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

**APRIL-** Azithro for Preventing the development of upper Respiratory tract Illness into Lower respiratory tract symptoms in children
Introduction

- Episodes of lower respiratory tract illness (LRTI) are common among preschoolers
  - Up to 14% to 26% of preschoolers present with recurrent wheezing during the first 6 years of life\textsuperscript{1,2}
- Substantial morbidity
  - Many are diagnosed with asthma\textsuperscript{3}
    - 20.9% seek emergency department care
    - 6.5% are hospitalized each year
Introduction

- The etiology of these LRTI has not been completely elucidated
  - Initial reports showed detection of respiratory viruses\(^4,5\)
  - Bacteria have more recently been detected.\(^6,7\)
    - Antibiotics have been shown to improve:
      - symptom scores\(^8\)
      - neutrophilic airway inflammation\(^9\)
Methods - Participants

- Eligible participants:
  - 12-71 month olds with **recurrent severe wheezing** in the context of clinically significant LRTIs that required systemic steroids and unscheduled medical care.

- Exclusion criteria:
  - > 4 courses of systemic corticosteroids in the past 12 months
  - > 1 hospitalization in the past 12 months
  - Use of long-term controllers for asthma for more than 8 months in the past 12 months
  - Receive systemic corticosteroids within the last 2 weeks
  - Received antibiotics for any indication in the last 4 weeks
  - ≥ 2 nocturnal awakenings in the last 2 weeks
  - Higher than NAEPP/EPR3 Step 2 therapy
Methods - Study Design

Episodic Therapy at Early Signs of RTI

Parent-Initiated therapy using a personalized Action Plan defining the child-specific early signs of a RTI

- Azithromycin 12 mg/kg/day + Albuterol 4 times daily + PRN
- Placebo + Albuterol 4 times daily + PRN

RTI Progresses to Severe Lower Respiratory Tract Illness when ANY of the following criteria are achieved:

a. Having symptoms that are more than mild after 3 albuterol treatments in 1 hour, OR
b. Requiring albuterol treatment more than once every 4 hours, OR
c. Requiring more than 6 albuterol treatments over a 24 hour period, OR
d. Having moderate-severe cough or wheeze for ≥ 5 days during which therapy was used.
Methods- Study Design

- The trial began in April 2011 with a follow-up period of 52 weeks
  - Study treatment used during a maximum of 3 treated RTIs not progressing to severe LRTI.
- In June 2012 the follow-up period was extended to 78 weeks for those participating in the study at that time (n = 164) or enrolled thereafter (n = 292)
  - Increased number of treated RTIs not progressing to a severe LRTI from 3 to 4.
Methods - Study Design

**Core Procedures**
- Short Physical Exam
- Height and Weight
- Review Diary Adherence
- Review Action Plan
### Methods

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated Respiratory Tract Illness (RTI)</td>
<td>Respiratory Tract Illness (RTI) for which the participant had opportunity to take more than one dose of study medication before meeting Study Failure criteria. Illnesses that progressed to Study Failure on the same day were not counted as Treated RTI. Note: Inclusion in the primary analysis was not dependent on actually taking any study medication, only on having the opportunity to take more than one dose.</td>
</tr>
<tr>
<td>Severe Lower Respiratory Tract Illness (SLRTI)</td>
<td>Clinically significant lower respiratory tract symptoms (also called APRIL Treatment Failure) occurring within 14 days of the start of a treated RTI.</td>
</tr>
<tr>
<td>Early termination</td>
<td>Study Failure occurring more than 14 days after the start of a treated RTI or on the same day that study medication was initiated.</td>
</tr>
<tr>
<td>End of follow-up</td>
<td>The end of the study follow-up period (either 52 or 78 weeks depending on whether it occurred prior to the protocol revision) or the occurrence of a 4th Treated RTI that did not progress to SLRTI.</td>
</tr>
<tr>
<td>Drop out</td>
<td>Lost to follow-up or withdrew consent (voluntarily or by study physician discretion) prior to the occurrence of Study Failure, 4th Treated RTI or reaching the end of the follow-up period.</td>
</tr>
</tbody>
</table>
Methods - Outcome Measures

- **Primary outcome measure**: the number of treated RTIs not progressing to severe LRTI
  - If the study physician concurred that the patient was experiencing LRTI the primary end point was reached.

- **Secondary pre-specified outcome measures**:
  - Number of urgent medical visits
  - Measures of disease impairment reflected by symptom severity and albuterol use during treated.
  - Rate of study failures during APRIL
  - Rate of drug side effects
  - Determine if demographic and patient characteristics will be associated with Azithromycin responsiveness.
    - Including IL-8 genotyping
  - Pharmoeconomic impacts of APRIL therapy
Methods- Microbial Data

- Cultures were performed on participants at randomization (n = 86) and at study completion (n = 81).
- Samples were inoculated onto sheep's blood agar containing Azithromycin.
  - The absence or presence of normal flora was assessed, and pathogenic organisms were isolated and identified.
Methods- *IL*-8 rs4073 Genotyping

• *A allele* for a variant at position -251 in the *promoter region of the IL-8 gene* (IL-8/-251) has been associated with increased transcription rates for IL-8 gene

• Participants were genotyped for the *IL*-8 rs4073 single-nucleotide polymorphism by PCR
Patients were classified for having a positive modified asthma predictive index (API)\textsuperscript{12}:

- at least 4 wheezing episodes in the past year \textbf{and} 1 major criterion \textbf{or} 2 minor criteria

- **Major criteria**
  - physician-diagnosed atopic dermatitis
  - parental history of asthma
  - allergic sensitization to $\geq$ 1 aeroallergen

- **Minor Criteria**
  - wheezing unrelated to colds
  - blood eosinophils $\geq$ 4%
  - allergic sensitization to milk, eggs, or peanuts
Methods - Statistical Analysis

- **Primary outcome:** similar to familiar “time to event” outcomes
- **Null hypothesis:** azithromycin and placebo do not differ using the following covariates:
  - study site
  - age at randomization (12-42 months vs 43-71 months)
  - modified API18 status
  - season during which the RTI occurred (a time-dependent covariate)
  - whether the child enrolled before or after the study was extended to 78 weeks.
Methods - Statistical Analysis

- **Secondary outcomes:** used repeated measures analysis of variance with compound symmetry to account for multiple treated RTIs in the same individual.

- Treatment-effect modification was explored in pre-specified subgroups:
  - defined by age at randomization
  - sex
  - modified API status
  - presence of viral infection during RTI
  - season during which the RTI occurred
  - *IL-8* rs4073 genotype.
Results - Participant's Study Enrollment and Outcomes
Results

- 708 enrolled → 607 were randomized
  - 140 excluded due to severity of symptoms
    - 12 had poor dairy adherence
    - 12 lost to follow up
    - 3 withdrew consent
    - 6 had physician initiated termination
- 164 did not experience a treated RTI
  - 84 Azithromycin group versus 80 Placebo group
- 109 met termination criteria
- 105 patients withdrew from the study
  - 51 in Azithromycin group versus 54 in Placebo group
Results - Participants

At Least 1 RTI versus No RTI

- Patients who experienced ≥1 RTI were more likely to be
  - White
  - Lower rates of tobacco exposure
  - Higher rates of ICS, oral steroid and/or Monteleukast use in the last year
- Otherwise characteristics were comparable between the two groups
Results - Participants

Azithromycin Group versus Placebo Group

- Higher rate of daycare attendance in Azithromycin group.
- Otherwise comparable distribution
- Overall high level of atopy
  - 52.7% sensitized to any allergen
  - 46.8% positive modified API

Table 2. Characteristics of Study Participants
Results - Primary Outcome

- Azithromycin (AZ) group had significantly lower risk of progressing to severe LRTI
- Absolute risk for first RTI:
  - AZ group: 0.05
  - Placebo group: 0.08
- Cumulative risk for severe LRTI over a max of 4 LRT:
  - AZ group: 0.24
  - Placebo group: 0.4
### Results - Viral Detection

<table>
<thead>
<tr>
<th></th>
<th>All RTIs</th>
<th>RTIs that Did Not Progress to Severe Lower Respiratory Tract Illness</th>
<th>RTIs that Did Progress to Severe Lower Respiratory Tract Illness</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Azithromycin</td>
<td>Placebo</td>
<td>Azithromycin</td>
</tr>
<tr>
<td>No Virus Present</td>
<td>77 (17.4%)</td>
<td>87 (19.9%)</td>
<td>72 (17.6%)</td>
</tr>
<tr>
<td>Adenovirus B</td>
<td>1 (0.2%)</td>
<td>0</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Adenovirus C</td>
<td>1 (0.2%)</td>
<td>0</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Bocavirus</td>
<td>2 (0.5%)</td>
<td>0</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Coronavirus HK</td>
<td>1 (0.2%)</td>
<td>0</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Coronavirus NL63</td>
<td>12 (2.7%)</td>
<td>5 (1.1%)</td>
<td>12 (2.9%)</td>
</tr>
<tr>
<td>Coronavirus OC43</td>
<td>10 (2.3%)</td>
<td>8 (1.8%)</td>
<td>10 (2.4%)</td>
</tr>
<tr>
<td>Enterovirus</td>
<td>12 (2.7%)</td>
<td>19 (4.3%)</td>
<td>9 (2.2%)</td>
</tr>
<tr>
<td>Enterovirus/Human Rhinovirus</td>
<td>66 (14.9%)</td>
<td>51 (11.7%)</td>
<td>64 (15.6%)</td>
</tr>
<tr>
<td>Influenza A</td>
<td>8 (1.8%)</td>
<td>6 (1.4%)</td>
<td>8 (2.0%)</td>
</tr>
<tr>
<td>Influenza B</td>
<td>2 (0.5%)</td>
<td>5 (1.1%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>Human Rhinovirus</td>
<td>181 (40.9%)</td>
<td>186 (42.6%)</td>
<td>165 (40.3%)</td>
</tr>
<tr>
<td>Metapneumovirus</td>
<td>17 (3.8%)</td>
<td>20 (4.6%)</td>
<td>14 (3.4%)</td>
</tr>
<tr>
<td>Parainfluenza 1</td>
<td>13 (2.9%)</td>
<td>12 (2.7%)</td>
<td>10 (2.4%)</td>
</tr>
<tr>
<td>Parainfluenza 2</td>
<td>7 (1.6%)</td>
<td>7 (1.6%)</td>
<td>7 (1.7%)</td>
</tr>
<tr>
<td>Parainfluenza 3</td>
<td>11 (2.5%)</td>
<td>9 (2.1%)</td>
<td>11 (2.7%)</td>
</tr>
<tr>
<td>Parainfluenza 4</td>
<td>5 (1.1%)</td>
<td>3 (0.7%)</td>
<td>5 (1.2%)</td>
</tr>
<tr>
<td>Parainfluenza 4b</td>
<td>3 (0.7%)</td>
<td>2 (0.5%)</td>
<td>3 (0.7%)</td>
</tr>
<tr>
<td>Respiratory Syncytial Virus A</td>
<td>10 (2.3%)</td>
<td>12 (2.7%)</td>
<td>9 (2.2%)</td>
</tr>
<tr>
<td>Respiratory Syncytial Virus B</td>
<td>6 (1.4%)</td>
<td>2 (0.5%)</td>
<td>6 (1.5%)</td>
</tr>
<tr>
<td>All</td>
<td>443 (100.0%)</td>
<td>437 (100.0%)</td>
<td>409 (100.0%)</td>
</tr>
</tbody>
</table>
## Results - Subgroup Analysis

**Figure 3. Potential Treatment-Effect Differences in Prespecified Subgroups for Risk of an Episode of Severe LRTI Among Preschool Children With a History of Severe LRTI**

<table>
<thead>
<tr>
<th>Subgroup Description</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>IL-8 genotype (rs4073)*</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*</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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<td></td>
</tr>
<tr>
<td>Positive*</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>

**Figure Legend:**
- **Hazards Ratio (95% CI):** Hazards ratio with 95% confidence intervals for each subgroup comparison.
Results - Secondary Outcomes

Figure 4. Symptom Scores Over the Duration of Treated RTIs Among Preschool Children With a History of Severe LRTI

![Graph showing symptom scores and treatments during illness for Azithromycin and Placebo groups.](image-url)
Results - Secondary Outcomes

- Healthcare Utilization
  - ED visits:
    - 3.6% in Azithromycin group
    - 5.4% in placebo group
  - Hospitalizations: 28
    - 13 in Azithromycin group
    - 15 in placebo group

- Microbial Resistance
  - At Randomization:
    - 5 of 41 (12.2%) in Azithromycin group
    - 4 of 45 (8.9%) placebo group
  - At Study completion:
    - 8 of 40 (20%) in Azithromycin group
    - 7 of 41 (17%) in placebo group

- Adverse Events:
  - Mild GI symptoms
Conclusion

- In preschool children with severe intermittent wheezing in the context of RTIs-
  - Azithromycin at first sign of RTI:
    - Reduces risk of progression to LRTI
    - Reduces symptoms severity of episodes of severe LRTI
  - Effects were detectable regardless of modified API status
Conclusion

- **Possible mechanisms:**
  - Antibacterial effects\(^7\)
  - Reduction of rhinovirus replication & increase INF gene expression??\(^{22}\)
  - Reduction of IL-8 levels in nasal secretions
    - Reducing neutrophilic inflammation caused by viruses
### Strengths and Limitations

#### Strengths
- Age of Participants
- Assessed for antimicrobial resistance
- Allowed for multiple treated RTIs per patient
- Treatment effect was present regardless of API status

#### Limitations
- Extension of study
- Study end point
- Inclusion criteria
- Parental reporting of symptoms
- Resistance patterns only done in one site
- Limited sputum studies
References

References