Pediatric vs. Adult Asthma: What is the Difference?

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Jeff Zobell, Pharm.D.
Objectives

• Discuss the differences between adult and pediatric asthma
• Describe the mechanisms of action of the different asthma medications
• List the limitations of the SMART study
Asthma Guidelines

- Asthma treatment guidelines were revised in 2007—called the Expert Panel Report 2007
- http://www.nhlbi.nih.gov/guidelines/asthma
- Main area of difference = goal of asthma therapy = ASTHMA CONTROL
Asthma Guidelines

• Four keys areas of asthma care to help achieve and maintain control
  – Assessment & Monitoring
  – Patient Education
  – Control of factors contributing to asthma severity
  – Pharmacologic Treatment
Figure 4–1a. Stepwise Approach for Managing Asthma in Children 0–4 Years of Age

Interruption Asthma

Persistent Asthma: Daily Medication
Consult with asthma specialist if step 3 care or higher is required.
Consider consultation at step 2.

Step 1
Preferred: Low-dose ICS
Alternative: Cromolyn or Montelukast

Step 2
Preferred: Medium-dose ICS

Step 3
Preferred: High-dose ICS + either LABA or Montelukast

Step 4
Preferred: Oral systemic corticosteroids

Step 5
Preferred: Oral systemic corticosteroids

Step 6
Preferred: Oral systemic corticosteroids

Patient Education and Environmental Control at Each Step

Quick-Relief Medication for All Patients
- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms.
- With viral respiratory infection: SABA q 4–6 hours up to 24 hours (longer with physician consult). Consider short course of oral systemic corticosteroids if exacerbation is severe or patient has history of previous severe exacerbations.
- Caution: Frequent use of SABA may indicate the need to step up treatment. See text for recommendations on initiating daily long-term control therapy.

Key: Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy. ICS, inhaled corticosteroid; LABA, inhaled long-acting beta₂-agonist; SABA, inhaled short-acting beta₂-agonist

Notes:
- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- If clear benefit is not observed within 4–6 weeks and patient/family medication technique and adherence are satisfactory, consider adjusting therapy or alternative diagnosis.
- Studies on children 0–4 years of age are limited. Step 2 preferred therapy is based on Evidence A. All other recommendations are based on expert opinion and extrapolation from studies in older children.
FIGURE 4–1b. STEPWISE APPROACH FOR MANAGING ASTHMA IN CHILDREN 5–11 YEARS OF AGE

Persistent Asthma: Daily Medication
Consult with asthma specialist if step 4 care or higher is required.
Consider consultation at step 3.

Step 1
Preferred: Low-dose ICS
Alternative: Cromolyn, LTRA, Nedocromil, or Theophylline

Step 2
Preferred: Low-dose ICS
Alternative: Cromolyn, LTRA, Nedocromil, or Theophylline
OR Medium-dose ICS

Step 3
Preferred: Medium-dose ICS + LABA
Alternative: Medium-dose ICS + either LTRA or Theophylline

Step 4
Preferred: High-dose ICS + LABA
Alternative: High-dose ICS + either LTRA or Theophylline

Step 5
Preferred: High-dose ICS + LABA + oral systemic corticosteroid
Alternative: High-dose ICS + either LTRA or Theophylline + oral systemic corticosteroid

Step 6
Step up if needed
(1st check adherence, inhaler technique, environmental control, and comorbid conditions)
Assess control
Step down if possible
(and asthma is well controlled for at least 3 months)

Each step: Patient education, environmental control, and management of comorbidities.
Steps 2–4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma
(see notes)

Quick-Relief Medication for All Patients
- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed.
- Caution: Increasing use of SABA or use >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.

Key: Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy. ICS, inhaled corticosteroid; LABA, inhaled long-acting beta₂-agonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting beta₂-agonist

Notes:
- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- Theophylline is a less desirable alternative due to the need to monitor serum concentration levels.
- Step 1 and step 2 medications are based on Evidence A. Step 3 ICS + adjunctive therapy and ICS are based on Evidence B for efficacy of each treatment and extrapolation from comparator trials in older children and adults—comparator trials are not available for this age group; steps 4–6 are based on expert opinion and extrapolation from studies in older children and adults.
- Immunotherapy for steps 2–4 is based on Evidence B for house-dust mites, animal danders, and pollens. Evidence is weak or lacking for molds and cockroaches. Evidence is strongest for immunotherapy with single allergens. The role of allergy in asthma is greater in children than in adults. Clinicians who administer immunotherapy should be prepared and equipped to identify and treat anaphylaxis that may occur.
Step 1

Preferred:

SABA PRN

For Children 0-11 years old
Short Acting Beta$_2$-Agonists

- Albuterol
- Levalbuterol
- Pirbuterol

**Mechanisms**

- **Bronchodilation.** Binds to the beta$_2$-adrenergic receptor, producing smooth muscle relaxation following adenylate cyclase activation and increase in cyclic AMP producing functional antagonism of bronchoconstriction.
Quick-relief Beta\textsubscript{2} Agonists
Spacers

www.google.com
accessed 1/30/07
Step 2

Preferred:
Low-dose ICS

Alternative:
Cromolyn or Montelukast

For Children 0-4 years old
Step 2

Preferred:
Low-dose ICS

Alternative:
Cromolyn, LTRA, Nedocromil, or Theophylline
Inhaled Corticosteroids

• Many different inhaled corticosteroids exist on the U.S. market
• All share the same mechanism of action
• Vary based on dosing (based on potency)

Mechanisms

■ Anti-inflammatory. Block late reaction to allergen and reduce airway hyperresponsiveness. Inhibit cytokine production, adhesion protein activation, and inflammatory cell migration and activation.
■ Reverse beta$_2$-receptor downregulation. Inhibit microvascular leakage.
Leukotriene Modifier

- Two medications exist in U.S. market that match this description
  - Zafirlukast (Accolate®)
  - Montelukast (Singular®)

**Leukotriene Receptor Antagonists (LTRAs)**

- **Mechanisms**
  - Leukotriene receptor antagonist; selective competitive inhibitor of CysLT₁ receptor.
Methylxanthines

- Theophylline
- Aminophylline

**Mechanisms**

- **Bronchodilation.** Smooth muscle relaxation from phosphodiesterase inhibition and possibly adenosine antagonism.

- May affect eosinophilic infiltration into bronchial mucosa as well as decreases T-lymphocyte numbers in epithelium.

- Increases diaphragm contractility and mucociliary clearance.
Step 3

Preferred:
Medium-dose ICS

For Children 0-4 years
Step 3

*Preferred:

EITHER:
Low-dose ICS + either LABA, LTRA, or Theophylline

OR
Medium-dose ICS

For Children
5-11 years
Long-Acting Beta\textsubscript{2}-Agonists

- Salmeterol
- Formoterol
- Combinations with ICS

\textit{Mechanisms}

- **Bronchodilation.** Smooth muscle relaxation following adenylate cyclase activation and increase in cyclic AMP, producing functional antagonism of bronchoconstriction.

- Compared to SABA, salmeterol (but not formoterol) has slower onset of action (15–30 minutes). Both salmeterol and formoterol have longer duration (>12 hours) compared to SABA.
Long Acting Beta$_2$ Agonists
Formoterol

Salmeterol

Fluticasone/Salmeterol

Budesonide/formoterol

www.allergy.peds.arizona.edu accessed 2/28/08
<table>
<thead>
<tr>
<th>Step 5</th>
<th>Step 6</th>
</tr>
</thead>
</table>
| **Preferred:**  
High-dose ICS + either LABA or Montelukast | **Preferred:**  
High-dose ICS + either LABA or Montelukast  
Oral systemic corticosteroids |

For Children 0-4 years
Step 5

*Preferred:*
High-dose ICS + LABA

*Alternative:*
High-dose ICS + either LTRA or Theophylline

Step 6

*Preferred:*
High-dose ICS + LABA + oral systemic corticosteroid

*Alternative:*
High-dose ICS + either LTRA or Theophylline + oral systemic corticosteroid

For Children 5-11 years
Oral Corticosteroids

- Methylprednisolone
- Prednisone
- Prednisolone

**Mechanisms**

- **Anti-inflammatory.** Block late reaction to allergen and reduce airway hyperresponsiveness. Inhibit cytokine production, adhesion protein activation, and inflammatory cell migration and activation.

- Reverse beta$_2$-receptor downregulation. Inhibit microvascular leakage.
Steps 2–4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma (see notes).
Immunotherapy

- Omalizumab (anti-IgE)

**Mechanisms**

- Binds to circulating IgE, preventing it from binding to the high-affinity (FcεRI) receptors on basophils and mast cells.
- Decreases mast cell mediator release from allergen exposure.
- Decreases the number of FcεR1s in basophils and submucosal cells.

www.google.com accessed 02/28/08
I HAVE ASTHMA BUT
ASTHMA DOESN'T HAVE
ME ME ME ME ME ME
## Classification of Asthma Severity

### ≥12 years of age

<table>
<thead>
<tr>
<th>Components of Severity</th>
<th>Intermittent</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Impairment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal FEV₁/FVC:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8–19 yr</td>
<td>≤2 days/week</td>
<td>&gt;2 days/week but not daily</td>
<td>Daily</td>
<td>Throughout the day</td>
</tr>
<tr>
<td>20–39 yr</td>
<td>≤2x/month</td>
<td>3–4x/month</td>
<td>&gt;1x/week but not nightly</td>
<td>Often 7x/week</td>
</tr>
<tr>
<td>40–59 yr</td>
<td>≤2 days/week</td>
<td>&gt;2 days/week but not daily, and not more than 1x on any day</td>
<td>Daily</td>
<td>Several times per day</td>
</tr>
<tr>
<td>60–80 yr</td>
<td>None</td>
<td>Minor limitation</td>
<td>Some limitation</td>
<td>Extremely limited</td>
</tr>
<tr>
<td>Lung function</td>
<td>Normal FEV₁ between exacerbations</td>
<td>FEV₁ &gt;80% predicted</td>
<td>FEV₁ &gt;60% but &lt;80% predicted</td>
<td>FEV₁ &lt;60% predicted</td>
</tr>
<tr>
<td></td>
<td>FEV₁/FVC normal</td>
<td>FEV₁/FVC normal</td>
<td>FEV₁/FVC reduced 5%</td>
<td>FEV₁/FVC reduced &gt;5%</td>
</tr>
<tr>
<td><strong>Risk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exacerbations</td>
<td>0–1/year (see note)</td>
<td>≥2/year (see note)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>requiring oral</td>
<td>Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category.</td>
<td>Relative annual risk of exacerbations may be related to FEV₁.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>systemic corticosteroids</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Recommended Step for Initiating Treatment

(See figure 4–5 for treatment steps.)

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3</th>
<th>Step 4 or 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>In 2–6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.</td>
<td>and consider short course of oral systemic corticosteroids</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Persistent Asthma: Daily Medication
Consult with asthma specialist if step 4 care or higher is required.
Consider consultation at step 3.

Step 1
Preferred: SABA PRN
Alternative: Cromolyn, LTRA, Nedocromil, or Theophylline

Step 2
Preferred: Low-dose ICS + LABA
OR
Medium-dose ICS
Alternative: Low-dose ICS + either LTRA, Theophylline, or Zileuton

Step 3
Preferred: Medium-dose ICS + LABA
AND
Consider Omalizumab for patients who have allergies

Step 4
Preferred: High-dose ICS + LABA + oral corticosteroid
AND
Consider Omalizumab for patients who have allergies

Step 5
Preferred: High-dose ICS + LABA + oral corticosteroid
AND
Consider Omalizumab for patients who have allergies

Step 6
Preferred: High-dose ICS + LABA + oral corticosteroid
AND
Consider Omalizumab for patients who have allergies

Quick-Relief Medication for All Patients
- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed.
- Use of SABA >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.

Each step: Patient education, environmental control, and management of comorbidities.
Steps 2–4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma (see notes).

Step up if needed (first, check adherence, environmental control, and comorbid conditions)
Assess control
Step down if possible (and asthma is well controlled at least 3 months)
# Classification of Asthma Control (≥12 years of age)

<table>
<thead>
<tr>
<th>Impairment</th>
<th>Well Controlled</th>
<th>Not Well Controlled</th>
<th>Very Poorly Controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>≤2 days/week</td>
<td>&gt;2 days/week</td>
<td>Throughout the day</td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>≤2x/month</td>
<td>1–3x/week</td>
<td>≥4x/week</td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>None</td>
<td>Some limitation</td>
<td>Extremely limited</td>
</tr>
<tr>
<td>Short-acting beta₂-agonist use for symptom control (not prevention of EIB)</td>
<td>≤2 days/week</td>
<td>&gt;2 days/week</td>
<td>Several times per day</td>
</tr>
<tr>
<td>FEV₁ or peak flow</td>
<td>&gt;80% predicted/personal best</td>
<td>60–80% predicted/personal best</td>
<td>&lt;60% predicted/personal best</td>
</tr>
</tbody>
</table>
| Validated questionnaires | ATAAQ
ACQ
ACT | 0
≤0.75*
≥20 | 1–2
≥1.5
16–19
≤15 |

<table>
<thead>
<tr>
<th>Risk</th>
<th>0–1/year</th>
<th>≥2/year (see note)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exacerbations requiring oral systemic corticosteroids</td>
<td>Consider severity and interval since last exacerbation</td>
<td></td>
</tr>
<tr>
<td>Progressive loss of lung function</td>
<td>Evaluation requires long-term followup care</td>
<td></td>
</tr>
<tr>
<td>Treatment-related adverse effects</td>
<td>Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.</td>
<td></td>
</tr>
</tbody>
</table>

### Recommended Action for Treatment
(see figure 4–5 for treatment steps)

- Maintain current step.
- Regular followups every 1–6 months to maintain control.
- Consider step down if well controlled for at least 3 months.
- Step up 1 step and Reevaluate in 2–6 weeks.
- For side effects, consider alternative treatment options.
- Consider short course of oral systemic corticosteroids.
- Step up 1–2 steps, and Reevaluate in 2 weeks.
- For side effects, consider alternative treatment options.
1. In the past 4 weeks, how much of the time did your **asthma** keep you from getting as much done as you would like at work, school or at home?

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

2. During the past 4 weeks, how often have you had shortness of breath?

<table>
<thead>
<tr>
<th>More than once a day</th>
<th>Once a day</th>
<th>3 to 6 times a week</th>
<th>Once or twice a week</th>
<th>Not at all</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3. During the past 4 weeks, how often did your **asthma symptoms** (coughing, wheezing, shortness of breath, chest tightness or pain in the morning) **wake you up at night or earlier than usual**?

<table>
<thead>
<tr>
<th>4 or more nights a week</th>
<th>2 or 3 nights a week</th>
<th>Once a week</th>
<th>Once or twice</th>
<th>Not at all</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

4. During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?

<table>
<thead>
<tr>
<th>3 or more times per day</th>
<th>1 or 2 times per day</th>
<th>2 or 3 times per week</th>
<th>Once a week or less</th>
<th>Not at all</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

5. How would you rate your **asthma control** during the past 4 weeks?

<table>
<thead>
<tr>
<th>Not controlled at all</th>
<th>Poorly controlled</th>
<th>Somewhat controlled</th>
<th>Well controlled</th>
<th>Completely controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

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Please enter your ZIP code: [ ]

[Why my ZIP Code?]
Stepping UP (EPR 3, 2007)

• Asthma NOT WELL CONTROLLED
  – Review adherence, inhaler technique, environmental control, co morbid conditions
  – Step up 1 step and reevaluate in 2-6 weeks

• Asthma VERY POORLY CONTROLLED
  – Review adherence, inhaler technique, environmental control, co morbid conditions
  – Consider short course of oral steroid
  – Step up 1 or 2 steps and reevaluate in 2 weeks
Persistent Asthma: Daily Medication

Consult with asthma specialist if step 4 care or higher is required.
Consider consultation at step 3.

Step 1
Preferred: SABA PRN

Step 2
Preferred: Low-dose ICS
Alternative: Cromolyn, LTRA, Nedocromil, or Theophylline

Step 3
Preferred: Medium-dose ICS + LABA
Alternative: Medium-dose ICS + either LTRA, Theophylline, or Zileuton

Step 4
Preferred: High-dose ICS + LABA
AND
Consider Omalizumab for patients who have allergies

Step 5
Preferred: High-dose ICS + LABA + oral corticosteroid
AND
Consider Omalizumab for patients who have allergies

Step 6
Step up if needed (first, check adherence, environmental control, and comorbid conditions)
Assess control
Step down if possible (and asthma is well controlled at least 3 months)

Each step: Patient education, environmental control, and management of comorbidities.
Steps 2–4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma (see notes).

Quick-Relief Medication for All Patients

- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed.
- Use of SABA >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.
<table>
<thead>
<tr>
<th>Study</th>
<th>FEV-1 AM/PM</th>
<th>PEF AM/PM</th>
<th>Asthma Symptoms</th>
<th>SABA Use</th>
<th>Exacerbation Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>VanNoord 1999 FP/SLM vs FP</td>
<td>↑</td>
<td>↑</td>
<td>↓ Daytime &amp; nighttime</td>
<td>↓</td>
<td>~</td>
</tr>
<tr>
<td>Baraniuk 1999 FP/SLM vs FP vs TAA</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>n/a</td>
</tr>
<tr>
<td>Wenzel 1998 SLM vs ALB</td>
<td>n/a</td>
<td>↑</td>
<td>↓</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Woolcock 1996 BDP/SALM vs BDP</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>n/a</td>
<td>~</td>
</tr>
<tr>
<td>Greening 1994 BDP/SALM vs BDP</td>
<td>n/a</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>~</td>
</tr>
</tbody>
</table>
ICS + LABA in asthma

<table>
<thead>
<tr>
<th>Study</th>
<th>FEV-1</th>
<th>PEF AM/PM</th>
<th>Asthma symptoms</th>
<th>Reliever medicine use</th>
<th>Exacerbation Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabe2006 BUD/FORM vs BUD (2x)</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>O'Byrne 2005 BUD/FORM vs BUD</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Lallo 2003 BUD/FORM vs BUD</td>
<td>~</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>O'Byrne 2001 BUD/FORM vs BUD</td>
<td>↑</td>
<td>n/a</td>
<td>↓</td>
<td>n/a</td>
<td>↓</td>
</tr>
<tr>
<td>Pauwels 1999 BUD/FORM vs BUD</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>
Stepping DOWN (GINA, 2009)
(asthma is controlled ≥3months)

• If pt on Medium-High dose
  – Reduce dose 50% at 3 month intervals (Evidence B)
• If control achieved on low dose
  – Switch to once daily (Evidence A)
• If pt taking ICS + LABA
  – Reduce ICS dose 50% + LABA (Evidence B)
  – Once control achieved on low dose + LABA (Evidence D)
    • Attempt to d/c LABA
• If pt taking ICS + other controller
  – Reduce ICS dose 50% + other controller (Evidence D)
  – Once control achieved on low dose + other controller (Evidence D)
    • Attempt to d/c other controller
• If pt on lowest dose of controller and no symptoms for 1 year
  – Attempt to d/c controller
Persistent Asthma: Daily Medication
Consult with asthma specialist if step 4 care or higher is required.
Consider consultation at step 3.

Step 1
Preferred: SABA PRN
Alternative: Low-dose ICS
Cromolyn, LTRA, Nedocromil, or Theophylline

Step 2
Preferred: Medium-dose ICS + LABA
Low-dose ICS + LABA OR
OR
Medium-dose ICS + either LTRA, Theophylline, or Zileuton
Alternative: Low-dose ICS + either LTRA, Theophylline, or Zileuton

Step 3
Preferred: Medium-dose ICS + LABA
AND
Consider Omalizumab for patients who have allergies

Step 4
Preferred: High-dose ICS + LABA + oral corticosteroid
AND
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Step 5
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Step 6
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Assess control
Step down if possible
(and asthma is well controlled at least 3 months)

Each step: Patient education, environmental control, and management of comorbidities.
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• Use of SABA >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.

EPR 3, 2007

- Salmeterol Multicenter Asthma Research Trial (SMART)
- 28-week, multi-center, randomized, double-blind, placebo-controlled, observational surveillance trial initiated in July 1996
- 6163 US sites; 1316 investigators
- Target enrollment: ~60,000 patients
- >12 yrs with asthma currently using prescription asthma medications
  - no history of previous salmeterol/formoterol use
- All therapy taken on outpatient basis
SMART Study Design

Usual Care + blinded salmeterol MDI (42mcg) BID

• No LABA

• ≥ 12 years of age
• No beta blockers

Phone contacts every 4 weeks

Usual Care + blinded placebo MDI BID

Study Visit 1
Day 0
Study procedures reviewed; 6 month supply of study medication provided

28 weeks
Study Endpoints

• Primary Endpoint
  – Combined number of respiratory-related deaths or respiratory-related life-threatening experiences (intubation and ventilation)

• Secondary Endpoints
  – Combined asthma-related deaths or life-threatening experiences
  – Asthma-related deaths
# Demographics

<table>
<thead>
<tr>
<th></th>
<th>Salmeterol</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=13,176)</td>
<td>(n=13,179)</td>
</tr>
<tr>
<td><strong>Age, mean</strong></td>
<td>39.2</td>
<td>39.1</td>
</tr>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>8334 (64)</td>
<td>8337 (64)</td>
</tr>
<tr>
<td>Male</td>
<td>4703 (36)</td>
<td>4686 (36)</td>
</tr>
<tr>
<td><strong>Ethnic Origin, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>9281 (71)</td>
<td>9361 (72)</td>
</tr>
<tr>
<td>African American</td>
<td>2366 (18)</td>
<td>2319 (18)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>996 (8)</td>
<td>999 (8)</td>
</tr>
<tr>
<td>Asian</td>
<td>173 (1)</td>
<td>149 (1)</td>
</tr>
<tr>
<td>Other</td>
<td>230 (2)</td>
<td>224 (2)</td>
</tr>
</tbody>
</table>
Baseline Asthma Characteristics in Caucasians and African Americans

<table>
<thead>
<tr>
<th></th>
<th>Caucasian (n=18,642)</th>
<th>African American (n=4683)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yrs), mean</strong></td>
<td>40.3</td>
<td>36.5</td>
</tr>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6733 (36)</td>
<td>1545 (33)</td>
</tr>
<tr>
<td>Female</td>
<td>11,718 (64)</td>
<td>3086 (67)</td>
</tr>
<tr>
<td><strong>PEF % Predicted</strong></td>
<td>85.3</td>
<td>78.1</td>
</tr>
<tr>
<td><strong>Baseline ICS Use</strong></td>
<td>49%</td>
<td>38%</td>
</tr>
<tr>
<td>≥1 ER visit in last 12 mths</td>
<td>22%</td>
<td>41%</td>
</tr>
<tr>
<td>≥1 ER visit in lifetime</td>
<td>59%</td>
<td>72%</td>
</tr>
<tr>
<td>≥1 hospitalization in last 12 mths</td>
<td>6%</td>
<td>15%</td>
</tr>
<tr>
<td>≥1 hospitalization in lifetime</td>
<td>30%</td>
<td>45%</td>
</tr>
<tr>
<td>≥1 intubation for asthma in lifetime</td>
<td>4%</td>
<td>8%</td>
</tr>
<tr>
<td>Nocturnal symptoms present</td>
<td>59%</td>
<td>67%</td>
</tr>
</tbody>
</table>
## SMART Results
### Total and Subgroups

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>RR (95% CI)</th>
<th>SAL n</th>
<th>PLA n</th>
</tr>
</thead>
<tbody>
<tr>
<td>1° Endpoint</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory Death or Life Threatening Experience</td>
<td>1.40 (0.91, 2.14)</td>
<td>50</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>1.05 (0.62, 1.76)</td>
<td>29</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>4.10 (1.54, 10.90)</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>5.82 (0.70, 48.37)</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1.08 (0.55, 2.14)</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>2.29 (0.94, 5.56)</td>
<td>16</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>3.88 (0.83, 18.26)</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>4.37 (1.25, 15.34)</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>5.82 (0.70, 48.37)</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>7.26 (0.89, 58.94)</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>2° Endpoints</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory Death</td>
<td>1.71 (1.01, 2.89)</td>
<td>37</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>1.08 (0.55, 2.14)</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>4.92 (1.68, 14.45)</td>
<td>19</td>
<td>4</td>
</tr>
<tr>
<td>Asthma Death or Life Threatening Experience</td>
<td>4.37 (1.25, 15.34)</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>5.82 (0.70, 48.37)</td>
<td>6</td>
<td>1</td>
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<td></td>
<td>7.26 (0.89, 58.94)</td>
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<td>1</td>
</tr>
</tbody>
</table>

- **Total**: N=13176, N=13179
- **Caucasian**: N=9281, N=9361
- **African American**: N=2366, N=2319
SMART Results
Total and Subgroups

1st Endpoint
- Respiratory Death or Life Threatening Experience
  - African American ICS (SAL N=906, PLA N=785)
  - African American Non-ICS (SAL N=1460, PLA N=1444)
  - Caucasian ICS (SAL N=4586, PLA N=4637)
  - Caucasian Non-ICS (SAL N=4695, PLA N=4724)
  - RR (95% CI) SAL n PLA n
    - 0.88 (0.42, 1.84) 13 15
    - 1.25 (0.60, 2.60) 16 13
    - 3.02 (0.82, 11.11) 9 3
    - 5.61 (1.25, 25.26) 11 2

2nd Endpoints
- Respiratory Death
- Asthma Death or Life Threatening Experience
  - RR (95% CI) SAL n PLA n
    - 2.31 (0.60, 8.93) 7 3
    - 2.29 (0.70, 7.42) 9 4
    - 3.12 (0.33, 29.92) 3 1
    - 4.43 (0.52, 37.89) 5 1

Asthma Death
  - RR (95% CI) SAL n PLA n
    - 0.68 (0.24, 1.90) 6 9
    - 1.62 (0.63, 4.17) 11 7
    - 3.02 (0.82, 11.11) 9 3
    - 10.46 (1.34, 81.58) 10 1

  - RR (95% CI) SAL n PLA n
    - 0.96 (0.06, 15.35) 1 1
    - 3.12 (0.33, 29.92) 3 1

- African American ICS (SAL N=906, PLA N=785)
- Caucasian ICS (SAL N=4586, PLA N=4637)
- African American Non-ICS (SAL N=1460, PLA N=1444)
- Caucasian Non-ICS (SAL N=4695, PLA N=4724)
Summary of SMART Results

• Total Population
  – No significant differences in the primary endpoint
  – A significant increase (?), in secondary endpoint of asthma-related deaths was observed in patients receiving salmeterol
    • 13 vs. 3 pts

• African Americans
  – Statistically significant increase in combined respiratory and asthma-related deaths
    • Worse asthma at baseline
    • NO baseline ICS led to increased risk
  – No difference in asthma-related death alone

• Caucasians
  – No significant increase in primary or secondary endpoint s
Safety LABA (EPR 3, 2007)

• If asthma not sufficiently controlled with ICS alone, the option of increasing the ICS dose to addition of LABA
  – Based Salmeterol Multicenter Asthma Research Trial (SMART) conducted by Nelson et al. Chest 2006
  – High dose formoterol trial conducted by Mann et al. Chest 2007

• In general do not exceed salmeterol 100mcg or 24mcg formoterol daily
Safety LABA (FDA, 2010)

- Use of a LABA alone without use of a long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated (absolutely advised against) in the treatment of asthma.
- LABAs should not be used in patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.
- LABAs should only be used as additional therapy for patients with asthma who are currently taking but are not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid.
Safety LABA (FDA, 2010)

- Once asthma control is achieved and maintained, patients should be assessed at regular intervals and step down therapy should begin (e.g., discontinue LABA), if possible without loss of asthma control, and the patient should continue to be treated with a long-term asthma control medication, such as an inhaled corticosteroid.

- Pediatric and adolescent patients who require the addition of a LABA to an inhaled corticosteroid should use a combination product containing both an inhaled corticosteroid and a LABA, to ensure adherence with both medications.
MDI-technique “Is significant”

  – 56% of patients made errors in MDI-technique which resulted in a 30% decrease in bronchodilation versus control (p<0.01)

  – 71% of patients misused MDI’s (47% due to poor coordination)
  – Asthma less stable in misusers (p<0.001)
  – Among misusers, asthma less stable in poor coordinators (p<0.001)
MDI technique

- 50% of adults and children do not perform all steps correctly (Crompton GK. Lung 1990;Suppl 168:658-662)
- Reasons for noncompliance
  - Not taking off cap
  - Not shaking
  - Failure to coordinate actuation with inspiration
  - Inhale through nose and not mouth
  - Inhale too fast
  - Failure to breath-hold after dose
  - “Cold freon” effect
  - Holding MDI upside down
MDI technique

  - 50% of patients reverted back to incorrect technique after one to 30 days after instruction.
  - Only 10.8% of patients performed all steps required for proper MDI-technique.
MDI technique

- Plaza et al. Resp 1998;65:195-198
  - 9% of patients, 15% of nurses, and 28% of physicians showed correct MDI-technique.

  - 65% of patients, 39% of housestaff, 82% of nurses were categorized as having “poor” MDI-technique.
Conclusions

• Asthma is a very serious problem
• Guidelines have been developed & recently amended to focus on control
• Medications vary by their mechanism of action & purpose
• Cooperation between patient, family, medical team is essential