Effective Treatment in Pediatric Asthma and Wheezing

A Focus on Preschool Children

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  - AAAAI Annual Meeting Planning Committee

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  - Nothing to Disclose

- **Other Interests**
  - Nothing to Disclose
Learning Objectives

- Differentiate the child with transient wheeze from those likely to have persistent asthma later in childhood and adolescence.
- Outline optimal intervention strategies for each group of patients.
Heterogeneity and the Phenotypes of Wheezing in Preschool Children
## Patterns of Early Childhood Wheezing

<table>
<thead>
<tr>
<th>Pattern of Wheeze During 1st 6 Years</th>
<th>0-3 Years</th>
<th>4-6 Years</th>
<th>% of Cohort</th>
<th>Relative Risk of Wheeze at 16 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never Wheeze</td>
<td></td>
<td></td>
<td>51%</td>
<td>1.0</td>
</tr>
<tr>
<td>Transient Early Wheeze</td>
<td>✔</td>
<td></td>
<td>20%</td>
<td>1.3</td>
</tr>
<tr>
<td>Late-Onset Wheeze</td>
<td></td>
<td>✔</td>
<td>15%</td>
<td>3.1*</td>
</tr>
<tr>
<td>Persistent Wheeze</td>
<td>✔ ✔</td>
<td>✔ ✔</td>
<td>14%</td>
<td>3.8*</td>
</tr>
</tbody>
</table>

* *p* < 0.001 compared with never wheezers

Martinez FD et al NEJM 1995;332:133

Morgan WJ et al AJRCCM 2005;172:1253

Tucson Children’s Respiratory Study
ALSPAC longitudinal birth cohort of 6265 children

Identified six wheezing phenotypes

- Four phenotypes very similar to Tucson study
- Two additional sub-phenotypes identified: intermediate and prolonged early

All wheezing phenotypes were associated with physician-diagnosed asthma, lower lung function, and greater AHR by 8-9 years compared to never/infrequent wheeze phenotype

Asthma Predictive Index (API)

Identifies High Risk Children Ages 2-3 Years

≥ 4 wheezing episodes in the past year (at least one must be MD diagnosed)

PLUS

One major criterion
- Parent with MD asthma
- MD atopic dermatitis
- Aeroallergen sensitivity

OR

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

**Asthma Predictive Index (API)**

<table>
<thead>
<tr>
<th>Active Asthma</th>
<th>OR (95% CI)</th>
<th>Positive Predictive Value (%)</th>
<th>Negative Predictive Value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At Yr 6</td>
<td>9.8 (5.6-17.2)</td>
<td>47.5%</td>
<td>91.6%</td>
</tr>
<tr>
<td>At Yr 13</td>
<td>5.7 (2.8-11.6)</td>
<td>51.5%</td>
<td>84.2%</td>
</tr>
</tbody>
</table>

Early Life Wheezing Phenotypes Correlate with Wheezing at 16 Years

1. Relative Risk for Wheeze at 16 years of age

<table>
<thead>
<tr>
<th>Wheeze Pattern Before 6 years of age</th>
<th>Never Wheeze</th>
<th>Transient</th>
<th>Late Onset</th>
<th>Persistent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative Risk for Wheeze at 16 years</td>
<td>1</td>
<td>1.3</td>
<td>3.1</td>
<td>3.8</td>
</tr>
</tbody>
</table>

* p<0.001 compared with never wheezers

Tucson Children’s Respiratory Study

Morgan WJ et al AJRCCM 2005;172:1253
Phenotypes of Atopy in Relation to Asthma

Manchester Allergy and Asthma Study – birth cohort with follow up at 1, 3, 5 and 8 yrs (n=1053)

At age 8 yrs
- 18% had current wheeze
- 13.7% were persistent wheezers
- 8.1% had asthma (symptoms + positive MCH)
- 38.9% atopic (positive SPT or sIgE)

Latent class analysis of sensitization state
- 2 class model (atopic or non-atopic)
- 5 class model (better captured the underlying structure of the data)

Simpson A et al. Am J Respir Crit Care Med 2010;181:1200-1206
Phenotypes of Atopy in Relation to Asthma

- 2 class model
  - 26.6% atopic vs. 73.4% nonatopic

- 5 class model
  - Non-dust mite atopic vulnerability (9.5%)
  - Dust mite atopic vulnerability (4.5%)
  - Multiple late atopic vulnerability (16.2%)
  - Multiple early atopic vulnerability (10.6%)
  - No latent vulnerability (59.2%)

- Of the 440 children classified as atopic ever (2 class), 61 classified as no latent vulnerability (5 class)

- Of the 322 children classified as atopic at 8 yrs (2 class), 36 classified as no latent vulnerability (5 class)

Simpson A et al. Am J Respir Crit Care Med 2010;181:1200-1206
Phenotypes of Atopy in Relation to Asthma

Relationships between atopy defined conventionally (yes/no), novel latent classes (2 and 5 class models), and clinical phenotypes associated with asthma (current wheeze, persistent wheeze, symptomatic AHR, hospital admission)

Simpson A et al. Am J Respir Crit Care Med 2010;181:1200-1206
Predicting vs. Diagnosing Asthma in Young Children

- Multiple phenotypes/patterns of early childhood wheeze described
- Common features across prediction models for persistent wheeze/asthma
  - All have relatively poor prediction capability (PPV <80%, sensitivity <50%)
  - Repeated wheezing episodes
  - Atopic features
    - Sensitization to multiple allergens early in life
- Thus, most of these models do not allow for the precise diagnosis of asthma
Managing Asthma among Preschool Children is Challenging

- A heterogeneous disorder with many phenotypic and variable expressions during early childhood
  - Cross-over between phenotypes
  - Compared to older school-age children: potential differences in disease pathophysiology and in the type of background airway inflammation

- Selection of asthma therapy is complicated by:
  - Lack of objective measurements and biomarkers
  - Many of the guideline recommendations are based on extrapolation from findings from the school-age population
Factors Contributing to Heterogeneity in Therapeutic Responses

- Trigger
- Gender
- Ethnicity
- Airway Inflammation/Pathophysiology
- Natural History
- Severity/Morbidity
- Age of Onset
- Atopy
- Genotype

Therapeutic Response
3 y/o male with history of asthma for the past year
- Need for albuterol treatments: 3 days/wk
- Over the past yr: 2 ED visits
- Meds: albuterol PRN, prednisolone during exacerbations (4x in past yr)
- Past Medical History: eczema since 4m/o
- Family History: mother has asthma
- PE: normal exam; Skin testing + for cat

Questions:
- *How should we classify his disease severity?*
- *Should we recommend daily treatment with an asthma controller medication? If yes, which?*
<table>
<thead>
<tr>
<th>Components of Severity</th>
<th>Classification of Asthma Severity (0-4 years of age)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intermittent</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
</tr>
<tr>
<td><strong>Impairment</strong></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>≤2 days/week</td>
</tr>
<tr>
<td>Nighttime Awakenings</td>
<td>0</td>
</tr>
<tr>
<td>Short-acting beta₂-agonist use for symptom control</td>
<td>≤2 days/week</td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>None</td>
</tr>
<tr>
<td><strong>Risk</strong></td>
<td></td>
</tr>
<tr>
<td>Exacerbations requiring oral corticosteroids</td>
<td>0-1/year</td>
</tr>
</tbody>
</table>

Stepwise Approach for Managing Asthma in Children 0-4 Years of Age

Open questions regarding the optimal step-2 therapy among preschool children:

- Evidence A for daily inhaled-corticosteroids (ICS), but:
  - Is daily low-dose ICS better than daily montelukast?
    - No randomized, double-blind trials in preschool children
  - What is the role of as-needed ICS + albuterol?

- Is there a “BEST” choice for step 2 asthma care? If so, for which patients?
  - A broad definition of asthma: wide range of phenotypes

Severe Intermittent (Episodic) Wheezing Phenotype

- Intermittent disease is common
  - Acute exacerbations of lower respiratory tract illnesses (LRTI) usually triggered by viral URIs
  - Many children have minimal (or no) symptoms between these acute episodes

- Disease severity is NOT mild
  - Severe morbidity during acute episodes:
    - 50% more ambulatory visits, ~2x ED visits, and ~3x hospitalization relative to school age children

Patient #2

- 3 y/o boy with recurrent (3 in past yr) episodes of wheezing in the context of URIs. He has had **minimal respiratory symptoms between these illnesses**
- One ED visit over the past year
- Meds: albuterol PRN, prednisolone during significant exacerbations (3 courses over the past year)
- PMH: eczema since 4m/o
- FH: mother has asthma
- PE: normal exam; skin tests are negative

**Question:**

- Should we recommend daily treatment with **ICS**?
Challenges Associated with Daily ICS

- Daily ICS therapy reduces the rate of severe exacerbations by approximately 40%, but does not completely prevent the exacerbations\(^1\)

- Suboptimal adherence: 40-45% adherence in a clinical trial that measured adherence\(^2\)

- Small but significant effect of ICS on reducing linear growth in preschool-aged children:
  - May be only partially reversed after discontinuation of ICS\(^3\)

- Additional strategies that effectively prevent/attenuate these exacerbations are needed

Intermittent ICS in Preschool Children Reduces Risk of Severe Exacerbation

**Intervention vs control**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A Pre-emptive ICS vs pre-emptive LTRA</strong></td>
<td></td>
</tr>
<tr>
<td>Bacharier (2008)</td>
<td>0.82 (0.59-1.15)</td>
</tr>
<tr>
<td><strong>B Pre-emptive ICS vs placebo</strong></td>
<td></td>
</tr>
<tr>
<td>Bacharier (2008)</td>
<td></td>
</tr>
<tr>
<td>Ducharme (2009)</td>
<td></td>
</tr>
<tr>
<td>Svedmyr (1999)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>0.68 (0.53-0.86)</td>
</tr>
<tr>
<td><strong>B Pre-emptive LTRA vs placebo</strong></td>
<td></td>
</tr>
<tr>
<td>Bacharier (2008)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.85 (0.61-1.18)</td>
</tr>
</tbody>
</table>

Daily or Intermittent Budesonide in Preschool Children with Recurrent Wheezing

- N=278; 12-53 months
- Number of wheezing episodes in the prior year: ≥4 or ≥3 with at least 3 months of asthma controller therapy
- Positive modified Asthma Predictive Index
- ≥1 severe exacerbation requiring systemic corticosteroids, urgent unscheduled, emergent visit or hospitalization in prior year
- No evidence of persistent symptomatic asthma during 2 week run-in on placebo

### Treatment Phase: 52 Weeks

<table>
<thead>
<tr>
<th>Randomized Treatment Group</th>
<th>Nightly EXCEPT During Respiratory Tract Illnesses</th>
<th>During Respiratory Tract Illnesses ONLY for 7 days</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Daily low-dose budesonide</strong></td>
<td>0.5 mg PM</td>
<td>Placebo AM 0.5 mg PM</td>
</tr>
<tr>
<td><strong>Intermittent high-dose budesonide</strong></td>
<td>Placebo PM</td>
<td>1.0 mg AM 1.0 mg PM</td>
</tr>
</tbody>
</table>

Zeiger RS et al. NEJM 2011;365:1990-2001
No Significant Differences Between Intermittent and Daily ICS

- No difference in
  - Time to 1st exacerbation
  - # of RTIs
  - % of RTIs requiring oral steroids (25%)
  - Severity of symptoms during RTI
  - Health care utilization
  - Growth

Intermittent group used less budesonide during trial (150mg vs 46mg)

Zeiger RS et al. NEJM 2011;365:1990-2001
Caveats to Alternative Non-Daily ICS Use

- Remember the efficacy and preferred position of daily ICS is based on a multitude of well-designed randomized trials over the entire asthma spectrum.

- Alternative strategies of ICS use are based on a handful of studies over the past few years.

- However, consistent demonstration of populations with mild asthma who do not appear to benefit with daily ICS over intermittent ICS.

- **Patient education** essential to help parents understand early signs of episodes and need to begin therapy.
Antibiotic use in wheezing illnesses is not recommended by national guidelines

However, antibiotics are commonly prescribed in clinical practice (1/6 US ambulatory visits for asthma)*

Viral infections are the most common trigger for acute wheeze, but bacteria have an emerging role in illness pathogenesis

Macrolides antibiotics have shown to provide benefits in other inflammatory airway diseases (e.g., CF)

Anti-bacterial and anti-inflammatory properties

Would early administration of azithromycin, started prior to the onset of severe lower respiratory tract symptoms, in preschool children with history of recurrent severe lower respiratory tract illnesses, can prevent the progression of these episodes?
Research

Original Investigation

Early Administration of Azithromycin and Prevention of Severe Lower Respiratory Tract Illnesses in Preschool Children With a History of Such Illnesses
A Randomized Clinical Trial

Leonard B. Bacharier, MD; Theresa W. Guilbert, MD; David T. Mauger, PhD; Susan Boehmer, MA; Avraham Beigelman, MD; Anne M. Fitzpatrick, PhD; Daniel J. Jackson, MD; Sachin N. Baxi, MD; Mindy Benson, MSN, RN; Carey-Ann D. Burnham, PhD; Michael Cabana, MD; Mario Castro, MD, MPH; James F. Chmiel, MD, MPH; Ronina Covar, MD; Michael Daines, MD; Jonathan M. Gaffin, MD, MMSc; Deborah Ann Gentile, MD; Fernando Holguín, MD; Elliot Israel, MD; H. William Kelly, PharmD; Stephen C. Lazarus, MD; Robert F. Lemanske Jr, MD; Ngoc Ly, MD; Kelley Meade, MD; Wayne Morgan, MD; James Moy, MD; Todd Olin, MD; Stephen P. Peters, MD; Wanda Phipatanakul, MD, MS; Jacqueline A. Pongracic, MD; Hengameh H. Raissy, PharmD; Kristie Ross, MD; William J. Sheehan, MD; Christine Sorkness, PharmD; Stanley J. Szefler, MD; W. Gerald Teague, MD; Shannon Thye, MD; Fernando D. Martinez, MD; for the National Heart, Lung, and Blood Institute’s AsthmaNet
Study Design & Protocol Treatments

- Randomized, double-blind, parallel group trial
- Azithromycin (AZM) 12mg/kg (maximum 500mg/d) or Placebo once daily for 5 days
  - Begin at onset of each RTI when patient developed signs or symptoms that parents defined as the patient’s usual starting point before development of LRT symptoms
  - Albuterol 4 times daily for 48 hours and as needed
- Duration - 52 weeks (3 treated RTIs), extended to 78 weeks (4 treated RTIs)

Primary Outcome

- The number of respiratory tract illnesses (RTIs) not progressing to severe lower respiratory tract illness (LRTI)
  - >6 albuterol treatments over a 24 hour period, OR
  - If symptoms are more than mild and not improved after 3 albuterol treatments in 1 hour, OR
  - Require albuterol more often than every 4 hours on 2 consecutive occasions, OR
  - Moderate-severe cough or wheeze for ≥5 days during which study therapy was used, OR
  - Need for acute/urgent/emergency care for respiratory symptoms, OR
  - Physician discretion

Reduction in Risk of Progression to Severe LRTI

**PLACEBO**

1st RTI
- 220
- 22 Severe LRTI

2nd RTI
- 147
- 19 Severe LRTI

3rd RTI
- 74
- 9 Severe LRTI

4th RTI
- 23
- 7 Severe LRTI

**AZM**

1st RTI
- 223
- 16 Severe LRTI

2nd RTI
- 146
- 13 Severe LRTI

3rd RTI
- 78
- 5 Severe LRTI

4th RTI
- 26
- 1 Severe LRTI

<table>
<thead>
<tr>
<th>No. of treated RTIs</th>
<th>223</th>
<th>220</th>
<th>146</th>
<th>147</th>
<th>78</th>
<th>74</th>
<th>26</th>
<th>23</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of SLRTIs</td>
<td>16</td>
<td>22</td>
<td>13</td>
<td>19</td>
<td>5</td>
<td>9</td>
<td>1</td>
<td>7</td>
</tr>
</tbody>
</table>

*Adjusted for study site, age, modified API status, season during which the RTI occurred, and whether the child enrolled before or after the study was extended to 78 weeks.

### Subgroup Analyses

<table>
<thead>
<tr>
<th></th>
<th>Azithromycin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>No. of RTIs</td>
</tr>
<tr>
<td>Overall</td>
<td>223</td>
<td>473</td>
</tr>
<tr>
<td><strong>IL-8 genotype (rs4073)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TT</td>
<td>41</td>
<td>80</td>
</tr>
<tr>
<td>AA/AT</td>
<td>82</td>
<td>178</td>
</tr>
<tr>
<td>Nasal virus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other virus b</td>
<td>46</td>
<td>119</td>
</tr>
<tr>
<td>Rhinovirus or enterovirus</td>
<td>123</td>
<td>247</td>
</tr>
<tr>
<td>No virus</td>
<td>39</td>
<td>77</td>
</tr>
<tr>
<td>Age group, mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>43-71</td>
<td>108</td>
<td>213</td>
</tr>
<tr>
<td>12-42</td>
<td>115</td>
<td>260</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Girls</td>
<td>84</td>
<td>172</td>
</tr>
<tr>
<td>Boys</td>
<td>139</td>
<td>301</td>
</tr>
<tr>
<td>mAPI status</td>
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</tr>
<tr>
<td>Positive c</td>
<td>104</td>
<td>221</td>
</tr>
<tr>
<td>Negative</td>
<td>119</td>
<td>252</td>
</tr>
<tr>
<td>Season</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sept-Nov</td>
<td>77</td>
<td>163</td>
</tr>
<tr>
<td>Dec-Feb</td>
<td>62</td>
<td>145</td>
</tr>
<tr>
<td>Mar-May</td>
<td>31</td>
<td>81</td>
</tr>
<tr>
<td>June-Aug</td>
<td>53</td>
<td>84</td>
</tr>
</tbody>
</table>

Reduction in Albuterol Use During Severe LRTIs

Azithromycin, started at the earliest signs of RTIs, was effective in reducing the risk of experiencing episodes of severe lower respiratory tract illnesses. Symptoms significantly less severe. No difference in response by API status. Well-tolerated with low rates of adverse effects.
Take-home Messages: Step 2 therapy in preschool children with persistent asthma

- A differential response in ~ ¾ of children.
  - Aeroallergen sensitization strongly predicts differential Step 2 treatment response in favor of daily ICS

- Preschool children with persistent asthma should be tested for aeroallergen sensitization:
  - If positive: Daily ICS is the preferred initial controller
  - A child with no sensitizations: Unknown
    - The choice of controller should be determined based on parent and clinician preferences

- If the child does not respond to the controller, explore other Step 2 therapies before moving to Step 3 therapies.
Take-home Messages: Preschool children with severe episodic wheeze

- A therapeutic trial of azithromycin, early in the course of respiratory tract illnesses (RTI), should be considered to prevent progression to severe lower-RTI and a need for OCS
  - Children who demonstrate an azithromycin response (less severe episodes of RTI) may benefit from repeating azithromycin with subsequent illnesses
  - Concern of antimicrobial resistance – monitor frequency of RTIs prompting azithromycin use and response to the intervention
    - More information is needed regarding the development of antibiotic resistant pathogens with this strategy
  - Unknown: efficacy of this prevention approach compared to the efficacy of daily (or intermittent) ICS therapy or role in patients already receiving controller therapy
Heterogeneity of early life wheezing adds complexity to asthma diagnosis and treatment
- Atopy as a dominant risk factor for disease persistence

Controller therapy for mild asthma
- ICS as the preferred controller
- Atopy as a strong predictor of ICS response

Emerging approaches for severe recurrent wheezing
- Episodic vs intermittent approaches effective, especially among atopic children
- Azithromycin early in development of RTI
  - Not just for atopic children