Management of Preschool Recurrent Wheezing and Asthma: A Phenotype-Based Approach

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Disclosures

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- Washington University

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- JACI – Associate Editor
- GINA – Science Committee

Gifts
- Nothing to Disclose

Other Interests
- Nothing to Disclose
Learning Objectives

- Describe the heterogeneity in the development & presentation of asthma in preschool children
- Outline optimal intervention strategies for preschool children with
  - Mild persistent asthma
  - Severe episodic wheezing
- Develop strategies for phenotype directed therapy in preschool children
<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

Modified Asthma Predictive Index (mAPI)

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>

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 guideline recommendations are based on extrapolation of findings from school-age children
Patient #1

- 3 y/o male with history of asthma for the past year
- Albuterol used for rescue 3 days/wk
- Over the past yr 2 ED visits for exacerbations
- 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

**Question:**
- *Is daily treatment with an asthma controller indicated? If so, which one?*
### Stepwise Approach – Pharmacotherapy (children ≤5 years)

#### PREFERRED CONTROLLER CHOICE

- **STEP 1**: Daily low dose ICS
  - **Leukotriene receptor antagonist (LTRA)**
  - **Intermittent ICS**

- **STEP 2**: As-needed short-acting beta$_2$-agonist (all children)

- **STEP 3**: Double 'low dose' ICS
  - **Low dose ICS + LTRA**
  - **Add LTRA Inc. ICS frequency**
  - **Add intermittent ICS**

- **STEP 4**: Continue controller & refer for specialist assessment

#### Other controller options

**CONSIDER THIS STEP FOR CHILDREN WITH:**

- **Infrequent viral wheezing and no or few interval symptoms**
  - Symptom pattern consistent with asthma and asthma symptoms not well-controlled, or ≥3 exacerbations per year
  - Symptom pattern not consistent with asthma but wheezing episodes occur frequently, e.g. every 6–8 weeks. Give diagnostic trial for 3 months.

- **Asthma diagnosis, and not well-controlled on low dose ICS**

- **First check diagnosis, inhaler skills, adherence, exposures**

- **Not well-controlled on double ICS**
Stepwise Approach – Pharmacotherapy (children ≤5 years)

**Open questions regarding 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?
**Individualized Therapy For Asthma in Toddlers (INFANT)**

300 children 12-59 mo necessitating treatment with Step 2 controller

### Run-In (2-8 weeks)
- **Placebo or Active Therapy**
  - Daily ICS
  - Placebo LTRA
  - As needed placebo ICS

### 16 weeks
- Placebo ICS
- Daily LTRA
- As needed placebo ICS

### 16 weeks
- Placebo ICS
- Placebo LTRA
- As needed active ICS

**Blood and urine sample collection for predictor analyses**

- Inhaled fluticasone (44 mcg/actuation) 2 inhalations twice daily
- Oral montelukast (4 mg) once daily HS
- As-needed albuterol plus inhaled fluticasone (44 mcg/actuation) 2 inhalations for every 2 inhalations albuterol

Primary Outcome: Differential Response

Differential response was a hierarchical composite variable of asthma control based on (in order of importance):

- **Risk domain**
  - Time from the start of the treatment period to an asthma exacerbation that requires systemic corticosteroids

- **Impairment domain**
  - Annualized number of Asthma Control Days within that treatment period

Primary Outcome Analysis Plan: 3 Stages

- Each child was identified as a **differential responder** if:
  - Time to an exacerbation was *at least 4 weeks longer*
  - Number of annualized asthma control days was *at least 31 days more*

- Rank order of the treatments from **best** to **worst** was determined for each differential treatment responder

- Among differential treatment responders, assessed 3 pre-specified primary predictors of differential response:
  - **Allergic sensitization, sex, previous exacerbation**

Which Step 2 Asthma Therapy is **BEST** for the Greatest Number of Children?

Hierarchical composite variable of time to exacerbations and number of asthma control days

**Differential response between at least two treatments was observed in**

**74% (170 of 230)**

of children who provided usable data for analysis

26% of children (60 of 230) did not have a differential response

Are there baseline characteristics that predict which treatment will produce the best response (for the greatest number of children)?

Aeroallergen sensitization & blood eosinophils ≥300/µL (but not exacerbation history or sex) associated with differential response favoring daily ICS

• In children with aeroallergen sensitization or eosinophilia: start with ICS first.

• In children who are not sensitized to aeroallergens or without eosinophilia: can choose any of these treatments.

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 3 episodes of wheezing in the context of URIs in the past year. He has had minimal/no 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 4 m/o

- FH: mother has asthma

- PE: normal exam; skin tests are negative

**Question:**

- *Should we recommend daily treatment with ICS?*
Phenotype: Positive Asthma Predictive Index
Modified Asthma Predictive Index (mAPI)

**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

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

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Treatment Phase:  
↓ Exacerbations  
(57.4/100 child-yrs vs 89.4/100 child-yrs)  
↓ Supplemental medications (ICS and LTRA)  
= bronchodilator use and unscheduled visits

Observation Phase:  
= Exacerbations  
= Supplemental medications (ICS and LTRA)  
= Bronchodilator use and unscheduled visits

EFD: No cough or wheeze, unscheduled clinic, urgent care, ED or hospital visits; no use of asthma medications

Guilbert TW et al. NEJM 2006;354:1985-97
### PEAK - Heterogeneity of ICS Response Within the mAPI+ Population

<table>
<thead>
<tr>
<th>Stratifying Variable</th>
<th>Percentage of Episode-Free Days</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ICS Mean (95% CI)</td>
<td>Placebo Mean (95% CI)</td>
<td>Difference (95% CI)</td>
<td>P-value (ICS vs Placebo)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>93 (92, 95)</td>
<td>86 (83, 89)</td>
<td>7.3 (3.9, 11.1)</td>
<td>0.0005</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>92 (89, 94)</td>
<td>92 (89, 94)</td>
<td>0.1 (-3.4, 3.5)</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>93 (91, 95)</td>
<td>84 (80, 88)</td>
<td>9.1 (4.8, 13.9)</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>Non-Caucasian</td>
<td>92 (89, 94)</td>
<td>93 (91, 94)</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>92 (90, 94)</td>
<td>84 (79, 87)</td>
<td>8.6 (4.2, 13.2)</td>
<td>0.0009</td>
<td></td>
</tr>
<tr>
<td>Run-In EFD ≥80%</td>
<td>93 (91, 95)</td>
<td>93 (91, 95)</td>
<td>0.0 (-2.5, 2.5)</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>ED/Hospitalization History</td>
<td>95 (93, 96)</td>
<td>87 (83, 90)</td>
<td>7.7 (3.9, 11.6)</td>
<td>0.0004</td>
<td></td>
</tr>
<tr>
<td>No ED/Hospitalization History</td>
<td>90 (87, 92)</td>
<td>91 (89, 93)</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>93 (91, 94)</td>
<td>86 (83, 89)</td>
<td>6.5 (3.2, 10.0)</td>
<td>0.0027</td>
<td></td>
</tr>
<tr>
<td>Negative Aeroallergen Skin Test</td>
<td>93 (90, 95)</td>
<td>92 (89, 94)</td>
<td>0.9 (-2.5, 4.4)</td>
<td>0.6</td>
<td></td>
</tr>
</tbody>
</table>

# PEAK - Heterogeneity of ICS Response Within the mAPI+ Population

<table>
<thead>
<tr>
<th>Stratifying Variable</th>
<th>Number of Prednisolone Bursts</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ICS Mean (95% CI)</td>
<td>Placebo Mean (95% CI)</td>
<td>Relative Rate (95% CI)</td>
<td>P-value (ICS vs Placebo)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.1 (0.9, 1.4)</td>
<td>1.8 (1.5, 2.2)</td>
<td>0.6 (0.5, 0.8)</td>
<td>0.0009</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.6 (1.2, 1.9)</td>
<td>1.4 (1.1, 1.7)</td>
<td>1.2 (0.8, 1.6)</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>1.4 (1.1, 1.7)</td>
<td>2.2 (1.9, 2.7)</td>
<td>0.6 (0.5, 0.8)</td>
<td>0.0004</td>
<td></td>
</tr>
<tr>
<td>Non-Caucasian</td>
<td>1.3 (1.0, 1.6)</td>
<td>1.1 (0.9, 1.4)</td>
<td>1.2 (0.8, 1.7)</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>ED/Hospitalization History</td>
<td>1.2 (0.98, 1.6)</td>
<td>2.3 (1.9, 2.8)</td>
<td>0.5 (0.4, 0.7)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>No ED/Hospitalization History</td>
<td>1.4 (1.1, 1.8)</td>
<td>1.1 (0.8, 1.3)</td>
<td>1.3 (0.97, 1.8)</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>≥1 Positive Aeroallergen Skin Test</td>
<td>1.3 (1.0, 1.5)</td>
<td>2.1 (1.7, 2.4)</td>
<td>0.6 (0.5, 0.8)</td>
<td>0.0003</td>
<td></td>
</tr>
<tr>
<td>Negative Aeroallergen Skin Test</td>
<td>1.4 (1.1, 1.8)</td>
<td>1.2 (0.9, 1.5)</td>
<td>1.2 (0.8, 1.7)</td>
<td>0.4</td>
<td></td>
</tr>
</tbody>
</table>

Challenges Associated with Daily ICS

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

- Suboptimal real world 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\(^3\)

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

Intermittent ICS in Preschool Children Reduce Risk of Severe Exacerbation

Subgroup analysis of children with intermittent asthma or viral-triggered wheezing showed reduced risk of exacerbation with preemptive high-dose intermittent ICS compared to placebo

(5 studies, N=422, RR 0.65, 95% CI 0.51-0.81, NNT=6)
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></th>
<th>Nightly EXCEPT During Respiratory Tract Illnesses</th>
<th>During Respiratory Tract Illnesses ONLY for 7 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized Treatment Group</td>
<td>0.5 mg PM</td>
<td>Placebo AM 0.5 mg PM</td>
</tr>
<tr>
<td><strong>Daily low-dose budesonide</strong></td>
<td></td>
<td></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
  - Albuterol use
  - 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
Potential Role of Macrolides for the Prevention of Acute Wheezing Illnesses in Preschool Children

- 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 and exacerbation risk
- Macrolides antibiotics have been 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, prevent the progression of these episodes?
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)
Study Population

- 12-71 months of age
- Recurrent clinically significant wheezing* in the past year (any of the following)
  - ≥3 episodes, ≥1 of which was clinically significant*; OR
  - ≥2 clinically significant* episodes; OR
  - ≥4 months of daily controller therapy AND ≥1 clinically significant* episode.

*Clinically significant episode: requiring any of the following: (1) systemic corticosteroids (oral or injectable), (2) unscheduled physician office, urgent care or ED visit, or (3) hospitalization.

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**

<table>
<thead>
<tr>
<th>1st RTI</th>
<th>2nd RTI</th>
<th>3rd RTI</th>
<th>4th RTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>220</td>
<td>147</td>
<td>74</td>
<td>23</td>
</tr>
<tr>
<td>22 Severe LRTI</td>
<td>19 Severe LRTI</td>
<td>9 Severe LRTI</td>
<td>7 Severe LRTI</td>
</tr>
</tbody>
</table>

**AZM**

<table>
<thead>
<tr>
<th>1st RTI</th>
<th>2nd RTI</th>
<th>3rd RTI</th>
<th>4th RTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>223</td>
<td>146</td>
<td>78</td>
<td>26</td>
</tr>
<tr>
<td>16 Severe LRTI</td>
<td>13 Severe LRTI</td>
<td>5 Severe LRTI</td>
<td>1 Severe LRTI</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>
<th>Favors Azithromycin</th>
<th>Favors Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>No. of RTIs</td>
<td>No. of Severe LRTIs</td>
<td>No. of Patients</td>
</tr>
<tr>
<td>Overall</td>
<td>223</td>
<td>473</td>
<td>35</td>
<td>220</td>
</tr>
<tr>
<td><em>IL-8 genotype (rs4073)</em>&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
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<tr>
<td>TT</td>
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<td>AA/AT</td>
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<td>Nasal virus</td>
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<tr>
<td>Other virus&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Rhinovirus or enterovirus</td>
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<td>No virus</td>
<td>39</td>
<td>77</td>
<td>5</td>
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<td>Age group, mo</td>
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<td>43-71</td>
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<td>12-42</td>
<td>115</td>
<td>260</td>
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<tr>
<td>Sex</td>
<td></td>
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</tr>
<tr>
<td>Girls</td>
<td>84</td>
<td>172</td>
<td>8</td>
<td>85</td>
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<tr>
<td>Boys</td>
<td>139</td>
<td>301</td>
<td>27</td>
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<tr>
<td>mAPI status</td>
<td></td>
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</tr>
<tr>
<td>Positive&lt;sup&gt;c&lt;/sup&gt;</td>
<td>104</td>
<td>221</td>
<td>19</td>
<td>104</td>
</tr>
<tr>
<td>Negative</td>
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<td>252</td>
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<tr>
<td>Season</td>
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<tr>
<td>Sept-Nov</td>
<td>77</td>
<td>163</td>
<td>20</td>
<td>75</td>
</tr>
<tr>
<td>Dec-Feb</td>
<td>62</td>
<td>145</td>
<td>6</td>
<td>53</td>
</tr>
<tr>
<td>Mar-May</td>
<td>31</td>
<td>81</td>
<td>5</td>
<td>43</td>
</tr>
<tr>
<td>June-Aug</td>
<td>53</td>
<td>84</td>
<td>4</td>
<td>49</td>
</tr>
</tbody>
</table>

[Diagram showing hazard ratio (95% CI)]

*AsthmaNetResearch.org*
Development of Azithromycin Resistance

81 subjects provided deep oropharyngeal samples at baseline and at final visit (≥14 days after final dose of study medication)

<table>
<thead>
<tr>
<th></th>
<th>Number (% of Subjects with an AZM-Resistant Organism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AZM-treated</td>
</tr>
<tr>
<td>Baseline</td>
<td>5/41 (12.2)</td>
</tr>
<tr>
<td>Final visit</td>
<td>8/40 (20.0)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Number (% of Subjects with Acquisition of an AZM-Resistant Organism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AZM-treated (N=36)</td>
</tr>
<tr>
<td></td>
<td>6 (16.7)</td>
</tr>
</tbody>
</table>

Summary

- Azithromycin, started at the earliest signs of RTIs, was effective in reducing the risk of experiencing episodes of severe lower respiratory tract illnesses
- No difference in response by API status
- Well-tolerated with low rates of adverse effects

Preschool Asthma Phenotypes and Treatment Options

Intermittent Disease

- mAPI NEGATIVE
  - Early Azithromycin
  - Intermittent Hi Dose ICS

- mAPI POSITIVE
  - Boys, Caucasian, More Symptoms, ED/Hosp, Sensitized
  - Daily ICS

Persistent Asthma

- Eosinophilia &/or Sensitized
  - Daily ICS

- No Eosinophilia or Sensitization
  - Daily ICS or Daily LTRA or Intermittent ICS
Take-home Messages: Step 2 therapy in preschool children with persistent asthma

- A differential response in ~ ¾ of children
  - **Aeroallergen sensitization &/or peripheral eosinophilia** strongly predict differential Step 2 treatment response in favor of daily ICS

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

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

- A trial of intermittent high dose ICS should be considered (particularly among mAPI positive children)
- 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 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 (AZM) prevention approach compared to the efficacy of daily (or intermittent) ICS therapy or role in patients already receiving controller therapy
Summary

- Heterogeneity of early life wheezing adds complexity to asthma diagnosis and treatment
- Controller therapy for mild persistent 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