Recurrent Wheezing in Preschool Children

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Disclosure

I have nothing to disclose related to this talk.
Background / Objectives

Asthma is the most common chronic disease of childhood.

Recurrent wheezing is common among preschool children.

The pathophysiology and treatment of these preschool episodes is likely different than those for older children or adults with well-established asthma.

This talk will focus on new advances in the treatment of these children with a direction towards personalized medicine.
Preschool Wheezing – Scope of Problem

Tucson Children’s Respiratory Study
Birth cohort of 826 children with follow up data at 2 points

Birth  3 years  6 years

0-3 years: Physician Diagnosis of LTR illness with wheeze?  6 years: Current wheezing?

No  No  Never Wheeze (51.5%)

Yes  No  Transient Early Wheeze (19.9%)

Yes  Yes  Persistent Wheeze (13.7%)

No  Yes  Late Onset Wheeze (15.0%)

Martinez FD, NEJM, 1995
Preschool Wheezing – Scope of Problem

- Approximately 50% of children had wheezing episode at some point in first 6 years of life.

- Almost 60% of those with wheeze in the first 3 years of life had outgrown this condition by 6 years of age.

**Transient Early Wheeze** were more likely to have:
- Diminished airway function at birth
- Mothers who smoked, but not mothers with asthma

**Persistent Wheeze** were more likely to have:
- Mother with a history of asthma
- Atopy: elevated serum IgE levels, eczema, rhinitis, + skin testing

Martinez FD, NEJM, 1995
At ages 2-5 years, all three of these phenotypes are prevalent... should we be treating children differently?
Preschool Wheezing – Scope of Problem

Preschool wheezers have the highest rates of healthcare utilization including:
- ED visits
- Hospitalizations

Goal is to implement personalized strategies in these children in order to control symptoms and/or prevent exacerbations

Akinbami L, Pediatrics, 2009
Children with Episodic Wheezing Episodes vs. Children with Persistent Symptoms

The best place to start for personalized medicine for these children is to differentiate children with intermittent disease from children with persistent disease.

**Intermittent Disease:**
- Children with recurrent flares of wheezing episodes
- High health care utilization – ED visits, hospitalizations
- Healthy in between episodes, minimal day-to-day symptoms

**Persistent Disease:**
- >2 days/week, 1-2 nights/month, limitations on normal activities
- +/- more severe wheezing exacerbations
Recent meta-analysis that examined the current evidence of the use of daily ICS, intermittent ICS, or montelukast

Focused on children with episodic wheezing episodes
  - Some analyses on children with more persistent disease

Focused on the outcome of preventing exacerbations
Daily ICS for Episodic Wheezing Episodes

- 30% reduction in the risk of exacerbation requiring systemic corticosteroids
- Number Needed to Treat (NNT): 9

Kaiser SV, Pediatrics, 2016
Prevention of Episodic Wheezing Episodes

- **Daily ICS vs. Placebo:**
  - 30% reduction in risk of exacerbation, NNT = 9

- **Intermittent ICS vs. Placebo:**
  - 36% reduction in risk of exacerbation, NNT = 6
  - High Doses: Budesonide 1 mg BID, Fluticasone 0.75 mg BID
  - First sign of URTI and continued for 7 days or until asymptomatic

- **Daily ICS vs. Intermittent ICS**
  - No significant differences in outcomes
  - Daily dosing was associated with increased exposure to ICS
  - Only 2 studies included

Kaiser SV, Pediatrics, 2016
Treatment of Children with Persistent Symptoms

Daily ICS vs. Placebo:
- 44% reduction in risk of exacerbation, NNT = 11

Daily ICS vs. Daily Montelukast:
- 41% reduction in risk of exacerbation for those on Daily ICS
- Only one study included
Summary of Recent Meta-Analysis

These analyses confirmed the role of ICS as the first-line therapy for preschool wheezers.

Daily ICS therapy should be considered for preschool children with persistent disease.

Intermittent ICS (pre-emptive high-dose) is a reasonable option for preschool children with intermittent disease.

Kaiser SV, Pediatrics, 2016
Biomarkers to Predict Success?

- **Step 1:** Differentiate intermittent vs. persistent disease

- **Step 2:** Biomarkers (?)

  Are there useful biomarkers that can predict successful response to the common therapies in this age group?

  A recent clinical trial attempted to answer this question.
INFANT Trial (NHLBI AsthmaNet)

- 300 children (ages 1-4 years)
- Persistent symptoms
  - Meeting criteria for Step 2 therapy (controller)
- Multicenter, blinded, randomized

Triple cross-over of three therapies (16 weeks each):
- Daily ICS
- Intermittent ICS
- Daily Montelukast

Primary Analyses:
1. Did children have a differential response to these treatments? (composite of exacerbations and daily symptoms)
2. Are there factors that are able to predict a differential response?

Fitzpatrick AM, JACI, 2016
Daily ICS was most likely the preferred therapy when all children were combined

- 74% of children had a preferred response to one treatment.

- Daily ICS was most likely the preferred treatment.

- Some children did have a preferential response to Intermittent ICS and Daily LTRA.

- 26% of children had no preferred choice (less severe).

Fitzpatrick AM, JACI, 2016
Aeroallergen Sensitization and Eosinophilia predicted better response to Daily ICS

Children with one or both of these biomarkers had a preferred response to Daily ICS

Children without these biomarkers had no preference among the three treatments

Fitzpatrick AM, JACI, 2016
Summary of the INFANT Trial

- Determining peripheral blood eosinophil counts and/or aeroallergen sensitivity may aid clinicians in choosing initial therapy for persistent asthma in preschoolers.
  - Positive testing $\rightarrow$ Child most likely to respond to Daily ICS
  - Negative testing $\rightarrow$ Child may be tried on any of the therapies

- If a child does not respond to the initial Step 2 controller therapy, an alternative Step 2 therapy should be considered before escalating to step 3 therapy.

Fitzpatrick AM, JACI, 2016
Other Predictors of Success with Daily ICS

Previous post-hoc analysis demonstrated that the following factors were also associated with a more favorable response to daily ICS:

- Boys
- White
- More symptoms at baseline
- ED visit or hospitalization within the past year
- Aeroallergen sensitization

Bacharier LB, JACI, 2009
Limitations of the Use of ICS

- ICS reduces the rate of exacerbations by approximately 30-40%, but does not completely prevent exacerbations.

- Daily ICS therapy has been associated with a small, but statistically significant, reduction in linear growth.

- Suboptimal adherence to Daily ICS is well documented.

- Is there a better way to treat children without persistent disease, but instead with only recurrent wheezing episodes especially those that are triggered by infections?
Macrolides have been shown to have beneficial anti-inflammatory effects in other inflammatory chronic lung disease.

Macrolides reduce neutrophilic inflammation which is prominent during respiratory infections.

Macrolides may have a beneficial effect on the airway microbiome.
APRIL Trial (NHLBI AsthmaNet)

- 607 children (ages 1-5 years)
- Episodic wheeze events, but minimal day-to-day symptoms
- Multicenter, blinded, randomized, placebo controlled

Azithromycin vs. Placebo
- Parent-initiated at the start of an upper respiratory tract infection
- 5 day course with each infection (12 mg/kg/day)
- Children were not on any controller therapies

Bacharier LB, JAMA, 2015
Intermittent azithromycin reduced the risk of progression to severe wheezing exacerbations.

Figure 2. Cumulative Risk of Experiencing an Episode of Severe LRTI Across Treated RTIs for Preschool Children With a History of Severe LRTI

Adjusted Cumulative Risk of Progressing to SLRTI

- Azithromycin
- Placebo

HR (95% CI), 0.64 (0.41-0.98), P = .04

<table>
<thead>
<tr>
<th>Treated RTI</th>
<th>No. of treated RTIs</th>
<th>No. of SLRTIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>223</td>
<td>16</td>
</tr>
<tr>
<td>Second</td>
<td>220</td>
<td>22</td>
</tr>
<tr>
<td>Third</td>
<td>146</td>
<td>13</td>
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<tr>
<td>Fourth</td>
<td>147</td>
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<td>Fourth</td>
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<td>Fourth</td>
<td>23</td>
<td>7</td>
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</tbody>
</table>

Bacharier LB, JAMA, 2015
Summary of the APRIL Trial

- Intermittent early initiation of azithromycin was able to reduce the risk of an upper RTI progressing to a severe wheezing episode by 36% (similar to ICS effect) when compared to placebo.

- Additionally, the azithromycin group had significantly decreased illness severity during episodes that progressed to an exacerbation.

- There was no difference in the treatment effects between children with and without a positive mAPI (modified Asthma Predictive Index)
  - Suggesting that azithromycin may be a good option for children with a negative mAPI (often under-represented in asthma studies)

Bacharier LB, JAMA, 2015
Macrolides as treatment for asthma

After the APRIL trial, similar beneficial results were reported from children aged 1-3 years in the Copenhagen Prospective Studies on Asthma in Childhood (COPSAC). These studies indicate that intermittent azithromycin therapy may be a therapeutic approach for young children with recurrent and severe episodic wheeze. Including those children with a negative mAPI.

Bacharier LB, JAMA, 2015
**mAPI: modified Asthma Predictive Index**

- Method for predicting asthma later in life
- In general, helps to identify young children with allergic-type asthma that will persist later in life
  - In contrast to infection-triggered wheezing that does not persist
- May help with personalized treatment approaches

<table>
<thead>
<tr>
<th><strong>Primary</strong></th>
<th>≥ 4 wheezing episodes in a year</th>
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<tbody>
<tr>
<td><strong>AND</strong></td>
<td></td>
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<tr>
<td><strong>Secondary</strong></td>
<td><strong>Major (at least 1)</strong> OR <strong>Minor (at least 2)</strong></td>
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<tr>
<td></td>
<td>Parental Asthma</td>
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<td></td>
<td>Eczema</td>
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<td></td>
<td>Aeroallergen Sensitization</td>
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<tr>
<td></td>
<td>Wheezing unrelated to colds</td>
</tr>
<tr>
<td></td>
<td>Eosinophils ≥ 4%</td>
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<tr>
<td></td>
<td>Food Allergen Sensitization</td>
</tr>
</tbody>
</table>
Let's try to put this all together

Personalized Medicine for Preschool Wheezers:

1. Disease Types:
   - Intermittent vs. Persistent

2. Predictive Factors:
   - mAPI, Eosinophilia, Aeroallergen Sensitization, Disease Burden

3. Treatments:
   - Daily ICS, Intermittent ICS, Montelukast (LTRA), Azithromycin
Personalized Medicine for Preschool Asthma

Intermittent Disease
- Negative mAPI → Azithromycin* early during the course or LRTI
- Positive mAPI → Intermittent ICS

Persistent Asthma
- Boys, Caucasian, more symptoms, ED/hospitalization, aeroallergen sensitization → Daily ICS
- Eosinophilia, aeroallergen sensitization → Daily ICS, LTRA, or Symptom-Driven Intermittent ICS
- No Eosinophilia, no aeroallergen sensitization

Beigelman A, Curr Opin Allergy Clin Immunol, 2017
Is this all too much?

Maybe (at least for now)
- That is why this is the “Future of Pediatrics” conference

The “one size fits all” treatment of asthma is clearly not the best approach.
- Such an approach would never be accepted in other diseases
  - Example: Anemia
“Asthma is heterogeneous, and there are many different forms of the disease. In fact, sometimes I tell audiences that, you know, until very late in the 19th century fever was considered a disease. The same will be said about asthma 20 or 30 or 50 years from now.”

Fernando Martinez, Lancet, 2006
PREVENTION?

Can we prevent wheeze/asthma in these young children?

Primary: Avoid the disease
Secondary: Interfere with natural progression of disease
Tertiary: Prevention of morbidity / disability

EXACERBATION
PARK Study (NIAID Multicenter Trial)  
Preventing Asthma in high Risk Kids

- Enroll 250 children aged 2-3 years at high risk for the development of asthma

- Randomize to two years blinded treatment of:
  - Omalizumab (anti-IgE) vs. Placebo

- Two years of treatment followed by two years of observation

- Outcomes are assessed two years after stopping therapy

- Start enrolling in 2018, results in 2024-2025

NCT 02570984
**ORBEX Study (NHLBI Multicenter Trial)**

**Oral Bacterial Extract for the Prevention of Wheezing Lower Respiratory Tract Illness**

Enroll 1,076 infants aged 6-17 months

At risk for development of asthma, but not yet wheezing
  - Infant has Eczema or Family History of Asthma

Randomize to two years blinded treatment of:
  - BronchoVaxom® (lyophilized bacterial extracts) vs. Placebo

Primary outcome measured after stopping therapy

Children’s National currently enrolling!
  - If interested: 202-476-2628

*Children's National Health System*

Breathe Easy Early
An ORBEX Study of Asthma & Wheezing

NCT 02148796
Summary

Wheezing in preschool children is the outward presentation of what is a diverse collection of pathophysiologic responses.

Efforts to personalize treatments targeted for these different underlying processes could help to improve health outcomes in an efficient manner.

Current research is underway to try to prevent wheezing in these children – and hopefully prevent asthma.
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