Asthma Pharmacology
What the Primary Care NP Needs to Know
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Disclosure
- No financial disclosure
- This presentation will disclose off label use of asthma medications in pediatrics
- Slides courtesy of:
  - Jessica Erkman, CPNP
  - NYU Hassenfeld Children’s Hospital

Objectives
- Be comfortable prescribing alternatives to nebulized medication
- Individualize asthma care
- Learn appropriate MDI use with spacer administration technique
- Understand importance of particle size on lung deposition
- Understand off label dosing of bronchodilators
Nebulizer: Yes or NO

Spacer: Yes or No

Presumption

- You know what asthma is
- You can diagnose text book asthma
- You follow the asthma guidelines
- You have a general idea of determining asthma severity
Asthma

- Prevalence in U.S. = 6.2 million/8.4%
- Total direct cost of pediatric asthma
  - US: $5.92 billion in 2013
- 80% develop asthma symptoms prior to 5 years of age
- "Asthmas" not asthma: not a homogeneous disease but many phenotypes

Goals of Asthma Therapy

- Control current disease
  - Symptom free
  - Good sleep
  - Normal growth and development
  - Able to participate in usual activities
  - Minimize exacerbations (use of systemic steroids)
  - Avoid hospitalizations
  - Avoid/minimize side effects of medications

Rule of Twos

You have poorly controlled asthma if:
- Take a quick relief (rescue) inhaler (like albuterol) for problems more than 2 times a week
- Awaken at night with asthma problems more than 2 times a month
- Refill a quick relief inhaler more than 2 times a year
Step 1: All Ages
- Short acting beta-agonist (SABA)
- Onset of action: 10 minutes
- Median time to peak effect: 30 minutes
- Duration of action: 4 hours
- Indication: relief of bronchospasm
- Use AS NEEDED for symptoms
- Frequent use indicates need to step up
- Dose and delivery matters
- Side effects increase with dose

Bronchodilators
There is no difference between side effect profile between albuterol and levalbuterol when equivalent dosing is used
- **Albuterol**
  - Never use oral
  - Nebulizer
    - 1.25mg, 2.5mg, 0.583%
  - HFA 90mcg/puff
    - ProAir, Ventolin, Proventil
  - Breath actuated 90mcg/puff (ProAir)
- **Levalbuterol (Xopenex)**
  - Nebulizer suspension: 31mg, 0.63mg, 1.25 mgs
  - HFA 45 mcg/puff
Step 2

**Age 0-4**
- Low dose ICS,
- Alternative
  - Montelukast *
  - Cromolyn**

*Always 2nd line choice
**Avoid Cromolyn and Theophylline

**Age >4**
- Low dose ICS
- Alternative
  - Montelukast*
  - Cromolyn**
  - Theophylline**

Inhaled Corticosteroids

- Preferred 1st line choice for controller
- Many options
- Various formulations: nebulizer suspension, DPI, HFA, breath actuated HFA
- They are not all created equal
- Particle size and delivery methods matter

Side Effects

- Low dose ICS for extended periods: safe
  - NO clinically serious adverse events
- Medium-high dose
  - Decreased growth velocity of 1 cm in 1st year, not progressive
  - Some formulations have higher incidence of oropharyngeal Candida infections
- Nebulizer vs DPI vs HFA
- Fluticasone
- Proper use
- No Candida reported with Beclomethasone or Ciclesonide
Nebulized

- Budesonide suspension: 0.25, 0.5, 1 mg
- Lots of equipment: compressor, kit
- Requires electricity
- Very variable particle size 1-10 µm
  - Droplets range from 14-500 µm
  - Significant oropharyngeal deposition

Dry Powder Inhalants

- Flow dependent
- Requires inhalation velocity of >60 L/min
  - Many adults cannot achieve this
- Increased oropharyngeal deposition (80% vs 10% depending on the study)
  - Potential increased side effects
- Smaller particle size than nebulizer, 4-5 µm
- May be contraindicated in severe milk protein allergy

How to Use DPI

- Get a patient trainer from pharmaceutical representative
- Need to be able to take strong, deep inhalations
- Patient needs to be able to follow sophisticated instructions
- Most require a cap/button/twist to activate
Dry Powder Inhalers

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Available</th>
<th>FDA Approved Age Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluticasone: Flovent Diskus</td>
<td>50, 100, 250 mcg</td>
<td>&gt; 4 yo</td>
</tr>
<tr>
<td>Pulmicort Flexhaler</td>
<td>90, 180 mcg</td>
<td>&gt; 6 yo</td>
</tr>
<tr>
<td>Mometasone: Asmanex Twixthaler</td>
<td>110, 220 mcg</td>
<td>&gt; 4 yo</td>
</tr>
<tr>
<td>Fluticasone furoate: Arnuity Ellipta</td>
<td>50, 100, 200 mcg</td>
<td>&gt; 5 yo</td>
</tr>
</tbody>
</table>

DPI “Low Dose” Dosage

<table>
<thead>
<tr>
<th>Drug</th>
<th>5-11 years of age</th>
<th>≥12 years of age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluticasone</td>
<td>100-200 mcg/day</td>
<td>100-300 mcg/day/divided</td>
</tr>
<tr>
<td>Mometasone</td>
<td>110 mcg (1 inhalation/day)</td>
<td>110-220mcg/day</td>
</tr>
<tr>
<td>Budesonide</td>
<td>180-360 mcg/day (1-2 inh/BID)</td>
<td>180-540 mcg/day 1-3 inh/BID</td>
</tr>
</tbody>
</table>

Hydrofluoroalkane (HFA)
Metered Dose Inhalers

- Most appropriate choice in pediatrics
- Requires inhalation timed with device actuation—USE WITH SPACER
- Smallest particle size: 1-3 µm = small airway deposition
### HFA Options

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Available</th>
<th>FDA Approved Age Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluticasone (Flovent)</td>
<td>44, 110, 220 mcg</td>
<td>&gt; 4 yo</td>
</tr>
<tr>
<td>Mometasone (Asmanex)</td>
<td>100, 200 mcg</td>
<td>&gt; 12 yo</td>
</tr>
<tr>
<td>Ciclesonide (Alvesco)</td>
<td>80, 160 mcg</td>
<td>&gt;12 yo</td>
</tr>
</tbody>
</table>

### HFA “Low Dose” Dosage

<table>
<thead>
<tr>
<th>Drug</th>
<th>0-4 years of age</th>
<th>5-11 years of age</th>
<th>≥12 years of age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluticasone (Flovent)</td>
<td>Off label 44 mcg</td>
<td>88-176 mcg 2x/day</td>
<td>88-264 mcg 2x/day</td>
</tr>
<tr>
<td>Mometasone (Asmanex)</td>
<td>Off label 1 puff daily</td>
<td>Off label 1 puff daily</td>
<td>110-220 mcg 2 puffs daily</td>
</tr>
<tr>
<td>Ciclesonide (Alvesco)</td>
<td>Off Label 80 mcg</td>
<td>80-160 mcg 2 puffs daily</td>
<td>160-320 mcg 2 puffs2x/day</td>
</tr>
</tbody>
</table>

### How to Use HFA

- Choose the right spacer
- Most children <8 need a mask
  - Small =infants <2 yrs
  - Medium =toddlers-school aged
  - Large=large school aged-adolescents
- Many teenagers need a face mask
- Teach patient about the dose counter:
  - Believe the Counter
Spacer Instructions

- **Shake, Squirt, Breathe, Repeat, Refresh**
  - **Shake:** 10 seconds, apply mask to face, insert mouthpiece in mouth
  - **Squirt:** press inhaler ONCE
  - **Breathe:**
    - Mask: count 8-10 breaths/30 seconds if calm or 1 minute if not
    - Mouthpiece: take long, slow inhale and hold breath 8-10 seconds
    - Repeat if needed
  - **Refresh:**
    - Brush teeth/Gargle/Drink something
    - Wipe mask/mouthpiece with damp cloth
    - Wash whole spacer weekly

**Breath Actuated HFA**

- **Beclomethasone (QVAR) 40 and 80 mcg**
- **FDA approved over 4 years**
- **NO spacer—medication is released when you inhale**
- **Requires inhalation velocity of 22-36 L/min**
- **Reported side effects include:**
  - Psychiatric/behavioral changes
HFA is better than DPI/HFA

- Cheaper
- Easier to use
- Faster
- Portable
- HFA has the smallest particle size for small airway disease

Does Size Matter

![Diagram showing nasal cavity, trachea, bronchi, and alveoli.]
### Does Size Matter

<table>
<thead>
<tr>
<th>Inhaled Steroid</th>
<th>MMAD (um)</th>
<th>Lung deposition value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluticasone DPI</td>
<td>~4.0</td>
<td>15%</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>4.5</td>
<td>14%</td>
</tr>
<tr>
<td>Budesonide nebulized</td>
<td>2.3</td>
<td>8-14%</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>2.6</td>
<td>13%</td>
</tr>
<tr>
<td>Flunisolide HFA</td>
<td>1.2</td>
<td>68%</td>
</tr>
<tr>
<td>Budesonide HFA</td>
<td>1.1</td>
<td>56%</td>
</tr>
<tr>
<td>Ciclesonide</td>
<td>1.0</td>
<td>52%</td>
</tr>
</tbody>
</table>

### Leukotriene Modifiers
- Montelukast (Singulair)
- 4 mg (chewable/powder packets)
- 5 mg (chewable)
- 10 mg (chewable/tablet)
- Leukotriene modifiers (LTRA) are less efficacious than ICS
- Better alternative choice if concomitant rhinitis
- Lack of evidence supporting efficacy of use as add on therapy in children not controlled with ICS
- Rare psychiatric/behavioral changes

### Assessing Asthma Control
- Onset of action of ICS–2 weeks
- Peak benefit 4-6 weeks
- Needs to be on daily ICS at consistent doses for 4-6 weeks before assessing effectiveness
- Assessment includes
  - Symptoms
  - Exacerbations
  - Use of albuterol
  - Need for systemic corticosteroids
  - ED visit/hospitalization
  - Adverse medication side effects
  - Medication adherence/technique
Before You Step Up

- Did you trial low dose ICS long enough?
- Are they taking their medication?
- Are they using the proper technique?
- Are using ICS with small particle size?
- Switch formulation, continue low dose

Assessing Symptoms

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Well Controlled Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytime Symptoms</td>
<td>≤ 2/week</td>
</tr>
<tr>
<td>Nighttime Awakenings/Symptoms</td>
<td>0-1 nights/month</td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>NONE</td>
</tr>
<tr>
<td>Need for Rescue Medication (SABA)</td>
<td>≤ 2/week</td>
</tr>
<tr>
<td>Lung Function (PEF or FEV1)</td>
<td>NORMAL</td>
</tr>
<tr>
<td>Exacerbations</td>
<td>NONE (0-1x/yr)</td>
</tr>
</tbody>
</table>

“Stepping Up” Therapy

- In general, when stepping up therapy you double the ICS dose
- Reassess in minimum 4-6 weeks
- No response:
  - Consider alternative diagnosis
  - Needs referral to pediatric pulmonologist
Step 3

<table>
<thead>
<tr>
<th>Age 0-4</th>
<th>Age &gt; 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medium dose ICS</td>
<td>Medium dose ICS</td>
</tr>
<tr>
<td>Low dose ICS + LABA or LTRA</td>
<td></td>
</tr>
</tbody>
</table>

Addition of LABA to low dose ICS is controversial across various guidelines. You can leave it to the experts.

### Medium Dose ICS Drug Doses

<table>
<thead>
<tr>
<th>Drug</th>
<th>0-4 yrs</th>
<th>5-11 yrs</th>
<th>≥12 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nebulized Budesonide</td>
<td>0.5-2 mg 2x/day</td>
<td>1 mg 2x/day</td>
<td>Should not be using</td>
</tr>
<tr>
<td>Fluticasone (Flovent)</td>
<td>110 mcg 1p/BID</td>
<td>110 mcg 1p/BID</td>
<td>110 mcg 2p/BID</td>
</tr>
<tr>
<td>Mometasone (Asmanex HFA)</td>
<td>Off label</td>
<td>100 mcg 1p/BID</td>
<td>100 mcg 2p/BID</td>
</tr>
<tr>
<td>Ciclesonide (AlvescoHFA)</td>
<td>Off label</td>
<td>80 mcg 2p/BID</td>
<td>160 mcg 2 puffs</td>
</tr>
<tr>
<td>Beclomethasone (Qvar Redhaler)</td>
<td>Off label</td>
<td>80 mcg 2p/BID</td>
<td>80 mcg 2p/BID</td>
</tr>
</tbody>
</table>

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Long Acting Beta-Agonist (LABA)

- Badger study showed better response when LABA was added to ICS vs increasing ICS dose or addition of LTRA in children aged 6-11
- LABA has onset of action of 15 minutes
- Black box warning label
- Common side effects: muscle cramps/spasms

LABA Medication

<table>
<thead>
<tr>
<th>Medication</th>
<th>Available Doses</th>
<th>FDA Approved Age Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Budesonide/Formoterol</td>
<td>80/4.5 and 160/4.5 mcg</td>
<td>&gt;6 years</td>
</tr>
<tr>
<td>Mometasone/Formoterol (Dulera)</td>
<td>100/5 and 200/5 mcg</td>
<td>≥12 years</td>
</tr>
<tr>
<td>Fluticasone/Salmeterol (Advair)</td>
<td>HFA 45/21, 113/14, 232/14 Mcg</td>
<td>12 years</td>
</tr>
<tr>
<td></td>
<td>Diskus DPI 100/50, 250/50, 500/50mcg</td>
<td>&gt; 4 years</td>
</tr>
<tr>
<td>Fluticasone/Salmeterol (AirDuo Respclick)</td>
<td>55/12, 113/14, 232/14 mcg</td>
<td>&gt; 12 years</td>
</tr>
</tbody>
</table>

Beyond Step 3

- Why haven’t you referred?
- Use of high dose ICS initially
- Quadruple the dose
- If true failure, then addition of other therapies
  - LABA and/or LAMA (long acting muscarinic antagonists)
  - Biologics: Omalizumab (≥6yrs) Nucala (≥12 yrs) Fasenra (≥12 yrs)
  - Systemic steroids
- Needs phenotyping of asthma first
  Individually therapy by pulmonologist
Asthma Exacerbations

- Home Albuterol 2-8 puffs Q4H
- OR Progressive worsening symptoms or persistent symptoms
- Provider visit Or ED

Asthma Exacerbation

Provider Visit Can manage
- Can improve air entry/sx with albuterol in office
- Decadron IM 0.3-1.7 mg/kg = 5 day oral steroid course
- Prednisone 1-2 mg/kg/day
- For 3-5 days

Provider Visit Send to ER
- Tachypnea despite treatment
- Hypoxia
- Respiratory distress without treatment response
- Worsening symptoms and systemic steroid failure

Use of “Pulse ICS”

- Use of ICS at onset of symptoms for short duration in children on Step 1
- Controversial at best
- Evidence supporting use in children under 5 yrs is lacking
- Take away: these children likely have asthma and should be put on daily ICS
- Use of temporary high dose ICS during onset of illness or asthma exacerbation
Tiotropium: Spiriva Respimat
This is for the Pulmonologist

- Long-acting anti-cholinergic (LAMA)
- Long acting maintenance bronchodilator
- Alternative to LABA or in addition to
- Dose: 1.25 mcg/day, max 2.5 mcg/day
- Approved for children >6 yrs
- Slow moving mist inhaler: No spacer
  - Complicated to set up
  - Utilize video instructions, get trainer

Omalizumab (Xolair)
For the Pulmonologist

- Indication: moderate to severe allergic asthma uncontrolled on ICS, allergic sensitivity to perennial aeroallergens
- Needs elevated serum IgE (>30IU/ml)
- Mechanism: anti-IgE antibody
- Adverse event: anaphylaxis possible, Give in clinical setting
- Approved >6 yrs
- SQ/IM injection every 2-4 weeks
  - Weight and IgE level based
  - New prefilled syringe formulation

Mepolizumab
Nucala

- Indication: add on maintenance treatment for severe eosinophilic asthma
- Mechanism: IL-5 antagonist monoclonal antibody
- Requirements:
  - Serum eos cells/µL
  - ≥2 hospitalizations/year or daily OCS
  - 2 or more controller medications
  - Approved ≥12 yrs
- Dosing: SQ injection q4 weeks
- Needs to be reconstituted
Benralizumab
Fasenra

- **Indication**: add on maintenance treatment for severe eosinophilic asthma
- **Binds to surface of eosinophils**
- **Mechanism**: IL-5 receptor alpha-directed cytolytic monoclonal antibody
- **Requirements**
  - Serum eos ≥ 300 cells/µL
  - ≥ 2 exacerbations
- **Dosing**: SQ injection, after 3rd dose, every 8 weeks
- Prefilled syringe
- Approved for ≥12yrs

References

- Papadopoulos, NG, Arakawa KH, Carlsen A. International consensus of (ICON) pediatric asthma. Allergy. 2012; 67:976-997
- Vaghi A, Berg E, Lijedahl S, Svensson JO. In vitro comparison of nebulized budesonide (Pulmicort Respules) and Beclomethasone dipropionate (Bclen per Aerosol). Pul Pharmcol Ther. 2006; 18 (2): 151-1