The Evolution of Childhood Wheezing to Asthma

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&

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AAAAAI 2014, San Diego CA
2501 Seminar
Saturday March 1st, 2014
Faculty Disclosure Information
Bradley Chipps, MD

- In the past 12 months, I have had the following financial relationships with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial service(s) discussed in this CME activity:

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  - AstraZeneca - Consultant, Speakers Bureau
  - GlaxoSmithKline - Consultant, Speakers Bureau
  - Novartis - Consultant, Speakers Bureau
  - Sunovion - Consultant, Speakers Bureau
  - Merck - Consultant, Speakers Bureau
  - Bausch+Lomb - Speakers Bureau
  - Dey - Consultant

- It is my obligation to disclose to you that I am on the Speakers Bureau for Genentech, AstraZeneca, GlaxoSmithKline, Novartis, Sunovion, Merck-Schering, & Bausch+Lomb. However, I acknowledge that today’s activity is certified for CME credit and thus cannot be promotional. I will give a balanced presentation using the best available evidence to support my conclusions and recommendations.

- I do not intend to discuss an unapproved/investigative use of a commercial product/device in my presentation.
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Leonard Bacharier, MD

- In the past 12 months, I have had the following financial relationships with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial service(s) discussed in this CME activity:

  - **GlaxoSmithKline** - Consultant, Speakers Bureau
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  - **Aerocrine** – Consultant
  - **Boeringher Ingelheim** - Consultant

I intend to discuss an unapproved/investigative use of a commercial product/device in my presentation.
At the conclusion of this session, the participant should be able to:

- Determine the diagnostic criteria for varied phenotypic expression of childhood asthma
- Examine the progression of immunopathologic events in the development of childhood asthma
- Examine the implication for treatment given the varied immunopathologic and phenotypic expressions
The Determinants and Pathophysiology of Asthma Involve Interacting Systems at Multiple Levels

Maternal Distress and Childhood Wheeze

Contributions of Viruses and Bacteria to the Development of Asthma

Tobacco Smoke Exposure Among Children

Percentage of Children Aged 3 to 19 Years Exposed to Environmental Tobacco Smoke, by Asthma Status, 1999-2010

- Children with asthma
  - 1999-2002: 57.9%
  - 2003-2006: 55.1%
  - 2007-2010: 54.0%

- Children without asthma
  - 1999-2002: 57.3%
  - 2003-2006: 54.3%
  - 2007-2010: 44.2%

Significant decreasing trend.
Data Source: Centers for Disease Control and Prevention, National Center for Health Statistics, National Health and Nutrition Examination Survey.

Interactions Between Early Respiratory Viral Infections and Atopic Sensitization on the Pathway to Persistent Asthma

Sensitization Leads to Viral Wheeze (the reverse does not appear to be true)

Jackson et al. AJRCCM 185:281, 2012
Hypothesis: Allergy Inhibits Innate Immune Responses Through FcεRI

- Expression of FcεRI
- Cross-linking of FcεRI

PBMCs

(Durrani et al, JACI 130:489, 2012)

- Type I & Type III IFN

More frequent and severe virus-induced wheezing
Prolonged inflammation
Possible airway remodeling and/or loss of lung function
HRV-Induced IFN’s are Lowest in Allergic Asthmatics

Durrani et al., *Journal of Allergy & Clinical Immunology* 2012
Multivariate Model for Factors Associated with Physician-Diagnosed and Active Asthma by the Seventh Birthday after Severe RSV Bronchiolitis

<table>
<thead>
<tr>
<th>RSV bronchiolitis</th>
<th>Baseline data</th>
<th>OR (95% CI)</th>
<th>P value</th>
<th>Age 3 y data</th>
<th>Variables</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 201</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White race</td>
<td>0.25 (0.11-0.57)</td>
<td>.001</td>
<td></td>
<td>White race</td>
<td>0.19 (0.04-0.93)</td>
<td>.041</td>
<td></td>
</tr>
<tr>
<td>Longer birth length per cm</td>
<td>0.86 (0.77-0.97)</td>
<td>.013</td>
<td></td>
<td>Day care by age 3 y</td>
<td>0.18 (0.04-0.84)</td>
<td>.029</td>
<td></td>
</tr>
<tr>
<td>History of maternal asthma at entry</td>
<td>5.21 (1.71-15.9)</td>
<td>.004</td>
<td></td>
<td>Positive response to ≥1 environmental allergen</td>
<td>10.7 (2.08-55.1)</td>
<td>.005</td>
<td></td>
</tr>
<tr>
<td>Exposure to levels of dog allergen &gt;8000 ng/g dust</td>
<td>3.15 (1.29-7.68)</td>
<td>.012</td>
<td></td>
<td>Wheezing (≥3 episodes before age 3 y)</td>
<td>7.31 (1.24-43.3)</td>
<td>.028</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 81</td>
<td>3.81 (2.07-7.01)</td>
<td>&lt;.001</td>
<td>With CCL5 included</td>
<td>n = 40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCL5</td>
<td></td>
<td></td>
<td></td>
<td>CCL5</td>
<td>6.52 (1.67-25.5)</td>
<td>.007</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 179</td>
<td></td>
<td></td>
<td></td>
<td>n = 104</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White race</td>
<td>0.39 (0.20-0.76)</td>
<td>.005</td>
<td></td>
<td>White race</td>
<td>0.15 (0.03-0.76)</td>
<td>.022</td>
<td></td>
</tr>
<tr>
<td>History of maternal asthma at entry</td>
<td>3.49 (1.59-7.65)</td>
<td>.002</td>
<td></td>
<td>Day care by age 3 y</td>
<td>0.14 (0.03-0.70)</td>
<td>.017</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 78</td>
<td>1.67 (1.19-2.36)</td>
<td>.003</td>
<td>With CCL5 included</td>
<td>n = 40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCL5</td>
<td></td>
<td></td>
<td></td>
<td>CCL5</td>
<td>15.1 (1.51-152)</td>
<td>.021</td>
<td></td>
</tr>
<tr>
<td>White race</td>
<td>0.24 (0.08-0.71)</td>
<td>.010</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Childhood Asthma-After Bacterial Colonization of the Airway in Neonates

1. Hypopharyngeal Culture at 1 mo age in 321/411
2. 21% S. pneumoniae, M. catarrhalis, H. influence, S. aureus
3. POS. culture (not s. aureus) associated with
   - Persistent wheeze       HR 2.4
   - Acute exacerbation      HR 2.99
   - Hosp. for wheeze       HR 3.85
4. At 5 yrs  Asthma 33 vs 10% ; B-Agonist 23 vs 18%

Risk of Recurrent Wheeze- Inverse Kaplan-Meier Plot

The Asthma Syndrome
Symptoms of asthma, variable airflow obstruction

Asthma phenotype characteristics
Observable characteristic with no direct relationship to a disease process. Includes physiology, triggers, inflammatory parameters

Asthma Endotypes
Distinct disease entities which may be present in clusters of phenotypes, but each defined by a specific biological mechanism

Endotype 1  Endotype 2  Endotype 3  Endotype 4  Endotype 5
Asthma Endotypes

1. ASA sensitive asthma
2. ABPM
3. Allergic asthma (adults)
4. API-positive preschool wheezer
5. Severe, late-onset hyper eos.
6. Cross-country skiers
Linear Representation of the Th2-Inflammation Hypothesis

- Allergen plus pre-disposition
- Th2
- Inflammation and damage
- Airway hyper-responsiveness plus mediators
- Symptoms

Open Framework Asthma Endotype Model

Multicentre Allergy Study (MAS)

1) Birth Cohort- 1314 “High Risk” Infants

2) 441 followed for 13 years

3) 315 (71.4%) no wheeze by 3 years

4) 126 (28.6%) onset wheeze by 3 years
Time of Sensitization and Degree of Exposure to Indoor Allergens and Lung Function Impairment at 7 yrs


![Graph showing FEV1 and MEF50 values with p-values](chart.png)
The Prevalence of Wheezing Varies Depending on Age and Atopic Status

Predictors of Remitting, Periodic, and Persistent Childhood Asthma

Baseline Predictors of Remitting, Periodic, or Persistent Asthma in Childhood

<table>
<thead>
<tr>
<th>Baseline measures</th>
<th>Remitting vs persistent</th>
<th>Periodic vs persistent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Mild vs moderate asthma</td>
<td>2.01 (1.08-3.74)</td>
<td>.03</td>
</tr>
<tr>
<td>Not sensitive or exposed to any indoor allergen*</td>
<td>3.23 (1.69-6.25)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>IgE &lt;502 ng/mL (median) vs ≥502 ng/mL</td>
<td>1.75 (0.90-3.45)</td>
<td>.10</td>
</tr>
<tr>
<td>Age at randomization (y)</td>
<td>1.23 (1.05-1.43)</td>
<td>.01</td>
</tr>
<tr>
<td>Pre-BD FEV₁ (% predicted)</td>
<td>1.05 (1.01-1.09)</td>
<td>.02</td>
</tr>
<tr>
<td>Pre-BD FVC (% predicted)</td>
<td>0.96 (0.92-1.00)</td>
<td>.04</td>
</tr>
<tr>
<td>Log methacholine FEV₁ PC₂₀ (mg/mL)</td>
<td>1.39 (1.03-1.87)</td>
<td>.03</td>
</tr>
</tbody>
</table>

Stepwise Approach for Managing Asthma (Age ≥ 12 years)

Step 1
Preferred: SABA PRN

Step 2
Preferred: Low-dose ICS
Alternative: Cromolyn, LTRA, Nedocromil, or Theophylline

Step 3
Preferred: Medium-dose ICS + LABA
Alternative: Medium-dose ICS + either LTRA, Theophylline or Zileuton

Step 4
Preferred: High-dose ICS + LABA
AND
Consider Omalizumab for patients who have allergies

Step 5
Preferred: High-dose ICS + LABA + oral corticosteroid
AND
Consider Omalizumab for patients who have allergies

Step 6
Preferred: High-dose ICS + LABA + oral corticosteroid
AND
Consider Omalizumab for patients who have allergies

Each step: Patient education, environmental control, and management of comorbidities.

Quick-Relief Medication for All Patients
• SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms; up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed.
• Use of SABA > 2 days a week for symptom relief generally indicates inadequate control and the need to step up treatment.

ICS Therapy in Preschool Children

- Multicenter double-blind randomized placebo controlled study designed to determine if ICS therapy can modify the subsequent development of asthma in high-risk children.

- Children with + API (ages 2-3, N=285) treated with either fluticasone 88 µg BID or placebo for 2 years followed by a year of observation.

- Primary outcome variable: Proportion of episode-free days.

Asthma Predictive Index

• Identify high risk children (ages 2 & 3):
  • ≥ 4 wheezing episodes in the past year
    (at least one must be MD diagnosed)
  PLUS

• One major criteria OR
  • Parent with Asthma
  • Atopic dermatitis
  • Aero-allergen sensitivity

• Two minor criteria
  • Food sensitivity
  • Peripheral eosinophilia (≥4%)
  • Wheezing not related to infection

Modified from: Castro-Rodriguez, AJRRCM, 2000
Score Chart of the Modified PIAMA Risk Score for Predicting Asthma in Preschool Children

<table>
<thead>
<tr>
<th>Score Factor</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>2</td>
</tr>
<tr>
<td>Medium/low parental education</td>
<td>1</td>
</tr>
<tr>
<td>Parental asthma</td>
<td>4</td>
</tr>
<tr>
<td>Preterm birth (&lt;37 wk)</td>
<td>1</td>
</tr>
<tr>
<td>Wheezing frequency</td>
<td></td>
</tr>
<tr>
<td>1-3 times/y</td>
<td>4</td>
</tr>
<tr>
<td>≥4 times/y</td>
<td>7</td>
</tr>
<tr>
<td>Wheezing/dyspnea apart from colds</td>
<td>2</td>
</tr>
<tr>
<td>Eczema</td>
<td>6</td>
</tr>
<tr>
<td>Range total score</td>
<td>0-23</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total score</th>
<th>Risk on asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-7</td>
<td>≤5%</td>
</tr>
<tr>
<td>8-15</td>
<td>6%-22%</td>
</tr>
<tr>
<td>16-23</td>
<td>25%-60%</td>
</tr>
</tbody>
</table>

Postterm delivery and respiratory tract infections were deleted from the original PIAMA risk score.

Predicted probability (as a percentage) for wheezing at age 8 years based on FENO values (parts per billion, log scale) measured at age 4 years, adjusted, and stratified for specific IgE levels, maternal allergy, doctor diagnosed eczema, and wheezing frequency at age 4 years.

Taylor, R. J Allergy Clin Immunol 2011;128:927-34.
Fluticasone had no Carryover Effect during the Observation Period

The increase in symptom-free days in the fluticasone cohort during the treatment period was lost in the 12 months subsequent during the observation period.

## Heterogeneity of ICS Response Within the API+ Population

<table>
<thead>
<tr>
<th>Stratifying Variable</th>
<th>Percentage of Episode-Free Days</th>
<th>Difference (ICS-Placebo) (95% CI)</th>
<th>P-value (ICS vs Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>7.3 (3.9, 11.1)</td>
<td>0.0005</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.1 (-3.4, 3.5)</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>9.1 (4.8, 13.9)</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>Non-Caucasian</td>
<td>-1.0 (-3.9, 1.7)</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>Run-In EFD &lt;80%</td>
<td>8.6 (4.2, 13.2)</td>
<td>0.0009</td>
<td></td>
</tr>
<tr>
<td>Run-In EFD ≥80%</td>
<td>0.0 (-2.5, 2.5)</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>ED/Hospitalization History</td>
<td>7.7 (3.9, 11.6)</td>
<td>0.0004</td>
<td></td>
</tr>
<tr>
<td>No ED/Hospitalization History</td>
<td>-1.1 (-4.4, 2.1)</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>≥1 Positive Aeroallergen Skin Test</td>
<td>6.5 (3.2, 10.0)</td>
<td>0.0027</td>
<td></td>
</tr>
<tr>
<td>Negative Aeroallergen Skin Test</td>
<td>0.9 (-2.5, 4.4)</td>
<td>0.6</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity of ICS Response Within the API+ Population

<table>
<thead>
<tr>
<th>Stratifying Variable</th>
<th>Number of Prednisolone Bursts</th>
<th>Relative Rate (ICS:Placebo) (95% CI)</th>
<th>P-value (ICS vs Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td></td>
<td>0.6 (0.5, 0.8)</td>
<td>0.0009</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>1.2 (0.8, 1.6)</td>
<td>0.4</td>
</tr>
<tr>
<td>Caucasian</td>
<td></td>
<td>0.6 (0.5, 0.8)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Non-Caucasian</td>
<td></td>
<td>1.2 (0.8, 1.7)</td>
<td>0.3</td>
</tr>
<tr>
<td>ED/Hospitalization History</td>
<td></td>
<td>0.5 (0.4, 0.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>No ED/Hospitalization History</td>
<td></td>
<td>1.3 (0.97, 1.8)</td>
<td>0.08</td>
</tr>
<tr>
<td>≥1 Positive Aeroallergen Skin Test</td>
<td></td>
<td>0.6 (0.5, 0.8)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Negative Aeroallergen Skin Test</td>
<td></td>
<td>1.2 (0.8, 1.7)</td>
<td>0.4</td>
</tr>
</tbody>
</table>

FEV1 % Change with Fluticasone Propionate

Summary - Characterization of within-subject responses to fluticasone and montelukast in childhood asthma

1) FP
   - High FeNO, EOS, IgE
   - Greater BHR
   - Lower FEV1

2) MTL
   - Younger age
   - Shorter duration of disease
   - High urine LTE

Changes in ACSs by Treatment Group

Distribution of Treatment Responses for FEV1

## Subject Characteristics and Bronchoscopic Features by Asthma Phenotype

<table>
<thead>
<tr>
<th></th>
<th>Healthy Control Subjects</th>
<th>Th2 Signature Low</th>
<th>Th2 Signature High</th>
<th>( P ) Value, Low vs. High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>28</td>
<td>20</td>
<td>22</td>
<td>—</td>
</tr>
<tr>
<td>Age, years</td>
<td>36 ± 9</td>
<td>36 ± 11</td>
<td>37 ± 12</td>
<td>0.98</td>
</tr>
<tr>
<td>Gender, M:F (% F)</td>
<td>12:16 (56)</td>
<td>6:14 (70)</td>
<td>11:11 (50)</td>
<td>0.19</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>20</td>
<td>9</td>
<td>9</td>
<td>0.98</td>
</tr>
<tr>
<td>African American</td>
<td>0</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>3</td>
<td>5</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Asian or Pacific Islander</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>FEV(_1), % predicted</td>
<td>107 (13)</td>
<td>90 (10)</td>
<td>85 (13)</td>
<td>0.85</td>
</tr>
<tr>
<td>( \Delta )FEV(_1) with albuterol (% of baseline)</td>
<td>2.7 ± 3.4</td>
<td>9.7 ± 7.4</td>
<td>12.5 ± 9.8</td>
<td>0.51</td>
</tr>
<tr>
<td>Methacholine PC(_{20})</td>
<td>64 (22–64)</td>
<td>0.93 (0.06–7.3)</td>
<td>0.27 (0.05–1.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IgE, IU/ml</td>
<td>27 (3–287); n = 26</td>
<td>125 (19–1,194)</td>
<td>244 (32–2,627)</td>
<td>0.031</td>
</tr>
<tr>
<td>Blood eosinophils, ( \times 10^9)/L</td>
<td>0.10 ± 0.07</td>
<td>0.23 ± 0.21</td>
<td>0.37 ± 0.22</td>
<td>0.027</td>
</tr>
<tr>
<td>BAL eosinophil %</td>
<td>0.26 ± 0.29; n = 22</td>
<td>0.42 ± 0.46; n = 16</td>
<td>1.9 ± 1.9; n = 20</td>
<td>0.001</td>
</tr>
<tr>
<td>RBM thickness, ( \mu m )</td>
<td>4.34 ± 1.11; n = 22</td>
<td>4.67 ± 0.99; n = 19</td>
<td>5.91 ± 1.72; n = 19</td>
<td>0.014</td>
</tr>
<tr>
<td>( \Delta )FEV(_1) with fluticasone at 4 wk, L</td>
<td>N/A</td>
<td>0.03 ± 0.12</td>
<td>0.35 ± 0.2;</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(−0.12 to 0.21); n = 6</td>
<td>(−0.02 to 0.73); n = 10</td>
<td></td>
</tr>
<tr>
<td>( \Delta )FEV(_1) with fluticasone at 8 wk, L</td>
<td>N/A</td>
<td>0.04 ± 0.12</td>
<td>0.25 ± 0.23;</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(−0.11 to 0.26); n = 6</td>
<td>(−0.18 to 0.52); n = 10</td>
<td></td>
</tr>
</tbody>
</table>

*Definition of abbreviations: BAL = bronchoalveolar lavage; PC\(_{20}\) = provocative concentration required to cause a 20% decline in FEV\(_1\); RBM = reticular basement membrane.

* Values are presented as mean ± SD or median (range) unless otherwise specified. \( P \) values are sidak corrected for multiple testing (across the three groups). For significance testing of PC\(_{20}\) and IgE, data were log transformed for normality. In case of missing data, the number of subjects for whom data exist is noted. \( P \) values relative to healthy control subjects are also depicted in Figures 2 and 3.
Subject Characteristics and Bronchoscopic Features by Asthma Phenotype

<table>
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<tr>
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<tr>
<td>Methacholine PC20</td>
<td>0.93 (0.06–7.3)</td>
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<tr>
<td>IgE, IU/ml</td>
<td>125 (19–1,194)</td>
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<td>RBM thickness, mm</td>
<td>4.67 ± 0.99; n = 19</td>
<td>5.91 ± 1.72; n = 19</td>
</tr>
<tr>
<td>ΔFEV1 with fluticasone 4wk, L</td>
<td>0.03 ± 0.12;</td>
<td>0.35 ± 0.2;</td>
</tr>
<tr>
<td></td>
<td>(−0.12 to 0.21); n = 6</td>
<td>(−0.02 to 0.73); n = 10</td>
</tr>
<tr>
<td>ΔFEV1 with fluticasone 8wk, L</td>
<td>0.04 ± 0.12;</td>
<td>0.25 ± 0.23;</td>
</tr>
<tr>
<td></td>
<td>(−0.11 to 0.26); n = 6</td>
<td>(−0.18 to 0.52); n = 10</td>
</tr>
</tbody>
</table>
ICS Response

![Graph showing changes in FEV1 over weeks with ICS initiation and cessation.](image)
Stepwise Approach for Managing Asthma

Step 1
- **Preferred:** Low-dose ICS
- **Alternative:** Cromolyn, LTRA, Nedocromil, or Theophylline

Step 2
- **Preferred:** Low-dose ICS + LABA
- **Alternative:** Medium-dose ICS

Step 3
- **Preferred:** Medium-dose ICS + LABA
- **Alternative:** Low-dose ICS + either LTRA, Theophylline or Zileuton

Step 4
- **Preferred:** High-dose ICS + LABA
  - **And:** Consider Omalizumab for patients who have allergies

Step 5
- **Preferred:** High-dose ICS + LABA
  - **And:** Consider Omalizumab for patients who have allergies

Step 6
- **Preferred:** High-dose ICS + LABA + oral corticosteroid

**Assess Control**
- Step up if needed first check adherence, environmental control and comorbid conditions
- Step down if possible and asthma is well controlled at least 3 months

**Quick-Relief Medication for All Patients**
- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms; up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed.
- Use of SABA >2 days a week for symptom relief generally indicates inadequate control and the need to step up treatment.

BADGER Trial

1. 182 Children (6-17 years of age), uncontrolled asthma, FP 100 µg BID, triple cross over design, 16 week period

2. FP 250 µg BID,
   FP 100 µg + SALM 50 µg BID,
   FP 100 µg BID + MTL 5 or 10 mg daily

3. 3 outcomes
   - Exacerbations
   - Symptom free days
   - FEV1 (Pre)

Probability of Best Response

Secondary Predictors of a Differential Response to Step-up Therapy

Can Formoterol/Budesonide be used “SMARTIly”
Individual patients with exacerbations requiring intervention

Weeks since randomisation

4 x BUD + SABA  294 events

Bud/Form + SABA  330 events

Bud/Form SMART  160 events

率 reduction 46 to 53% vs both groups; p<0.001

Severe Asthma in Children: Is it Time to Adjust the Paradigm?

Current assumptions of treatment:

- Asthma is a unified disorder with a common inflammatory mechanism
- There is concordance between inflammation and symptoms
- The nature of the inflammation is corticosteroid responsive
Severe Asthma in Children May be Associated With a Different Inflammatory Phenotype

CHILDHOOD ASTHMA

Persistent Asthma

Th2 phenotype

Eosinophils

Severe Asthma

Mixed phenotype?

Neutrophils?

The Unexpected Importance of Innate Immunity in Asthma Severity and Reduced Steroid Sensitivity

Demographic and clinical characteristics of children and adolescents with severe or difficult-to-treat asthma
Methods

- Cross-sectional baseline data analyzed
- TENOR patients between 6 and 17 years of age included (N=1,261)
- Patients categorized into four age groups by gender:

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Males (N=791) n (%)</th>
<th>Females (N=470) n (%)</th>
<th>Total (N=1,261) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-8</td>
<td>145 (18)</td>
<td>88 (19)</td>
<td>233 (18)</td>
</tr>
<tr>
<td>9-11</td>
<td>282 (36)</td>
<td>120 (26)</td>
<td>402 (32)</td>
</tr>
<tr>
<td>12-14</td>
<td>240 (30)</td>
<td>171 (36)</td>
<td>411 (33)</td>
</tr>
<tr>
<td>15-17</td>
<td>124 (16)</td>
<td>91 (19)</td>
<td>215 (17)</td>
</tr>
</tbody>
</table>
Healthcare Utilization by Long-Term Controller Use, Ages 6-11 & 12-17
### Baseline Characteristics of Study Subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Children, no. (%)</th>
<th>Adolescents and adults, no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>169 (32.6)</td>
<td>2402 (66.5)</td>
</tr>
<tr>
<td>Male</td>
<td>349 (67.4)</td>
<td>1210 (33.5)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>316 (61.0)</td>
<td>2789 (77.2)</td>
</tr>
<tr>
<td>Nonwhite</td>
<td>202 (39.0)</td>
<td>823 (22.8)</td>
</tr>
<tr>
<td><strong>Age of onset</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3 y</td>
<td>290 (56.0)</td>
<td>600 (16.6)</td>
</tr>
<tr>
<td>3-11 y</td>
<td>228 (44.0)</td>
<td>923 (25.6)</td>
</tr>
<tr>
<td>12-17 y</td>
<td>—</td>
<td>260 (7.2)</td>
</tr>
<tr>
<td>≥18 y</td>
<td>—</td>
<td>1829 (50.6)</td>
</tr>
<tr>
<td><strong>Obese</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes*</td>
<td>159 (30.7)</td>
<td>2071 (57.3)</td>
</tr>
<tr>
<td>No</td>
<td>359 (69.3)</td>
<td>1541 (42.7)</td>
</tr>
<tr>
<td><strong>Passive smoke exposure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>133 (25.7)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>385 (74.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Active smoking</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>—</td>
<td>1232 (34.1)</td>
</tr>
<tr>
<td>No</td>
<td>—</td>
<td>2380 (65.9)</td>
</tr>
<tr>
<td><strong>Atopy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥3 Allergic triggers</td>
<td>220 (42.5)</td>
<td>2084 (57.7)</td>
</tr>
<tr>
<td>% Allergic rhinitis</td>
<td>356 (68.7)</td>
<td>2778 (76.9)</td>
</tr>
<tr>
<td>% Atopic dermatitis</td>
<td>172 (33.2)</td>
<td>793 (22.0)</td>
</tr>
<tr>
<td><strong>Total IgE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥100 IU/mL</td>
<td>145 (28.0)</td>
<td>784 (21.7)</td>
</tr>
<tr>
<td>&lt;100 IU/mL</td>
<td>373 (72.0)</td>
<td>2828 (78.3)</td>
</tr>
<tr>
<td><strong>Aspirin sensitivity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>—</td>
<td>432 (12.0)</td>
</tr>
<tr>
<td>No</td>
<td>—</td>
<td>3180 (88.0)</td>
</tr>
<tr>
<td><strong>Abnormal FEV₁/FVC ratio†</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>342 (66.0)</td>
<td>1828 (50.6)</td>
</tr>
<tr>
<td>No</td>
<td>176 (34.0)</td>
<td>1784 (49.4)</td>
</tr>
</tbody>
</table>

Characteristics of 5 Clusters in 518 Children Ages 6-11 Years

<table>
<thead>
<tr>
<th>Feature</th>
<th>Cluster 1</th>
<th>Cluster 2</th>
<th>Cluster 3</th>
<th>Cluster 4</th>
<th>Cluster 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients (%)</td>
<td>115 (22.2)</td>
<td>81 (15.6)</td>
<td>162 (31.3)</td>
<td>87 (16.8)</td>
<td>73 (14.1)</td>
</tr>
<tr>
<td>% Boys</td>
<td>100†</td>
<td>0†</td>
<td>64.2</td>
<td>65.5</td>
<td>100†</td>
</tr>
<tr>
<td>% White race</td>
<td>100†</td>
<td>58.0</td>
<td>58.0</td>
<td>69.0</td>
<td>0†</td>
</tr>
<tr>
<td>% Onset &lt;3 y old</td>
<td>46.1</td>
<td>54.3</td>
<td>58.0</td>
<td>57.5</td>
<td>67.1</td>
</tr>
<tr>
<td>Obese BMI &gt; 95th percentile</td>
<td>20.0</td>
<td>28.4</td>
<td>34.6</td>
<td>35.6</td>
<td>35.6</td>
</tr>
<tr>
<td>Mean (SD) BMI</td>
<td>18.8 ± 3.7</td>
<td>19.9 ± 5.2</td>
<td>20.4 ± 5.2</td>
<td>22.2 ± 10.4</td>
<td>20.2 ± 4.5</td>
</tr>
<tr>
<td>% Passive smoke exposure</td>
<td>0†</td>
<td>0†</td>
<td>28.4</td>
<td>100†</td>
<td>0†</td>
</tr>
<tr>
<td>Atopy ≥3 Allergic triggers</td>
<td>49.6</td>
<td></td>
<td></td>
<td>39.5</td>
<td>25.3‡$§‖‖</td>
</tr>
<tr>
<td>% Allergic rhinitis</td>
<td>100†</td>
<td>100†</td>
<td>0†</td>
<td>100†</td>
<td>100†</td>
</tr>
<tr>
<td>% Atopic dermatitis</td>
<td>40.0</td>
<td>37.0</td>
<td>2.8‡$§‖#</td>
<td>36.8</td>
<td></td>
</tr>
<tr>
<td>IgE % Total IgE ≥100</td>
<td>73.0</td>
<td>64.2</td>
<td>60.5</td>
<td>73.6</td>
<td>80.8</td>
</tr>
<tr>
<td>Mean (SD) IgE</td>
<td>505 ± 792</td>
<td>393 ± 520</td>
<td>469 ± 722</td>
<td>787 ± 1593</td>
<td>757 ± 1180</td>
</tr>
<tr>
<td>FEV1:FVC ratio</td>
<td>57.4</td>
<td>50.6</td>
<td>73.5</td>
<td>72.4</td>
<td>72.6</td>
</tr>
<tr>
<td>% &lt;normal for age</td>
<td>82.2 (9.5)</td>
<td></td>
<td>83.4 (9.3)</td>
<td></td>
<td>78.0 (10.6)</td>
</tr>
</tbody>
</table>

Characteristics of 5 Clusters in 3612 Adolescents and Adults Ages \( \geq 12 \) Years

**TABLE III.** Characteristics of 5 clusters in 3612 adolescents and adults ages \( \geq 12 \) years

<table>
<thead>
<tr>
<th>Feature</th>
<th>Cluster 1</th>
<th>Cluster 2</th>
<th>Cluster 3</th>
<th>Cluster 4</th>
<th>Cluster 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients (%)</td>
<td>1262 (34.9)</td>
<td>659 (18.2)</td>
<td>664 (18.4)</td>
<td>596 (16.5)</td>
<td>431 (11.9)</td>
</tr>
<tr>
<td>% Girls and women</td>
<td>100†</td>
<td>67.5†</td>
<td>0†</td>
<td>61.1†</td>
<td>76.8§</td>
</tr>
<tr>
<td>% White race</td>
<td>100†</td>
<td>83.2†</td>
<td>100†</td>
<td>0†</td>
<td>73.1§</td>
</tr>
<tr>
<td>% Onset ( \geq 18 ) years old</td>
<td>61.0§</td>
<td></td>
<td>/¶</td>
<td>38.5¶#</td>
<td>43.7¶#</td>
</tr>
<tr>
<td>BMI % Obese (BMI &gt; 30 kg/m²)</td>
<td>57.5</td>
<td>52.1</td>
<td>54.8</td>
<td>62.6</td>
<td>61.7</td>
</tr>
<tr>
<td>Mean (SD) BMI</td>
<td>30.0 ± 7.9</td>
<td></td>
<td></td>
<td>29.0 ± 8.0</td>
<td></td>
</tr>
<tr>
<td>% Smokers</td>
<td>35.7</td>
<td>27.5</td>
<td>36.8§</td>
<td>36.7</td>
<td>31.8</td>
</tr>
<tr>
<td>Atopy ≥3 Allergic triggers</td>
<td>56.7‡§</td>
<td></td>
<td></td>
<td>68.9¶#</td>
<td>47.9‡‡§#</td>
</tr>
<tr>
<td>% Allergic rhinitis</td>
<td>75.9§¶</td>
<td>85.1¶#</td>
<td>74.0‡¶</td>
<td>68.6‡§#</td>
<td>83.3‡¶</td>
</tr>
<tr>
<td>% Atopic dermatitis</td>
<td>0†</td>
<td>100†</td>
<td>0†</td>
<td>5.5†</td>
<td>23.4¶</td>
</tr>
<tr>
<td>IgE % Total IgE ≥100</td>
<td>25.3</td>
<td>42.2</td>
<td>41.6</td>
<td>48.7</td>
<td>30.4</td>
</tr>
<tr>
<td>Mean (SD) IgE</td>
<td>204 ± 437¶</td>
<td></td>
<td></td>
<td>512 ± 1302¶</td>
<td></td>
</tr>
<tr>
<td>% Aspirin sensitive</td>
<td>0†</td>
<td>0.2</td>
<td>0†</td>
<td>0†</td>
<td>100†</td>
</tr>
<tr>
<td>FEV(_1)/FVC ratio</td>
<td>43.0</td>
<td>49.5</td>
<td>61.8</td>
<td>54.2</td>
<td>52.7</td>
</tr>
<tr>
<td>Mean (SD) FEV(_1)/FVC</td>
<td>72.5 ± 11.7¶</td>
<td></td>
<td></td>
<td>72.9 ± 12.1¶</td>
<td></td>
</tr>
</tbody>
</table>

A Comparison of the Clusters Identified in the Current TENOR Cohort Analysis and those Identified in Adults in SARP

<table>
<thead>
<tr>
<th>Cluster</th>
<th>TENOR (n = 3612)</th>
<th>SARP (n = 726)</th>
<th>Similarities</th>
<th>Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>3</td>
<td>Female, late onset, less atopy</td>
<td>Obese (SARP)</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>1, 2</td>
<td>Female, early onset, atopic</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>4</td>
<td>Highest nonwhite, severe</td>
<td>Atopic (SARP)</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>5</td>
<td>Female, white, late-onset, severe</td>
<td>Aspirin sensitive (TENOR)</td>
</tr>
</tbody>
</table>

Airway inflammation in asthma underlying chronic airflow obstruction, airway hyperresponsiveness, and mucus hypersecretion, focusing on T-helper-2 cytokines

## Phenotype-Targeted Treatments in Asthma

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>Specifically-targeted treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Allergic asthma</strong></td>
<td>Anti-immunoglobulin E (omalizumab)</td>
</tr>
<tr>
<td>High serum immunoglobulin E; atopy;</td>
<td></td>
</tr>
<tr>
<td>high blood eosinophil</td>
<td></td>
</tr>
<tr>
<td><strong>Eosinophilic asthma</strong></td>
<td>Anti-interleukin-4 receptor α (dupilumab)</td>
</tr>
<tr>
<td>Recurrent exacerbations; sputum eosinophils;</td>
<td></td>
</tr>
<tr>
<td>steroid-dependent asthma</td>
<td></td>
</tr>
<tr>
<td><strong>Neutrophilic asthma</strong></td>
<td>Macrolide antibiotics (azithromycin)</td>
</tr>
<tr>
<td>Sputum neutrophils</td>
<td></td>
</tr>
<tr>
<td><strong>Chronic airflow obstruction</strong></td>
<td>Anti-interleukin-13 (lebrikizumab)</td>
</tr>
<tr>
<td>Airway wall remodelling; low FEV₁;</td>
<td></td>
</tr>
<tr>
<td>high serum periostin</td>
<td></td>
</tr>
<tr>
<td><strong>Recurrent exacerbations</strong></td>
<td>Anti-interleukin-5 (mepolizumab)</td>
</tr>
<tr>
<td>Sputum eosinophils; oral corticosteroid dose</td>
<td></td>
</tr>
</tbody>
</table>

FEV₁ = forced expiratory volume in 1 s.

*Table: Phenotype-targeted treatments in asthma*

Causes and putative molecular mechanisms of corticosteroid insensitivity underlying severe asthma

Proposed management pathway with new treatments, focusing on characteristics and biomarkers

IgE for Asthma- Inner City

1. 419 Patients
   10.8 ± 3.4 years
   Approx. 60% African Americans
   7 Year duration
   FEV1 92%
   FEV1/FVC 77%

2. 73% moderate to severe disease

3. Protocol anti-IgE for 60 weeks

Number of Days with Symptoms in a 2-Week Interval, Frequency of Exacerbations, and Dose of Inhaled Glucocorticoids over the Course of the Study.
Seasonal Variation in Days with Symptoms, Frequency of Exacerbations, and Dose of Inhaled Glucocorticoids. The width of the bands represents the 95% confidence interval.
# Stepwise Management of Asthma in 3 Strategies

<table>
<thead>
<tr>
<th>STEP-UP LONG-TERM (SLT)</th>
<th>STEP-UP SHORT-TERM (SST)</th>
<th>STEP-UP INTERMITTENT (SUI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>increase in therapy for uncontrolled asthma (weeks)</td>
<td>increase in therapy for brief loss of control (days)</td>
<td>increase in therapy for variable symptoms (day-to-day)</td>
</tr>
<tr>
<td>persistent loss of control</td>
<td>brief loss of control (upper respiratory tract infections, pet exposure)</td>
<td>mild symptoms</td>
</tr>
<tr>
<td>step-down therapy when control achieved after 3-6 months</td>
<td>step-down therapy when control achieved after 3-10 days</td>
<td>intermittent use</td>
</tr>
</tbody>
</table>

Summary - Predicting Persistence of Wheezing

1. Family history of asthma
2. Recurrent lower airway symptoms in infancy
3. Atopic sensitization before 4 years and early exposure
4. Eczema
5. Exposure to ETS
Summary- Predicting Persistence of Wheezing

6. Females post puberty
7. Obesity
8. Acetaminophen ?
9. Vitamin D ?
10. Maternal Diabetes & Folate Def
Evolution of Childhood Wheezing to Asthma
Phenotypic Expressions of Childhood Wheezing Disorders

1. Viral induced wheezing
2. Severe Intermittent Wheezing
3. Persistent Asthma
4. Severe Asthma
Viral Induced Wheezing

1. Triggered by viral infections
2. Non-Atopic
3. Remission in childhood
Infants
Role of Viral Infections
Host Factors and HRV Infections

1. 630 infants with URI or Bronchilitis in 2004-2008
2. 162 (26%) HRV- 18% bronchilitis; 47% URI
3. 104 (64%) HRV only- 44 (42%) Hosp.
4. HRV-C assoc. with more severe illness

Risk Factors for HRV-assoc. Infant Respiratory Tract Disease Severity
RV Wheezing vs. RSV Wheezing in First 3 Years and Asthma at Age 6 Years

Jackson DJ et al. AJRCCM 2008; 178: 667
RV Wheeze vs. RSV Wheeze

Severe Intermittent Wheezing
AIMS – Primary Hypothesis

- In young children with recurrent severe wheezing, intervention with an ICS or LTRA at the onset of respiratory tract illness (RTI)-associated symptoms will increase the proportion of episode-free days over a 12 month period compared with conventional therapy*.

*Conventional therapy - inhaled bronchodilator followed by the sequential addition of systemic corticosteroids
Persistent Asthma
Multicentre Allergy Study (MAS)

1) Birth Cohort- 1314 “High Risk” Infants

2) 441 followed for 13 years

3) 315 (71.4%) no wheeze by 3 years

4) 126 (28.6%) onset wheeze by 3 years

Time of Sensitization and Degree of Exposure to Indoor Allergens and Lung Function Impairment at 7 yrs

Illi et al. Lancet
2006;368:763-770.
The Prevalence of Wheezing Varies Depending on Age and Atopic Status

Incidence of Wheezing up to the age of 13 years in the MAS Study Cohort

Graphic representation of a hidden Mardov model

Association between atopic groups

Kaplan-Meier estimates of cumulative risk of hospital admission

Melbourne Epidemiological Study

![Lung Function Over Time by Classification at Recruitment](image)

**FIG 2.** FEV$_1$ 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.
Defining the Asthma Syndrome

1. Phenotypes
2. Endotypes
3. Cluster Analysis
The Asthma Syndrome
Symptoms of asthma, variable airflow obstruction

Asthma phenotype characteristics
Observable characteristic with no direct relationship to a disease process. Includes physiology, triggers, inflammatory parameters

Asthma Endotypes
Distinct disease entities which may be present in clusters of phenotypes, but each defined by a specific biological mechanism

Endotype 1  Endotype 2  Endotype 3  Endotype 4  Endotype 5
Asthma Endotypes

1. ASA sensitive asthma
2. ABPM
3. Allergic asthma (adults)
4. API-positive preschool wheezer
5. Severe, late-onset hyper EOS.
6. Cross-country skiers

Linear Representation of the Th2-Inflammation Hypothesis

1. Allergen plus pre-disposition
2. Th2
3. Inflammation and damage
4. Airway hyper-responsiveness plus mediators
5. Symptoms

Open Framework Asthma Endotype Model

Relationship between Nitric Oxide, Atopy, AHR, Eosinophilic Inflammation & Asthma

- AHR
- Asthma
- NO
- Eosinophilic Inflammation
- Atopy
Relationship between Nitric Oxide, Atopy, AHR, Eosinophilic Inflammation & Asthma
# Subject Characteristics and Bronchoscopic Features by Asthma Phenotype

## Table 2. Subject Characteristics and Bronchoscopic Features by Asthma Phenotype

<table>
<thead>
<tr>
<th></th>
<th>Healthy Control Subjects</th>
<th>Th2 Signature Low</th>
<th>Th2 Signature High</th>
<th>P Value, Low vs. High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>28</td>
<td>20</td>
<td>22</td>
<td>—</td>
</tr>
<tr>
<td>Age, years</td>
<td>36 ± 9</td>
<td>36 ± 11</td>
<td>37 ± 12</td>
<td>0.98</td>
</tr>
<tr>
<td>Gender, M:F (% F)</td>
<td>12:16 (56)</td>
<td>6:14 (70)</td>
<td>11:11 (50)</td>
<td>0.19</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>20</td>
<td>9</td>
<td>9</td>
<td>0.98</td>
</tr>
<tr>
<td>African American</td>
<td>0</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>3</td>
<td>5</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Asian or Pacific Islander</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>FEV₁, % predicted</td>
<td>107 (13)</td>
<td>89 (10)</td>
<td>85 (13)</td>
<td>0.85</td>
</tr>
<tr>
<td>ΔFEV₁ with albuterol (% of baseline)</td>
<td>2.7 ± 3.4</td>
<td>9.7 ± 7.4</td>
<td>12.5 ± 9.8</td>
<td>0.51</td>
</tr>
<tr>
<td>Methacholine PC₂₀</td>
<td>64 (22–64)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgE, IU/ml</td>
<td>27 (3–287); n = 26</td>
<td>125 (19–1,194)</td>
<td>244 (32–6,267)</td>
<td>0.031</td>
</tr>
<tr>
<td>Blood eosinophils, × 10⁹/L</td>
<td>0.10 ± 0.07</td>
<td>0.23 ± 0.21</td>
<td>0.37 ± 0.22</td>
<td>0.027</td>
</tr>
<tr>
<td>BAL eosinophil %</td>
<td>0.26 ± 0.29; n = 22</td>
<td>0.42 ± 0.46; n = 16</td>
<td>1.9 ± 1.9; n = 20</td>
<td>0.001</td>
</tr>
<tr>
<td>RBM thickness, µm</td>
<td>4.34 ± 1.11; n = 22</td>
<td>4.67 ± 0.99; n = 19</td>
<td>5.91 ± 1.72; n = 19</td>
<td>0.014</td>
</tr>
<tr>
<td>ΔFEV₁ with fluticasone at 4 wk, L</td>
<td>N/A</td>
<td>0.03 ± 0.12;</td>
<td>0.35 ± 0.2;</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(–0.12 to 0.21); n = 6</td>
<td>(–0.02 to 0.73); n = 10</td>
<td></td>
</tr>
<tr>
<td>ΔFEV₁ with fluticasone at 8 wk, L</td>
<td>N/A</td>
<td>0.04 ± 0.12;</td>
<td>0.25 ± 0.23;</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(–0.11 to 0.26); n = 6</td>
<td>(–0.18 to 0.52); n = 10</td>
<td></td>
</tr>
</tbody>
</table>

Definition of abbreviations: BAL = bronchoalveolar lavage; PC₂₀ = provocative concentration required to cause a 20% decline in FEV₁; RBM = reticular basement membrane.

* Values are presented as mean ± SD or median (range) unless otherwise specified. P values are sidak corrected for multiple testing (across the three groups). For significance testing of PC₂₀ and IgE, data were log transformed for normality. In case of missing data, the number of subjects for whom data exist is noted. P values relative to healthy control subjects are also depicted in Figures 2 and 3.
## Subject Characteristics and Bronchoscopic Features by Asthma Phenotype

### Subjects with Asthma

<table>
<thead>
<tr>
<th>Measure</th>
<th>Th2 Signature Low</th>
<th>Th2 Signature High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methacholine PC20</td>
<td>0.93 (0.06–7.3)</td>
<td>0.27 (0.05–1.9)</td>
</tr>
<tr>
<td>IgE, IU/ml</td>
<td>125 (19–1,194)</td>
<td>244 (32–2,627)</td>
</tr>
<tr>
<td>Blood eosinophils, 3109/L</td>
<td>0.23 ± 0.21</td>
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<td>BAL eosinophil %</td>
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<td>RBM thickness, mm</td>
<td>4.67 ± 0.99; n = 19</td>
<td>5.91 ± 1.72; n = 19</td>
</tr>
<tr>
<td>DFEV1 with fluticasone 4wk, L</td>
<td>0.03 ± 0.12;</td>
<td>0.35 ± 0.2;</td>
</tr>
<tr>
<td></td>
<td>(−0.12 to 0.21); n = 6</td>
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<td>DFEV1 with fluticasone 8wk, L</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Markers of Allergy, Eosinophilic Inflammation, and Airway Remodeling are Increased in Th2-high Asthma

ICS Response

Severe Asthma
Severe Asthma

- Refractory
- Difficult to control asthma
- Uncontrolled asthma refractory to conventional treatment
- Frequent exacerbations
- ? Distinct phenotype or subgroup
Reasons for Failure to Achieve Control

- Compliance
- Asthma heterogeneity
- Wrong diagnosis
- Wrong target
- Failure to deliver drug to the target site
ID of Asthma Phenotypes Using Cluster Analysis in SARP

1. 726 patients > 12 yrs old; 304 patients w/ severe asthma
2. 34 phenotypic variables

Moore et al. Am J Respir Crit Care 2010; Vol 181: 315-23
Unsupervised Cluster Analysis Reveals 4 Phenotypes of Childhood Asthma

Demographics
- Asthma duration
- Symptom frequency
- ICS dose
- Number of controller medications
- Healthcare utilization
- Atopic sensitization
- Lung function
- Exhaled nitric oxide

Fitzpatrick AM et al., J Allergy Clin Immunol, 2011; 127: 130-137
Duration of Asthma

Cluster 1: Low-medium dose ICS
Later-onset symptomatic asthma with normal lung function

Cluster 2: Medium-dose ICS
Early-onset atopic asthma with normal lung function

Cluster 3: Medium/high-dose ICS
Early-onset atopic asthma with mild airflow limitation

Early-onset atopic asthma with advanced airflow limitation

Tree Analysis

Moore et al. Am J Respir Crit Care 2010; Vol 181: 315-23
Cluster- SARP

1. 110 early onset atopic asthma and PFT; 2 or fewer controllers- little HCU

2. 321 #1 with more medication use

Moore et al. Am J Respir Crit Care 2010; Vol 181: 315-23
Tree Analysis

Moore et al. Am J Respir Crit Care 2010; Vol 181: 315-23
Cluster- SARP

3. 59 older obese women, late onset; non atopic- mod FEV1 ↓, freq OCS

Moore et al. Am J Respir Crit Care 2010; Vol 181: 315-23
Tree Analysis

Moore et al. Am J Respir Crit Care 2010; Vol 181: 315-23
Cluster- SARP

4. 120 severe obst. (<65%) with no response, ↑ atopy

5. 116 severe obst. (<65%), ↑ HCU, ↑ sputum neutrophils, ↓ atopy, ↑ pulmonary infection

Moore et al. Am J Respir Crit Care 2010; Vol 181: 315-23
Tree Performance

Moore et al. Am J Respir Crit Care 2010; Vol 181: 315-23
Demographics and Clinical Characteristics of the SARP subjects

Airflow Limitation and Air Trapping are Most Pronounced in Clusters 3 and 4

FEV$_1$ (% predicted)

RV / TLC

p < 0.001

p < 0.05

Fitzpatrick AM et al., J Allergy Clin Immunol, 2011; 127: 382-389
Allergic Sensitization Does Not Differentiate the Pediatric Asthma Clusters

Fitzpatrick AM et al., J Allergy Clin Immunol, 2011; 127: 382-389
Asthma Cluster Assignments Do Not Agree With NAEPP EPR-3 Definitions of Asthma Severity for Children

Frequency (%)

Mild persistent asthma
Moderate persistent asthma
Severe persistent asthma

Cluster 1  Cluster 2  Cluster 3  Cluster 4
Asthma Clusters Are Differentiated By Symptom Burden and the Need for High-Intensity Treatment

Oral corticosteroid bursts (previous year)

Daily dose of inhaled fluticasone equivalent (µg)

Fitzpatrick AM et al., J Allergy Clin Immunol, 2011; 127: 382-389
Severe Asthma in Children May be Associated With a Different Inflammatory Phenotype

Severe Asthma in Children: Is it Time to Adjust the Paradigm?

Current assumptions of treatment:

- Asthma is a unified disorder with a common inflammatory mechanism
- There is concordance between inflammation and symptoms
- The nature of the inflammation is corticosteroid responsive
Demographic and clinical characteristics of children and adolescents with severe or difficult-to-treat asthma
Methods

- Cross-sectional baseline data analyzed
- TENOR patients between 6 and 17 years of age included (N=1,261)
- Patients categorized into four age groups by gender:

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Males (N=791) n (%)</th>
<th>Females (N=470) n (%)</th>
<th>Total (N=1,261) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-8</td>
<td>145 (18)</td>
<td>88 (19)</td>
<td>233 (18)</td>
</tr>
<tr>
<td>9-11</td>
<td>282 (36)</td>
<td>120 (26)</td>
<td>402 (32)</td>
</tr>
<tr>
<td>12-14</td>
<td>240 (30)</td>
<td>171 (36)</td>
<td>411 (33)</td>
</tr>
<tr>
<td>15-17</td>
<td>124 (16)</td>
<td>91 (19)</td>
<td>215 (17)</td>
</tr>
</tbody>
</table>
Spirometry by Age and Gender

Pre-Bronchodilator—Percent Predicted FEV₁/FVC Ratio
- Male □ Female

Post-Bronchodilator—Percent Predicted FEV₁/FVC Ratio
- Male □ Female

Pre-Bronchodilator—Percent Predicted FEV₁
- Male □ Female

Post-Bronchodilator—Percent Predicted FEV₁
- Male □ Female

Age Group (years):
- 6-8
- 9-11
- 12-14
- 15-17

Ratio x 100
- 100
- 90
- 80
- 70
- 60

Percent Predicted
- 100
- 90
- 80
- 70
- 60
Medication Use by Age

*Based on test for linear trend, a statistically significant age trend (P < .05) was seen for methylxanthines and long-acting β-agonists.
Healthcare Utilization by Long-Term Controller Use, Ages 6-11 & 12-17

- Ever Intubated
  - 1 Controller (n=59): 3.4%
  - 2 Controllers (n=204): 8.8%
  - ≥3 Controllers (n=369): 10.3%

- ER Visit in Last 3 Mo.
  - 1 Controller (n=35): 2.9%
  - 2 Controllers (n=180): 11.1%
  - ≥3 Controllers (n=408): 15.0%

- Overnight Hospitalization in Last 3 Mo.
  - 1 Controller: 8.5%
  - 2 Controllers: 16.7%
  - ≥3 Controllers: 25.5%

- Corticosteroid Burst in Last 3 Mo.
  - 1 Controller (n=59): 47.5%
  - 2 Controllers (n=204): 44.1%
  - ≥3 Controllers (n=369): 53.4%

- Unscheduled Office Visit/Contact in Last 3 Mo.
  - 1 Controller (n=35): 52.5%
  - 2 Controllers (n=180): 47.1%
  - ≥3 Controllers (n=408): 48.2%
Summary - Predicting Persistence of Wheezing

1. Family history of asthma
2. Recurrent lower airway symptoms in infancy
3. Absence of nasal symptoms at 1 year
4. Atopic sensitization before 4 years and early exposure
5. Eczema
Summary- Predicting Persistence of Wheezing

6. Exposure to ETS
7. Females post puberty
8. Acetaminophen ?
9. Vitamin D ?
10. Obesity
Thank You
Change in corticosteroid adherence over time with respect to the first asthma exacerbation in SAPPHIRE participants.

Relationship between level of ICS adherence (ie, percentage of prescribed ICS medication taken) and the likelihood of an asthma exacerbation (ie, burst oral steroid use, asthma-related ED visit, or asthma-related hospitalization).

Spirometry by Age and Gender

[Graphs showing spirometry data by age and gender pre- and post-bronchodilator.]
High Rate of Allergic Sensitization Among API+ Children

- Food: 5%
- Food and Aeroallergen: 26%
- Aeroallergen: 29%
- Neither: 40%

Phenotypes Related to Response to Leukotriene Receptor Antagonists
Response to Montelukast Among Subgroups of Children 2 to 14 Years With Asthma

- Review of 2 clinical trials in children 2-14 yrs old
  - 2-5yr olds – 2 week run-in followed by 12 week double-blind placebo controlled trial
    - Montelukast 4mg once daily vs placebo
- No evidence that the effect of treatment with montelukast (percentage of asthma free days) was modified by any baseline variables:
  - Family history of asthma, smoking in household, asthma duration, concurrent ICS use, rhinitis, eczema, positive RAST test, eosinophilia, or baseline symptom frequency

Distinguishing Phenotypes of Childhood Wheeze & Cough Using Latent Class Analysis

- 1650 white children recruited in 1990 at age 0-5yrs
- 3 Phenotypes for Wheeze Identified
  - Atopic Persistent Wheeze – attacks with and without colds. Nocturnal symptoms present. Lower lung function and greater BHR.
  - Transient viral wheeze – attacks prior to 1st survey & subsided by 2nd survey. Only with colds. Normal lung function, but slightly greater BHR.

Spycher BD et al. ERJ 2008;31:974-981
Prednisolone Reduces Recurrent Wheezing after a First Wheezing Episode Associated with Rhinovirus Infection or Eczema

- 118 children followed for 1 year after initial wheezing episode treated in hospital with either oral prednisolone or placebo
- 37% experienced recurrent wheezing
- Prednisolone therapy decreased the probability of recurrent wheezing among children with eczema (HR 0.15) compared to those without eczema (HR 1.89) (p-value for interaction 0.007)

PACT: Study Overview

2 clinic visits

8 study encounters at 6-week intervals

All participants receive:
- morning diskus
- evening diskus
- evening capsule
- albuterol prn
- ICS fluticasone fluticasone placebo
- LTRA placebo placebo montelukast

285 children 6-14 years of age with uncontrolled mild-moderate asthma

FEV₁ ≥80% predicted

Methacholine PC₂₀ ≤12.5 mg/mL

Modified from Sorkness CA et al. J Allergy Clin Immunol 2007;119:64-72
PACT: Asthma Control Days

Percent Asthma Control Days

- Fluticasone: 64%
- Montelukast: 51%

Effect Size: Asthma Control Days/year

- Fluticasone: 234
- Montelukast: 186

48 MORE ACDs


p = 0.0011
Therapeutic Response Varies by Baseline FeNO Level

- Entire Cohort:
  - Mucosapone: 64%
  - Montelukast: 51%

- FeNO <25ppb:
  - Mucosapone: 55%
  - Montelukast: 57%

- FeNO ≥25ppb:
  - Mucosapone: 70%
  - Montelukast: 43%
Asthma Phenotypes

**CLINICAL FEATURES**
- Age of onset
- Triggers
  - Allergen
  - Infection
  - Exercise
- Atopic vs non-atopic
- Natural history
- Severity
- Exacerbation-prone
- Response to therapy

**PATHOPHYSIOLOGY**
- Pattern of inflammation
  - Eosinophilic
  - Neutrophilic
  - Pauci-granulocytic
- Biomarkers
  - eNO, EBC, ULTE$_4$
- Lung function
  - Normal vs abnormal
  - Reversible vs fixed obstruction (BD, steroids)
  - AHR

**GENOTYPES**
- Disease susceptibility
- Pharmacogenetics

**Asthma Is A Heterogeneous Disorder**
Strength and Direction of Associations Between Derived Phenotypes and Clinical Outcomes

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Asthma</th>
<th>Atopy</th>
<th>FEV\textsubscript{1}</th>
<th>FEF\textsubscript{25-75}</th>
<th>AHR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient Early</td>
<td>+</td>
<td>No Association</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Prolonged Early</td>
<td>++</td>
<td>No Association</td>
<td>↓</td>
<td>↓↓</td>
<td>↑</td>
</tr>
<tr>
<td>Intermediate Onset</td>
<td>++++</td>
<td>++</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↑↑</td>
</tr>
<tr>
<td>Late Onset</td>
<td>+++</td>
<td>++</td>
<td>↓</td>
<td>↓</td>
<td>↑↑</td>
</tr>
<tr>
<td>Persistent</td>
<td>+++++</td>
<td>+</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↑↑</td>
</tr>
</tbody>
</table>

Risk of Asthma Exacerbations at the Month 30 Visit Associated with Consistently VPC Asthma

Predictors of Future Exacerbations

Folate & Asthma

Blatter et al. Am J Respir Crit Care 2013;188: 12-17.
- Severe Intermittent Wheezing
MIST

1. 12 month R, DB, active control - 278 children (12-53 months)
2. 4 episodes wheezing last year - Pos. mAPI
   • 1 episode - OCS, ED, Urgent Care or Hosp.
3. Primary Outcome - exacerbation with OCS

<table>
<thead>
<tr>
<th>Run in: 2 weeks</th>
<th>Treatment phase: 52 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pbo run-in nightly + Albuterol PRN</strong></td>
<td><strong>Randomized Treatment Group</strong></td>
</tr>
<tr>
<td></td>
<td>Daily low dose Budesonide</td>
</tr>
<tr>
<td></td>
<td>Intermittent high dose Budesonide</td>
</tr>
</tbody>
</table>

MIST – Frequency of Exacerbations

1. Exacerbations 0.95/patient yr; p=0.6
MIST- Time to First Exacerbation

2. Similar time to first exacerbation, $p=0.87$

MIST- Frequency of Treatments for Respiratory Tract Illness

3. No difference in treatment failures or episode free days

MIST- Time to First Treatment for Respiratory Tract Illness

4. $H_t = 0.26$ cm avg. difference; $W_t = 0.16$ Kg avg. difference

Phenotypes Related to Response to Systemic Corticosteroids
Prednisolone Reduces Recurrent Wheezing after a First Wheezing Episode Associated with Rhinovirus Infection or Eczema

- 118 children followed for 1 yr after initial wheezing episode treated in hospital with either oral prednisolone or placebo
- 37% experienced recurrent wheezing
- Prednisolone therapy decreased the probability of recurrent wheezing
  - among children with rhinovirus (HR 0.19) but not with RSV (HR 2.12) or no virus (HR 2.03) (p-value for interaction 0.017)
  - among children with eczema (HR 0.15) compared to those without eczema (HR 1.89) (p-value for interaction 0.007)

Risk of Recurrent Wheezing

Censored cases marked with vertical lines.

Oral Prednisolone for Preschool Children with Acute Virus-Induced Wheezing

- 700 children 10-60 hospitalized for acute viral-induced wheezing
- Randomized, double-blind, placebo-controlled trial
- 5-day course of oral prednisolone (10 mg daily for children 10-24 months and 20 mg daily for older children) vs. placebo
- Primary outcome: duration of hospitalization

Panickar J et al. NEJM 2009;360:329-38
Oral Prednisolone for Preschool Children with Acute Virus-Induced Wheezing

- No significant difference in duration of hospitalization or time until ready for discharge

- 1/3 were first time wheezers

- Among the subgroup at high risk for asthma (API+), no difference in time to discharge between treatment groups

Panickar J et al. NEJM 2009;360:329-38