The Asthma Guidelines: Ambulatory Management of Asthma

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Objectives

- Review the medications available to treat asthma;
- Summarize use of these medications in a step-care approach to treatment of asthma.
Models for Categorizing Asthma Medications

- **Old Model:** Anti-inflammatory vs. bronchodilator
- **Current Model:** Controller vs. Quick reliever

**Quick-acting bronchodilators**

**Beta-agonist bronchodilators:**

<table>
<thead>
<tr>
<th></th>
<th>alpha (blood vessel)</th>
<th>beta-1 (heart)</th>
<th>beta-2 (bronchi)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>++ +</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>--</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Albuterol</td>
<td>--</td>
<td>+</td>
<td>+++</td>
</tr>
</tbody>
</table>
### Other selective beta-2 agonist bronchodilators

<table>
<thead>
<tr>
<th>Medication</th>
<th>MDI</th>
<th>Nebulizer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albuterol (ProAir, Ventolin, Proventil)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Pirbuterol (Maxair)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Levalbuterol (Xopenex)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**RACEMIC ALBUTEROL**

- All β-agonists are racemates
- All marketed forms of albuterol are racemates composed of a 50:50 mixture of (R)- and (S)-albuterol isomers
Albuterol-HFA

- MDI inhalers contain propellants, traditionally CFCs.
- New, environmentally-friendly propellants (HFAs) are replacing CFCs.
- For albuterol, these are:
  - ProAir-HFA, Proventil-HFA, and Ventolin-HFA (as of yet, no generic albuterol-HFA)

Three Things to Know about Albuterol-HFA

1. They are equally effective as albuterol-CFC.
2. They have a different feel; a less forceful, less cold “plume” of medication.
3. The plastic holder needs to be cleaned to prevent plugging of medication.
Other Quick-Acting Bronchodilators (not recommended)

- **Anticholinergic**: Ipratropium (Atrovent)
- **Oral beta agonist**: albuterol tablets, syrup; terbutaline tablets (Brethine)
- **Quick-release theophylline**: Elixophylline

  → slower in onset; less powerful bronchodilation; more side effects

Anti-Inflammatory Therapy

- Mast cell stabilizers
- Corticosteroids
- Anti-IgE monoclonal antibody
Anti-Inflammatory Therapy

Mast cell stabilizers: Cromolyn (Intal)  
Nedocromil (Tilade)

- block the release of inflammatory mediators from mast cells – purely preventive
- need to be taken 4 times daily
- weakly effective

Inhaled Steroid Preparations

- Budesonide DPI* (Pulmicort) 90, 180
- Mometasone DPI† (Asmanex) 110, 220
- Beclomethasone MDI-HFA (Qvar) 40, 80
- Fluticasone MDI-HFA (Flovent) 44, 110, 220
- Flunisolide MDI (Aerobid) 250
- Triamcinolone MDI (Azmacort) 100
- Ciclesonide MDI† (Alvesco) 80, 160

*category B in pregnancy
†approved for once-daily dosing
Benefits of Inhaled Corticosteroids

- Improved lung function
- Decreased bronchial hyperresponsiveness
- Fewer asthmatic symptoms
- Improved health-related quality of life
- Fewer asthmatic exacerbations
- Decreased risk of death or near-death from asthma

Inhaled Corticosteroids and Risk of Hospitalization for Asthma

Donahue et al., JAMA 1997; 277:887.
Dosing of Inhaled Corticosteroids

- Twice-daily dosing (not 2 puffs 4 times a day!)
- In mild-to-moderate asthma, mometasone (Asmanex) and ciclesonide (Alvesco) are approved for once-daily dosing.
- Other inhaled corticosteroids can likely be used equally effectively in the same way.

Steroid-Induced Side-Effects

- Oral candidiasis (thrush)
- Hoarse voice (dysphonia)
- Systemic effects? – at high doses
  - Eyes (cataracts, glaucoma)
  - Bones (osteoporosis)
  - Easy bruisability (ecchymoses)
Other Controller Medications

- Long-acting bronchodilators
- Leukotriene modifiers
Adding Salmeterol vs. Increasing the Dose of Inhaled Corticosteroids

- 426 patients at 99 general practitioner centers
- Symptomatic despite beclomethasone (BDP) 400 μg/day
- Randomized to:
  - BDP 400 μg/day plus salmeterol 50 μg BID
  - vs. BDP 1000 μg/day
- Double-blind, double-dummy 6 months trial.

Salmeterol in Moderate Asthma: Peak Flow

Mean Morning PEF

Change in PEF (L/min)

Weeks of Treatment

Greening et al., Lancet 1994; 344:291
Long-Acting Inhaled Beta Agonists in Moderate and Severe Persistent Asthma

- Used in combination with inhaled steroids to improve asthma control and minimize the dose of inhaled steroids
- Effective control of nocturnal symptoms
- Not appropriate for monotherapy (that is, only to be used together with an anti-inflammatory agent)

Long-Acting Inhaled Beta Agonists

- Salmeterol (Serevent)
- Formoterol (Foradil)

Other long-acting bronchodilators (not recommended):
- oral beta-agonists (Volmax, VoSpire ER)
- theophylline (Uniphyl, Theo-24, etc.)
Black-Box Warning for all LABAs

**WARNING:** DATA FROM A LARGE PLACEBO-CONTROLLED US STUDY THAT COMPARED THE SAFETY OF SALMETEROL (SEREVENT® INHALATION AEROSOL) OR PLACEBO ADDED TO USUAL ASTHMA THERAPY SHOWED A SMALL BUT SIGNIFICANT INCREASE IN ASTHMA-RELATED DEATHS IN PATIENTS RECEIVING SALMETEROL (13 DEATHS OUT OF 13,176 PATIENTS TREATED FOR 28 WEEKS) VERSUS THOSE ON PLACEBO (3 OF 13,179) (SEE WARNINGS AND CLINICAL TRIALS: ASTHMA: SALMETEROL MULTI-CENTER ASTHMA RESEARCH TRIAL).

Salmeterol Multicenter Asthma Research Trial (SMART)

- 26,000 subjects (of planned 60,000) randomized to salmeterol vs placebo plus “usual care” for 6 months
- Outcomes: respiratory/asthma deaths and near-deaths (respiratory failure)
Salmeterol Multicenter Asthma Research Trial (SMART)

• Findings at time of study termination:
  -- more asthma deaths (13 vs. 3) and more life-threatening or fatal asthma events (37 vs. 22) in the salmeterol-treated group.

• Subgroups at particular risk:
  -- African-Americans
  -- those not on inhaled steroids

<table>
<thead>
<tr>
<th></th>
<th>Salmeterol (N=13,176)</th>
<th>Placebo (N=13,179)</th>
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<tbody>
<tr>
<td>Baseline ICS Use</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>No Baseline ICS Use</td>
<td>9</td>
<td>0</td>
</tr>
</tbody>
</table>
Combination ICS and LABA

<table>
<thead>
<tr>
<th>Combination</th>
<th>Brand name</th>
<th>Dose per inhalation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluticasone + salmeterol</td>
<td>Advair Diskus, Advair HFA</td>
<td>100/50, 250/50, 500/50, 44/21, 115/21, 230/21</td>
</tr>
<tr>
<td>Budesonide + formoterol</td>
<td>Symbicort HFA</td>
<td>80/4.5, 160/4.5</td>
</tr>
</tbody>
</table>

New Model of Asthma Therapy

**Controllers (Preventers)**
- Inhaled steroids
- Long-acting bronchodilators
- Leukotriene blockers
  *take every day

**Relievers**
- Quick-acting bronchodilators
  +Use only as needed
Other Controller Medications

- Long-acting bronchodilators
- Leukotriene modifiers

Arachidonic Acid Pathway

- Membrane Phospholipids
  - Phospholipase A₂
  - Arachidonic Acid
    - Cyclooxygenase
    - 5-lipoxygenase
      - Prostaglandins
      - Thromboxanes
      - Leukotrienes C₄, D₄, E₄
    - Cysteinyl leukotriene receptor
Leukotriene-Modifying Drugs

- Leukotriene receptor blockers
  - Zafirlukast (Accolate): twice-daily tablet
  - Montelukast (Singulair): once-daily tablet, chewtab, or sprinkles

- Lipoxygenase inhibitor
  - Zileuton (Zyflo): twice-daily extended release tablet newly available

Use of Leukotriene Blocking Drugs: One Viewpoint

- Aspirin-sensitive asthma
- Mild-to-moderate asthma in persons fearful or intolerant of inhaled steroids
- Add-on therapy with inhaled steroids
- Helps with allergic rhinitis

Step 1: Intermittent asthma

- Quick-acting bronchodilator as needed
- Can use quick-acting bronchodilator preventively, such as 5-10 minutes prior to exercise.
Step 2 (Mild persistent asthma)

Preferred: Low-dose inhaled corticosteroid

Alternatives:

- Leukotriene modifier, mast cell stabilizer, theophylline

Use quick-acting bronchodilator as needed

Step 3 (Moderate Persistent Asthma)

- Low dose inhaled corticosteroid plus long-acting inhaled bronchodilator; or
- Medium-dose inhaled corticosteroid.

Alternative:

- Low-dose inhaled steroid plus leukotriene modifier or theophylline

Use quick-acting bronchodilator as needed
Step 4 (Moderate-Severe Persistent Asthma)

- Medium-dose inhaled corticosteroid plus long-acting inhaled bronchodilator.

Alternative:
- Medium-dose inhaled corticosteroid plus leukotriene modifier or theophylline
  Use quick-acting bronchodilator as needed

Step 5: Severe Persistent Asthma

- High-dose inhaled corticosteroid plus long-acting inhaled bronchodilator.

Consider:
- Anti-IgE therapy with omalizumab (Xolair)
  Use quick-acting bronchodilator as needed
Step 6: Severe Persistent Asthma

- Add *regular* oral corticosteroids to
- High-dose inhaled corticosteroid *plus* long-acting inhaled bronchodilator.

Consider:
- Anti-IgE therapy with omalizumab (Xolair)
  Use quick-acting bronchodilator as needed

Stepping-Down Therapy

- Once asthma has been well controlled for 3-6 months, it may be possible to reduce or “step-down” asthma medications;
- The goal of stepping-down treatment is to minimize potential long-term side effects, cost, and inconvenience … while maintaining good asthma control.
Anti-IgE Monoclonal Antibody

- Anti-IgE humanized recombinant monoclonal antibody
- Binds to free circulating IgE at the same site as high-affinity IgE receptor
- Reduces circulating IgE levels by 95% and leads to a reduction in the number of receptor binding sites on mast cells.

IgE Binds to Mast Cells at the High Affinity Receptor (FcεRI)

- IgE molecule bound to mast cell
- FcεRI receptor
- FcεRI binding site
- IgE molecule
Blocks IgE Binding to Mast Cells

- IgE molecule
- Omalizumab
- FcεRI receptor
- Mast cell

Omalizumab (Xolair): Outcomes

Outcomes:

- Fewer, shorter asthmatic exacerbations
- Reduced doses of inhaled steroids
- Less need for rescue bronchodilator
- Improved lung function and symptom scores

Omalizumab (Xolair): Other Considerations

- Side effects: rare anaphylaxis (0.1%)
- Great expense ($10,000 – $30,000/yr)
- Indications: moderate-to-severe allergic asthma poorly controlled on conventional therapy.
- Other potential indications: other atopic diseases, including food allergies

Conclusions:

- Asthma medications can be divided into controllers and relievers;
- Conventional controller medications include inhaled corticosteroids, long-acting inhaled beta agonists, and leukotriene modifiers. Others are the mast cell stabilizers and anti-IgE therapy.
Conclusions:

- Treatment is “stepped-up” in order to achieve asthma control; and can be “stepped-down” once well-controlled asthma is achieved.