Prevention of Allergy

Hugo Van Bever
Department of Pediatrics
NUHS - Singapore
“The prevalence of allergic diseases has been increasing dramatically during the last decades, and we can’t prevent or cure this.”
Prevalence of allergy and its impact on prevention strategies

- Variations in allergy prevalence
- Singapore: HDM allergy – no GP allergy
- Singapore: food allergy is low
GUSTO: Positive SPT at 18 and 36 months

% of participants with positive SPT at 18 and 36 months for different allergens:

- Any food
- milk
- egg
- peanut
- Any HDM
- Der p
- Der f
- Blom t

n = 848
Allergy – contributors
PAST: “genes and allergens”

- GENES

- ENVIRONMENT
  (- life style)
  - Allergen exposure
  - Microbes
  - Viruses
  - Pollution
  - Dietary factors
Genetic spectrum of allergy

Mild to moderate allergic constitution

Healthy  10% - 20%

60% - 70%

Mild to moderate allergic constitution

Severe allergy  < 10%

= manipulable

... in theory!
Different approaches in the prevention of allergy...

Key: stimulating **Th1** immune responses

→ Studies on the role of **bacterial products**
Allergen exposure

new concepts...

1. What is exposure?
2. How to measure it?
Prevention of allergy and role of breast feeding

... even totally breast fed babies develop allergy.

Q: But are they exclusively breast fed?
Peanut protein in household dust is related to household peanut consumption and is biologically active

Helen A. Brough, MRCPCH, MSc,a,b Alexandra F. Santos, MD, MSc,a,c,d Kerry Makinson, MSc,a Martin Penagos, MD, MSc,a Alick C. Stephens, PhD,a Abdel Douiri, PhD,a Adam T. Fox, MD, MSc,a George Du Toit, FRCPCH,a Victor Turcanu, PhD,aa and Gideon Lack, MD, FRCPCH** London and Southampton, United Kingdom, and Coimbra and Lisbon, Portugal

**rs=0.698

**rs=0.672

FIG 1. Correlation between combined parental peanut consumption (grams per week) over 6 months and peanut protein levels in the maternal bed (A; n = 41; r_s = 0.698; 95% CI, 0.460-0.811; P < .001) and paternal bed (B; n = 37; r_s = 0.672; 95% CI, 0.475-0.829; P < .001). Axes are displayed in log scale.

Conclusions: We have shown that an infant’s environmental exposure to peanut is most likely to be due to HPC. Peanut protein in dust is biologically active and should be assessed as a route of possible early peanut sensitization in infants. (J Allergy Clin Immunol 2013;132:630-8.)
Allergens are everywhere!

Different routes

- eating, drinking
- inhaling – smelling
- transcutaneous (eczema)
- prenatal
- through breast milk

UNMEASURABLE
Primary Prevention of Allergy
FIVE classical preventive measures

- recent conclusions -

• Bacterial products *may* prevent eczema

• HA-milks *may* prevent CMA / eczema

• Early pet exposure *may* prevent allergy

• Early moisturizing *may* prevent eczema

• Early food exposure *may* prevent food allergy (Leap study)
Prevention of AD with **bacterial products**
(most studies are on probiotics)

- Started prenatally
- In combination with breast feeding
- **Q**: Best? Dose? Onset? Duration?
FIVE classical preventive measures

- recent conclusions -

• Bacterial products *may* prevent eczema

• HA-milks *may* prevent CMA / eczema (?)

• Early pet exposure *may* prevent allergy (?)

• Early moisturizing *may* prevent eczema

• Early food exposure *may* prevent food allergy (Leap study)
Randomized Trial of Peanut Consumption in Infants at Risk for Peanut Allergy

George Du Toit, M.B., B.Ch., Graham Roberts, D.M., Peter H. Sayre, M.D., Ph.D., Henry T. Bahnson, M.P.H., Suzana Radulovic, M.D., Alexandra F. Santos, M.D., Helen A. Brough, M.B., B.S., Deborah Phippard, Ph.D., Monica Basting, M.A., Mary Feeney, M.Sc., R.D., Victor Turcanu, M.D., Ph.D., Michelle L. Sever, M.S.P.H., Ph.D., Margarita Gomez Lorenzo, M.D., Marshall Plaut, M.D., and Gideon Lack, M.B., B.Ch., for the LEAP Study Team
Figure 2. Primary Outcome.

The prevalence of peanut allergy at 60 months of age is shown among participants who had a negative result on the skin-prick test at baseline, among those who had a positive result at baseline, and in both groups combined, in the intention-to-treat analysis (Panel A) and the per-protocol analysis (Panel B). Among the 640 participants who underwent randomization, peanut-allergy status was determined by means of an oral food challenge in 617 (96.4%) and by means of a diagnostic algorithm in 11 (1.7%). Peanut allergy could not be evaluated with the use of the diagnostic algorithm in 2 participants (0.3%). A total of 10 participants (1.6%) voluntarily withdrew or were lost to follow-up. The worst-case imputation analysis (Panel C) assumes that participants with missing data in the peanut-consumption group would have been allergic to peanuts and that participants with missing data in the peanut-avoidance group would have been nonallergic. P values are based on chi-square analyses.
To prevent a food allergy:

→ expose!
Early moisturizing prevents eczema - JACI October 2014 - 2 studies

Atopic dermatitis and skin disease

Emollent enhancement of the skin barrier from birth offers effective atopic dermatitis prevention

Eric L. Simpson, MD, MCR, Joanne R. Chalmers, PhD, Jon M. Hanifin, MD, Kim S. Thomas, PhD, Michael J. Cork, PhD, FRCP, W. H. Irwin McLean, FRSE, FMedSci, Sara J. Brown, MRCP, MD, Zunqiu Chen, MS, Yiyi Chen, PhD, and Hywel C. Williams, DSc, FMedSci

Portland, Ore, and Nottingham, Sheffield, and Dundee, United Kingdom

Application of moisturizer to neonates prevents development of atopic dermatitis

Kenta Horimukai, MD,* Kumiko Morita, MD, Masami Narita, MD, PhD, Mai Kondo, MD, Hiroshi Kitazawa, MD, PhD, Makoto Nozaki, MD, Yukiko Shigematsu, MD, Kazue Yoshida, MD, PhD, Hironori Niizeki, MD, PhD, Ken-ichiro Motomura, MD, Haruhiko Sago, MD, PhD, Tetsuya Takimoto, MD, PhD, Eisuke Inoue, PhD, Norio Kamemura, PhD, Hiroshi Kido, MD, Junzo Hisatsune, PhD, Motoyuki Sugai, DDS, PhD, Hiroyuki Murota, MD, PhD, Ichiro Katayama, MD, PhD, Takashi Sasaki, PhD, Masayuki Amagai, MD, PhD, Hideaki Morita, MD, PhD, Akio Matsuda, PhD, Kenji Matsumoto, MD, PhD, Hiroisa Saito, MD, PhD, and Yukihiro Ohya, MD, PhD

Tokyo, Tokushima, Hiroshima, and Osaka, Japan
Early moisturizing:
can we do better?
Effects of nonpathogenic gram-negative bacterium *Vitreoscilla filiformis* lysate on atopic dermatitis: a prospective, randomized, double-blind, placebo-controlled clinical study

A. Gueniche, B. Knaudt,* E. Schuck,* T. Volz,* P. Bastien, R. Martin, M. Röcken,* L. Breton and T. Biedermann*

L’Oréal Recherche, Clichy, France

*Department of Dermatology, Eberhard Karls University Tübingen, Liebermeisterstr. 25, 72076 Tübingen, Germany

N = 75 – DBPC local treatment

Results: improvement in symptoms (SCORAD) improvement in TEWL
Idea for a new study!

Early moisturizing with probiotic-containing cream
Breastfeeding in the prevention of allergy

- Breast milk is the best
- Breast milk is the only living milk
- No other formula milk will ever be better for babies than breast milk

How to make it more anti-allergic?
A systematic review of the importance of milk TGF-β on immunological outcomes in the infant and young child

range of immunological outcomes in infancy and early childhood, such as wheeze, atopy, eczema and the immunoglobulin switch. Twelve human studies were included in the review and 67% showed a positive association with TGF-β1 or TGF-β2 demonstrating protection against allergy-related outcomes in infancy and early childhood. High

Oddy & Rosales, PAI 2009
Supplementation with *Lactobacillus rhamnosus* or *Bifidobacterium lactis* probiotics in pregnancy increases cord blood interferon-γ and breast milk transforming growth factor-β and immunoglobulin A detection


*School of Paediatrics and Child Health, University of Western Australia, Perth, Australia, †Wellington Asthma Research Group, Wellington School of Medicine and Health Sciences, University of Otago, Wellington, New Zealand, ‡Department of Pharmacology and Clinical Pharmacology, University of Auckland, Auckland, New Zealand, §Department of Paediatrics, Wellington School of Medicine and Health Sciences, University of Otago, Wellington, New Zealand, ¶Department of Paediatrics, University of Auckland, Auckland, New Zealand and ‖Immunology Department, Auckland Hospital, Auckland, New Zealand
“To improve the anti-allergic qualities of breast milk”

- On the Research Agenda -

- Diets (?)
- Supplements (PUFA) (?)
- Bacterial products
- Helminths
- Allergens
Primary prevention...

1. Early bacterial products (start earlier?)
   *(cfr Bifidobacteriae dynamics in pregnancy)*

2. Early moisturizer

3. Breastfeeding (increase anti-allergic features)

4. Early exposure to allergenic foods

FUTURE: early IT (?)
Early Immunotherapy

= prevention & cure

→ The future!
Allergen Immunotherapy

AR > AA > AD...

U. Wahn, Stallergenes Symposium, EAACI, June 2014
Allergen Immunotherapy

- Is effective (30% - 40%)
- But... *doesn’t cure*
- Changes immune direction (Th2 $\rightarrow$ Th1)
- Adjuvants are needed to induce a strong (and permanent Th1-booster / T-reg-booster)
Immunotherapy → change direction and go in the new direction!
Future of IT

ALLERGEN + ADJUVANTS = Th1 – Treg BOOST

- Bacterial antigens (toxins)
- Probiotics - prebiotics
- Helminthic proteins
- Other
Administration of a probiotic with peanut oral immunotherapy: a randomized trial.

*Mimi Tang et al. JACI 2015*

- DBPC trial (2 groups) of the probiotic *Lactobacillus rhamnosus* CGMCC 1.3724 and peanut OIT, in 62 children → 56 reached the study’s end.

- Possible sustained unresponsiveness was achieved in 82.1% receiving PPOIT and 3.6% receiving placebo (P < .001) (i.e. 9 children need to be treated for 7 to achieve sustained unresponsiveness)

- Criticism: no OIT group
Transcutaneous immunotherapy (?)

- Allergen
- Mitogen
- Th1 stimulant
- Th2 suppressant
- T-reg stimulant
- ... & ...
(TOOLS) Interventions – overview.

- Early bacterial products
- Breast feeding (or HA-milk) (4 – 6 months)
- Tailored weaning
- Early moisturizing (new creams?)
- Vaginal seeding (caesarean section)
- New types of immunotherapy *(FUTURE)*

→ The tools are available for the appropriate construction
Primary Prevention

- FOOD ALLERGY: almost there!

- INHALANT ALLERGY: still a way to go!

(# role of *respiratory viruses* – role of pollution, and allergen exposure)
### Summary – primary prevention

<table>
<thead>
<tr>
<th>INTERVENTION</th>
<th>EFFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Breast feeding during 4 – 6 months</td>
<td>To all infants (especially those at risk for allergy)</td>
</tr>
<tr>
<td>2. Probiotics</td>
<td>Prevents AD (might prevent FA) no effect on respiratory allergy (asthma – rhinitis)</td>
</tr>
<tr>
<td>(best is to start during pregnancy, and to continue in combination with breast milk)</td>
<td></td>
</tr>
<tr>
<td>3. Early moisturizing</td>
<td>Prevents AD (in short follow-up studies)</td>
</tr>
<tr>
<td>4. Early introduction of peanut - egg</td>
<td>Prevents FA (in specific at risk infants)</td>
</tr>
<tr>
<td>5. Vaginal seeding</td>
<td>In infants born by caesarean section</td>
</tr>
<tr>
<td>6. Hydrolysed formula</td>
<td>In cases were breast feeding is impossible.</td>
</tr>
<tr>
<td></td>
<td>Prevents AD and cow’s milk allergy.</td>
</tr>
</tbody>
</table>

### Future Research

1. Combination of interventions / 2. Exploring the role of early IT / 3. Exploring the role of immunomodulatory treatments (helminths, etc.)
Incidence of eczema at 2 years in children given probiotics from birth

Figure 2: Treatment effect of *Lactobacillus GG* on atopic disease
Bars are 95% CI.

Kalliomaki M, Lancet. 2001; 357:1076
Time has come to set up...

National Programs on Primary Prevention of Allergy

Thank You!
Primary Prevention

- FOOD ALLERGY: almost there!

- INHALANT ALLERGY: still a way to go!

(# role of respiratory viruses – role of pollution, and allergen exposure)