Asthma Medications & Devices

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Objectives

• Describe the mechanism of action of the different asthma medications
• Explain where the various medications fit into the asthma guidelines
• Differentiate between the different delivery devices utilized in asthma
Pathophysiology

• Asthma is a chronic inflammatory disorder of the airways
  – Airflow obstruction, bronchospasm

• Several factors may play a part in the increasing the risk of developing and triggering asthma

• These factors can be divided into host factors (genetic) and environmental factors

www.ginasthma.org accessed 03/14/15
National Heart, Lung and Blood Institute
HOST FACTORS
Genetic, e.g.,
• Genes pre-disposing to atopy
• Genes pre-disposing to airway hyperresponsiveness
Obesity
Sex

ENVIRONMENTAL FACTORS
Allergens
• Indoor: Domestic mites, furred animals (dogs, cats, mice), cockroach allergen, fungi, molds, yeasts
• Outdoor: Pollens, fungi, molds, yeasts
Infections (predominantly viral)
Occupational sensitizers
Tobacco smoke
• Passive smoking
• Active smoking
Outdoor/Indoor Air Pollution
Diet

www.ginasthma.org accessed 11/18/2012
Pathophysiology

Asthma Trigger (antigen) → Inflammatory response in airways

- Inflammatory cells (i.e. mast cells)
- Inflammatory mediators (i.e. cytokines)
- Airway structural changes (i.e. Smooth muscle hypertrophy)

- Airway edema
- Airway smooth muscle contraction
- Airway thickening
- & Mucus hypersecretion
Pathophysiology

Asthma Trigger (antigen) → Inflammatory response in airways

- Inflammatory cells (i.e. mast cells)
- Inflammatory mediators (i.e. cytokines)
- Airway structural changes (i.e. Smooth muscle hypertrophy)

Airway edema, Airway smooth muscle contraction, Airway thickening, & Mucus hypersecretion → Airway Narrowing, Airway Hyperresponsiveness → ASTHMA
Asthma Guidelines

• GINA Asthma treatment guidelines were revised in 2014
  • http://www.ginasthma.org
• 2007 Expert Panel Report by NIH
  • 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
STEP-WISE APPROACH TO THERAPY

Persistent Asthma: Daily Medication
Consult 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 + LABA
OR – Medium 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
Preferred: High dose ICS + LABA + oral corticosteroid
AND
Consider Omalizumab for patients who have allergies

Each Step: Patient Education and Environmental Control and management of comorbidities
Steps 2 – 4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma

2007 NAEPP Guidelines, EPR-3 – Section 4, pg 343.
Short-Acting Beta$_2$ Agonists (SABA)

www.allergy.peds.arizona.edu
accessed 2/19/2011
Short Acting Beta$_2$-Agonists (SABA)

Types of SABAs
- Albuterol (Ventolin HFA, ProAir HFA)
- Levalbuterol (Xopenex, Xopenex HFA)

Common ADRs
- Tachycardia
- Tremor
- Shakiness
- Cough

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.
## Figure 4-4c. Usual Dosages for Quick-Relief Medications in Children

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage Form</th>
<th>0–4 Years</th>
<th>5–11 Years</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhaled Short-Acting Beta₂-Agonists</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albuterol CFC</td>
<td>90 mcg/puff, 200 puffs/canister</td>
<td>1-2 puffs 5 minutes before exercise</td>
<td>2 puffs 5 minutes before exercise</td>
<td>Differences in potencies exist, but all products are essentially comparable on a per puff basis. An increasing use or lack of expected effect indicates diminished control of asthma. Not recommended for long-term daily treatment. Regular use exceeding 2 days/week for symptom control (not prevention of EIB) indicates the need for additional long-term control therapy. May double usual dose for mild exacerbations. Should prime the inhaler by releasing 4 actuations prior to use. Periodically clean HFA actuator, as drug may plug orifice. Children &lt;4 years may not generate sufficient inspiratory flow to activate an auto-inhaler. Nonselective agents (i.e., epinephrine, isoproterenol, metaproterenol) are not recommended due to their potential for excessive cardiac stimulation, especially in high doses.</td>
</tr>
<tr>
<td>Albuterol HFA</td>
<td>90 mcg/puff, 200 puffs/canister</td>
<td>2 puffs every 4-6 hours as needed</td>
<td>2 puffs every 4-6 hours as needed</td>
<td></td>
</tr>
<tr>
<td>Levalbuterol HFA</td>
<td>45 mcg/puff, 200 puffs/canister</td>
<td>Safety and efficacy not established in children &lt;4 years</td>
<td>2 puffs every 4–6 hours as needed</td>
<td></td>
</tr>
<tr>
<td>Pirbuterol CFC</td>
<td>200 mcg/puff, 400 puffs/canister</td>
<td>Safety and efficacy not established</td>
<td>Safety and efficacy not established</td>
<td></td>
</tr>
<tr>
<td>Autohaler</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nebulizer solution</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albuterol</td>
<td>0.63 mg/3 mL</td>
<td>0.63–2.5 mg in 3 cc of saline q 4–6 hours, as needed</td>
<td>1.25–5 mg in 3 cc of saline q 4–8 hours, as needed</td>
<td>May mix with cromolyn solution, budesonide inhalant suspension, or ipratropium solution for nebulization. May double dose for severe exacerbations.</td>
</tr>
<tr>
<td></td>
<td>1.25 mg/3 mL</td>
<td>0.63 mg/3 mL</td>
<td>1.25 mg/0.5 mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.5 mg/3 mL</td>
<td>1.25 mg/3 mL</td>
<td>1.25 mg/3 mL</td>
<td></td>
</tr>
<tr>
<td>Levalbuterol (R-Albuterol)</td>
<td>0.31 mg/3 mL</td>
<td>0.31–1.25 mg in 3 cc q 4–6 hours, as needed</td>
<td>0.31–0.63 mg, q 8 hours, as needed</td>
<td>Does not have FDA-approved labeling for children &lt;6 years of age. The product is a sterile-filled preservative-free unit dose vial. Compatible with budesonide inhalant suspension.</td>
</tr>
</tbody>
</table>
### Inhaled Short-Acting Beta<sub>2</sub>-Agonists (SABA)

<table>
<thead>
<tr>
<th>Product</th>
<th>MDI</th>
<th>Applies to all four SABAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albuterol CFC</td>
<td>90 mcg/puff, 200 puffs/canister</td>
<td>■ 2 puffs 5 minutes before exercise</td>
</tr>
<tr>
<td>Albuterol HFA</td>
<td>90 mcg/puff, 200 puffs/canister</td>
<td>■ An increasing use or lack of expected effect indicates diminished control of asthma.</td>
</tr>
<tr>
<td>Pirbuterol CFC</td>
<td>200 mcg/puff, 400 puffs/canister</td>
<td>■ Not recommended for long-term daily treatment. Regular use exceeding 2 days/week for symptom control (not prevention of EIB) indicates the need to step up therapy.</td>
</tr>
<tr>
<td>Levalbuterol HFA</td>
<td>45 mcg/puff, 200 puffs/canister</td>
<td>■ Differences in potency exist, but all products are essentially comparable on a per puff basis.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ May double usual dose for mild exacerbations.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ Should prime the inhaler by releasing 4 actuations prior to use.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ Periodically clean HFA activator, as drug may block/plug orifice.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ Nonselective agents (i.e., epinephrine, isoproterenol, metaproterenol) are not recommended due to their potential for excessive cardiac stimulation, especially in high doses.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nebulizer solution</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Albuterol</td>
<td>0.63 mg/3 mL 1.25 mg/3 mL 2.5 mg/3 mL 5 mg/mL (0.5%) 1.25–5 mg in 3 cc of saline q 4–8 hours as needed</td>
<td>■ May mix with budesonide inhalant suspension, cromolyn or ipratropium nebulizer solutions. May double dose for severe exacerbations.</td>
</tr>
<tr>
<td>Levalbuterol (R-albuterol)</td>
<td>0.31 mg/3 mL 0.63 mg/3 mL 1.25 mg/0.5 mL 1.25 mg/3 mL 0.63 mg–1.25 mg q 8 hours as needed</td>
<td>■ Compatible with budesonide inhalant suspension. The product is a sterile-filled, preservative-free, unit dose vial.</td>
</tr>
</tbody>
</table>
**STEP-WISE APPROACH TO THERAPY**

**Persistent Asthma: Daily Medication**
Consult 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 + LABA
*Alternative:* Medium dose ICS
*Alternative:* Medium-dose ICS + either LTRA, Theophylline, or Zileuton

**Step 3**
*Preferred:* Low-dose ICS + LABA
*Alternative:* Medium dose ICS

**Step 4**
*Preferred:* Medium Dose ICS + LABA
*Alternative:* Medium dose ICS + either LTRA, Theophylline, or Zileuton

**Step 5**
*Preferred:* High Dose ICS + LABA
*Alternative:* Medium dose ICS + either LTRA, Theophylline, or Zileuton

**Step 6**
*Preferred:* High dose ICS + LABA + oral corticosteroid
*Alternative:* High dose ICS + LABA

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

Each Step: Patient Education and Environmental Control and management of comorbidities
Steps 2 – 4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma

2007 NAEPP Guidelines, EPR-3 – Section 4, pg 343.
Inhaled Corticosteroids (ICS)
ICS’s

- Many different inhaled corticosteroids exist on the U.S. market
  - Beclomethasone (Qvar)
  - Budesonide (Pulmicort Flexhaler)
  - Ciclesonide (Alvesco)
  - Flunisolide (Aerospan)
  - Fluticasone (Flovent HFA)
  - Mometasone (Asmanex)

- These vary based on dosing (due to varied potency)

ADRs
- Dysphonia
- Oral candidiasis (thrush)
- Cough
- URTIs

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 beta₂-receptor downregulation.** Inhibit microvascular leakage.
**Low-Dose ICS**

**Figure 4-4b. Estimated Comparative Daily Dosages for Inhaled Corticosteroids in Children**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Low Daily Dose</th>
<th>Medium Daily Dose</th>
<th>High Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Child 0–4</td>
<td>Child 5–11</td>
<td>Child 0–4</td>
</tr>
<tr>
<td><strong>Beclohexone HFA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 or 80 mcg/puff</td>
<td>NA</td>
<td>80–160 mcg</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Budesonide DPI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90, 180, or 200 mcg/inhalation</td>
<td>NA</td>
<td>180–400 mcg</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Budesonide inhaled</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhalation suspension for nebulization (child dose)</td>
<td>0.25–0.5 mg</td>
<td>0.5 mg</td>
<td>&gt;0.5–1.0 mg</td>
</tr>
<tr>
<td><strong>Flunisolide</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>250 mcg/puff</td>
<td>NA</td>
<td>500–750 mcg</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Flunisolide HFA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80 mcg/puff</td>
<td>NA</td>
<td>160 mcg</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Fluticasone</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HFA/MDI: 44, 110, or 220 mcg/puff</td>
<td>176 mcg</td>
<td>88–176 mcg</td>
<td>&gt;176–352 mcg</td>
</tr>
<tr>
<td>DPI: 50, 100, or 250 mcg/inhalation</td>
<td>NA</td>
<td>100–200 mcg</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Mometasone DPI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>200 mcg/inhalation</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
### FIGURE 4–8b. ESTIMATED COMPARATIVE DAILY DOSAGES FOR INHALED CORTICOSTEROIDS FOR YOUTHS ≥12 YEARS OF AGE AND ADULTS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Low Daily Dose Adult</th>
<th>Medium Daily Dose Adult</th>
<th>High Daily Dose Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone HFA 40 or 80 mcg/puff</td>
<td>80–240 mcg</td>
<td>&gt;240–480 mcg</td>
<td>&gt;480 mcg</td>
</tr>
<tr>
<td>Budesonide DPI 90, 180, or 200 mcg/inhalation</td>
<td>180–600 mcg</td>
<td>&gt;600–1,200 mcg</td>
<td>&gt;1,200 mcg</td>
</tr>
<tr>
<td>Flunisolide 250 mcg/puff</td>
<td>500–1,000 mcg</td>
<td>&gt;1,000–2,000 mcg</td>
<td>&gt;2,000 mcg</td>
</tr>
<tr>
<td>Flunisolide HFA 80 mcg/puff</td>
<td>320 mcg</td>
<td>&gt;320–640 mcg</td>
<td>&gt;640 mcg</td>
</tr>
<tr>
<td>Fluticasone HFA/MDI: 44, 110, or 220 mcg/puff</td>
<td>88–264 mcg</td>
<td>&gt;264–440 mcg</td>
<td>&gt;440 mcg</td>
</tr>
<tr>
<td></td>
<td>DPI: 50, 100, or 250 mcg/inhalation</td>
<td>100–300 mcg</td>
<td>&gt;300–500 mcg</td>
</tr>
<tr>
<td>Mometasone DPI 200 mcg/inhalation</td>
<td>200 mcg</td>
<td>400 mcg</td>
<td>&gt;400 mcg</td>
</tr>
</tbody>
</table>
Leukotriene Modifying Agents

• Two medications exist on U.S. market
  – Zafirlukast (Accolate®)
  – Montelukast (Singular®)

• ADRs
  – URTIs, headache, abdominal pain, Incr. LFTs, dizziness, pharyngitis, sinusitis

Leukotriene Receptor Antagonists (LTRAs)

Mechanisms

- Leukotriene receptor antagonist; selective competitive inhibitor of CysLT$_1$ receptor.
# Leukotriene Modifying Agents

## Leukotriene Receptor Antagonists (LTRAs)

<table>
<thead>
<tr>
<th></th>
<th>0-4 years</th>
<th>5-11 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Montelukast</strong></td>
<td>4 mg or 5 mg chewable tablet 4 mg granule packets</td>
<td>4 mg qhs (1–5 years of age) 5 mg qhs (6–14 years of age)</td>
</tr>
<tr>
<td><strong>Zafirlukast</strong></td>
<td>10 mg tablet</td>
<td>Safety and efficacy not established 10 mg bid (7–11 years of age)</td>
</tr>
</tbody>
</table>

- Montelukast exhibits a flat dose-response curve.
- No more efficacious than placebo in infants 6–24 months (van Adelsberg et al. 2005).
- For zafirlukast, administration with meals decreases bioavailability; take at least 1 hour before or 2 hours after meals.
- Monitor for signs and symptoms of hepatic dysfunction.

EPR-2007
## Leukotriene Modifying Agents

### Adults

#### Leukotriene Receptor Antagonists

<table>
<thead>
<tr>
<th>Leukotriene Modifiers</th>
<th>Dosage</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Montelukast</td>
<td>4 mg or 5 mg chewable tablet, 10 mg tablet</td>
<td>10 mg qhs</td>
</tr>
<tr>
<td>Zafirlukast</td>
<td>10 or 20 mg tablet</td>
<td>40 mg daily (20 mg tablet bid)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Methylxanthines

RX
Purdue Pharmaceutical Products L.P.

400 mg
U 400
P 400

600 mg
U 600
P 600

Controlled-Release Tablets
Uniphyll®
(theophylline, anhydrous)

Aminophylline
20 mL
Usual dose via:
For slow IV use

Theo-Dur
100
200
300
450

www.google.com
accessed 01/30/14
Methylxanthines

- Theophylline (Elixophyllin, Theolair, Theo-24,
- Aminophylline

**ADRs**
- Nausea, headache, tachycardia, insomnia, tremor, nervousness
- Signs of toxicity: persistent vomiting, Vtach, seizures

**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.
# Methylxanthines

<table>
<thead>
<tr>
<th>0-4 years</th>
<th>5-11 years</th>
</tr>
</thead>
</table>

**Methylxanthines**

<table>
<thead>
<tr>
<th>Theophylline</th>
<th>Liquids, sustained-release tablets, and capsules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting dose</td>
<td>10 mg/kg/day; usual maximum:</td>
</tr>
<tr>
<td>&lt;1 year of age</td>
<td>0.2 (age in weeks) + 5 = mg/kg/day</td>
</tr>
<tr>
<td>≥1 year of age</td>
<td>16 mg/kg/day</td>
</tr>
</tbody>
</table>

- Adjust dosage to achieve serum concentration of 5–15 mcg/mL at steady-state (at least 48 hours on same dosage).
- Due to wide interpatient variability in theophylline metabolic clearance, routine serum theophylline level monitoring is essential.
- See next page for factors that can affect theophylline levels.

EPR-2007
## Methylxanthines

### Adults

<table>
<thead>
<tr>
<th>Methylxanthines</th>
<th>Theophylline</th>
<th>Liquids, sustained-release tablets, and capsules</th>
<th>Starting dose 10 mg/kg/day up to 300 mg maximum; usual maximum 800 mg/day</th>
</tr>
</thead>
</table>

- Adjust dosage to achieve serum concentration of 5–15 mcg/mL at steady-state (at least 48 hours on same dosage).
- Due to wide interpatient variability in theophylline metabolic clearance, routine serum theophylline level monitoring is important.
- See next page for factors that can affect theophylline levels.
Long-Acting Beta$_2$-Agonists (LABA)
Long-Acting Beta$_2$-Agonists (LABA)

- Salmeterol (Serevent Diskus)
- Formoterol (Foradil Aerolizer)
- Combinations with ICS

ADRs
- Same as SABAs (tremor, cough, increased heart rate, etc)

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.
LABA’s

- Formoterol (Foradil aerolizer):
  - DPI: 1 capsule via inhaler BID (>5yrs)
  - Indicated for asthma and exercise induced bronchospasm

- Salmeterol (Serevent diskus):
  - DPI: 1 puff BID (>4-11yrs)
  - Indicated for asthma and exercise induced bronchospasm

- DO NOT USE FOR ACUTE EXACERBATIONS

- ADR
  - Same as SABAs (tremor, cough, increased heart rate, etc)
STEP-WISE APPROACH TO THERAPY

Intermittent Asthma

Consult 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

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
Preferred:
High dose ICS + LABA + oral corticosteroid

AND
Consider Omalizumab for patients who have allergies

Each Step: Patient Education and Environmental Control and management of comorbidities
Steps 2 – 4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma

Step up if needed
(first, check adherence, environmental control & comorbid conditions)

Assess control

Step down if possible
(and asthma is well controlled at least 3 months)

2007 NAEPP Guidelines, EPR-3 – Section 4, pg 343.
Combination therapy (ICS+ LABA)

- Fluticasone/salmeterol
- Budesonide/formoterol
- Mometasone/formoterol
- Fluticasone/salmeterol
Combination therapy (ICS + LABA)

• Fluticasone/Salmeterol (Advair)
  – DPI (Advair diskus)-Dose 1 puff BID
    • 100/50mcg (>4-11yrs)
    • 250/50mcg (>12yrs)
    • 500/50mcg (>12yrs)
  – MDI (Advair HFA)-Dose 2 puffs BID
    • 45/21mcg (>12yrs)
    • 115/21mcg (>12yrs)
    • 230/21mcg (>12yrs)

• Budesonide/Formoterol
  – MDI (Symbicort HFA)- 2 puffs BID
    • 80/4.5mcg, 160/4.5mcg (>12yrs)
Combination therapy (ICS+ LABA)

- Mometasone/Formoterol
  - MDI (Dulera)- 2 puffs BID
    - 100/5mcg, 200/5mcg (>12yrs)

- ADR
  - see LABA & ICS
# Medium-Dose ICS

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**Fig. 4-4b. Estimated Comparative Daily Dosages for Inhaled Corticosteroids in Children**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Low Daily Dose</th>
<th>Medium Daily Dose</th>
<th>High Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Child 0–4</td>
<td>Child 5–11</td>
<td>Child 0–4</td>
</tr>
<tr>
<td>Beclomethasone HFA</td>
<td>NA</td>
<td>80–160 mcg</td>
<td>NA</td>
</tr>
<tr>
<td>40 or 80 mcg/puff</td>
<td>80–160 mcg</td>
<td></td>
<td>&gt;160–320 mcg</td>
</tr>
<tr>
<td>Budesonide DPI</td>
<td>NA</td>
<td>180–400 mcg</td>
<td>NA</td>
</tr>
<tr>
<td>90, 180, or 200 mcg/inhalation</td>
<td></td>
<td>&gt;400–800 mcg</td>
<td>NA</td>
</tr>
<tr>
<td>Budesonide inhaled</td>
<td>0.25–0.5 mg</td>
<td>0.5 mg</td>
<td>&gt;0.5–1.0 mg</td>
</tr>
<tr>
<td>Inhalation suspension for nebulization (child dose)</td>
<td></td>
<td>1.0 mg</td>
<td>&gt;1.0 mg</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>NA</td>
<td>500–750 mcg</td>
<td>NA</td>
</tr>
<tr>
<td>250 mcg/puff</td>
<td>NA</td>
<td>1,000–1,250 mcg</td>
<td>NA</td>
</tr>
<tr>
<td>Flunisolide HFA</td>
<td>80 mcg/puff</td>
<td>160 mcg</td>
<td>NA</td>
</tr>
<tr>
<td>80 mcg/puff</td>
<td>NA</td>
<td>320 mcg</td>
<td>NA</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>176 mcg</td>
<td>88–176 mcg</td>
<td>&gt;176–352 mcg</td>
</tr>
<tr>
<td>HFA/MDI: 44, 110, or 220 mcg/puff</td>
<td></td>
<td>&gt;176–352 mcg</td>
<td>&gt;352 mcg</td>
</tr>
<tr>
<td>DPI: 50, 100, or 250 mcg/inhalation</td>
<td></td>
<td></td>
<td>&gt;352 mcg</td>
</tr>
<tr>
<td>Mometasone DPI</td>
<td>100–200 mcg</td>
<td>NA</td>
<td>&gt;200–400 mcg</td>
</tr>
<tr>
<td>200 mcg/inhalation</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

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EPR-2007
### Medium-Dose ICS

**FIGURE 4–8b. ESTIMATED COMPARATIVE DAILY DOSAGES FOR INHALED CORTICOSTEROIDS FOR YOUTHS ≥12 YEARS OF AGE AND ADULTS**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Low Daily Dose Adult</th>
<th>Medium Daily Dose Adult</th>
<th>High Daily Dose Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beclomethasone HFA</strong></td>
<td>80–240 mcg</td>
<td>&gt;240–480 mcg</td>
<td>&gt;480 mcg</td>
</tr>
<tr>
<td>40 or 80 mcg/puff</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Budesonide DPI</strong></td>
<td>180–600 mcg</td>
<td>&gt;600–1,200 mcg</td>
<td>&gt;1,200 mcg</td>
</tr>
<tr>
<td>90, 180, or 200 mcg/inhalation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Flunisolide</strong></td>
<td>500–1,000 mcg</td>
<td>&gt;1,000–2,000 mcg</td>
<td>&gt;2,000 mcg</td>
</tr>
<tr>
<td>250 mcg/puff</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Flunisolide HFA</strong></td>
<td>320 mcg</td>
<td>&gt;320–640 mcg</td>
<td>&gt;640 mcg</td>
</tr>
<tr>
<td>80 mcg/puff</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fluticasone</strong></td>
<td>88–264 mcg</td>
<td>&gt;264–440 mcg</td>
<td>&gt;440 mcg</td>
</tr>
<tr>
<td>HFA/MDI: 44, 110, or 220 mcg/puff</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DPI: 50, 100, or 250 mcg/inhalation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mometasone DPI</strong></td>
<td>200 mcg</td>
<td>400 mcg</td>
<td>&gt;400 mcg</td>
</tr>
<tr>
<td>200 mcg/inhalation</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Intermittent Asthma
Consult 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 + LABA
  - OR – Medium 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
- **Alternative:** Consider Omalizumab for patients who have allergies

**Step 5**
- **Preferred:** High dose ICS + LABA + oral corticosteroid
- **AND**

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

Each Step: Patient Education and Environmental Control and management of comorbidities
Steps 2 – 4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma

2007 NAEPP Guidelines, EPR-3 – Section 4, pg 343.
### Figure 4-4b. Estimated Comparative Daily Dosages for Inhaled Corticosteroids in Children

<table>
<thead>
<tr>
<th>Drug</th>
<th>Low Daily Dose</th>
<th>Medium Daily Dose</th>
<th>High Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Child 0–4</td>
<td>Child 5–11</td>
<td>Child 0–4</td>
</tr>
<tr>
<td><strong>Beclomethasone HFA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 or 80 mcg/puff</td>
<td>NA</td>
<td>80–160 mcg</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Budesonide DPI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90, 180, or 200 mcg/inhalation</td>
<td>NA</td>
<td>180–400 mcg</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Budesonide inhaled</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhalation suspension for nebulization (child dose)</td>
<td>0.25–0.5 mg</td>
<td>0.5 mg</td>
<td>&gt;0.5–1.0 mg</td>
</tr>
<tr>
<td><strong>Flunisolide</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>250 mcg/puff</td>
<td>NA</td>
<td>500–750 mcg</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Flunisolide HFA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80 mcg/puff</td>
<td>NA</td>
<td>160 mcg</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Fluticasone</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HFA/MDI: 44, 110, or 220 mcg/puff</td>
<td>176 mcg</td>
<td>88–176 mcg</td>
<td>&gt;176–352 mcg</td>
</tr>
<tr>
<td>DPI: 50, 100, or 250 mcg/inhalation</td>
<td>NA</td>
<td>100–200 mcg</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Mometasone DPI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>200 mcg/inhalation</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
# High-Dose ICS

## Figure 4–8b. Estimated Comparative Daily Dosages for Inhaled Corticosteroids for Youths ≥12 Years of Age and Adults

<table>
<thead>
<tr>
<th>Drug</th>
<th>Low Daily Dose Adult</th>
<th>Medium Daily Dose Adult</th>
<th>High Daily Dose Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone HFA</td>
<td>80–240 mcg</td>
<td>&gt;240–480 mcg</td>
<td>&gt;480 mcg</td>
</tr>
<tr>
<td>40 or 80 mcg/puff</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Budesonide DPI</td>
<td>180–600 mcg</td>
<td>&gt;600–1,200 mcg</td>
<td>&gt;1,200 mcg</td>
</tr>
<tr>
<td>90, 180, or 200 mcg/inhalation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flunisolide</td>
<td>500–1,000 mcg</td>
<td>&gt;1,000–2,000 mcg</td>
<td>&gt;2,000 mcg</td>
</tr>
<tr>
<td>250 mcg/puff</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flunisolide HFA</td>
<td>320 mcg</td>
<td>&gt;320–640 mcg</td>
<td>&gt;640 mcg</td>
</tr>
<tr>
<td>80 mcg/puff</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluticasone</td>
<td>88–264 mcg</td>
<td>&gt;264–440 mcg</td>
<td>&gt;440 mcg</td>
</tr>
<tr>
<td>HFA/MDI: 44, 110, or 220 mcg/puff</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DPI: 50, 100, or 250 mcg/inhalation</td>
<td></td>
<td></td>
<td>&gt;500 mcg</td>
</tr>
<tr>
<td>Mometasone DPI</td>
<td>200 mcg</td>
<td>400 mcg</td>
<td>&gt;400 mcg</td>
</tr>
<tr>
<td>200 mcg/inhalation</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Oral Corticosteroids

Types
- Methylprednisolone
  - (Solu-Medrol, Medro Dosepak)
- Prednisone
- Prednisolone
  - (Orapred, Prelone)

Short-term ADRs
- Incr. appetite, weight gain
- Fluid retention
- Mood changes
- Insomnia
- GI upset

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 beta2-receptor downregulation. Inhibit microvascular leakage.
Oral Corticosteroids

• Dose varies by patient response and severity
• Used for acute exacerbations and in very severe disease (Step 6)
• Used in asthma action plans for use at home if needed
**Oral Corticosteroids**

0-4 years  5-11 years

<table>
<thead>
<tr>
<th>Systemic Corticosteroids</th>
<th>0-4 years</th>
<th>5-11 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylprednisolone</td>
<td>2, 4, 8, 16, 32 mg tablets</td>
<td>0.25–2 mg/kg daily in single dose in a.m. or qod as needed for control</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>5 mg tablets, 5 mg/5 cc, 15 mg/5 cc</td>
<td>0.25–2 mg/kg daily in single dose in a.m. or qod as needed for control</td>
</tr>
<tr>
<td>Prednisone</td>
<td>1, 2.5, 5, 10, 20, 50 mg tablets; 5 mg/cc, 5 mg/5 cc</td>
<td>Short-course “burst”: 1–2 mg/kg/day, maximum 30 mg/day for 3–10 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Short-course “burst”: 1–2 mg/kg/day, maximum 60 mg/day for 3–10 days</td>
</tr>
</tbody>
</table>

*(Applies to all three corticosteroids)*

- For long-term treatment of severe persistent asthma, administer single dose in a.m. either daily or on alternate days (alternate-day therapy may produce less adrenal suppression).
- Short courses or “bursts” are effective for establishing control when initiating therapy or during a period of gradual deterioration.
- There is no evidence that tapering the dose following improvement in symptom control and pulmonary function prevents relapse.
- Patients receiving the lower dose (1 mg/kg/day) experience fewer behavioral side effects (Kayani and Shannon 2002), and it appears to be equally efficacious (Rachelefsky 2003).
- For patients unable to tolerate the liquid preparations, dexamethasone syrup at 0.4 mg/kg/day may be an alternative. Studies are limited, however, and the longer duration of activity increases the risk of adrenal suppression (Hendeles 2003).
# Oral Corticosteroids

## Adults

<table>
<thead>
<tr>
<th>Systemic Corticosteroids</th>
<th>Adults' Dosage</th>
<th>(Applies to all three corticosteroids)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylprednisolone</td>
<td>2, 4, 8, 16, 32 mg tablets</td>
<td>7.5–60 mg daily in a single dose in a.m. or qod as needed for control</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>5 mg tablets, 5 mg/5 cc, 15 mg/5 cc</td>
<td>Short-course “burst”: to achieve control, 40–60 mg per day as single or 2 divided doses for 3–10 days</td>
</tr>
</tbody>
</table>
| Prednisone               | 1, 2.5, 5, 10, 20, 50 mg tablets; 5 mg/cc, 5 mg/5 cc | - For long-term treatment of severe persistent asthma, administer single dose in a.m. either daily or on alternate days (alternate-day therapy may produce less adrenal suppression). Short courses or “bursts” are effective for establishing control when initiating therapy or during a period of gradual deterioration.  
- There is no evidence that tapering the dose following improvement in symptom control and pulmonary function prevents relapse. |

EPR-2007
Anti-IgE Therapy

- Omalizumab (Xolair)

**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 FcεRIs in basophils and submucosal cells.

[Image of Omalizumab (Xolair) box]
Omalizumab (Xolair)

- Only used in moderate-severe persistent asthma who are inadequately controlled on inhaled steroids (step 5 or 6).
- Given in doctor’s office
- ADRs
  - Headache, URTIs, viral infection, sinusitis, arthralgia
- Black Box Warning
  - Anaphylaxis (including delayed-onset)
Inhaler Devices & Technique
Factors affecting lung deposition

• Only 5-15% of metered dose reaches the lungs

• Two main factors
  – Particle size
  – Speed of inhalation

• Additional factors
  – Breath holding for a minimum of 2 seconds
  – Allow at least 30 seconds between consecutive doses
The Importance of Inhaler technique

“There are well designed studies that demonstrate that the medicine has to be in you to be effective!”

Dr. Wayne Samuelson, MD
Professor of Medicine
University of Utah
University of Utah Adult Asthma Center Director
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

• 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.
9-steps of MDI-technique

1. Stand or sit upright with your head and neck straight or tilted slightly back.
2. Hold the canister upright and shake the inhaler well. Remove the mouthpiece cap.
3. Breathe out normally through your mouth.
4. With the canister upright, position inhaler either 1-2 inches away from “open mouth” or in the mouth with lips closed tightly around the inhaler mouthpiece “closed mouth”
5. As you start to breathe in slowly, press down on the top of the inhaler firmly once. Continue to breathe in slowly (over 3-5 seconds) and deeply until your lungs are full of air.
6. Hold your breath for 5-10 seconds or as long as you can and exhale slowly.
7. If more than one puff is needed, wait 1 minute before taking your next puff and repeat step 1-7.
8. Rinse your mouth out with water and spit.
9. Replace the mouthpiece cap after you are finished.
Spacer/Holding Chambers

• Advantages
  - Increase lung deposition 10-15%
  - Eliminate need for coordination
  - Reduce cough and “cold freon” effect

• Disadvantages
  - Not “cool”
  - Not compact enough
  - Not compatible with all inhalers
  - Require regular cleaning
Dry-Powdered Inhalers (DPI)
DPI

• **Advantages**
  – eliminates the need for coordination
  – may reduce incidence of local adverse effects
  – “environmentally friendly”
  – easy to use
  – not affected by cold air
  – useful in arthritic or elderly patients

• **Disadvantages**
  – must generate required inspiratory flow rate
  – may be affected by humidity
  – each device has unique dose loading system
  – may waste medication if device is turned upside down
9-steps of DPI-technique

1. Remove the cover.
2. Load a single dose according to the specific device used.
3. Breathe out normally through your mouth.
4. Put the inhaler mouthpiece into your mouth, closing your lips tightly around it.
5. Inhale deeply and forcefully.
6. Hold your breath for 5-10 seconds or as long as you can and then exhale slowly.
7. If more than one dose is needed, wait 1 minute before taking your next dose and repeat steps 2-7.
8. Rinse your mouth out with water and spit.
9. Replace the mouthpiece cap after you are finished.
Peak flow meters
Recommended Peak Flow Monitoring (NAEPP, 2007)

- Patients who have moderate or severe persistent asthma
- Patients who have a history of severe exacerbations
- Patients who poorly perceive airflow obstruction and worsening asthma
- Patients who prefer this monitoring method
Peak flow meters

• Advantages:
  – gives objective measure of the patients condition
  – helps patient predict impending exacerbation's
  – helps patients identify possible asthma triggers
  – helps patients decide if condition is serious enough to seek medical attention

• Disadvantages:
  – highly effort dependent
  – patients must be highly motivated and interested in their disease process
8-Steps to Peak Flow Monitoring

1. Place the pointer at the bottom of the numbered scale (set it to zero).

2. Stand or sit upright.

3. Take a deep breath, filling your lungs completely.

4. Place the meter in your mouth and close your lips around the mouthpiece. DO NOT put your tongue inside the hole.

5. Blow out as hard and as fast as you can.

6. Write down the number indicated by the pointer.

7. Repeat steps 1-6 two more times.

8. Write down the highest of the three numbers in your peak flow diary.
Education Resources

• Google: Asthma Care Pharmacy Utah or
  – http://health.utah.gov/asthma/professionals/pharmacy.htm

• Inhaler technique
  – https://www.youtube.com/watch?v=Rdb3p9RZoR4
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
References
