Evolution of asthma from childhood

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• **Questionnaire data**
  - Symptoms occurring once or several times at follow-up (wheeze, dyspnea, cough, nocturnal symptoms)
  - Self-reported asthma
  - Use of asthma treatment (eg. salbutamol use)
  - Video questionnaire
  - Doctor diagnosis

• **Intermediate phenotypes of asthma**
  - Airway hyper-responsiveness
    • Direct (methacoline, histamine)
    • Indirect (exercise, mannitol, cold-air challenge)
  - Reversibility on β2-agonist
  - Variability of peak expiratory flow rate (PEFR)
  - Lung function (eg. FEV1, FEF 25-75, PEF)

• **Combination of questionnaires and phenotypes intermediates**
  (asthma scores and asthma algorithm)
Global studies on allergy and asthma

- Different profiles of allergy across the world were showed throughout several authors.
- Role of “westernization” is important for developing allergic disease.
- Significant difference among countries and regions.
- Different prevalence of self-reported asthma and current wheeze among migrant children compared with those born in native country.
- Different prevalence of migrant children depends on their origin country. Perhaps misdiagnosis and underdiagnosis in their countries of origin can explain the differences.
Regional differences in asthma prevalence and socio-economic factors like lifestyle and domestic exposures differences need more studies.

The greater risk of developing atopy and asthma among children with high standard of life while exposure to general urban deprivation and pollution is associated with an increase risk of respiratory symptoms and infections but a more modest increase in allergic diseases.

Allergic diseases in the setting of urban poverty may be more severe and result in greater morbidity and mortality owing to poor access to care, unavailability of medication and problems with adherence and risk avoidance.
• ISAAC phase III conducted 8-10 years later confirmed the high prevalence of asthma symptoms in some of developing country centers

• A stabilization or decrease on asthma prevalence was observed in the majority of centers in industrialized countries

• The moderate or high prevalence of asthma in some developing countries is already being reflected by a significant demand for health services

• Asthma, from childhood to adulthood in several developing countries is the first cause of consultations for chronic respiratory disease in primary healthcare settings (WHO report 2004)
Gene By Environment Interactions, a Key feature of Asthma Genetic  
(Weiss ST, 2004)
Atopic immune systems don’t mature normally

(Lemanske R, JACI 109(6)
Asthma Phenotype

Childhood
- Transient infant wheezing
- Non atopic wheezing toddler
- Persistent atopic wheezing

Adulthood
- Adult onset asthma
  - Aspirin induced
  - Intrinsic
  - Occupational
- Late onset childhood asthma

Adapted from Bel EH Curr Opin Pulm Med 2004
Despite the fact that certain levels of allergens may prove to be protective, allergen exposure is still the major risk factor for the development of allergy.

In the absence of allergens, no allergy develops, and above and allergen-specific threshold, the risk of sensitization increase in parallel with exposure.

To measure allergen in environment is important to establish dose-response relationships between exposure on the one hand and sensitization and clinical allergy on the other hand.
Wheezing is Common in Early Life

- Late onset wheezing: 15%
- Persistent wheezing: 20%
- Transient early wheezing: 14%
- Never wheezed: 51%

N=1246 newborns
Tucson Children’s Respiratory Study
Martinez FD et al NEJM 1995;332:133
### Transient vs. Persistent Wheezers

#### Transient Wheezers
- Diminished lung function at birth, at 6, 13 & 16 yrs of age
- Mother who smoked
- Mothers without asthma
- Normal IgE levels
- Negative skin tests

#### Persistent Wheezers
- Normal lung function at birth but diminished at 6, 13 & 16 yrs of age
- Mothers with asthma
- Elevated IgE levels at 9 months and 6 yrs
- Positive skin tests at 6 yrs of age

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Tucson Children’s Respiratory Study
Prevalence – Wheezing Evolution

Transient wheezers
Asthma
Non-atopic wheezers

Age - Years
Asthma Prevalence in Schoolchildren (5.386)

Nunes C et al RPIA, 1996
**Asthma predictive index**

**Major criteria**
- Parental history of physician diagnosed asthma
- Physician diagnosed asthma with atopic dermatitis

**Minor criteria**
- Wheezing apart colds
- Blood eosinophilia $\geq 4\%$
- Physician-diagnosed allergic rhinitis

The child must have a history of early frequent wheezing during first 3 years of life plus one major criterion or two minor criteria

*Adapated from Castro Rodrigues et al. Am J Respir Crit Care Med 2000;162:1403-6*
Predictors of persistence and severity of childhood asthma

More severe and frequent wheezing episodes during preschool age
Onset during school age
Family history of asthma and allergy
Elevated serum IgE
Early development of positive skin test results
Early development of bronchial hyperresponsiveness
Frequency of respiratory infections
Lack of contact with older children
Parenting difficulties
Greater childhood psychological risk
• Strong oxidative stress in children with asthma and the oxidant/antioxidant imbalance increases with asthma severity.
  
  (Ercan et al. JACI 2006;118:1097-104)

• Early deterioration on lung function, high IgE levels, and persistent cough/mucus hypersecretion are strong markers of moderate/severe asthma.
  
  (de Marco et al JACI 2006;117:1249-56)
Asthma evolution

We could estimate 2 out of 3 children with asthma outgrow their symptoms

Risk factors for asthma persisting into adulthood

- Female
- Eczema
- Onset after age of 3 years
- Severe disease
- Parental history of atopy / asthma
• High endotoxin exposition, pet ownership, atopy and wheezing in high-risk infants has no effect on aeroallergen sensitisation or wheezing during infancy
  
  (Campo et al. JACI 2006;118:1271-8)

• House dust avoidance and dietary fatty acid modification in the first 5 yrs of life has no effect to prevent the onset of asthma, eczema or atopy
  
  (Marks et al JACI 2006;118:53-61)
Persistence of Asthma from Childhood to Adulthood

- 613 N. Zealand children followed from age 3 yrs to 26

- At age 26,
  - 42% no symptoms and no challenged wheezing
  - 31% transient or intermittent wheezing
  - 12% relapsing symptoms (wheezing stopped after childhood, then recurred)
  - 15% persistent wheezing.

FIG 1. Histogram showing pattern of asthma at age 42 years in subjects from original recruitment groups. *MWB*, Mild wheezy bronchitis; *WB*, wheezy bronchitis; *A*, asthma; *SA*, severe asthma; *NRA*, no recent asthma; *IA*, infrequent episodic asthma; *FA*, frequent episodic asthma; *PA*, persistent asthma.
Sensitivity of Early Symptoms for Predicting Later Asthma

<table>
<thead>
<tr>
<th>Start and end ages of study</th>
<th>Symptom / outcome</th>
<th>Number in Study</th>
<th>Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2 to 11 yrs</td>
<td>wheeze / AHR*</td>
<td>397</td>
<td>Tucson</td>
</tr>
<tr>
<td>0-7 to 32 yrs</td>
<td>attacks / asthma</td>
<td>1494</td>
<td>Tasmania</td>
</tr>
<tr>
<td>0-5 to 18 yrs</td>
<td>frequent symptoms / asthma</td>
<td>273</td>
<td>Tucson</td>
</tr>
<tr>
<td>0-7 to 23 yrs</td>
<td>allergic symptoms / asthma</td>
<td>7225</td>
<td>OAD</td>
</tr>
<tr>
<td>0-10 to 25 yrs</td>
<td>wheeze / asthma</td>
<td>862</td>
<td>Algarve</td>
</tr>
<tr>
<td>6 to 11 yrs</td>
<td>wheeze / AHR*</td>
<td>397</td>
<td>Britain</td>
</tr>
<tr>
<td>6-8 to 20 yrs</td>
<td>wheeze / wheeze</td>
<td>498</td>
<td>Japan</td>
</tr>
<tr>
<td>-10 to 25 yrs</td>
<td>wheeze / asthma</td>
<td>406</td>
<td>Belmont</td>
</tr>
</tbody>
</table>

*AHR = airway hyperresponsiveness

Adapted from Peat JK, Toelle BG, Mellis CM. JACI 2000
Aeroallergen Sensitisation throughout age

Oryszczin et al. EGEA JACI 2007; 119:57-63
Lung Function in Children: “Natural History”

- Never
- Late Onset
- Persistent
- Transient Early

Age, yrs

Z-Score

*p<0.05 vs. never
**p<0.05 vs. never, late and persistent
***p<0.05 vs. late

Childhood Asthma Research and Education Network. Tucson Children’s Respiratory Study.
• Reduced lung function at birth was associated with an increased risk of asthma at 10 yrs


• Chronic course of asthma with airway hyper-responsiveness and impairment at school age is determined by continuing allergic airway inflammation beginning in the first 3 yrs of life

(Illi et al Lancet 2006;368:763-70)
FEV₁ / FVC ratio is diminished in children with asthma because of slower FEV₁ and greater FVC development with age

*NHBLI - CAMP Research*
Fev$_1$ versus height throughout age

Control

Asthmatics

Oryszczin et al EGEA JACI 2007; 119:57-63
Cohort of 165 asthmatics children versus 148 non-asthmatics during 20 years

Pulmonary Function FEV25-75

Age-Years

Control Asthma

Nunes C et al JIACI, 2002
Cohort of 165 asthmatics children versus 148 non-asthmatics during 20 years

Pulmonary Function FEV1

Nunes C et al JIACI, 2002
FIG 2. FEV₁ percent predicted at ages 7, 10, 14, 21, 28, 35, and 42 years in subjects in their recruitment groups. C, Control; MWB, mild wheezy bronchitis; WB, wheezy bronchitis; A, asthma; SA, severe asthma.
## Visits per year/sex/age
Cohort of 165 asthmatics children during 20 years

<table>
<thead>
<tr>
<th>Morbidity</th>
<th>Male</th>
<th>Female</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalisations</td>
<td>0.17</td>
<td>0.09</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Asthma Crises</td>
<td>2.46</td>
<td>1.95</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Respiratory Inf.</td>
<td>12.18</td>
<td>10.27</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>ENT Infections</td>
<td>2.73</td>
<td>2.90</td>
<td>NS</td>
</tr>
<tr>
<td>Other Infections</td>
<td>3.03</td>
<td>3.33</td>
<td>NS</td>
</tr>
<tr>
<td>Eczema</td>
<td>0.57</td>
<td>0.43</td>
<td>NS</td>
</tr>
<tr>
<td>Others</td>
<td>1.52</td>
<td>1.51</td>
<td>NS</td>
</tr>
</tbody>
</table>

Nunes C et al JIACI, 2002
Clinical observations of a cohort
165 asthmatics versus 148 non-asthmatics
during 20 years

Nunes C et al JIACI, 2002
• In outpatients with moderate and severe asthma the annual mean is 7.4 visits per year. This mean is 3.4 fold of the general population.

• There is a annual mean of 3.7 visits in mild asthma.

• There is an annual mean of 0.7 visits to emergency rooms.

• A mean of 0.04 internments per asthmatic/year.
Psychological disorders often present in children and adolescents with asthma

<table>
<thead>
<tr>
<th></th>
<th>With acute asthma</th>
<th>Asymptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>86.4 %</td>
<td>47.7 %</td>
</tr>
<tr>
<td>Anxiety</td>
<td>36.4 %</td>
<td>45.5 %</td>
</tr>
<tr>
<td>Overprotection</td>
<td>37.0 %</td>
<td>29.5 %</td>
</tr>
<tr>
<td>Isolation</td>
<td>47.0 %</td>
<td>41.7 %</td>
</tr>
<tr>
<td>Dependence</td>
<td>85.6 %</td>
<td>47.2 %</td>
</tr>
<tr>
<td>Defective Perception</td>
<td>35.2 %</td>
<td>38.6 %</td>
</tr>
</tbody>
</table>

Revino MB ACAI 2006, P124
Who Has Asthma Remissions?

- **Very Likely**
  - Mild Intermittent
  - Mild Persistent
  - Moderate Persistent
  - Severe Persistent

Adapted from: Szefer SJ. Advances in Pediatrics 2000; 47: 273-308
Who Has Asthma Remissions?

- Mild Intermittent
- Mild Persistent
- Moderate Persistent
- Severe Persistent

Adapted from: Szefer SJ. Advances in Pediatrics 2000; 47: 273-308
Who Has Asthma Remissions?

Duration of Asthma (years)

Mild Intermittent
Mild Persistent
Moderate Persistent
Severe Persistent

Unlikely
Airway Remodeling

Adapted from: Szefler SJ. Advances in Pediatrics 2000; 47: 273-308
Conclusions

- Early intervention with inhaled corticosteroids in childhood asthma reduces morbidity but does not alter the natural history of asthma.

- Symptom questionnaires are predictive of subsequent asthma episodes in people older than 10 years old, but not in young children.

- In children with asthma, FEV₁/FVC is a more reliable inclusion criterion for clinical studies as well as an assessment measure for clinical control.
Evaluation and management of severe asthma in children include verification of the diagnosis, assessment for coexisting illnesses, and identification of effective treatment strategies directed to adherence, medication delivery, and combination therapy.

Responsiveness to asthma treatment is heterogeneous even among patients with asthma of similar severity. This heterogeneity calls attention to the importance of assessing control and adjusting treatment accordingly.

We are now moving toward an individualized approach to asthma therapy and searching for biomarkers and genetics as a resource to guide treatment.