that the processes leading to egg sensitisation are already strongly established by this age in many infants, and that much earlier preventive interventions will ultimately be needed. Importantly, in all cases there was no previous history known direct ingestion of egg by the infant, indicating previous exposure through other routes potentially through breast milk or across the placenta. While cutaneous sensitisation has been proposed in children with eczema, this does not appear to explain rates of reactivity in children with no eczema. Differences in neonatal immune function of these individuals (including effector and regulatory T cell function) suggest these events are initiated in utero and consolidated in the very early postnatal period.

Previous strategies to prevent food allergy through “allergen avoidance” have not only failed, but have instead been associated with increased risk of disease. This together with other observations in humans and animals has suggested two main avenues of research, 1) the role of earlier introduction of allergenic foods, and 2) a range of other environmental strategies to promote more tolerogenic conditions during initial allergen encounter

Environmental and lifestyle interventions currently under investigation include microbial agents (probiotics), dietary and nutritional modulation (vitamin D, oligosaccharide prebiotics and long chain fatty acids) in pregnancy and the early postnatal period. Observational studies also suggest that adverse conditions such as stress (raised cortisol levels) in pregnancy and infancy, and exposure to pro-inflammatory agents (such as cigarette smoking and diesel exhaust) are also associated with and increase risk of allergic disease. Investigating the relative contribution of these and other environmental factors as “causes” and/or “solutions” to the rise in food allergy remains an enormous challenge that may take many decades to unravel. In the process we need a more thorough understanding of the developing immune system and the events that lead to oral tolerance. This should ideally include identification of predisposing genes, critical environmental determinants and maternal-fetal interactions which pave pathways to disease.

References:
Prenatal events in the development of Food Allergy

PROF SUSAN PRESCOTT

Changing allergy patterns in developed regions
Food allergy: a new wave in the allergy epidemic

RESPIRATORY ALLERGY EPIDEMIC

FOOD ALLERGY EPIDEMIC

Prevalence (%)

YEAR

Asthma

Eczema

Food allergy

Example countries: Australia, Singapore, New Zealand, Hong Kong

Dramatic increase in food allergy and eczema in the last 10 years

ALLERGY REFERRALS

Eczema

Food allergy

YEAR

Maline, MJA 2007; 186: 618-621 (Australian data)
Dramatic increase in severe reactions (anaphylaxis)

5-fold rise in preschoolers over 10 yrs

Mukher, MJA 2007; 186: 918-921 (Australian data)

Food sensitisation: a very early event

- RCT: start egg/placebo at 4-6 months
- 22% reaction rate at randomization (prior to the intervention)
- 1.2% anaphylaxis Rx adrenaline
- On first known oral exposure to egg
- 'Early feeding' already too late in these children

Implies much earlier allergen exposure: pregnancy, lactation, transcutaneous

Neonatal differences in immune function point to the importance of in utero events

Presymptomatic differences at birth in allergic individuals:

- Increased inflammatory responses
  Prescott JMD 2006 132 239
- Immature Th1 function
  Prescott 1998 and others
- Immature T reg function (?)
  Saphir Prescott 2008 127 340
  Schall 2008 127 1491

Gene-environmental interactions in utero. Epigenetic influences?

Innate inflammatory responses (IL-6, TNF-α)

Subsequent Allergic response
Fetus: highly developed regulatory responses

- Not an 'immature' version of adults
- Highly responsive to antigens
- Strong bias to Treg differentiation (tolerogenic milieu: TGFβ, TSLP)
- Higher % circulating Treg than adults

→ Wave of promiscuously responsive cells
→ Gives rise to a broad repertoire of Treg (self antigens)

Dispels myth that the fetus has reduced ability to respond.

Does tolerance to exogenous antigens (allergens) begin during this period?

- Allergens cross the placenta
  → detected in cord blood, placenta and amniotic fluid
- Fetus can generate long-lived CD4+CD25+FoxP3+ Tregs
  → to exogenous antigens (alloantigens, microbial Ag)¹²
  → can modulate postnatal responses
- Fetal allergen-specific responses
  → generate Treg in vitro¹

Fetal Treg response
- Allergens
- Microbial antigens
- Allergens

The role of the thymus?

- Autoreactive clones
  - Deleted (high affinity)
  - Converted to Treg (medium affinity)
  → periphery (tolerance)
- Surprising new studies:
  - T cells/DC re-enter thymus (physiological)
    → deliver Ag from periphery¹
  - DC can carry allergen (OVA) from tissues
    → to the thymus (experimental)²
    → regulatory response

Challenges notion of unidirectional role of thymus: New perspectives for tolerance to exogenous Ag?
Exposures in very early development can increase risk of future diseases

Early environment (diet, microbes, toxins, stress)

Risk of later disease (heart disease, obesity, dementia, diabetes, allergy, asthma)

How is this happening?

Early exposures (diet, microbes, toxins, stress)

Changes in gene expression

The environment can change the epigenetic code which determines patterns of gene expression in each cell.

Risk of later disease (heart disease, obesity, dementia, diabetes, allergy, asthma)

Good news: ‘plasticity’ means opportunity for change

Opportunities may be greater during early development

GENES

Epigenetic effects

ENVIRONMENT

Changing pattern of gene expression

Changing disease predisposition

Opportunities for change! (Prevention and re-programming)
Logical preventive approaches
Restoring environment balance

- Pollutants
  - Reduce avoidable exposure
    - individual and societal
  - Reduce unnecessary use
    - individual and HCP

- Pharmaceuticals
  - Strategies to restore balance
    - probiotics, prebiotics, other?

- Microbial exposure
  - Anti-inflammatory nutrients
    - n-3 PUFA, fibre, antioxidants

- Traditional diets
  - Behavioural strategies
    - exercise, 'de-stress', sun in moderation, vitamin D?

Smoking and Pollutants

Cigarette Smoking:
- MANY adverse effects on the fetus
- effects on placental function
- abnormal lung development / asthma risk

Diesel exhaust particles:
- immune effects and increased asthma risk

Organic pollutants (pesticides / industrial chemicals):
- persistent and lipid soluble
  - detected in cord blood, placenta and breast milk
- suspected role in immune disease

All have epigenetic effects
Avoidance strongly recommended

Other adverse modern exposures

The public has many candidates:
- Chemicals and food additives
- Cleaning products
- Electromagnetic radiation (mobile phones, WiFi, microwaves)

But virtually no studies:
- No clear evidence either way.

EM radiation in animals:
- No clear immune effects in mature animals
- Some effects on newborn mice
- Effects in pregnancy: not known

Difficult to exclude effects of these modern exposures
Medications in pregnancy and allergy risk

Paracetamol:
- increased asthma risk
- seen in multiple studies
- abnormal

Anti-acid medications:
- increased allergy
- increased asthma

Antibiotics:
- some evidence of increased asthma and allergy risk

Logical to avoid unnecessary medications in pregnancy

Role of fermented foods and probiotics

Microbes essential for normal development

- Now >19 probiotic prevention studies (pregnancy and newborns)
- Conflicting results: depends on the strains and the population and lots of other factors
- Summary (Cochrane Review)
  - Some strains better (L. rhamnosus)
  - Effects only on eczema (not in all studies)
  - No reproducible effects of any other probiotics
  - No probiotics prevent other allergic diseases

Still no definitive benefits or recommendations

Need better strategies to define and restore microbial balance?

Restoring levels of soluble dietary fibre using ‘prebiotics’

More refined modern diets (less fibre)
- Less favourable colonisation
- Less substrate for SCFA formation

Prebiotics (naturally in breast milk)
Promote favourable colonisation
Fermentation products → anti-inflammatory

Prebiotic studies in newborns:
early promise in allergy prevention
### Restoring n-3 PUFA status (fish oil)

**N-3 PUFA**
- Clear anti-inflammatory effects: many health benefits
- Deficient in western diets

**Population studies (fish intake)**
- Many studies showing allergy protection (esp. pregnancy)

**Clinical trials (fish oil)**
- Allergy protection (supplementation in pregnancy)

No official recommendations yet, but logical to restore n-3 PUFA (closer to traditional levels)

### Reducing stress!!?

**Stress affects immune function**
- Effects in pregnancy
- Long-term effects in offspring
- Some evidence in humans

**Maternal stress and allergies**
- Higher IgE levels in newborns
- Risk of wheeze and asthma

**Infant stress levels**
- Cortisol levels indicate stress in babies, and higher allergy risk!

Logical to reduce stress for many health benefits

### Restoring Vitamin D status?

**Lifestyle changes: reduced sun exposure**
- Declining vitamin D levels
- Rising rates of deficiency

**Immune effects:**
- Important for immune regulation

**Implicated in allergy and asthma:**
- Associations but no proven links
- Conflicting reports

➡️ Prevention studies (vitamin D in pregnancy): underway
In conclusion

- One of the greatest challenges of modern medicine is to learn how we can live in the new world we have created.

- We need:
  - A better understanding of our effects on the environment, as well as its effects on us!
  - To restore a form of 'immune balance' so that we are less prone to the growing number of modern diseases (NCDs) that result from inflammation and immune dysregulation.

- Restoring balance may improve many aspects of human health...

A healthy environment = healthy humans?

Book released September 2011
(all author proceeds donated to research)

- Paperback book
  - Can be ordered on-line
  - Publisher (UWA Press)
  - Amazon / other on-line outlets

- E-Books

My hope: valuable, interesting resource for the public / patients / students / everyone!

Contact me (or the publisher)
if you need more information:
sprescott@meddent.uwa.edu.au
Early Dietary Exposures and Feeding Practices

Scott H. Sicherer, MD
Clinical Professor of Pediatrics, Jaffe Food Allergy Institute, Division of Pediatric Allergy and Immunology
Mount Sinai School of Medicine
New York, New York, USA

Abstract:
Food allergy prevalence varies geographically and appears to be increasing in “westernized” areas. This lecture focuses on the role of early dietary exposures (infant feeding) and feeding practices (timing and types of foods chosen) on food allergy. Recent Guidelines from the US have addressed diet as a means of allergy prevention. Emphasis is placed upon encouraging breast feeding and considering the use of “hypoallergenic” infant formulas for infants “at risk” if the infant is not breast fed. New guidelines in the US rescind prior recommendations that suggested avoidance of potentially allergenic foods for prolonged periods in infants at risk; for example prior suggestions to avoid milk until age 1, egg until age 2 and fish, peanut or nuts to age 3 years. The reversal substantially matches approaches that were in place in most countries outside of the US. Study after study appears to be substantiating the impression that waiting longer to introduce dietary “allergens” may be counterproductive for atopy outcomes (e.g., and others). There are likely numerous dietary reasons, besides dietary allergen exposure per se, that can affect allergy outcomes. We will explore how feeding practices themselves (using manufactured foods, cultural and regional differences) may have influenced allergy outcomes as well.

References
World Allergy Forum
Food Allergy: Pathogenesis and Prevention
Early Dietary Exposures and Feeding Practices
Scott H. Sicherer, MD
Clinical Professor of Pediatrics
Jaffe Food Allergy Institute
Mount Sinai School of Medicine
New York

AAAI Orlando 2012: Session 3307

Disclosures

• NIH-NIAID Funding for studies
• Food Allergy Initiative Consultant and funding for studies
• Food Allergy & Anaphylaxis Network Medical Advisor

Learning Objectives

• Understand the current data on atopy prevention through infant diet
• Advise families on dietary approaches with regard to food allergy prevention

Suggested References:
and
Prevention Through Diet

- Prevention of...
  - Sensitization
  - Inflammation
  - Disease

- Through “ingestion”...
  - Pregnancy
  - Breastfeeding
  - Breastfeeding-with Maternal diet alteration
  - Choice of breast milk substitution
  - Complementary foods
  - When/what

What are “normal” feeding practices?

- Breast feed
- Weaning
- Solids that are easily managed by an infant
- Progression as teeth erupt

Breast Feeding (focus on eczema)

- 18 prospective studies (Gdavelich JAAD 2001; 45:520-7)
  - Atopic (OR 0.58; 95% CI, 0.41-0.92)
  - Non-atopic (OR 0.84; 95% CI, 0.59-1.19)
- 21 studies (Yang YW BJD 2009; 161:373-383)
  - Overall OR 0.89 (95% CI 0.75-1.04)
  - vs. formula OR 0.7 (95% CI 0.50-0.99)
  - (but p=NS removing Chandra)

- ISAAC Study (Floh C BJD 2011;165:1280-9)
  - 51,119 children. No evidence of overall protection.
  - Recent studies suggest genetic differences affect risk
    (Hong et al JACI 2011;128:374-81)
Meta-Analysis: Maternal Diet Restriction While Breast Feeding

- Insufficient evidence that maternal allergen avoidance prevents atopic disease
- Possible exception for atopic dermatitis
- 2 studies
  Kramer Kakuma Cochrane database 2006
- 2010 Food Allergy Guidelines: Not recommended to reduce FA

The German Infant Nutritional Intervention Study

- “At risk” for atopy (one 1st degree)
- Randomized to study formula (within context of instruction to breast-feed)
  - Cow’s milk formula (CMF)
  - Extensively hydrolyzed casein (eHF-C)
  - Extensively hydrolyzed whey (eHF-W)
  - Partially hydrolyzed whey (pHF-W)

Von Berg A JACI 2003; 111:533
Von Berg JACI 2007
Von Berg JACI 2006

The German Infant Nutritional Intervention Study

- Lesson #1: Cannot assume a formula’s effect (e.g., eHF-W)
- Lesson #2: Impact on subtypes of risk*

*Trends
Randomized Trial of 3 Formulas if Weaning

- 620 infants positive family history atopy
- Cow’s milk vs. soy vs partially hydrolyzed whey at weaning
- Followed age 2 years (93%) and age 7 (80%)
- 50% exposed ~5 months, ~75% 1 year
- No differences in AD, food skin tests, asthma, rhinitis

Lowe et al JACI 2011;128:360-5

Prevention Formulas

- Soy not recommended for “prevention” (AAP, NIAID)
- “Hydrolyzed infant formulas” recommended over whole cow’s milk protein for “at risk” (NIAID Guideline) and some evidence for reduced atopic dermatitis (slight advantage of extensive casein hydrolysate versus partial whey hydrolysate weighed by cost (AAP)

Dietary Prevention Program, US

- Randomized, prospective, 288 subjects, one parent with atopy and sensitization
- Program:
  - Pregnancy, 3rd trimester-no milk, egg, peanut, reduced soy/wheat
  - Lactation, avoid same, supplement casein hydrolysate
  - Solids at 6 mo, 12 mo-CM, wheat, soy, 24 mo-egg, 36 mo-peanut, fish
- Followed to age 7 years

Zeiger JACI 1989;Zeiger PAl 1992;Zeiger JACI 1995
Dietary Prevention Program, US Period Prevalence of Disorders


“Prevention”
AAP Committee on Nutrition, 2000

- Breastfeed 1 year
- If supplement, “hypoallergenic formula”
- Solids delay to age 6 mo
- Should eliminate Peanut, Tree nuts, and consider eliminate egg, milk, fish “others” while nursing
- No Cow's milk to 12 mo
- No Egg to age 2 yr
- No Peanut, Tree Nuts, fish to 3 yr
- Pregnancy: consider peanut exclusion

Suggestions aimed at “high risk”

Solid Foods

Age of Solid food Introduction

Ferguson et al Clls Allergy 1991
Kajosaari & Saarinen Acta Ped Scand 1983

Rate of Eczema

Atopic Dermatitis OR (95% CI)

Veg (>4 mo)
Egg (>8 mo)

Zutavern et al ADC 2004
Solid Food Post 2000

- **Germany** (J Pediatr 2007;151:262)
  - 4753 infants (birth cohort): Among "at risk" atopy if waited on giving egg (RR 1.8, 95% CI: 1.2-2.6)
- **Belgium** (Pediatrics 2010;21:74)
  - Case Control: Solids before 4 months, less eczema (OR 0.49; 95% CI 0.3-0.7)
- **Finland** (New Am J Pediatr 2010;125:G0)
  - Cohort 994: Later introduction of solid foods associated with higher food sensitization
- **Netherlands** (J Pediatr Cardiol 2011;103:233)
  - Cohort 6905: No relationship of eczema/wheeze to receiving milk, egg, soy, nut, wheat prior to age 8 months

Complementary feeding and food sensitization: Detroit

- Enrolled 1258 women, 44.9% parental atopy
- Dietary inclusion of complementary foods at < 4 months versus food sensitization at age 2-3 years
- 74.2% with data for this analysis

<table>
<thead>
<tr>
<th>Family Atopy</th>
<th>IgE &gt; 0.7 kU/L E/RM &gt; 0.35 peanut</th>
<th>Adjusted odds ratio</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Yes</td>
<td>Egg/milk</td>
<td>0.5 (0.3-0.9)</td>
<td>0.023</td>
</tr>
<tr>
<td>Yes</td>
<td>Peanut</td>
<td>0.2 (0.1-0.7)</td>
<td>0.007</td>
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<tr>
<td>No</td>
<td>Egg/milk</td>
<td>1.0 (0.6-2.0)</td>
<td>0.894</td>
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<tr>
<td>No</td>
<td>Peanut</td>
<td>1.3 (0.6-2.7)</td>
<td>0.544</td>
</tr>
</tbody>
</table>

Joseph et al JACI 2011;127:1203-10

Egg Introduction and Egg Allergy

"HealthNuts" study, 2589 infants population-based, cross-sectional study

- Effects seen in high-risk and low-risk infants with cooked egg introduction
- Adjusted for confounding factors
- Confirmed egg allergy

Koplin et al JACI 2010
Cereal Grain Introduction and Wheat Allergy

"Daisy" study (US), 1612 infants, birth cohort observational study

0-6 mo
≥7 mo

- Parent reported wheat allergy in 1%, 4 with positive wheat-IgE
- Adjusted for parental allergic diseases and any food allergy < 6 mo of age
- Designed to investigate natural hx of diabetes and celiac disease in a HLA-predisposed population

Poole et al Pediatrics 2006

Cow's Milk Introduction and Milk Allergy

Prospective feeding study of 13019 infants in Israel, telephone interview, encourage to breast feed

- Low prevalence of IgE-mediated allergy 0.5%, which confirmed milk allergy
- Regards parental atopy as a potential confounding factor
- Nursery milk exposures not considered

Katz et al JACI 2010

Introduction of milk/milk products and atopy outcomes

- KOALA Birth cohort (n=2558, Netherlands)
- Followed to age 2: Delayed milk/milk products associated with eczema; delayed "other foods" with atopy, prolonged BFing-protective.

Snijders et al Pediatrics 2008;122:e115-22

Age at introduction of milk protein (mo)
Government and Pediatric Society Response To Peanut Allergy “Epidemic”

- Avoid peanut during pregnancy, lactation and wait to age 3 years to feed it
- American Academy of Pediatrics 2000
- Committee on Toxicology (UK) 1999

Ingestion is bad...Uh oh...?

Percent peanut allergy in children

After Advice to avoid

Before Advice to avoid

Maybe if you don’t eat it, you touch it, have accidental periodic ingestions that are all sensitizing?

Sicherer et al JACI 2003; 2010 Grundy et al JACI 2002; Du Toit JACI 2005; Fox JACI 2009

Urbanization

What are “normal” feeding practices?

- Breast feed
- Weaning
- Solids that are easily managed by an infant
- Progression as teeth erupt

Weaning Foods

- Thailand-coconut, chili, tamarind, lemon grass
- Africa-meat
- China-rice, fish, vegetables, meat
- India-wheat, rice, milk, egg, fish, legumes
- Japan-rice, soy, fish

Characteristics Mothers Completing the Questionnaire Asking Whether They Have Ever Given Pre-masticated Food to Their Children

- Anonymous survey
- 90, HIV infected mothers
- Brooklyn, NY
- Overall, 18% pre-masticated

<table>
<thead>
<tr>
<th>N = 90</th>
<th>Yes, Premasticates</th>
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<tbody>
<tr>
<td>Born US</td>
<td>18%</td>
</tr>
<tr>
<td>Born Caribbean or Central America</td>
<td>13%</td>
</tr>
<tr>
<td>Born Africa</td>
<td>29%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>7%</td>
</tr>
<tr>
<td>African American</td>
<td>30%</td>
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<tr>
<td>African</td>
<td>29%</td>
</tr>
<tr>
<td>Mother Pre-masticated</td>
<td>42%</td>
</tr>
<tr>
<td>Mother did not Premasticate</td>
<td>12%</td>
</tr>
</tbody>
</table>


ENDS: MEANS

- Prevention of...
  - Sensitization
  - Inflammation
  - Disease

- Through ingestion...
  - Pregnancy
  - Breast feeding
  - Breast feeding with Maternal diet alteration
  - Choice of breast milk substitution
  - Complementary foods

ENDS: MEANS

- Prevention of...
  - Good for everyone, exclusive to 4-6 mo
  - Certain Hydrolyzed formulas, not soy, not cow's milk

- Through ingestion...
  - Pregnancy
  - Breast feeding
  - Breast feeding with Maternal diet alteration
  - No obvious Effect (?)
  - Choice of breast milk substitution
  - Complementary foods
  - Nothing special (exceptions?)
Abstract:
In analysing the relationship between food allergy (FA) and atopic eczema (AE), there are various possibilities to consider; firstly FA may cause or be an exacerbating factor for AE. The second possibility is that AE may lead to FA. The third possibility is that they mutually contribute to each other.

There is strong evidence of an association between FA and AE. Children with FA more commonly have a history of AE; whereas children with AE very frequently have proven FA. A recent study in 2008 showed that early age of onset and eczema severity were both associated with FA.1 Furthermore in oral provocation studies done by different groups,2-4 about half of the positive food challenges resulted in delayed eczematous lesions. These eczematous responses were induced mainly by milk, egg, wheat, and soya. It is therefore surprising that intervention studies to eliminate allergens from the diet of children with AE have had very limited success. Most studies are uncontrolled and suffer from methodological limitations due to lack of blinding, lack of confirmation of FA, selection bias, and different criteria for the diagnosis of AE.5

In animal models, there is literature suggesting that cutaneous exposure to allergen can lead to the production of allergen specific IgE, particularly in the context of inflamed or abraded skin.6,7 More recently, Chan et al8 showed that T lymphocyte responses in peanut allergic children were predominant in the CLA+ population consistent with the hypothesis that sensitisation to peanut occurs in the skin. It has also been observed that use of arachis oil is increased in children who develop peanut allergy.9 More recently, it has been shown that environmental exposure to peanut as measured by a Food Frequency Questionnaire of peanut consumption in the home, was linked to peanut consumption as a risk factor for the development of peanut allergy.10

The discovery of the importance of filaggrin null mutations in AE provides a biological basis for the possibility of cutaneous sensitisation. These mutations affect up to 50% of Caucasian individuals with moderate to severe AE. Patients with filaggrin null mutations have a deficiency in the skin barrier (irrespective of the presence of eczema), and it has been shown that infants with this mutation have increased Trans Epidermal Water Loss even in the absence of detectable eczema.11 It has been shown that the filaggrin null mutation increases the risk of peanut allergy (OR 5.3)12 and the association remained significant after controlling for coexistent AE.

In summary, FA and AE are clearly associated. There is evidence that FA can exacerbate eczema, and perhaps the strongest direct evidence comes from food challenge studies. There is however a lack of well-conducted interventional dietary elimination studies. There is growing circumstantial data to support the potential role of AE and defects in the skin barrier as a cause of FA.

References
Food Allergy and Atopic Eczema

Professor Gideon Lack
King’s College London

Relationship between Food Allergy & Atopic Dermatitis

- Food allergy → Atopic dermatitis
- Atopic dermatitis → Food allergy
- Atopic dermatitis ↔ Food allergy

Prevalence of AD in FA

[Graph showing prevalence of AD in FA]
Prevalence of food allergy* and atopic dermatitis

- Sampson 1985 56%
- Sampson 1995 73%
- Eigenmann (Baltimore) 1998 37%
- Eigenmann (Geneva) 2000 27%
- Niggemann 1999 81%
- Roehr 2001 55%

* Proven by DBPCFC

The relationship between eczema severity and the frequency of high-risk IgE food sensitization (HR-IgE-FS) to foods according to the age of onset of eczema is shown. The children with the most severe eczema (≥5), and the earliest age of onset (3 months), had the greatest frequency of HR-IgE-FS.


Does food allergy cause atopic dermatitis?

- Oral Provocation Studies
- Interventional Studies
Oral Provocation Studies

- 139 children, mean age 13 months
- Mild AD 59%, Moderate 32%, Severe 9%
- Suspected food involvement by doctor or parent

DBPCFC to milk, egg, wheat and soy in children median age 2 years with AD and suspected FA

Causes of late eczematous reactions
Does food allergy cause atopic dermatitis?

- Oral Provocation Studies
- Interventional Studies

Interventional studies: Can Dietary Restriction Improve Atopic Dermatitis?

- 16 interventional studies to address this
- No meta-analyses
- Varying
  - Study populations
  - Intervention
  - Design
  - Outcome measures

Review of Studies

- 15 of 16 studies report some response, but variable
- Interventions most effective in infants
- Successful interventions include egg, milk & wheat avoidance
- Effect is generally small
CLA+ and CD8+ proliferation as a percentage of total CLA+ and CD8+ proliferation to 400μg/ml peanut in each patient on day 5, showing proliferation to peanut predominating in the CLA subset of PA patients and a more mixed response in peanut tolerant (NA) patients.


Peanut allergy is associated with:

- Eczema: OR = 2.6, 95%CI 1.4 - 5.0
- Oozing crusted rash: OR = 5.2, 95%CI 2.7 - 10.2
- Topical Arachis oil: OR = 6.8, 95%CI 1.4 - 32.9


Proportion of allergic children with peanut allergy as a function of household peanut consumption during infancy, and as a function of maternal peanut consumption during pregnancy

Filaggrin

- Filaggrin forms a dense protein lipid matrix regulating permeability of the skin to water and external particles

- Loss-of-function filaggrin mutations:
  - Common (up to 10%) in Caucasian populations
  - Associated with up to 50% of moderate-severe eczema
  - Associated with peanut allergic (OR 5.3; CI 3.8-10.2) in UK and Canada even after controlling for coexistent eczema (p=0.0008)

Sandilands A et al. Nature Genetics 2007; 39: 850-4
Brown SJ et al. JACI 2011; 127(3-4): 651-667
Summary

- Food allergy → Atopic dermatitis
- Atopic dermatitis → Food allergy
- Atopic dermatitis ↔ Food allergy
EAACI-WAO World Allergy & Asthma Congress
22 - 26 June 2013
Milan, Italy

Abstract Submission Deadline: 21 January 2013

www.eaaci-wao2013.com
Severe Allergies, Severe Asthma: 
New Strategies for Optimal Treatment & Prevention

Hyderabad, India
6-9 December 2012

www.worldallergy.org/wisc2012
“Food Allergy: Pathogenesis and Prevention”

Program

Moderators:
Ruby Pawankar
Nippon Medical School
Tokyo, Japan

Dennis K. Ledford
University of South Florida College of Medicine
Tampa, FL, USA

1. Welcome to the World Allergy Forum Symposium and Introduction to “Food Allergy: Pathogenesis and Prevention”
   Ruby Pawankar and Dennis Ledford

2. Prenatal Events and Development of Food Allergies
   Susan Prescott
   University of Western Australia School of Paediatrics and Child Health
   Perth, Australia

3. Early Dietary Exposures and Feeding Practices
   Scott H. Sicherer
   Mount Sinai School of Medicine
   New York, NY, USA

4. Food Allergy and Atopic Eczema
   Gideon Lack
   St. Thomas Hospital
   London, UK

Upon completion of this session, participants should be able to:
• Describe the genetic and environmental events which predispose individuals to food allergy;
• Identify the possible dietary and environmental interventions to prevent food sensitization;
• Recognize when food allergy is implicated in the patient with atopic eczema.
**Mission of the World Allergy Organization**

WAO’s mission is to be a global resource and advocate in the field of allergy, advancing excellence in clinical care through education, research and training as a world-wide alliance of allergy and clinical immunology societies.

**WAO Meetings**

**World Allergy Congress™ (WAC)**
WAO hosts the World Allergy Congress™ (WAC) — its main scientific meeting — biennially in different regions of the world. Please join us in Milan, Italy in 2013 and Seoul, South Korea in 2015.

**WAO International Scientific Conference (WISC)**
In 2010, WAO launched its theme-based scientific conferences alternating with and complementing WAO’s biennial World Allergy Congresses. The 2nd WAO International Scientific Conference on Severe Allergies, Severe Asthma: New Strategies for Optimal Treatment and Prevention will be held in Hyderabad, India — 6-9 December 2012. The 2012 Conference will provide a forum for the most useful combination of the latest research, review of current theory and practice, and hands-on, problem-based learning. For more information, visit www.worldallergy.org/wisc2012.

**World Allergy Organization Journal**

The World Allergy Organization Journal (WAO Journal) provides a global forum for the exchange of research and information on allergy, asthma, and clinical immunology. The journal supports this scientific interaction among members of the World Allergy Organization, an alliance of 89 societies worldwide, through publication of original research, clinical reviews, position papers, and epidemiological studies that contribute to current knowledge in patient care. Articles cover diagnosis, therapeutic options, crisis management, and treatment efficacy. Authors and reviewers represent all geographic regions, providing a truly global perspective. Published monthly online, with access on computers and mobile devices, the journal ensures the widest availability of practice-relevant science at the point of care. In 2010, the WAO Journal launched a new feature, Chief Editor Podcasts, consisting of audio downloads of interviews with authors of recently published articles on the latest research. www.waojournal.org

**WAO Online Resources**

As a leading global online destination for allergy, asthma and clinical immunology the WAO website supports and enhances WAO educational activities and provides materials specifically designed for continued medical training.

Popular resources include:
- Specially commissioned educational synopses on major topics posted in the Allergic Diseases Resource Center
- Interactive case studies that challenge allergists to diagnose unusual cases
- Online learning programs including the Immunology Online Lecture Series, Asthma and Allergic Rhinitis Online Lecture Series, and the interactive learning modules with CME on Food Allergy and Drug Allergy
- An archive of webinars recorded at major meetings, and audio recordings of interviews with key opinion leaders around the world
- A special section, Defining the Specialty, which provides easy access to WAO publications and other resources that help to define the specialty of allergy and immunology including the WAO White Book on Allergy
- Disease-specific sections of the website including the Allergic Rhinitis Working Group, Small Airways Working Group, and HAE Alliance.

The WAO website is HONcode certified. www.worldallergy.org

**WAO Programs for Education, Research and Patient Care**

**Global Resources in Allergy™ (GLORIA)**
GLORIA promotes best practices in the management of allergic disease through programs developed by international advisory expert panels. Modules are created from established guidelines and recommendations to address different aspects of allergy-related patient care. GLORIA is presented at national and regional allergy society meetings throughout the world and also at regional, state and local society meetings within the United States. All current GLORIA modules are available for free download at www.worldallergy.org/gloria.

**World Allergy Forum® (WAF)**
The World Allergy Forum® (WAF) program brings cutting edge symposia to major allergy meetings throughout the world. 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. WAF is the longest running educational program series sponsored by WAO and currently provides two or three placements a year with up to 1,000 attendees at each program. WAF is supported by an unrestricted educational grant from Novartis. View presentations for free at www.worldallergy.org/waf.
WAO Programs for Education, Research and Patient Care (continued)

Emerging Societies Program (ESP)
In order to advance the WAO mission of supporting developments that will enable allergists to better serve patients now and in the future, the Emerging Societies Program (ESP) aims to disseminate information on and share experiences about new treatments for allergic disease and about new indications for available therapies. As a response to an area of need identified by ESP Delegates, the ESP has also started to offer World Allergy Training Schools (WATS) in various regions of the world. All ESP meetings and training schools are conducted with the help and support of WAO Member Societies and held in conjunction with a Member Society’s annual meeting and in partnership with the American College of Allergy, Asthma and Immunology (ACAAI). View all ESP activities at www.worldallergy.org/.

WAO Publications
WAO papers support and promote the specialty of allergy and help set standards for clinical practice and training. A full bibliography is available at www.worldallergy.org/publications/.

World Allergy Week
In 2011, based on feedback from WAO Member Societies over recent years, WAO inaugurated the first annual World Allergy Week as a way for WAO Member Societies to collaborate in a global effort to disseminate information of worldwide importance about allergic and immunologic diseases and asthma. Participation covered a wide spectrum of activities including promotions through websites and social media avenues, patient information sessions, and interviews for radio and television programs. The next World Allergy Week will be held from 16 to 22 April 2011. Watch for updates and view last year’s activities at www.worldallergy.org/worldallergyweek/.

WAO Junior Members Group
www.worldallergy.org/juniormembers/
The WAO Junior Members Group aims to support and encourage young scientists and clinicians by providing the opportunity for them to contribute to the ongoing work of the WAO - and become future WAO leaders! Applicants must be working in the field of allergy/clinical immunology, be 35 years of age or under and/or within 5-years of their latest degree, and a current member of a WAO Member Society. Visit www.worldallergy.org/juniormembers/ for further information or to apply.
March 4, 2012

Dear Colleagues,

A warm welcome to the forty-first symposium in the World Allergy Forum (WAF) series: Food Allergy: Pathogenesis and Prevention. Recognizing the importance of food allergy, the World Allergy Organization (WAO) is delighted to bring this symposium to the 2012 Annual Meeting of the American Academy of Allergy, Asthma and Immunology (AAAAI).

WAO is proud to announce that the year 2012 marks the 15th anniversary of the World Allergy Forum. The first WAF was presented at the AAAAI Annual Meeting in San Francisco in 1997 and WAO is appreciative that this symposium is an annual event at the AAAAI Annual Meeting. Since 1997, WAF has flourished and become the longest continuing educational program of World Allergy Organization (WAO).

The area of food allergy has always been considered one of the most important and complex areas of allergic disease and its escalating prevalence in recent years makes it a growing public health concern. This WAF Symposium will examine the pathogenesis and prevention of food allergy. Prof. Susan Prescott will begin the symposium by examining the events responsible for this dramatic increase in food allergy and explore earlier preventive strategies. Dr. Scott H. Sicherer will focus on the role of early dietary exposures (infant feeding) and feeding practices (timing and types of foods chosen) on food allergy. Prof. Gideon Lack will conclude today’s symposium by examining the relationship between food allergy and atopic eczema. There will be an open discussion following the formal lectures.

The WAO Board hopes that you enjoy today’s program with its wealth of information and if you would like to access the faculty materials after the session they will be available at: www.worldallergy.org/waf.

WAO gratefully acknowledges the unrestricted educational grant from Novartis that supports educations programs such as this conjoint program at the AAAAI meeting.

With best regards,

Ruby Pawankar, MD, PhD, FAAAAI
President
World Allergy Organization

Dennis Ledford, MD, FAAAAI
President
American Academy of Allergy, Asthma and Immunology
Prenatal Events and the Development of Food Allergies

Professor Susan Prescott, PhD, MD
Paediatric Immunologist, Princess Margaret Hospital for Children, and
Winthrop Professor, School of Paediatrics and Child Health
University of Western Australia
Perth, Australia

Abstract:
Food allergy is now a substantial and evolving public health issue, recently emerging as a poorly understood ‘second wave’ of the allergy epidemic 1. In regions like Australia, there has been a 5-fold increase in food anaphylaxis in preschool children over the last decade 2 and challenge-proven IgE-mediated food allergy now affects up to 10% of infants 3. The greatest burden of this new epidemic is in young children, who are not only experiencing the most dramatic increase in food allergy, but also earlier presentations 2 and increasing persistence 4 of disease. As these younger generations reach adulthood, the burden of allergic diseases is expected to increase even more.

This dramatic and unprecedented rise in food allergy reinforces the pressing need to better define the events responsible in order to instigate earlier preventive strategies. There is no doubt that modern environmental changes need to better define the natural processes of oral tolerance in very early infancy. New data generated from our randomised controlled trials aimed at earlier introduction of allergenic foods have revealed worrying new evidence that a significant proportion of 4-6 month old infants already have established egg-sensitisation and clinical reactivity prior to the randomisation process. In some cases, the “first” introduction of egg at <5 months induced anaphylaxis. This clearly indicates that the processes leading to egg sensitisation are already strongly established by this age in many infants, and that much earlier preventive interventions will ultimately be needed. Importantly, in all cases there was no previous history known direct ingestion of egg by the infant, indicating previous exposure through other routes potentially through breast milk or across the placenta. While cutaneous sensitisation has been proposed in children with eczema, this does not appear to explain rates of reactivity in children with no eczema. Differences in neonatal immune function of these individuals (including effector 5 and regulatory T cell function6) suggest these events are initiated in utero and consolidated in the very early postnatal period.

Previous strategies to prevent food allergy through ‘allergen avoidance’ have not only failed, but have instead been associated with increased risk of disease 7. This together with other observations in humans and animals has suggested two main avenues of research, 1) the role of earlier introduction of allergenic foods, and 2) a range of other environmental strategies to promote more tolerogenic conditions during initial allergen encounter 8. Environmental and lifestyle interventions currently under investigation include microbial agents (probiotics), dietary and nutritional modulation (vitamin D, oligosaccharide prebiotics and long chain fatty acids) in pregnancy and the early postnatal period. Observational studies also suggest that adverse conditions such as stress (raised cortisol levels) in pregnancy and infancy, and exposure to pro-inflammatory agents (such as cigarette smoking and diesel exhaust) 9 are also associated with and increase risk of allergic disease. Investigating the relative contribution of these and other environmental factors as “causes” and/or “solutions” to the rise in food allergy remains an enormous challenge that may take many decades to unravel. In the process we need a more thorough understanding of the developing immune system and the events that lead to oral tolerance. This should ideally include identification of predisposing genes, critical environmental determinants and maternal-fetal interactions which pave pathways to disease.

References:
Prenatal events in the development of Food Allergy

Changing allergy patterns in developed regions
Food allergy: a new wave in the allergy epidemic

e.g. Australia, Singapore, New Zealand, Hong Kong

Dramatic increase in food allergy and eczema in the last 10 years

Malini, MJA 2007; 186: 618-621 (Australian data)
Dramatic increase in severe reactions (anaphylaxis)

5-fold rise in preschoolers over 10 yrs

Malins, MJA 2007: 186: 918-921 (Australian data)

Food sensitisation: a very early event

- RCT: start egg/placebo at 4-6 months
- 22% reaction rate at randomization (prior to the intervention)
- 1.2% anaphylaxis Rx adrenaline
- On first known oral exposure to egg
- ‘Early feeding’ already too late in these children

Implies much earlier allergen exposure: pregnancy, lactation, transcutaneous

Neonatal differences in immune function point to the importance of in utero events

Presymptomatic differences at birth in allergic individuals:
- Increased inflammatory responses
  Prescott JFO 2006; 122: 291
- Immature Th1 function
  Ng 2006; Archer Ria: Amende 1999
  Prescott 1998 and others
- Immature T reg function (?)
  Smith Prescott 2008; 121:748

Gene-environmental interactions in utero. Epigenetic influences?
**Fetus: highly developed regulatory responses**

- Not an 'immature' version of adults
- Highly responsive to antigens
- Strong bias to Treg differentiation (tolerogenic milieu: TGFβ, TSLP)
- Higher % circulating Treg than adults

→ Wave of promiscuously responsive cells
→ Gives rise to a broad repertoire of Treg (self antigens)

**Does tolerance to exogenous antigens (allergens) begin during this period?**

- Allergens cross the placenta → detected in cord blood, placenta and amniotic fluid
- Fetus can generate long-lived CD4+CD25+FoxP3+ Tregs → to exogenous antigens (alloantigens, microbial Ag) → can modulate postnatal responses
- Fetal allergen-specific responses → generate Treg in vitro

**The role of the thymus?**

- Autoreactive clones
  - Deleted (high affinity)
  - Converted to Treg (medium affinity) → periphery (tolerance)
- Surprising new studies:
  - T cells/DC re-enter thymus (physiological) → deliver Ag from periphery
  - DC can carry allergen (OVA) from tissues to the thymus (experimental) → regulatory response


**Challenges notion of unidirectional role of thymus: New perspectives for tolerance to exogenous Ag?**
New evidence of differences in thymic development in allergy

- TSLP
- IL-7
- Th2 milieu in neonatal thymus
- Capacity for Treg: TSLP level
- Atopic children
  - Reduced Treg (% and function)
  - Reduced TSLP
  - Evident in neonatal period
  - Reflects in utero environment
- Postnatal period
  - Breast milk IL-7 crosses intestine
  - Influences thymic size / T cell function

Environmental effects on thymic milieu may alter T reg development


Common risk factors
For many modern diseases

- Δ microbial balance
- Δ dietary profile
  - Saturated fat
  - Dietary fibre
  - n3 PUFA
  - Fresh foods
- Δ Sunlight (vitamin D)
- Δ Exercise patterns
- Δ Pollutants
  - Smoking
  - Toxins & POPs
  - EM radiation?

= Common interventions for prevention

Central role of the gut and nutrition
In maintenance of immune and metabolic homeostasis
(adverse exposures lead to inflammation and metabolic dysregulation)
Exposures in very early development can increase risk of future diseases

Early environment
(diet, microbes, toxins, stress)

Risk of later disease
(heart disease, obesity, dementia
diabetes, allergy, asthma)

How is this happening?

Early exposures
(diet, microbes, toxins, stress)

Changes in gene expression

The environment can change the epigenetic code which
Determines patterns of gene expression in each cell.

Risk of later disease
(heart disease, obesity, dementia
diabetes, allergy, asthma)

Good news:
‘plasticity’ means opportunity for change

Opportunities may be greater during early development

GENES  ➔  ENVIRONMENT

Changing pattern of gene expression

Changing disease predisposition

Opportunities for change
(Prevention and re-programming)
Logical preventive approaches

Restoring environment balance

↑ Pollutants ▼ Reduce avoidable exposure (individual and societal)

↑ Pharmaceuticals ▼ Reduce unnecessary use (individual and HCP)

↓ Microbial exposure → Strategies to restore balance
   probiotics, prebiotics, other?

↓ Traditional diets → Anti-inflammatory nutrients
   n-3 PUFA, fibre, antioxidants.

↑ Sedentary lifestyles → Behavioural strategies
   exercise, ‘de-stress’,
   sun in moderation, vitamin D?

---

Smoking and Pollutants

Cigarette Smoking:
- MANY adverse effects on the fetus
  - effects on placental function
  - abnormal lung development / asthma risk

Diesel exhaust particles:
- immune effects and increased asthma risk

Organic pollutants (pesticides / industrial chemicals):
- persistent and lipid soluble
  - detected in cord blood, placenta and breast milk
- suspected role in immune disease

All have epigenetic effects
Avoidance strongly recommended

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Other adverse modern exposures

The public has many candidates:
- Chemicals and food additives
- Cleaning products
- Electromagnetic radiation (mobile phones/WiFi/microwaves)

But virtually no studies:
- No clear evidence either way.

EM radiation in animals:
- No clear immune effects in mature animals
- Some effects on newborn mice
- Effects in pregnancy: not known

Difficult to exclude effects of these more modern exposures
Medications in pregnancy and allergy risk

Paracetamol:
- increased asthma risk
- seen in multiple studies
- abnormal

Anti-acid medications:
- increased allergy
- increased asthma

Antibiotics:
- some evidence of increased asthma and allergy risk

Logical to avoid unnecessary medications in pregnancy

Role of fermented foods and probiotics

Microbes essential for normal development

- Now >19 probiotic prevention studies (pregnancy and newborns)
- Conflicting results: depends on the strains and the population and lots of other factors
- Summary (Cochrane Review)
  - Some strains better (L. rhamnosus)
  - Effects only on eczema (not in all studies)
  - No reproducible effects of any other probiotics
  - No probiotics prevent other allergic diseases

Still no definitive benefits or recommendations
Need better strategies to define and restore microbial balance?

Restoring levels of soluble dietary fibre using ‘prebiotics’

More refined modern diets (less fibre)
- Less favourable colonisation
- Less substrate for SCFA formation

Prebiotics (naturally in breast milk)
Promote favourable colonisation
Fermentation products → anti-inflammatory

Prebiotic studies in newborns:
early promise in allergy prevention
Restoring n-3 PUFA status (fish oil)

N-3 PUFA
- Clear anti-inflammatory effects: many health benefits
- Deficient in western diets

Population studies (fish intake)
- Many studies showing allergy protection (esp. pregnancy)

Clinical trials (fish oil)
- Allergy protection (supplementation in pregnancy)

No official recommendations yet, but logical to restore n-3 PUFA (closer to traditional levels)

Reducing stress!!?

Stress affects immune function
- Effects in pregnancy
- Long-term effects in offspring
- Some evidence in humans

Maternal stress and allergies
- Higher IgE levels in newborns
- Risk of wheeze and asthma

Infant stress levels
- Cortisol levels indicate stress in babies, and higher allergy risk!

Logical to reduce stress for many health benefits

Restoring Vitamin D status?

Lifestyle changes: reduced sun exposure
- Declining vitamin D levels
- Rising rates of deficiency

Immune effects:
- Important for immune regulation

Implicated in allergy and asthma:
- Associations but no proven links
- Conflicting reports

➡️ Prevention studies (vitamin D in pregnancy): underway
In conclusion

- One of the greatest challenges of modern medicine is to learn how we can live in the new world we have created.

- We need:
  - A better understanding of our effects on the environment, as well as its effects on us!
  - To restore a form of ‘immune balance’ so that we are less prone to the growing number of modern diseases (NCDs) that result from inflammation and immune dysregulation.

- Restoring balance may improve many aspects of human health…

A healthy environment = healthy humans?

Book released September 2011
(all author proceeds donated to research)

- Paperback book
  - Can be ordered on-line
  - Publisher (UWA Press)
  - Amazon / other on-line outlets

- E-Books

My hope: valuable, interesting resource for the public / patients / students / everyone!

Contact me (or the publisher) if you need more information:
sprescott@meddent.uwa.edu.au
Abstract:
Food allergy prevalence varies geographically and appears to be increasing in “westernized” areas. This lecture focuses on the role of early dietary exposures (infant feeding) and feeding practices (timing and types of foods chosen) on food allergy. Recent Guidelines from the US have addressed diet as a means of allergy prevention. Emphasis is placed upon encouraging breast feeding and considering the use of “hypoallergenic” infant formulas for infants “at risk” if the infant is not breast fed. New guidelines in the US rescind prior recommendations that suggested avoidance of potentially allergenic foods for prolonged periods in infants at risk; for example prior suggestions to avoid milk until age 1, egg until age 2 and fish, peanut or nuts to age 3 years. The reversal substantially matches approaches that were in place in most countries outside of the US. Study after study appears to be substantiating the impression that waiting longer to introduce dietary “allergens” may be counterproductive for atopy outcomes (e.g., and others). There are likely numerous dietary reasons, besides dietary allergen exposure per se, that can affect allergy outcomes. We will explore how feeding practices themselves (using manufactured foods, cultural and regional differences) may have influenced allergy outcomes as well.

References
World Allergy Forum
Food Allergy: Pathogenesis and Prevention
Early Dietary Exposures and Feeding Practices

Scott H. Sicherer, MD
Clinical Professor of Pediatrics
Jaffe Food Allergy Institute
Mount Sinai School of Medicine
New York

Disclosures

- NIH-NIAID Funding for studies
- Food Allergy Initiative Consultant and funding for studies
- Food Allergy & Anaphylaxis Network Medical Advisor

Learning Objectives

- Understand the current data on atopy prevention through infant diet
- Advise families on dietary approaches with regard to food allergy prevention

Suggested References:
Prevention Through Diet

- Prevention of...
  - Sensitization
  - Inflammation
  - Disease
- Through “ingestion”...
  - Pregnancy
  - Breast feeding
  - Breast feeding-with Maternal diet alteration
  - Choice of breast milk substitution
  - Complementary foods
  - When/what

What are “normal” feeding practices?

- Breast feed
- Weaning
- Solids that are easily managed by an infant
- Progression as teeth erupt

Breast Feeding (focus on eczema)

- 18 prospective studies (Gdalevich JAAD 2001; 45:520-7)
  - Atopic (OR 0.58; 95% CI, 0.41-0.92)
  - Non-atopic (OR 0.84; 95% CI, 0.59-1.19)
- 21 studies (Yang YW BJD 2009; 161:373-383)
  - Overall OR 0.89 (95% CI 0.75-1.04)
  - vs. formula OR 0.7 (95% CI 0.50-0.99)
  *(but p=NS removing Chandra)

- ISAAC Study (Flohr C BJD 2011;165:1280-9)
  - 51,119 children. No evidence of overall protection.

Recent studies suggest genetic differences affect risk
(Hong et al JACI 2011;128:374-81)
Meta-Analysis: Maternal Diet Restriction While Breast Feeding

- Insufficient evidence that maternal allergen avoidance prevents atopic disease
- Possible exception for atopic dermatitis
- 2 studies
  - Kramer Kakuma Cochrane database 2006
- 2010 Food Allergy Guidelines: Not recommended to reduce FA

The German Infant Nutritional Intervention Study

- "At risk" for atopy (one 1st degree)
- Randomized to study formula (within context of instruction to breast-feed)
  - Cow’s milk formula (CMF)
  - Extensively hydrolyzed casein (eHF-C)
  - Extensively hydrolyzed whey (eHF-W)
  - Partially hydrolyzed whey (pHF-W)

- Trends

Von Berg A. JACI 2003; 111:633
Von Berg JACI 2006

The German Infant Nutritional Intervention Study

- Lesson #1: Cannot assume a formula’s effect (e.g., eHF-W)
- Lesson #2: Impact on subtypes of risk*
Randomized Trial of 3 Formulas if Weaning

- 620 infants positive family history atopy
- Cow’s milk vs. soy vs partially hydrolyzed whey at weaning
- Followed age 2 years (93%) and age 7 (80%)
- 50% exposed ~5 months, ~75% 1 year
- No differences in AD, food skin tests, asthma, rhinitis

Lowe et al JACI 2011:128:360-5

Prevention Formulas

- Soy not recommended for “prevention” (AAP, NIAID)
- “Hydrolyzed infant formulas” recommended over whole cow’s milk protein for “at risk” (NIAID Guideline) and some evidence for reduced atopic dermatitis (slight advantage of extensive casein hydrolysate versus partial whey hydrolysate weighed by cost (AAP)

Dietary Prevention Program, US

- Randomized, prospective, 288 subjects, one parent with atopy and sensitization
- Program:
  - Pregnancy, 3rd trimester-no milk, egg, peanut, reduced soy/wheat
  - Lactation, avoid same, supplement casein hydrolysate
  - Solids at 6 mo, 12 mo-CM, wheat, soy, 24 mo-egg, 36 mo-peanut, fish
- Followed to age 7 years

**Dietary Prevention Program, US Period Prevalence of Disorders**

- **Asthma**

- **Atopic dermatitis**

**“Prevention”**

AAP Committee on Nutrition, 2000

- Breast feed 1 year
- If supplement, “hypoallergenic formula”
- Solids delay to age 6 mo
- Should eliminate Peanut, Tree nuts, and consider eliminate egg, milk, fish “others” while nursing
- No Cow’s milk to 12 mo
- No Egg to age 2 yr
- No Peanut, Tree Nuts, fish to 3 yr
- Pregnancy: consider peanut exclusion

Suggestions aimed at “high risk”

**Solid Foods**

- Rate of Eczema
- Age of Solid food introduction

- Ferguson et al CIBA Allergy 1981
- Kajosaari & Saarinen Acta Ped Scand 1983

- Veg (>4 mo)
- Egg (>8 mo)

Zutavern et al ABC 2004
Solid Food Post 2000

- **Germany** (Frijters J Pediatr 2007;151:202)
  - 4753 infants (birth cohort). Among “at risk” atopy if waited on giving egg (RR 1.8, 95% CI: 1.2-2.6)

- **Belgium** (Sud et al PM 2010;2174)
  - Case Control: Solids before 4 months, less eczema (OR 0.49; 95% CI 0.3-0.7)

- **Finland** (Naru et al Pediatrics 2010;125:50)
  - Cohort 994: Later introduction of solid foods associated with higher food sensitization

- **Netherlands** (Tromp et al Pediatr Allergy Immunol 2011:103-933)
  - Cohort 6903: No relationship of eczema/wheeze to receiving milk, egg, soy, nut, wheat prior to age 8 months

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**Complementary feeding and food sensitization: Detroit**

- Enrolled 1258 women, 44.9% parental atopy

- Dietary inclusion of complementary foods at < 4 months versus food sensitization at age 2-3 years

- 74.2% with data for this analysis

<table>
<thead>
<tr>
<th>Family Atopy</th>
<th>IgE &gt; 0.7 kU/L EIA, &gt;0.35 peanut</th>
<th>Adjusted odds ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes Egg/milk</td>
<td>0.5 (0.3-0.9)</td>
<td>0.023</td>
<td></td>
</tr>
<tr>
<td>Yes Peanut</td>
<td>0.2 (0.1-0.7)</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>No Egg/milk</td>
<td>1.0 (0.6-2.0)</td>
<td>0.894</td>
<td></td>
</tr>
<tr>
<td>No Peanut</td>
<td>1.3 (0.6-2.7)</td>
<td>0.544</td>
<td></td>
</tr>
</tbody>
</table>

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**Egg Introduction and Egg Allergy**

"HealthNuts" study, 2589 infants population-based, cross-sectional study

- Effects seen in high-risk and low-risk infants with cooked egg introduction
- Adjusted for confounding factors
- Confirmed egg allergy

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Joseph et al. JACI 2011;127:1203-10

Kaplin et al. JACI 2010
Cereal Grain Introduction and Wheat Allergy

"Daisy" study (US), 1612 infants, birth cohort observational study

- 0-6 mo
- ≥7 mo

- Parent reported wheat allergy in 1%, 4 with positive wheat-IgE
- Adjusted for parental allergic diseases and any food allergy <6 mo of age
- Designed to investigate natural hx of diabetes and celiac disease in a HLA-predisposed population

Poole et al. Pediatrics 2006

Cow's Milk Introduction and Milk Allergy

Prospective feeding study of 13019 infants in Israel, telephone interview, encourage to breast feed

- Low prevalence of IgE-mEDIATE allergy 0.5%, which confirmed milk allergy
- Regards parental atopy as a potential confounding factor
- Nursery milk exposures not considered

Katz et al. JACI 2010

Introduction of milk/milk products and atopy outcomes

- KOALA Birth cohort (n=2558, Netherlands)
- Followed to age 2: Delayed milk/milk products associated with eczema; delayed "other foods" with atopy, prolonged BFing-protective.


Age at introduction of milk protein (mo)
Government and Pediatric Society Response To Peanut Allergy “Epidemic”

- Avoid peanut during pregnancy, lactation and wait to age 3 years to feed it
- American Academy of Pediatrics 2000
- Committee on Toxicology (UK) 1999

Ingestion is bad...Uh oh...?

Percent peanut allergy in children

After Advice to avoid

Before Advice to avoid

Maybe if you don’t eat it, you touch it, have accidental periodic ingestions that are all sensitizing?


Urbanization

What are “normal” feeding practices?

- Breast feed
- Weaning
- Solids that are easily managed by an infant
- Progression as teeth erupt

Weaning Foods

- Thailand-coconut, chilis, tamarind, lemon grass
- Africa-meats
- China-rice, fish, vegetables, meat
- India-wheat, rice, milk, egg, fish, legumes
- Japan-rice, soy, fish

Characteristics Mothers Completing the Questionnaire Asking Whether They Have Ever Given Pre-masticated Food to Their Children

- Anonymous survey
- 90, HIV infected mothers
- Brooklyn, NY
- Overall, 18% pre-masticated

<table>
<thead>
<tr>
<th></th>
<th>Yes, Premasticates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Born US</td>
<td>18%</td>
</tr>
<tr>
<td>Born Caribbean or Central America</td>
<td>13%</td>
</tr>
<tr>
<td>Born Africa</td>
<td>29%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>7%</td>
</tr>
<tr>
<td>African American</td>
<td>30%</td>
</tr>
<tr>
<td>African</td>
<td>29%</td>
</tr>
<tr>
<td>Mother Pre-masticated</td>
<td>42%</td>
</tr>
<tr>
<td>Mother did not Pre-masticate</td>
<td>12%</td>
</tr>
</tbody>
</table>


ENDS: MEANS

- Prevention of...
  - Sensitization
  - Inflammation
  - Disease

- Through ingestion...
  - Pregnancy
  - Breast feeding
  - Breast feeding with Maternal diet alteration
  - Choice of breast milk substitution
  - Complementary foods
    - When/what

ENDS: MEANS

- Prevention of...
  - Good for everyone, exclusive to 4-6 mo
  - Certain Hydrolyzed formulas, not soy, not cow’s milk

- Through ingestion...
  - No obvious Effect (?)
  - No, but for high risk maybe (AD)
  - Nothing special (exceptions?)
Food Allergy and Atopic Eczema

Gideon Lack, MD
MRC Asthma UK Centre in Allergic Mechanisms of Asthma, King’s College London
Guy’s & St Thomas’ NHS Foundation Trust, Children’s Allergies Department
London, UK

Abstract:
In analysing the relationship between food allergy (FA) and atopic eczema (AE), there are various possibilities to consider; firstly FA may cause or be an exacerbating factor for AE. The second possibility is that AE may lead to FA. The third possibility is that they mutually contribute to each other. There is strong evidence of an association between FA and AE. Children with FA more commonly have a history of AE; whereas children with AE very frequently have proven FA. A recent study in 2008 showed that early age of onset and eczema severity were both associated with FA. Furthermore in oral provocation studies done by different groups, about half of the positive food challenges resulted in delayed eczematous lesions. These eczematous responses were induced mainly by milk, egg, wheat, and soya. It is therefore surprising that intervention studies to eliminate allergens from the diet of children with AE have had very limited success. Most studies are uncontrolled and suffer from methodological limitations due to lack of blinding, lack of confirmation of FA, selection bias, and different criteria for the diagnosis of AE. In animal models, there is literature suggesting that cutaneous exposure to allergen can lead to the production of allergen specific IgE, particularly in the context of inflamed or abraded skin. More recently, Chan et al showed that T lymphocyte responses in peanut allergic children were predominant in the CLA+ population consistent with the hypothesis that sensitisation to peanut occurs in the skin. It has also been observed that use of arachis oil is increased in children who develop peanut allergy. More recently, it has been shown that environmental exposure to peanut as measured by a Food Frequency Questionnaire of peanut consumption in the home, was linked to the development of peanut allergy. The discovery of the importance of filaggrin null mutations in AE provides a biological basis for the possibility of cutaneous sensitisation. These mutations affect up to 50% of Caucasian individuals with moderate to severe AE. Patients with filaggrin null mutations have a deficiency in the skin barrier (irrespective of the presence of eczema), and it has been shown that infants with this mutation have increased Trans Epidermal Water Loss even in the absence of detectable eczema. It has been shown that the filaggrin null mutation increases the risk of peanut allergy (OR 5.3) and the association remained significant after controlling for coexistent AE.

In summary, FA and AE are clearly associated. There is evidence that FA can exacerbate eczema, and perhaps the strongest direct evidence comes from food challenge studies. There is however a lack of well-conducted interventional dietary elimination studies. There is growing circumstantial data to support the potential role of AE and defects in the skin barrier as a cause of FA.

References
Food Allergy and Atopic Eczema

Professor Gideon Lack
King's College London

Relationship between Food Allergy & Atopic Dermatitis

- Food allergy → Atopic dermatitis
- Atopic dermatitis → Food allergy
- Atopic dermatitis ↔ Food allergy

Prevalence of AD in FA
Prevalence of food allergy* and atopic dermatitis

- Sampson 1985 56%
- Sampson 1995 73%
- Eigenmann (Baltimore) 1998 37%
- Eigenmann (Geneva) 2000 27%
- Niggemann 1999 81%
- Roehr 2001 55%

* Proven by DBPCFC

The relationship between eczema severity and the frequency of high-risk IgE food sensitization (HR-IgE-FS) to foods according to the age of onset of eczema is shown. The children with the most severe eczema (G3), and the earliest age of onset (3 months), had the greatest frequency of HR-IgE-FS.


Does food allergy cause atopic dermatitis?

- Oral Provocation Studies
- Interventional Studies
Oral Provocation Studies

- 139 children, mean age 13 months
- Mild AD 59%, Moderate 32%, Severe 9%
- Suspected food involvement by doctor or parent

DBPCFC to milk, egg, wheat and soy in children median age 2 years with AD and suspected FA

- 100 challenges in 45 patients
- 185 food challenges
- 122 failures
- 54% Treatment
- 47% Median
- 61% Median
- 10% Definitive</p>

Causes of late eczematous reactions

- Milk 23%
- Egg 27%
- Wheat 31%
- Soy 9%
- Other 15%
Does food allergy cause atopic dermatitis?

- Oral Provocation Studies
- Interventional Studies

Interventional studies: Can Dietary Restriction Improve Atopic Dermatitis?

- 16 interventional studies to address this
- No meta-analyses
- Varying
  - Study populations
  - Intervention
  - Design
  - Outcome measures

Review of Studies

- 15 of 16 studies report some response, but variable
- Interventions most effective in infants
- Successful interventions include egg, milk & wheat avoidance
- Effect is generally small
CLA+ and δ4δ7+ proliferation as a percentage of total CLA+ and δ4δ7+ proliferation to 4000μg/ml peanut in each patient on day 5, showing proliferation to peanut predominating in the CLA subset of PA patients and a more mixed response in peanut tolerant (NA) patients.


Peanut allergy is associated with:

- Eczema:  OR = 2.6, 95%CI 1.4 - 5.0
- Oozing crusted rash:  OR = 5.2, 95%CI 2.7 - 10.2
- Topical Arachis oil:  OR = 6.8, 95%CI 1.4-32.9

Lack G et al. NEM. 2003; 348:977-985

Proportion of allergic children with peanut allergy as a function of household peanut consumption during infancy, and as a function of maternal peanut consumption during pregnancy

Filaggrin

- Filaggrin forms a dense protein lipid matrix regulating permeability of the skin to water and external particles

- Loss-of-function filaggrin mutations:
  - Common (up to 10%) in Caucasian populations
  - Associated with up to 50% of moderate-severe eczema
  - Associated with peanut allergic (OR 5.3; CI 3.8-10.2) in UK and Canada even after controlling for coexistent eczema (p<0.0008)

Brown SJ et al. JACI 2011; 127(4):691-697
Summary

- Food allergy → Atopic dermatitis
- Atopic dermatitis → Food allergy
- Atopic dermatitis ↔ Food allergy
Notes
EAACI-WAO Congress 2013

Allergy: A Global Health Challenge

Abstract Submission Deadline: 21 January 2013

www.eaaci-wao2013.com