Treatment of Recurrent Wheezing in Preschool Children

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Wheezing in Preschool Children

Introduction

Clinical Scenarios
Pathophysiology of Wheezing

\[ \Delta P = KV \]

\[ \dot{V} = S \cdot \nu \uparrow \]

Re = 2rvd/n > 2000

\[ \Delta P = KV^2 \]
Clinical Case 1

- 12 mo ♀ with 3 episodes of cough over the last year
- Association with viral respiratory infections
Recurrent Viral-Associated Wheezing

Bisgaard et al. AJRCCM 2005:171:315
Clinical Case 2

- 6 mo ♂ - cough for 2 months (↑ at night)
- “Congested” chest
- Clear nasal drainage
- Maternal asthma
Wheezing in Preschool Children

Wheezing and Anti-inflammatory Treatment
Anti-inflammatory Medications for Wheezing to Preschool Children: Why?

- Ameliorate symptoms associated with lower airway obstruction
- Prevent recurrences and improve quality of life
- Prevent deficits in lung function growth
To maximize efficacy of anti-inflammatory medications and to minimize side effects we need to know:

- Which preschool children will develop asthma?
- Which subjects are at risk for deficits in growth of lung function?
- Which wheezing phenotypes are responsive to anti-inflammatory medications?
- What are the possible side effects of ICS in relation to duration of treatment?
Definition of Bronchial Asthma

- Recurrent episodes of reversible lower airway obstruction (without/without treatment)
- Inflammation of the lower airways (eosinophils, mastocytes, lymphocytes)
- Bronchial hyperresponsiveness
Outcome of Wheezing in the First 6 Yrs of Life
Morgan et al. AJRCCM 2005;172:1253
Children < 3 yo at High Risk for Wheeze after 6 Years of Age

**Major criteria (at least 1)**
- > 3 episodes/y + parental hx of asthma
- > 3 episodes/y + atopic dermatitis

**OR**

> 3 episodes/y +

**Minor criteria (at least 2)**
- Allergic rhinitis
- Wheezing apart from colds
- Eosinophilia (≥ 4%)

Outcome of Wheezing in the First 6 Yrs of Life
Morgan et al. AJRCCM 2005;172:1253
### Study groups
- Viral-associated wheeze
- Frequent recurrences-persistent symptoms
- Frequent recurrences with risk factors for asthma *(Tuscon’s criteria)*

### Interventions
- Inhaler/spacer device vs. nebulizer
- Corticosteroids vs. non-steroidal medications
- High vs. low dosages
- Variable duration
Published Evidence (II)

Outcomes

- Expiratory flow function
- Hospitalizations
- ER visits
- Steroid courses
- Symptom-free days
- Nights with symptoms
- Need for bronchodilators
- Clinical scores
Infant Pulmonary Function Testing
ERS/ATS Task Force on Standards for Infant PFT.
ERJ 2000;16:731
Wheezing in Preschool Children

Anti-inflammatory Medications - Indications
Available Anti-Inflammatory Medications

- No passive smoking
- Systemic corticosteroids
- Inhaled corticosteroids
- Cromolyn, nedocromil
- Leukotriene receptor antagonists
Systemic Corticosteroids for Viral-Associated Wheezing

- **Webb et al.** Arch Dis Child 1986; 61:15
  38 children (3-17 mo) with wheezing
  
  *Clinical score*
  
  Prednisolone 2 mg/kg/d for 5 d = Placebo for 5 d

- **Tal et al.** Pediatrics 1990; 86:350
  74 children (7-54 mo) with wheezing
  
  *Admission rate*
  
  Methyprednisolone 4 mg/kg IM < Placebo IM
Inhaled Corticosteroids for Viral-Associated Wheeze

- **Episodic High-Dose ICS**
  - 2 RCTs-infants with viral wheeze
  - Beclomethasone or budesonide 0.8-3.2 mg/d PRN

  Reduced need for po steroids  RR 0.53 (CI 0.27-1.04)

- **Low-Dose Maintenance ICS**
  - 2 RCTs-infants and children with viral wheeze
  - Budesonide 0.4 mg/d for 4 m

  Courses of po steroids  RR 0.82 (CI 0.23-2.9)
  No. of admissions  RR 0.21 (CI 0.01-4.11)

McKean et al. Cochrane 2000:CD001107
Prophylactic Intermittent Inhaled Corticosteroids for Viral-Associated Wheezing

- 55 children 1-3 yo
- Study duration: 1 y
- Budesonide 0.8-1.6 mg vs. Placebo PRN
- Reduced clinical score for budesonide
- No difference in ER visits-hospitalizations

Montelukast for Viral-Associated Wheezing in Preschool Children

549 children; 2-5 yo
1 year
Montelukast
1.6 episodes
Placebo
2.34 episodes

Bisgaard et al. AJRCCM 2005:171:315
Inhaled Corticosteroids for Frequent/Persistent Wheeze

- **Systematic review**
  - 24 RCTs-1087 children with asthma
  - 10/24 RCTs with preschool children
  - Placebo, beclomethasone 0.15-0.4 mg/d or budesonide 0.3-2 mg/d for 4-24 wks

- ICS compared to placebo
  - *Improved symptom score* -50% (CI 49%-51%)
  - *Improved PEFR* +11% (CI 9.5%-12.5%)
  - *Reduced use of po steroids* RR 0.68 (CI 0.66-0.70)

Calpin et al. J Allergy Clin Immunol 1997;100:452
Fluticasone for Children < 2 yo with Wheezing and Risk Factors for Asthma

26 children < 2 yo + r.wheezing + family hx of asthma/rhinitis/eczema
Fluticasone 250 mcg/Placebo for 6 m
Exacerbations 2.1 ± 1.7 vs 4.1 ± 3

Teper et al. AJRCCM 2005:171:587
Montelukast for Persistent Asthma in Preschool Children

- 689 children; 2-5 yo
- 12 wks
- Montelukast
  Days with symptoms: 59%
- Placebo
  Days with symptoms: 64%

Budesonide or Nedocromil in Children with Mild-to-Moderate Asthma

1041 children
5-12 yo
Study duration: 4-6 y
Budesonide 200 mcg bid
Nedocromil 8 mg bid
Placebo bid

CAMP. NEJM 2000:343:1054
Budesonide or Nedocromil in Children with Mild-to-Moderate Asthma

<table>
<thead>
<tr>
<th># /100 children/y</th>
<th>Budesonide</th>
<th>Nedocromil</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>po steroids</td>
<td>70 *</td>
<td>102 *</td>
<td>122</td>
</tr>
<tr>
<td>ER visits</td>
<td>12 *</td>
<td>16 *</td>
<td>22</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>2.5 *</td>
<td>4.3</td>
<td>4.4</td>
</tr>
</tbody>
</table>

CAMP. NEJM 2000:343:1054
Cromolyn in Children 1-4 yo with Persistent Asthma

218 children
1-4 yo
5 m
Cromolyn 10 mg tid
Placebo tid

Wheezing in Preschool Children

Inhaled Corticosteroids - Safety
Long-Term Use of ICS: Standing Height

1041 children
5-12 yo
4-6 y
Budesonide, Nedocromil, Placebo

CAMP. NEJM 2000:343:1054
Long-Term Use of ICS:
Other Potential Side-Effects

- Bone density
  (CAMP. NEJM 2000:343:1054)

- Cataracts, glaucoma
  (CAMP. NEJM 2000:343:1054)

- HPA axis
Relative Potency of ICS
(NHLBI 2002 Update)

<table>
<thead>
<tr>
<th>Dose (mcg)</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDP <em>inh</em></td>
<td>&lt;400</td>
<td>400-800</td>
<td>&gt;800</td>
</tr>
<tr>
<td>BUD <em>neb</em></td>
<td>500</td>
<td>1000</td>
<td>2000</td>
</tr>
<tr>
<td>FP <em>inh</em></td>
<td>&lt;200</td>
<td>200-400</td>
<td>&gt;400</td>
</tr>
</tbody>
</table>
Wheezing in Preschool Children

Treatment Guidelines
<table>
<thead>
<tr>
<th>Classify Severity: Clinical Features Before Treatment or Adequate Control</th>
<th>Medications Required To Maintain Long-Term Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms/Day</strong></td>
<td><strong>Daily Medications</strong></td>
</tr>
<tr>
<td><strong>Symptoms/Night</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Step 4</strong></td>
<td>Continual</td>
</tr>
<tr>
<td>Severe Persistent</td>
<td>Frequent</td>
</tr>
<tr>
<td></td>
<td>- Preferred treatment:</td>
</tr>
<tr>
<td></td>
<td>- High-dose inhaled corticosteroids AND</td>
</tr>
<tr>
<td></td>
<td>- Long-acting inhaled beta₂-agonists AND, if needed,</td>
</tr>
<tr>
<td></td>
<td>- Corticosteroid tablets or syrup long term (2 mg/kg/day, generally do not exceed 60 mg per day). (Make repeat attempts to reduce systemic corticosteroids and maintain control with high-dose inhaled corticosteroids.)</td>
</tr>
<tr>
<td><strong>Step 3</strong></td>
<td>Daily</td>
</tr>
<tr>
<td>Moderate Persistent</td>
<td>&gt;1 night/week</td>
</tr>
<tr>
<td></td>
<td>- Preferred treatments:</td>
</tr>
<tr>
<td></td>
<td>- Low-dose inhaled corticosteroids and long-acting inhaled beta₂-agonists OR</td>
</tr>
<tr>
<td></td>
<td>- Medium-dose inhaled corticosteroids.</td>
</tr>
<tr>
<td></td>
<td>- Alternative treatment:</td>
</tr>
<tr>
<td></td>
<td>- Low-dose inhaled corticosteroids and either leukotriene receptor antagonist or theophylline.</td>
</tr>
<tr>
<td></td>
<td>If needed (particularly in patients with recurring severe exacerbations):</td>
</tr>
<tr>
<td></td>
<td>- Preferred treatment:</td>
</tr>
<tr>
<td></td>
<td>- Medium-dose inhaled corticosteroids and long-acting beta₂-agonists.</td>
</tr>
<tr>
<td></td>
<td>- Alternative treatment:</td>
</tr>
<tr>
<td></td>
<td>- Medium-dose inhaled corticosteroids and either leukotriene receptor antagonist or theophylline.</td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
<td>&gt;2/week but &lt;1x/day</td>
</tr>
<tr>
<td>Mild Persistent</td>
<td>&gt;2 nights/month</td>
</tr>
<tr>
<td></td>
<td>- Preferred treatment:</td>
</tr>
<tr>
<td></td>
<td>- Low-dose inhaled corticosteroids (with nebulizer or MDI with holding chamber with or without face mask or DPI).</td>
</tr>
<tr>
<td></td>
<td>- Alternative treatment (listed alphabetically):</td>
</tr>
<tr>
<td></td>
<td>- Cromolyn (nebulizer is preferred or MDI with holding chamber) OR leukotriene receptor antagonist.</td>
</tr>
<tr>
<td><strong>Step 1</strong></td>
<td>≤2 days/week</td>
</tr>
<tr>
<td>Mild Intermittent</td>
<td>≤2 nights/month</td>
</tr>
<tr>
<td></td>
<td>- No daily medication needed.</td>
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Which Children should be treated with Anti-inflammatory Medications

- Symptomatic treatment required > 2/wk
- Severe exacerbations < 6 wks apart
- > 3 episodes/y (affecting sleep) + risk factors for asthma
Conclusions

- Heterogeneity between studies:
  wheezing phenotypes, interventions, outcomes

- Infrequent, mild, viral-associated wheeze
  may not be related to asthma

- Frequent/severe/persistent symptoms +
  personal hx of atopy/family hx of asthma:
  ↓ quality of life, ↓ lung growth,
  ↑ cost for family/health care system

- Inhaled/systemic corticosteroids probably
  most effective in preventing/controlling symptoms