Allergen and Environment in Severe Asthma

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Role of Allergen in Asthma Pathogenesis

*Early response of allergen exposure*

Role of Allergen in Asthma Pathogenesis

**Chronic stage allergen-induced airway**

Atopy and asthma

- **Atopy**
  - Risk factor of asthma
  - But the relationship is not always obvious
  - **Childhood**
    - Strong influence on the emergence of persistent asthma
    - Sensitization to aeroallergens in the home
  - **Adult**
    - Less important
    - Aspirin and NSAIDs intolerance
    - Occupational exposure
Asthma, Severe Asthma

- Asthma is a heterogeneous mix of several endotypes, so severe is not a single disease process.
  

- WHO universal definition of severe asthma
  - Untreated severe asthma
  - Difficult to treat severe asthma
  - Treatment resistant severe asthma

  Bousquet J, et al. JACI, 2010

Pathogenesis of Severe Asthma

Cytokine Signaling Pathways of Severe Asthma

• IL-4/IL-13
  – Allergen associated symptoms, high serum IgE
  – Murine OVA asthma model

• IL-5/IL-33
  – Non-atopic late onset eosinophilic severe asthma
  – IL-4 independent Th2
  – Resistant to high dose ICS but responsive to systemic CS

• IL-17
  – Sputum neutrophilia
  – Resistant to CS and responsive to macrolide

• Th1 - IL-18/INF-γ

Phenotype and Endotype

[Diagram showing phenotype and endotype of severe asthma with characteristics, symptoms, exacerbations, inflammation, low FEV1, early onset, eosinophilic, obese, neutrophilic, mild, moderate, late onset, AERO/AERD-like, obes, female, late onset, less eosinophilic]
Atopy in Severe Asthma

<table>
<thead>
<tr>
<th></th>
<th>ENFUMOSA</th>
<th>SARP</th>
<th>COREA</th>
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<tr>
<td>Age</td>
<td>No difference</td>
<td>Older</td>
<td>Older</td>
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<tr>
<td>Sex</td>
<td>More females</td>
<td>No difference</td>
<td>No difference</td>
</tr>
<tr>
<td>BMI</td>
<td>Increased (♀)</td>
<td>No difference</td>
<td>No difference</td>
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<tr>
<td>Atopy</td>
<td>Decreased</td>
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<tr>
<td>Aspirin sensitivity</td>
<td>Increased</td>
<td>Increased</td>
<td>Not reported</td>
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<tr>
<td>Sinusitis</td>
<td>Increased (♀)</td>
<td>Increased</td>
<td>No difference</td>
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<tr>
<td>GERD</td>
<td>Not reported</td>
<td>Increased</td>
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► Common misunderstanding:
'Severe asthma is usually non-allergic'

Atopy and Severe Asthma

SARP data
*Moore WC, et al. 2007 JACI*

ENFUMOSA
*Holgate ST, et al. 2003 ERJ*
Severe Asthma and Allergen

1. **Inhalant allergens**
   - Perennial Indoor
   - Seasonal (usually outdoor)

2. **Fungal allergens**
   - Growing in the lungs (ABPA, ABPM)
   - Dermatophytes (Trichophyton)

3. **Samter’s triad**
   - Sinusitis with nasal polyp, ASA intolerance

4. **Non-inflammatotary**
   - Upper airway dysfunction
   - Obesity

**Role of Allergens in Severe Asthma**

*All that glitter is not gold.*

*All that allergen is not cause of asthma.*

- Does allergen exposure matter for the occurrence of severe asthma?
Exposure to domestic allergens

- Asthmatics exposed in their homes to sensitized allergens have a more severe form of the disease.  
  *Langley SJ, et al. JACI, 2003*

- Significantly more severe bronchial reactivity in non-sensitized, atopic asthmatic subjects when exposed to high levels of domestic allergens.  

Allergic Triggers and Poor Control of Asthma

*Haselkorn T, et al. JACI, 2009*
Allergen in Severe Asthma

High dose
Exacerbation of Asthma

Low dose
Persistent Asthma

Viral infection

Allergen

Difficult to treat asthma

Sensitization Triggering

Treatment resistant asthma

Can we turn it off?
Allergen Avoidance

Primary exposure  2ndary exposure  Tertiary exposure
Sensitization    Inflammation    Aggravation

When, what degree, how long?
Early, complete, and life-long.

Various aspects of allergen control

1. Environmental control measures
2. Allergen level in environment
3. Allergen level in person
4. Allergen control & management of allergic diseases
5. Allergen control & prevention of allergic diseases
Environmental Control Measures

• Different approaches are needed to different allergens.
  
  – Mite
  – Pet
  – Cockroach
  – Fungi…

Control Mite Allergens

• Impermeable covers for mattress, pillows, and duvet
• Carpets, upholstery, fabric curtain: remove
• Washing at high temperature (55°C), steam cleaning, freezing with liquid nitrogen
• Chemicals: acaricides
• Intensive vacuum cleaning with HEPA filter
• Special ventilating system to reduce humidity
Pet Allergen Avoidance

- Basically, complete avoidance is impossible
  - ‘Remove pet’ is the best way
  - Exposed even in homes without pet, public buildings, and public transport
  - Wash pets (2/wk): short-lived effect
  - Fel d 1: major cat allergen, affected by testosterone (need castration)
How to control cockroach allergen?

• Physical and chemical procedure
• Sealing cracks and holes
• Pesticides
• Household cleaning

• Reductions in cockroach allergen levels by intervention: none or modest.
• Objective studies are rare.

Other allergen and more…

• Indoor allergens
  – Acarids, insects, domestic animals, fungi

• Other allergens from outside
  – Rodents, pollens
  – Closing windows and doors
  – Remaining indoors

• ETS, indoor air pollution (NO$_2$, O$_3$), endotoxin
16th Century
The 1st environmental control for asthma patient

Gerolamo Cardano (1501–1576)
Italian mathematician, physician, astrologer and gambler.

John Hamilton, Archbishop
St. Andrews Castle, Scotland

“Allergen free environment

“Asthmatic persons are so capricious that each patient has to find out for himself; a given asthmatic may lose his asthma at Davos. Only young persons should try the experiment, and persons free from emphysema”.

Allbutt C. The past winter in Davos. Lancet 1879
Effective Allergen Avoidance at High Altitude Reduces Allergen-Induced Bronchial Hyperresponsiveness

DIEGO G. PERONI, ATTILIO L. BONER, GRAZIANO VALLONE, IVANA ANTOLINI, and JOHN O. WARNER

Allergen free condition for extended period: high altitude

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<th>October</th>
<th>January</th>
<th>June</th>
<th>September</th>
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<tr>
<td>(n = 22)</td>
<td>(n = 22)</td>
<td>(n = 22)</td>
<td>(n = 14)</td>
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<tr>
<td>Total serum IgE</td>
<td>886 ± 800</td>
<td>585 ± 434</td>
<td>463 ± 350</td>
<td>877 ± 701</td>
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<tr>
<td>levels, IU/ml</td>
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<tr>
<td>Opt-specific IgE</td>
<td>35.0 ± 8.6</td>
<td>33.2 ± 6.3</td>
<td>29.6 ± 6.7</td>
<td>25.6 ± 8.5</td>
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<tr>
<td>levels, IU/ml</td>
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<tr>
<td>PEF decreases after exercise, %</td>
<td>27.8 ± 20.8</td>
<td>13.8 ± 15.9</td>
<td>14.2 ± 12.3</td>
<td>27.9 ± 12.1</td>
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<tr>
<td>Methacholine</td>
<td>124 ± 213</td>
<td>463 ± 612</td>
<td>586 ± 664</td>
<td>140 ± 125</td>
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<tr>
<td>PD_{ach}-FEV_{1}, sg/ml</td>
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Peroni DG et al. Am J Respir Crit Care Med, 1994

REDUCTION OF BRONCHIAL HYPERREACTIVITY DURING PROLONGED ALLERGEN AVOIDANCE

THOMAS A. E. PLATTS-MILLS  
E. BRUCE MITCHELL  
PAMELA NOCK

EUGAN R. TOVEY  
HELEN MOKOZO  
SUSAN R. WILKINS

Staying in allergen free hospital room for extended period improves airway hyperresponsiveness

Multifaceted intervention trials

Results of a Home-Based Environmental Intervention among Urban Children with Asthma

Wayne J. Morgan, M.D., C.M., Ellen F. Grin, M.D., Ph.D., Rebecca S. Gruchalla, M.D., Ph.D., George T. O’Connor, M.D., Mayer Kattan, M.D., C.M., Richard Evans III, M.D., M.P.H., James Stout, M.D., M.P.H., George Malindzak, Ph.D., Ernestine Smartt, R.N., Marshall Paut, M.D., Michelle Walter, M.S., Benjamin Vaughn, M.S., and Herman Mitchell, Ph.D., for the Inner City Asthma Study Group*  

- Randomized controlled trial of environmental intervention  
- 937 children (5-11 years) with persistent asthma  
- Intervention: Remediation of exposure to dust mites, passive smoking, cockroach, pets, rodents, and molds, combined with education and attitude change  
- Outcomes: Asthma Symptoms and health-care use, environmental exposures  
  

Nocturnal temperature controlled laminar airflow

Boyle RJ et al. Thorax, 2012

Air filtration pillow

Stillerman A et al.  
Ann Allergy Asthma Immunol 2010
Conditions to succeed in avoidance

✔ Clinically relevant allergen
✔ Covers all sensitized allergens
✔ Reduce allergen exposure level sufficiently
✔ Reduce other environmental triggering factors
✔ Maintain long-term avoidance with adequate compliance
✔ As early as possible before the disease becomes self-perpetuating chronic course

Conclusion

• No study convincingly evaluated benefit of allergen avoidance in severe asthma yet.

• Nonetheless, allergen and environmental control seem to be helpful at least in allergic subtypes of severe asthma.

• Clinical implication of allergen avoidance need more evidences to be accepted as a standard management for severe asthma.