Recent Advances in the Treatment of Asthma

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Asthma is Inflammation

Mild to moderate asthma

When does it start?
Can it be prevented?
Can it be reversed?
Can certain therapies make it worse?

JEFFERY PK. AJRCCM 2001; 164:S28-S38
NHLBI Asthma Guidelines

National Asthma Education and Prevention Program: Expert Panel Report #3

1991 Asthma is an inflammatory disease

1997 Early recognition and treatment

2002 Update on selected topics

2007 EPR-3
New Concepts

- Recommendations are now made using 3 age ranges, not 2 (0-4, 5-11, ≥ 12 yrs)
- Concept of severity and control
- Evaluation of both severity and control using two domains:
  - Impairment
  - Risk

Severity, Control and Responsiveness

Severity
- Intrinsic intensity of the disease process
- Severity is most easily and directly measured in patients not receiving long-term therapy
- *Guides clinical decisions during the initial evaluation and prior to start of controller therapy*

Control
- Degree to which asthma-related symptoms, functional impairment, and risk of untoward events are minimized and the goals of therapy are met
- *Guides clinical decisions to either maintain or adjust therapy once therapy is initiated*

Responsiveness
- Ease with which asthma control is achieved by therapy
- Responsiveness to asthma treatment is highly variable
Current Impairment and Future Risk

Both severity and control include the domains of **current impairment** and **future risk**

**Impairment (cross-sectional)**
- Frequency and intensity of symptoms and functional limitations (pulmonary function, quality of life) the patient is currently experiencing or has recently experienced

**Risk (longitudinal)**
- Likelihood of asthma exacerbations, progressive decline in lung function, or risk of adverse effects from medications

Primary Goal of Therapy: Achieving and Maintaining Asthma Control

- Primary goal of asthma therapy is to enable a patient to achieve and maintain control over their asthma
  - Eliminate impairments including symptoms, functional limitations, poor quality of life, and other manifestations of asthma
  - Reduce risk of exacerbations, ED use, and hospitalizations
- Treatment goals are identical for all levels of asthma severity

Short acting beta agonists (SABAs)
Safety and Efficacy of Therapies Used to Treat Mild to Moderate Asthma: Beta Agonists

Question: Is treatment with regularly scheduled albuterol safe?

Answer: Not harmful; not beneficial

BAGS (Beta Agonist Study) Trial

NEJM 335:841, 1996
**Question**: Do beta receptor polymorphisms influence response to chronic treatment with beta agonists?

**Answer**: Yes. Patients with the Arg/Arg genotype at codon 16 may be at increased risk of loss of asthma control.

AJRCCM 162:75, 2000
Run out

Weeks after Randomization

Arg/Arg-PRN
Gly/Gly-Regular
Arg/Arg-Regular

Israel E et al., AJRCCM 2000; 162:75-80
Safety and Efficacy of Therapies Used to Treat Mild to Moderate Asthma: *Beta Agonists*

**BARGE (Beta Adrenergic Response by Genotype) Trial**

- **Question:** Does the B16 loci influence asthma outcome measures other than PEF?

  *First asthma clinical trial in which patients were randomized by genotype*

- **Answer:** Yes. Subjects with the Arg/Arg genotype have better control when regularly scheduled albuterol is stopped. Subjects with the Gly/Gly genotype have improved control with regular use.

*Lancet 364:1505, 2004*
Long acting beta agonists (LABAs)
Question: In patients with mild persistent asthma, well controlled on ICS, can salmeterol replace the ICS and be used as monotherapy?

Answer: No. Salmeterol monotherapy increases the risk of loss of asthma control.

JAMA 285:2583, 2001
Combination Therapy
More ICS or add a LABA?

  - Improved impairment; no difference in risk domain

  - Improved impairment; no difference in risk domain
FACET Study: Formoterol and Budesonide in Moderate Asthma

Budesonide 100mcg/400mcg BID Formoterol 12mcg BID

**p=0.01

**

Safety and Efficacy of Therapies Used to Treat Mild to Moderate Asthma: *Beta Agonists*

**Question:**
ICS (uncontrolled) →
add salmeterol (improved control) →
can ICS dose be reduced and/or eliminated?

**Answer:** Reduction, yes. Elimination, no.

SLIC (Salmeterol ± Inhaled Corticosteroids)

*JAMA 285:2594, 2001*
**SOCS/SLIC Retrospective Genotype Analysis**

**Questions:**
- Are the adverse effects of chronic albuterol treatment in patients with the Arg/Arg genotype at B16 also demonstrable with the LABA salmeterol?
- If so, does concomitant treatment with ICS alter these effects?

**Answers:**
- Similar adverse effects are seen with salmeterol in Arg/Arg patients.
- The effect is not prevented by ICS treatment.

AJRCCM 173:519, 2006
Question: Are there genotype attributable adverse effects on control due to beta receptor polymorphisms in patients receiving LABAs in combination with ICS?

Answer: NO. Addition of salmeterol to ICS for 18 weeks produced similar improvements in airway caliber in both Arg/Arg and Gly/Gly genotype groups. Exacerbation rates were also similar.

Manuscript in preparation
LABA and Beta-Adrenergic Genotype

**Design:** Subjects (n = 183) currently receiving short-acting beta2-agonists were randomized to twice-daily therapy with salmeterol, 50 μg, administered with fluticasone propionate, 100 μg, in a single inhaler or daily therapy with montelukast for 12 weeks, followed by a 2- to 4-day run-out period.

**Results:** Response to therapy NOT dependent on B16 genotype or haplotype

**Conclusion:** Response to salmeterol does not vary between beta adrenergic genotypes after chronic dosing with an inhaled corticosteroid

Bleecker ER et al. JACI 118:809, 2006
Why were no differences observed?

- Genotype-specific differences only occur with short-acting beta-agonists but not with long-acting beta-agonists when used with inhaled corticosteroids.
- Higher doses of ICS blunt a genotype-specific effect of salmeterol.
- Higher doses of ICS delay a genotype-specific effect of salmeterol.
- Genotype-specific effects may be more prominent in sub-populations underrepresented in the study.
Combination Therapy in Children
Salmeterol Powder for Pediatric Asthma

**Patient Criteria**

- 4 to 16 years of age
- Currently taking inhaled corticosteroids $\geq 400$ mcg/day
  - beclomethasone or budesonide
- PEFR % predicted $\leq 90\%$
- Diurnal variation in PEFR $\geq 15\%$

Randomized, Double-Blind

210 children

2-week baseline

Salmeterol Powder
50 mcg b.i.d.

Placebo b.i.d.

12-week treatment

Addition of salmeterol powder (50 mcg b.i.d.) to ≥400 mcg/day of BDP or BUD therapy significantly:

- Improved morning PEFR
- Reduced asthma symptoms
- Reduced daytime rescue albuterol use

Evening PEFR, nighttime asthma symptoms, and nighttime rescue albuterol use followed a similar pattern, but were not significant after the first 4 weeks.

The overall incidence of adverse events was similar in both groups; however, headaches were more common in the salmeterol group.

Addition of Salmeterol vs Doubling the Dose of Beclomethasone in Children with Asthma

- 177 children (6-16 yrs) with mild-moderate asthma (ATS) with FEV$_1$ 55-90% predicted and using 200-800 mcg of ICS for at least 3 months
- Demonstration of reversibility ($\geq 10\%$) and methacholine hyperresponsiveness $\geq 2$ SD below mean of healthy children
- 6 week run-in on beclomethasone (BDP) 200 $\mu$g BID monotherapy, then treated for 54 weeks with: (Rotadisks® in combination with a Diskhaler®)
  - Placebo (BDP 200 $\mu$g BID)
  - BDP 200 $\mu$g BID (BDP 400 $\mu$g BID)
  - Salmeterol 50 $\mu$g BID + placebo (BDP 200 $\mu$g BID)

Verberne AAPH et al. AJRCCM 158:213, 1998
Combination Salmeterol + Beclomethasone in Childhood Asthma: Effect on Prebronchodilator \( \text{FEV}_1 \)

\[
\begin{align*}
\bullet &= \text{B (400 } \mu\text{g)} + \text{S} \\
o &= \text{B (400 } \mu\text{g)} \\
\blacksquare &= \text{B (800 } \mu\text{g)}
\end{align*}
\]

Verberne A et al. AJRCCM 156:688, 1997
Combination Salmeterol + Beclomethasone in Childhood Asthma: Effect on Growth

Verberne A et al. AJRCCM 156:688, 1997

- = B (400 μg) + S
○ = B (400 μg)
■ = B (800 μg)
Childhood Asthma Research and Education Network (CARE)

**Clinical Centers**
- Denver: National Jewish Medical & Research Center
- Madison: University of Wisconsin
- San Diego: University of California Kaiser Permanente California
- St. Louis: Washington University
- Tucson: University of Arizona

**Data Coordinating Center**
- Hershey: Penn State University

**NIH Funding Agency**
- Bethesda, MD: NHLBI
PACT (Pediatric Asthma Controller Trial)

What is the best choice of therapy for the treatment of mild persistent asthma in children?

- ICS monotherapy
- Combination therapy (ICS + LABA)
- Monotherapy with montelukast?
PACT: Study Schematic

2-week run-in

- 2 clinic visits
- All participants receive Albuterol prn
- placebo diskus in the morning and evening
- placebo capsule in the evening

Randomization

48-week treatment period

- 8 study encounters (5 clinic and 3 telephone) at 6-week intervals

<table>
<thead>
<tr>
<th>Morning Diskus</th>
<th>Evening Diskus</th>
<th>Evening Capsule</th>
</tr>
</thead>
<tbody>
<tr>
<td>fluticasone</td>
<td>fluticasone</td>
<td>placebo</td>
</tr>
<tr>
<td>ICS 50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>fluticasone/salmeterol</td>
<td>salmeterol</td>
<td>placebo</td>
</tr>
<tr>
<td>LTRA</td>
<td>placebo</td>
<td>montelukast</td>
</tr>
</tbody>
</table>

Sorkness CA et al. JACI 119:64, 2007
Primary Outcome

- Percent of *Asthma Control Days (ACD)* during the 12-month treatment period
- Using self-reported daily diary data, an *ACD was defined as a day without*:
  - Albuterol use (permitted pre-exercise)
  - Use of non-study asthma medications
  - Daytime or nighttime asthma symptoms
  - Unscheduled health care provider visits for asthma
  - School absenteeism for asthma

Sorkness CA et al. JACI 119:64, 2007
Comparison of PACT Therapies

<table>
<thead>
<tr>
<th>Asthma Burden</th>
<th>Favors fluticasone over montelukast</th>
<th>Favors fluticasone over combination</th>
<th>Favors combination over montelukast</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACD over 12 months</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACQ</td>
<td></td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Time to prednisone burst</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to treatment failure</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of treatment failures</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AM and PM PEF</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>FEV₁ and FEV₁/FVC</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>eNO</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>PC₂₀</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Pulmonary Function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max BD response</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
</tbody>
</table>

Sorkness CA et al. JACI 119:64, 2007
### Stepwise Approach for Managing Asthma in Children 5-11 Years of Age

<table>
<thead>
<tr>
<th>Intermittent Asthma</th>
<th>Persistent Asthma: Daily Medication</th>
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</thead>
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<tr>
<td>Consult with asthma specialist if step 4 care or higher is required. Consider consultation at step 3.</td>
<td></td>
</tr>
</tbody>
</table>

#### Step 1
- **Preferred:** SABA PRN
- **Alternative:**
  - Low-dose ICS (A)
  - Cromolyn (B), LTRA (B), Nedocromil (B), or Theophylline (B)

#### Step 2
- **Preferred:**
  - Low-dose ICS (A)
- **Alternative:**
  - Cromolyn (B), LTRA (B), Nedocromil (B), or Theophylline (B)

#### Step 3
- **Preferred:**
  - Medium-dose ICS + either LABA (B), LTRA (B), or Theophylline (B)
- **Alternative:**
  - Medium-dose ICS + either LABA (B), LTRA (B), or Theophylline (B)

#### Step 4
- **Preferred:**
  - High-dose ICS + LABA (B)
- **Alternative:**
  - High-dose ICS + either LTRA (B) or Theophylline (B)

#### Step 5
- **Preferred:**
  - High-dose ICS + LABA (B)
- **Alternative:**
  - High-dose ICS + either LTRA (B) or Theophylline (B)

#### Step 6
- **Preferred:**
  - High-dose ICS + LABA (B) + Oral Systemic Corticosteroid (D)
- **Alternative:**
  - High-dose ICS + either LTRA or Theophylline and Oral Systemic Corticosteroid (D)

#### 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 of use of SABA or use >2 days a week for symptom relief (not prevention of EIB) indicates inadequate control and the need to step up treatment

---

CARE Trial in Progress

Adjusting therapy based on asthma CONTROL

Stepping down

ACRN

CARE

BADGER

Stepping up

Step 1

Step 2

Step 3

Step 4

Step 5

Step 6

Intermittent Asthma

Persistent Asthma
Research Question: Children

BADGER

Best Add-on Therapy Giving Effective Responses

- In patients receiving daily low dose ICS treatment who are not well controlled, what are the next best treatment options?
BADGER Protocol: Overview

Double blind 3 way cross-over

3 Treatment Periods → 6 Sequences

Run-in period on 1xICS to demonstrate lack of control

Run-in Period 2-8 weeks

Period 1
- 2x ICS or
- 1x ICS + LABA or
- 1 x ICS + LTRA

16 weeks

Period 2
- 2x ICS or
- 1x ICS + LABA or
- 1 x ICS + LTRA

16 weeks

Period 3
- 2x ICS or
- 1x ICS + LABA or
- 1 x ICS + LTRA

16 weeks

Randomization
BADGER: Outcome measures to determine differential response

- 3 outcome measures defined a priori:
  - **Exacerbations:**
    - occurs when the total amount of prednisone prescribed to control asthma symptoms is at least 180 milligrams less on one treatment than on either of the other two treatments
  - **FEV$_1$:**
    - occurs when the FEV1 change is at least 5.0% higher on one treatment than on either of the other two treatments
  - **Asthma Control Days:**
    - occurs when the number of annualized ACD (AACD) achieved is at least 31 days more on one treatment than on either of the other two treatments
If children demonstrate a preferential response to one treatment, they will then be evaluated using secondary outcomes to determine if there are phenotypic and/or genotypic characteristics that are associated with this positive response.
ACRN and CARE Trials Summary

Intermittent
Step 1
Step 2
Step 3
Step 4
Step 5
Step 6
Persistent Asthma

ACRN
CARE
BAGS
SOCS
PACT
BADGER
SLIC
LARGE

Intermittent Asthma
Persistent Asthma
Beta Agonists + ICS: Maintenance and Reliever Therapy?
Combination Therapy: STAY Study

Severe Asthma Exacerbations

O’Byrne PM et al. AJRCCM 171:129, 2005
Is a Long Acting Beta Agonist Necessary for Control?

- Mild asthma subjects (n=455)
- Six months treatment
- Primary outcome: AM PEF

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Scheduled</th>
<th>As needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Placebo</td>
<td>BDP 250 mcg + Albuterol 100 mcg</td>
</tr>
<tr>
<td>B</td>
<td>Placebo</td>
<td>Albuterol 100 mcg</td>
</tr>
<tr>
<td>C</td>
<td>BDP 250 mcg</td>
<td>Albuterol 100 mcg</td>
</tr>
<tr>
<td>D</td>
<td>BDP 250 mcg +</td>
<td>Albuterol 100 mcg</td>
</tr>
<tr>
<td></td>
<td>Albuterol 100 mcg</td>
<td></td>
</tr>
</tbody>
</table>

Results:

- AM PEF and Exacerbations: Group A = C = D > B
- Cumulative dose of ICS lower in Group A compared to C and D

Research Question: Children

In patients receiving daily low dose ICS treatment who are well controlled, can ICS doses be reduced and, if possible, what is the best strategy for doing so?
TREXA Protocol: Overview

Major outcome measure: 
Asthma exacerbations

Treatment Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Daily Therapy</th>
<th>Relief</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>ICS BID</td>
<td>ICS + Alb</td>
</tr>
<tr>
<td>B</td>
<td>ICS BID</td>
<td>Placebo ICS + Alb</td>
</tr>
<tr>
<td>C</td>
<td>Placebo ICS BID</td>
<td>ICS + Alb</td>
</tr>
<tr>
<td>D</td>
<td>Placebo ICS BID</td>
<td>Placebo ICS + Alb</td>
</tr>
</tbody>
</table>

Randomize

Run-in to demonstrate control on low dose ICS

8 weeks

44 weeks
Beta Agonists: Conclusions

- LABAs should not be used as monotherapy

- Combination therapy significantly improves asthma control in both the current impairment and future risk domains

- Are responses to therapy based on beta adrenergic receptor genotype different with SABAs than with LABAs?

- Do children respond differently to LABAs (not adversely but therapeutically)?

- Concept of maintenance and reliever with ICS + beta agonist needs further study
Thank you
# Classifying Severity in Patients 5-11 Years of Age
Not Currently Taking Long-Term Controllers

<table>
<thead>
<tr>
<th>Components of Severity</th>
<th>Intermittent</th>
<th>Persistent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Impairment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>≤2 days/week</td>
<td>&gt;2 days/week but not daily</td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>≤2x/month</td>
<td>3-4x/month</td>
</tr>
<tr>
<td>SABA use for symptom control (not prevention of EIB)</td>
<td>≤2 days/week</td>
<td>&gt;2 days/week but not daily</td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>None</td>
<td>Minor limitation</td>
</tr>
<tr>
<td><strong>Lung Function</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal FEV₁ between exacerbations</td>
<td></td>
<td>FEV₁ ≥80% predicted</td>
</tr>
<tr>
<td>FEV₁ &gt;80% predicted</td>
<td></td>
<td>FEV₁/FVC &gt;80%</td>
</tr>
<tr>
<td>FEV₁/FVC &gt;85%</td>
<td></td>
<td>FEV₁ = 60%-80% predicted</td>
</tr>
<tr>
<td>FEV₁ &lt;60% predicted</td>
<td></td>
<td>FEV₁/FVC = 75%-80%</td>
</tr>
<tr>
<td>FEV₁ &lt;60% predicted</td>
<td></td>
<td>FEV₁/FVC &lt;75%</td>
</tr>
<tr>
<td><strong>Risk</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exacerbations requiring oral systemic corticosteroids</td>
<td>0-1/year</td>
<td>≥2/year Consider severity and interval since last exacerbation Frequency and severity may fluctuate over time for patients in any severity category</td>
</tr>
<tr>
<td>Relative annual risk of exacerbations may be related to FEV₁</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Recommended Step for Initiating Treatment</strong></th>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3, medium-dose ICS option and consider short course of oral systemic corticosteroids</th>
<th>Step 3, medium-dose ICS option, or Step 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>In 2 to 6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FVC = forced vital capacity.

# Assessing Asthma Control in Patients 5-11 Years of Age

<table>
<thead>
<tr>
<th>Components of Control</th>
<th>Well Controlled</th>
<th>Not Well Controlled</th>
<th>Very Poorly Controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impairment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>≤2 days/week but not &gt; than 1x on each day</td>
<td>&gt;2 days/week or multiple times on ≤2 days/week</td>
<td>Throughout the day</td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>≤1x/month</td>
<td>≥2x/month</td>
<td>≥2x/week</td>
</tr>
<tr>
<td>Interference with nl activity</td>
<td>None</td>
<td>Some limitation</td>
<td>Extremely limited</td>
</tr>
<tr>
<td>SABA 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>Lung function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁ or peak flow</td>
<td>&gt;80% predicted/ personal best &gt;80%</td>
<td>60%-80% predicted/ personal best 75%-80%</td>
<td>&lt;60% predicted/ personal best &lt;75%</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk</th>
<th>0-1/year</th>
<th>≥2/year</th>
<th>Consider severity and interval since last exacerbation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exacerbations</td>
<td></td>
<td></td>
<td>Evaluation requires long-term follow-up</td>
</tr>
<tr>
<td>requiring oral systemic corticosteroids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduction in lung growth</td>
<td></td>
<td></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>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommended Action for Treatment</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintain current step</td>
<td>Step up at least 1 step and step up 1 or 2 steps, and</td>
</tr>
<tr>
<td>Regular follow-up every 1 to 6 months</td>
<td>Reevaluate in 2 to 6 weeks, and Reevaluate in 2 weeks</td>
</tr>
<tr>
<td>Consider step down if well controlled for at least 3 months</td>
<td>For side effects, consider alternative rx options, and For side effects, consider alternative rx options</td>
</tr>
</tbody>
</table>

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Stepwise Approach for Managing Asthma in Children 5-11 Years of Age

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<thead>
<tr>
<th>Step 1</th>
<th>Preferred: Low-dose ICS (A) or SABA PRN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alternative</td>
<td>Cromolyn (B), LTRA (B), Nedocromil (B), or Theophylline (B)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 2</th>
<th>Preferred: Low-dose ICS + LABA (B)</th>
<th>Alternative: Medium-dose ICS + either LABA (B), LTRA (B), or Theophylline (B)</th>
</tr>
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<tbody>
<tr>
<td>Step 3</td>
<td>Preferred: Medium-dose ICS + LABA (B)</td>
<td>Alternative: Medium-dose ICS + either LABA (B), LTRA (B), or Theophylline (B)</td>
</tr>
<tr>
<td>Alternative</td>
<td>Low-dose ICS + either LABA (B), LTRA (B), or Theophylline (B)</td>
<td>OR Medium-dose ICS (B)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 4</th>
<th>Preferred: High-dose ICS + LABA (B)</th>
<th>Alternative: High-dose ICS + either LTRA (B) or Theophylline (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alternative</td>
<td>High-dose ICS + either LTRA (B) or Theophylline (B)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 5</th>
<th>Preferred: Medium-dose ICS + LABA (B)</th>
<th>Alternative: Medium-dose ICS + either LTRA (B) or Theophylline (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alternative</td>
<td>High-dose ICS + either LTRA or Theophylline and Oral Systemic Corticosteroid (D)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 6</th>
<th>Preferred: High-dose ICS + LABA + Oral Systemic Corticosteroid (D)</th>
<th>Alternative: High-dose ICS + either LTRA or Theophylline and Oral Systemic Corticosteroid (D)</th>
</tr>
</thead>
</table>

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 of use of SABA or use >2 days a week for symptom relief (not prevention of EIB) 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.

Assess Control
- Step Up if Needed (first, check adherence, inhaler technique, environmental control, and comorbid conditionals)
- Step Down if Possible (and asthma is well-controlled at least 3 months)

### Baseline Characteristics at the Start of the Run-in Period and at Randomization by Treatment Group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BDP 400 + Salm</th>
<th>BDP 800</th>
<th>BDP 400</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Start of run-in</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prebronch FEV$_1$ (% pred)</td>
<td>87.2 (13)</td>
<td>85.3 (13.8)</td>
<td>86.5 (13.2)</td>
</tr>
<tr>
<td>Postbronch FEV$_1$ (% pred)</td>
<td>103.2 (14.1)</td>
<td>100.9 (12.3)</td>
<td>102.2 (12.0)</td>
</tr>
<tr>
<td>Meth PD$_{20}$ (μg)</td>
<td>24.5 (11-47.5)</td>
<td>22.5 (7.5-42.5)</td>
<td>26 (12-38)</td>
</tr>
<tr>
<td><strong>At randomization</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prebronch FEV$_1$ (% pred)</td>
<td>89.7 (11.8)</td>
<td>87.4 (12.3)</td>
<td>89.2 (13.4)</td>
</tr>
<tr>
<td>Postbronch FEV$_1$ (% pred)</td>
<td>103.5 (14.1)</td>
<td>102.3 (11.4)</td>
<td>103.0 (13.6)</td>
</tr>
<tr>
<td>Meth PD$_{20}$ (μg)</td>
<td>29 (9-59)</td>
<td>20 (6-56)</td>
<td>27 (16.5-44)</td>
</tr>
<tr>
<td>Days in 2 wks with symptoms</td>
<td>6 (3-11)</td>
<td>5 (1.5-10)</td>
<td>4 (1-9)</td>
</tr>
<tr>
<td>Nights in 2 wks with symptoms</td>
<td>6 (3-10)</td>
<td>4.5 (1-11)</td>
<td>5 (1-9)</td>
</tr>
</tbody>
</table>

Verberne AAPH et al. AJRCCM 158:213, 1998