Treatment Approaches to Preschool Wheezing Illnesses

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Disclosures

Employment
Washington University

Financial Interests
Consultant: DBV, Merck, Boehringer Ingelheim, Vectura, Sanofi, Genentech/Novartis
Honoraria/ Speakers Bureau: Teva, BI, Astra Zeneca, Genentech
Research Support: None

Research Interests
NIH/NHLBI, NIAID

Organizational Interests
AAAAI Annual Meeting Planning Committee
Director, ABAI

Gifts
Nothing to Disclose

Other Interests
Nothing to Disclose

Learning Objectives

Examine strategies for the management of acute severe wheezing illnesses in preschool children.
Explore the role of azithromycin in the prevention and attenuation of wheezing illnesses.
**Background**

- Severe episodes of lower respiratory tract symptoms are common in early childhood
- Disproportionate healthcare resource utilization in this age group
- Viral infection most common trigger, but bacteria have an emerging role in illness pathogenesis
- More evidence is needed to guide practitioners for episode management and prevention

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**Are Oral Corticosteroids Effective in Episodes of Wheezing in Preschool Children?**

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**Oral Corticosteroids (OCS) for Acute Wheezing Episodes**

- Recommended by asthma guidelines for asthma exacerbations: children and adults
- Efficacy is well proven for acute asthma exacerbations among school-age children and adolescents (acute care setting):
  - Lower risk of relapse, fewer hospitalizations, and less need for β₂-agonist treatments
- OCS have traditionally been used for treatment of acute episodic wheezing in preschool children, mainly based on their benefits in older children with asthma

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Systemic Corticosteroids in Preschool Children

- Early parent-initiated OCS treatment (home)
  - Does not prevent urgent visits\(^1\)
  - Potentially higher rate of urgent visits\(^2\)
  - Does not improve respiratory symptoms\(^1\)
  - Low compliance\(^1\)
- Emergency Department
  - Reduced rate of hospitalization (approx 50\%)\(^3\)


700 preschool children (10-60 mo) hospitalized for acute wheezing episode preceded by viral URI symptoms
- ~30% were first time wheezers
- RDBPC: 5-day course of oral prednisolone vs. placebo
  - 10 mg daily for children 10-24 months
  - 20 mg daily for older children
- Primary outcome: duration of hospitalization


No Significant Reduction in Episode Severity

No significant difference in duration of hospitalization (or time until ready for discharge) - 11.0 hrs vs. 13.9 hrs (p=0.18)

No difference between groups in:
- Use of albuterol
- Rescue open-label OCS
- PRAM score at 4, 12, 24 hrs
- Rate of readmission
- No difference in outcomes based on API status

Do Oral Corticosteroids Reduce Severity of Acute LTRI in Preschool Children?

- *Post hoc* analyses in 2 outpatient cohorts of preschool children participating in Childhood Asthma Research and Education (CARE) Network clinical trials
  - Initial cohort (AIMS study) & validation cohort (MIST study)
  - Participants: 1-5 y/o children with history of episodic wheezing in the context of RTIs
  - Prednisolone (4 days): rescue treatment (protocol criteria)
    - Significant lower respiratory tract illness (LRTI) after consultation with study physician

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Total Symptom Scores Were Not Lower Among Episodes Treated With OCS

- No significant difference in cough score, wheeze score, trouble breathing score, or interference with activity score

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Summary: Uncertain Efficacy of OCS in Preschool Children with Episodic Wheezing

- Outpatient (home) setting
  - Did not improve respiratory symptoms
  - Potentially associated with higher rates of ED visits
- ED setting
  - One study showed reduced rate of hospitalization
- Hospital setting
  - Did not reduce duration of hospitalization or improve respiratory symptoms
- Very little evidence to support the efficacy of OCS in preschool children with episodic wheezing
**Potential Explanations for OCS Findings in Preschool Children**

- Different wheezing/asthma phenotypes with potentially different mechanisms and thus response to interventions
- Episodic/"severe intermittent" wheezing
  - Dominance of the "risk domain"
    - Significant morbidity during acute wheezing episodes
    - Minimal persistent asthma symptoms
  - Potentially more background and acute neutrophilic\(^1,2\) and less eosinophilic airway inflammation


**Potential Role of Macrolides for the Prevention of Acute Wheezing**

- Antibiotic use in wheezing illnesses is not recommended by national guidelines
  - 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


**ARS SLIDE #1**

For preschool children with recurrent severe lower respiratory tract illnesses, the NAEPP Guidelines do not recommend antibiotics as a component of episode management. How often do you prescribe an antibiotic for significant lower respiratory tract illnesses in this population?

A. Never, ever, under any circumstances
B. <25% of the time
C. 25-50% of the time
D. 50-75% of the time
E. >75% of the time
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?


**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

<table>
<thead>
<tr>
<th>PLACEBO</th>
<th>AZM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st RTI</td>
<td>220</td>
</tr>
<tr>
<td>2nd RTI</td>
<td>147</td>
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<tr>
<td>3rd RTI</td>
<td>76</td>
</tr>
<tr>
<td>4th RTI</td>
<td>26</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 by 12 weeks

Subgroup Analyses
Reduction in Albuterol Use During Severe LRTIs


Summary

- 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

Azithromycin for episodes with asthma-like symptoms in young children aged 1-3 years: a randomised, double-blind, placebo-controlled trial


- Double blind placebo controlled trial among COPSAC2010 1-3yrs with recurrent asthma-like symptoms (n=72)
- After >3 days of asthma-like symptoms, AZM 10mg/kg/d or placebo for 3 days
  - Concurrent ICS in 82% of episodes, LTBA in 60%
- Primary outcome: duration of episode after start of therapy

63.3% reduction in duration in AZM group (p=0.0001)
Azithromycin for episodes with asthma-like symptoms in young children aged 1-3 years: a randomised, double-blind, placebo-controlled trial

- Greater effect when AZM started before day 6 of episode
- No differential effect if:
  - Evidence of pneumonia
  - Detectable wheezing
  - Use of ICS or LTRA
  - Presence of bacteria (other than was more effective if H. influenzae detected in hypopharyngeal aspirate)
  - No difference based upon presence or absence of viral infection
  - No effect on time to next episode


Summary: Preschool Children with Severe Wheezing Episodes

- 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 prevention approach compared to the efficacy of daily (or intermittent) ICS therapy or role in patients already receiving controller therapy