Allergy in young children

Hugo Van Bever
National University
Singapore

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APAPARI - Education

1. Joint meetings with National Allergy Societies

- 2002: Japan (Tokyo)
- 2003: Singapore (workshop)
- 2004: Hong Kong (IPRAIC)
- 2005: S-Korea (Seoul)
- 2006: Indonesia (Jakarta)
- 2007: Philippines (Manila) & WAO (Bangkok)

2. Training courses on pediatric allergy

- 2006: Indonesia (Jakarta) / Borneo
- 2007: Cambodia / Jakarta / Vietnam
Allergy = a feature and **NOT** a disease!

= ... the ability to produce specific antibodies (IgE) to different substances of the environment (inhalant and food allergens)...

\[
\text{IgE} \quad \rightarrow \quad \text{inflammation} \quad = \quad \text{swelling - narrowing}
\]

\[
\downarrow
\]

\[
\text{shock organs} \quad \rightarrow \quad \text{symptoms}
\]
Allergic diseases...

- eczema
- asthma
- urticaria
- conjunctivitis
- migraine
- rhinitis
- enteritis
- healthy

ALLERGY
Positive skin tests in 273 HEALTHY children at the age 6-7 years (Belgium - 1996).

<table>
<thead>
<tr>
<th>ALLERGEN</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>- HDM</td>
<td>21</td>
<td>8%</td>
</tr>
<tr>
<td>- Cat dander</td>
<td>6</td>
<td>2%</td>
</tr>
<tr>
<td>- Birch pollen</td>
<td>1</td>
<td>0%</td>
</tr>
<tr>
<td>- Grass pollen</td>
<td>8</td>
<td>3%</td>
</tr>
<tr>
<td>- ANY</td>
<td>29</td>
<td>11%</td>
</tr>
</tbody>
</table>
Allergy, one feature with many faces

SKIN

AIRWAYS
Allergy: ... mild to severe
“The Allergic March”

Typical evolution of allergic diseases

Prevalence of allergic symptoms

- Allergic rhinitis
- Asthma
- Atopic dermatitis
- Food allergy

0 1 3 7 15 years

Adapted from Holgate S. Church MK. eds. Allergy. London: Gower Medical Publishing, 1993
# The Allergic March

<table>
<thead>
<tr>
<th></th>
<th>START</th>
<th>STOP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Intestinal symptoms</td>
<td>0 - 3 months</td>
<td>1 yr</td>
</tr>
<tr>
<td>2. Eczema</td>
<td>1 - 6 months</td>
<td>7 yr</td>
</tr>
<tr>
<td>3. Asthma</td>
<td>1 - 3 yr</td>
<td>14 yr</td>
</tr>
<tr>
<td>4. Hay fever</td>
<td>4 - 7 yr</td>
<td>40 yr</td>
</tr>
</tbody>
</table>
Environmental substances
= allergens (proteins...)

1. **Inhalant allergens**
   - house dust mites, pollen
   - pets, moulds

2. **Food allergens**
   - egg, cow’s milk, soy, wheat (< 3 yrs)
   - peanuts, fish, shrimp (> 3 yrs)
House Dust Mites

*Blomia tropicalis*  
*Dermatophagoides farinae*
Asthma
Rhinitis
Eczema
House Dust Mites in Singapore

- High temp and humidity provides perfect environment for HDMs
- High counts (> 100 mites/g dust) of HDM are isolated in Singapore
- A wide variety of mite species is isolated other than Dermatophagoides.
- *Blomia tropicalis* is predominant.
### Mite Species Present in Singaporean Mattresses

<table>
<thead>
<tr>
<th>Species</th>
<th>%  (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. tropicalis</td>
<td>94</td>
</tr>
<tr>
<td>D. pteronyssinus</td>
<td>80</td>
</tr>
<tr>
<td>S. brasiliensis</td>
<td>84</td>
</tr>
<tr>
<td>T. granarius</td>
<td>44</td>
</tr>
<tr>
<td>D. farinae</td>
<td>26</td>
</tr>
<tr>
<td>A. malaysiensis</td>
<td>20</td>
</tr>
<tr>
<td>C. malaccensis</td>
<td>24</td>
</tr>
<tr>
<td>M. intermedius</td>
<td>12</td>
</tr>
</tbody>
</table>

Chew FT 1999 Clin Exp Allergy 29:201-206
The increase of allergic diseases.
Inverse relation between the incidence of infectious diseases and immune disorders (Bach JF, NEJM 2002, 347, 911)
Increasing hospital admissions for systemic allergic disorders in England: analysis of national admissions data

Direction of immune responses in early life

Factors
1. constitution
2. bacterial load
3. allergen exposure
The $T_{h1} - T_{h2}$ immune system around birth.
Hygiene hypothesis

Bacterial load vs. allergen contacts
Hygiene levels in a contemporary population cohort are associated with wheezing and atopic eczema in preschool children.

**Increasing hygiene scores**

- wheezing \( \text{OR} = 1.04 \ (95\% \ CI: \ 1.00 - 1.08) \)
- atopic eczema \( \text{OR} = 1.04 \ (95\% \ CI: \ 1.01 - 1.07) \)
Hygiene hypothesis

Have bacterial load and/or antigen exposure changed since the 80s???

NO EVIDENCE
The increase of allergic diseases.

1960                1980
1990               2000

**PARACETAMOL**
**BROADSPECTRUM ANTIBIOTICS**
**ALLERGEN AVOIDANCE**
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Title</th>
</tr>
</thead>
</table>
Does the use of antibiotics in early childhood increase the risk of asthma and allergic disease?

Droste JHJ, Wieringa MH, Weyler JJ, Nelen VJ, Vermeire PA, Van Bever HP.

Clin Exper Allergy 2000, 30, 1547 - 1553.
Does the use of antibiotics in early childhood increase the risk of asthma and allergic disease?

Clin Experim Allergy 2000, 30, 1547 - 1553.

* p < 0.05
Does the use of antibiotics in early childhood increase the risk of asthma and allergic disease?

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* p < 0.05
Does the use of antibiotics in early childhood increase the risk of asthma and allergic disease?

Clin Experim Allergy 2000, 30, 1547–1553.

Parental hay fever + Early usage of antibiotics

Increased risk for...
Asthma
Hay fever
Eczema
... at the age of 7–8 yrs
Antibiotica use during infancy promotes a shift in the Th1/Th2 balance toward Th2-dominant immunity in mice.

Paracetamol...
Sale of analgesics in Norway

The graph shows the sale of analgesics in Norway from 1979 to 1999. The y-axis represents DDD/1000 inhabitants/observation day (DDD), and the x-axis represents the years from 1979 to 1999. The graph indicates a significant increase in the sale of certain analgesics over this period.

Key points:
- Paracetamol (N02BE01)
- Ibuprofen (M01AE01)
- Fenazone/propyfenazone (N02BB)
- Acetylsalicylsyre usammensatte (N02BA01)
Paracetamol sales and atopic disease in children and adults: an ecological analysis.

“... the possibility is raised that variation in paracetamol usage may explain some of the variation in atopic disease prevalence between countries...”
A matched patient-sibling study on the usage of paracetamol and the subsequent development of allergy and asthma.

Riece K, Huak CY, Ning TT, Van Bever HP. A matched patient-sibling study on the usage of paracetamol and the subsequent development of allergy and asthma.

Koniman Riece¹, Chan Yiong Huak², Tan Teng Ning¹ and Hugo P. Van Bever¹

¹Department of Paediatrics and ²Biostatistics Unit, National University Singapore, Singapore
... Significant and relevant results

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Outcomes of interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older sibling (7-10 y.o)</td>
<td>Asthma, allergic asthma</td>
</tr>
<tr>
<td>Young maternal age at delivery</td>
<td>Asthma</td>
</tr>
<tr>
<td>Low allergen exposure (≤ 6 mths old)</td>
<td>Asthma</td>
</tr>
<tr>
<td>Paracetamol (≤ 6 mths old, 4-6 mths old)</td>
<td>Asthma</td>
</tr>
<tr>
<td>Paracetamol (pregnancy)</td>
<td>Allergic asthma</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>Allergy</td>
</tr>
</tbody>
</table>
Hypothesis

**Antibiotics**
- Decreased bacterial load

**Paracetamol**
- Decreased TNF-\(\alpha\) secretion

**Decreased Th\(_1\) stimulation**
Primary prevention of allergy...

**Allergen exposure**

- INCREASE ???

How to measure allergen exposure?
Prenatal sensitization to allergens...does it exist?

1. clinical evidence
   (peanuts - ovalbumin - pollen - house dust mite - cat - dog)

2. allergens in amniotic fluid & cord blood

3. active transport through placenta
Recent studies on prenatal allergen exposure


Recent studies on prenatal allergen exposure


   ... a short-lasting protective effect of exposure to dog on total IgE and early sensitization.


   ... in utero factors (maternal IgE, colds, eczema) increase the risk of eczema.


   ... prenatal exposure to HDM is associated with higher IgE levels at birth.
Exposure to peanuts in utero and in infancy and the development of sensitization to peanut allergens in young children.


... mothers who consumed peanuts more than once a week during pregnancy were more likely to have a peanut-allergic child than mothers who consumed peanuts less than once a week (odds ratio=3.97, 98% confidence interval 0.73-24).

Positive maternal blood samples (21%)

** Der p 1
- amniotic fluid 24 / 43 (56%)
- cord blood 15 / 24 (63%)

2 routes of allergen transfer
- transamniotic
- transplacental
Prenatal sensitization does exist...

1. Food allergens (milk, egg, peanut)

2. Inhalant allergens (HDM, pollen, pets)

... but, allergen exposure is difficult to measure
Early postnatal allergen exposure...
Sensitisation, asthma, and a modified Th2 response in children exposed to cat allergen: a population-based cross-sectional study

Non-linear allergic response to cat allergen

Thomas Platts-Mill, John Vaughan, Susan Squillace, Judith Woodfolk, Richard Sporik

Lancet 2001
Primary prevention of allergy by house dust mite avoidance

- Contradictory results
- Positive results are borderline
- No data on HDM exposure in young children
- Prenatal exposure has been shown.
Woodcock A, Lowe LA, Murray CS, Simpson BM, Pipis SD, Kissen P, Simpson A, Custovic A; NAC Manchester Asthma and Allergy Study Group.

Early life environmental control: effect on symptoms, sensitization, and lung function at age 3 years.

Conclusion

... stringent environmental control in newborns was associated with an increased risk of mite sensitization at the age of 3 years.
Impossible to avoid
Sensitization to allergens...

IgE

sensitization

allergen concentration

high risk zone

symptoms

in sensitized subjects...

allergen concentration

allergen avoidance
Attempts to avoid HDM may result in increased sensitization...
Consequences of allergen avoidance...

1. In primary prevention
   results in exposure to a low dose of allergen = IgE response
   (high dose = IgG response - tolerance)

2. In secondary - tertiary prevention (after sensitization)
   results in less symptoms
   (cfr. dose - response curve)