News and Views on Asthma Education

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Pediatric Pulmonology
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Aims

- Identify different phenotypes of asthma and its comorbidities.
- Review different inhaled medications and inhalation techniques.
- Review recent literature on asthma medications.
On average, 3 children in a classroom of 30 are likely to have asthma.*
Infant to Preschool wheezers

- 50% of children wheeze within first year of age

ERS definitions:
- Episodic wheezer
  - Only wheeze in discrete periods of time
  - Usually associated with viral infections
- Multi-trigger wheezer
  - Wheeze in between episodes
  - Triggered by smoke exposure, allergens, exercise, viruses

Wheezing in childhood

Asthma Phenotypes using cluster analysis

• 3 variables
  • Baseline FEV1
  • Maximal FEV1
  • Age of onset of asthma

Phenotype based on bronchoscopy

- GERD
- Subacute bacterial infection
- Tissue eosinophilia
- Combination
- Non-specific

Many Paths to Asthma

• Chronic, immunologically mediated condition with a disturbance of normal airway repair mechanisms
  – Inflammatory changes and airway remodeling
• Multiple etiologies and pathogenic mechanisms are involved.
• Patients may exhibit disparate clinical courses, and diverse dimensions are being used to describe its manifestations.
Airway dysfunction in asthma: spontaneous variation of airway caliber

Diurnal variability

Short-term variability

Homeokinesis

Que et al. J Appl Physiol 2001
What are small airways?

- < 2mm in diameter (8th generation)
- Collectively huge surface area
- Laminar flow or diffusion
- Traditionally contribute very little to airway resistance (<10%)
Structural Alterations in Small Airways

Bronchiole (small airway) (200X magnification H&E stain) from a 9 years old child with severe persistent asthma demonstrating airway inflammation, smooth muscle hyperplasia and epithelial sloughing characteristic of significant small airway involvement.
Comorbid conditions

Boulet, LP. Eur Respir J 2009; 33: 897–906
Comorbid GERD

- Prevalence with asthma is high: 34-89%
- Steroids and beta-agonists decrease LES pressure

Bronchospasm from microaspiration and neurally mediated reflex

↑ Intrathoracic pressure from uncontrolled asthma worsens GERD
GERD

- Effect of GERD on asthma is unclear
  - improvement in asthma following GERD treatment is variable
    - different from one patient to another
- A medication trial may be the best way in which to assess the influence of GERD on asthma
Comorbid OSA

- About 35% of those diagnosed with OSA also have asthma
- Etiology uncertain:
  - Adenotonsillar hypertrophy
  - Inflammation
- When to screen:
  - Overweight
  - Asthma not well controlled
Poorly controlled asthma (PCA) and obstructive sleep apnea (OSA)

- 92 children with PCA underwent NPSG; obesity noted in 36%
- OSA diagnosed in 58 cases, i.e., 63% (OSA in non-asthmatics: 4%)
- Worse asthma in OSA (+) than in OSA (-) children.
- In children with OSA, T&A improved asthma outcomes

Comorbid Allergic Rhinitis

• Up to 95% of allergic asthmatic patients also suffer from rhinitis
• Rhinitis is also common in nonallergic asthma
  • Underdiagnosed
• Children and adults with this comorbidity have:
  • more frequent physician’s and ER visits
  • hospital admissions for asthma
  • higher asthma-related drug expenses
Allergic Rhinitis/Sinusitis: One airway

- The degree of inflammation in asthma correlates highly with the level of inflammation in the nose
- Allergen challenge of the nose leads to hyperresponsiveness in the lungs
- Allergen challenge in the lung leads to inflammation in the nose

**Central mechanism** links airway inflammation
Comorbid Obesity

- Specific phenotype:
  - Breathing at low lung volumes
  - Systemic inflammatory process that may possibly influence airways
  - Reduced response to asthma medications
  - Improving weight improves asthma symptoms

21
Asthma prevalence is increased in obese and morbidly obese children

17,944 children aged 4 to 12 yrs in West Virginia.
Obesity: 20.9%
Asthma: 14%

Comorbid psychological problem

- Anxiety
- Depression
- Panic disorders

More frequent than in the general population
Talking to patients about asthma

- Educate on basic asthma physiology
- Learn to recognize symptoms
- Learn to avoid (or work around) triggers
- Set goals for control
- Review inhalation techniques
- Identify adherence issues
What is asthma control?
As defined by the Global Initiative for Asthma (GINA), 2007

- Minimal to no daytime asthma symptoms
- No limitations on activities
- No nocturnal symptoms or awakenings
- Minimal to no need for reliever or rescue therapy
- Normal lung function (FEV₁ or PEF)
- No exacerbations
Compliance

When a patient says “My asthma medicine is not working!”

What does this mean?

Adapted from Dr. Bruce Rubin’s Lecture “My asthma medication is not working”
“My asthma medicine is not working”

- “I don’t like it” (This really means: “I’m not using it.”)

- Why?
  - This takes too much time
  - This is too much of a bother
  - I don’t believe in medications

These often mean
“I’m afraid of side effects”
Side effects

- Immune suppression
- Big muscles
- I might become addicted!
- Growth!
Side effects

- Local adverse reactions
  - Hoarseness
  - Oral candidiasis
- HPA axis suppression
- Growth
- Bone metabolism
- Skin atrophy and bruising
- Glaucoma
Systemic absorption

Figure 1 Schematic representation of the fate of an ICS. [53,58] Adapted from Derendorf et al., 2006 [53]; Derendorf, 1997 [58].
<table>
<thead>
<tr>
<th></th>
<th>Oral Bioavailability (%)</th>
<th>Lung Deposition (%)</th>
<th>Particle size (microns)</th>
<th>Protein-binding (% not bound)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone</td>
<td>40</td>
<td>50-60</td>
<td>&lt;2</td>
<td>13</td>
</tr>
<tr>
<td>Budesonide</td>
<td>11</td>
<td>15-30</td>
<td>&gt;2.5</td>
<td>12</td>
</tr>
<tr>
<td>Ciclesonide</td>
<td>&lt;1</td>
<td>50</td>
<td>&lt;2</td>
<td>1</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>&lt;1</td>
<td>20</td>
<td>2.8</td>
<td>10</td>
</tr>
</tbody>
</table>

Ahmet et al. Allergy, Asthma & Clinical Immunology 2011. 7:13
Minimize side effects:

- Use a spacer device and rinse the mouth after inhalation
- Use the lowest possible dose of ICS to maintain control
- Consider additional therapies before increasing the ICS dose
Adrenal Axis suppression

- Extremely rare
  - Related to high doses over long periods of time
  - 4 case reports of adrenal insufficiency in children on fluticasone HFA
    - 500-1500 ug/day for over 6 months
- Symptoms
  - Headache, hypoglycemia, nausea, fatigue, myalgia
Effect of Budesonide on Adult Height

Beclomethasone and Growth

• Camargos PA and Lasmar LM. Respiratory Medicine 2010; 104(7):951-956

• Prospective study following 82 children for 5 years

• Height and weight were not affected by dose or duration of beclomethasone therapy

• Severe persistent asthma associated with lower height
# Dose comparison of common ICS

<table>
<thead>
<tr>
<th>ICS</th>
<th>formulation</th>
<th>Low daily dose</th>
<th>Medium daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone/</td>
<td>40 mcg</td>
<td>8-160 mcg</td>
<td>160-320 mcg</td>
</tr>
<tr>
<td>QVAR HFA</td>
<td>80 mcg</td>
<td>160-320 mcg</td>
<td></td>
</tr>
<tr>
<td>Budesonide/</td>
<td>0.25 mg neb</td>
<td>0.5 mg</td>
<td>1 mg</td>
</tr>
<tr>
<td>Pulmicort respule</td>
<td>0.5 mg neb</td>
<td>1 mg</td>
<td></td>
</tr>
<tr>
<td>Budesonide/</td>
<td>90 mcg</td>
<td>180-400 mcg</td>
<td>400-800 mcg</td>
</tr>
<tr>
<td>Pulmicort DPI</td>
<td>180 mcg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>200 mcg</td>
<td></td>
<td></td>
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<tr>
<td>Fluticasone/</td>
<td>44 mcg</td>
<td>88-176 mcg</td>
<td>176-352 mcg</td>
</tr>
<tr>
<td>Flovent HFA</td>
<td>110 mcg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>220 mcg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mometasone DPI/</td>
<td>220 mcg</td>
<td>220 mcg</td>
<td>440 mcg</td>
</tr>
<tr>
<td>Asmanex Twisthaler</td>
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</tbody>
</table>

“My asthma medicine is not working”

I don’t feel it or taste it

Understand the difference between bronchodilator and anti inflammatories
“My asthma medicine is not working”

No one showed me how to use this thing!
Effective aerosol therapy

• 47% of parents given an aerosol device by their child’s pediatrician received no training in administering the treatment.

Some keys to know about aerosol deposition

- Distress in infant – a particular form of non-compliance
pMDI-VHC in sleeping infants

- N=30 ages 6-23 mos
- Filter dose
- Awake: 29% poor cooperation
- Asleep: 69% awoke with ¾ “distressed”

Aerosol administration in a young sleeping child.

Esposito-Festen J et al. Chest 2006;130:487-492
Some keys to know about aerosol deposition

- **Inspiratory flow matters**
- **Metered-dose inhalers with spacer**
  - Slow and deep
  - Breath hold
- **Breath-actuated**
  - Slow and deep
  - No spacer
- **Dry powder inhalers**
  - Fast flow
  - Move tongue out of the way!
Albuterol delivery in vitro model

Asthma Control Medications

- Inhaled steroids
- Long-acting bronchodilators
- Leukotriene receptor antagonists
- Anti-IgE agents
- Theophylline, nedocromil, cromolyn

Other:
- Vitamin D???
Ciclesonide (Alvesco) MDI

- Smaller particle size
- Inactive parent compound converted to active metabolite by esterases in the airway
- Cleared by the liver rapidly
- Greater plasma protein binding

= decreased side effects

Kaliner MA. Clin Ther. 2006 Mar; 28(3):319-31
### Current knowledge on ICS

<table>
<thead>
<tr>
<th>What is known</th>
<th>What is new</th>
<th>What is uncertain</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICS are the cornerstone of asthma treatment</td>
<td>Early ICS use does not prevent asthma</td>
<td>VEW and MTW are distinct phenotypes</td>
</tr>
<tr>
<td>ICS reduce symptoms, exacerbations, improve lung function in school aged children</td>
<td>Phenotypes: VEW MTW</td>
<td>MTW = asthma</td>
</tr>
<tr>
<td>ICS are safe in low to moderate dose</td>
<td>ICS in EVW not efficacious</td>
<td>Physician confirmed wheezing = asthma</td>
</tr>
<tr>
<td></td>
<td>MTW resembles asthma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Parent reported wheeze is not reliable</td>
<td></td>
</tr>
</tbody>
</table>

**VEW**: viral episodic wheezer  
**MTW**: multiple trigger wheezer
Long-acting bronchodilators

- Black box warning
  - Based on SMART trial 2006
    - 60,000 asthma patients
    - 28 weeks long
  - Salmeterol 42 mcg BID vs. placebo
    - About half of patients were taking ICS
    - Increased risk of asthma-related death or life-threatening experience

LABA adverse events mechanisms

- Subsensitization of response of airway smooth muscle
  - Receptor down-regulation
  - Receptor internalization

- Genotype of receptor appears to make a difference in subsensitization

- “Mask” airway inflammation
  - Stabilize airway smooth muscle
  - If ICS not used inflammation still present
LABA opinion

- ICS/LABA are not first-line treatment for asthma
- Patients on LABA should be evaluated frequently and step down of therapy attempted
- Consider use of anticholinergics
Leukotriene Modifiers

- Singulair (Montelukast)
- Accolate (Zafirlukast)
- Zyflo (Zileutin)

Therapeutic issues

✓ Drug interactions, monitor hepatic enzymes (esp. Zyflo)
ADHD increased with LI
Saricoban HE. Annal Asthma Allergy Immun
Vitamin D status and risk of asthma exacerbation

- 560 Puerto Rican children, 6 to 14 years of age, with (n = 287) and without (n=273) asthma.

- Vitamin D insufficiency (serum 25(OH)D <30 ng/ml) was noted in 47% of asthmatic children and 44% of controls.

- In asthmatic children, vitamin D insufficiency was associated with increased likelihood of severe AEs in the prior year (OR: 2.6), atopy, and decreased FEV₁/FVC ratio.

- After stratification for atopy, the relationship between vitamin D insufficiency and severe exacerbation was greater in nonatopics (6.2) than in atopic children (OR: 2).

Brehm JM, et al. Am J Respir Crit Care Med 2012; 186: 140-146
Resources

- National Asthma Education and Prevention Program
  - http://www.nhlbi.nih.gov/about/naepp/
- Asthma and Allergy Foundation of America
  - http://www.aafa.org
- American Lung Association
  - http://www.lungusa.org
- American Academy of Allergy, Asthma, and Immunology
  - http://www.aaaai.org
- Not One More Life – offers free CME
  - http://notonemorelife.org
Asthma Control Questionnaires

- Asthma Control Test (ACT): www.asthmacontrol.com
- Childhood Asthma Control test (C-Act)
- Asthma Control Questionnaire (ACQ): www.qoltech.co.uk/Asthma1.htm
- Asthma Therapy Assessment Questionnaire (ATAQ):
  - www.ataqinstrument.com
- Asthma Control Scoring System