Update on Asthma Pharmacotherapy and Review of Treatment Recommendations from the 2007 NIH Asthma Guidelines

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Note: The speaker has no actual or potential conflicts of interest in relation to this presentation to disclose.
Asthma Statistics

- 22.2 million persons with asthma in the U.S.
- Most common chronic disease in children (approximately 6.5 million children < 18 yoa)
- 14.7 million outpatient asthma visits in 2004
- 750,000 ER visits per year in children < 15 yoa
- 497,000 (198,000 peds) of 1.8 million who seek ER care annually require hospitalization (> $1.6 billion)
- 12.8 million school days missed in 2003
- 10.1 million work days missed in 2003

National Center for Health Statistics, Centers for Disease Control, 2005.
Summary Health Statistics for U.S. Adults: National Health Interview Survey, 2005
Summary Health Statistics for U.S. Children: National Health Interview Survey, 2006
National Hospital Ambulatory Medical Care Survey: 2005 Summary
National Hospital Ambulatory Medical Care Survey: 2005 Outpatient Department Summary
National Hospital Ambulatory Medical Care Survey: 2005 Emergency Department Summary
Initial Classification of Asthma Severity

• “Severity” = Intrinsic intensity of the disease
• Must consider:
  – Impairment (Present)
    • Frequency and intensity of symptoms
    • Impact on quality of life
  – Risk (Future)
    • Exacerbations
    • Loss of pulmonary function
    • Risk of ADRs
• Clinically, classification of severity is most useful for **initiating controller therapy**
## Classification of Severity: 1997/2002 vs. 2007 NIH Recommendations

<table>
<thead>
<tr>
<th>1997/2002 (EPR-2)</th>
<th>2007 (EPR-3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>❖ Mild Intermittent</td>
<td>❖ Intermittent</td>
</tr>
<tr>
<td>❖ Mild Persistent</td>
<td>❖ Mild Persistent</td>
</tr>
<tr>
<td>❖ Moderate Persistent</td>
<td>❖ Moderate Persistent</td>
</tr>
<tr>
<td>❖ Severe Persistent</td>
<td>❖ Severe Persistent</td>
</tr>
</tbody>
</table>
Perception of Risk of Death from Childhood Asthma is Underestimated

Clinical Assessment of Asthma Severity in Children with Asthma Who Died

Goals of Therapy: Decreasing Impairment

- Prevent symptoms
  - No need for reliever medications (2x or less per week)
  - No daytime symptoms (2x or less per week)
  - No nighttime symptoms (2x or less per week)

- Maintain “normal” pulmonary function

- Maintain normal activity/lifestyle
  - No limitations in daily activities
  - No limitations in exercise

- Meet patients’ and families’ expectations
Goals of Therapy: Decreasing Risk

• Prevent recurrent exacerbations
• Decrease ED visits and hospitalizations
• Prevent progressive loss of lung function
• Achieve maximal pharmacotherapeutic benefit with minimal side effects / ADRs

“NEW” CONCEPTS INTRODUCED IN 1997

• Major emphasis on:
  • Meeting patients’ expectations
  • Providing patient education
  • Developing a written, long-term action plan
  • Using peak flow meters
  • Avoiding asthma triggers

“NEW” CONCEPTS INTRODUCED IN 1997

- New classification of drugs:
  - “quick relief” vs. “bronchodilators”
  - “long-term control” vs. “anti-inflammatories”

“Quick relief” drugs are for **TREATMENT**!
“Long-term control” drugs are for **PREVENTION**!
### Classification of Meds

<table>
<thead>
<tr>
<th>Quick Relief</th>
<th>Long-Term Control</th>
</tr>
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<tbody>
<tr>
<td>• Short-Acting β₂-Agonists</td>
<td>• Inhaled Corticosteroids</td>
</tr>
<tr>
<td>• Anticholinergics</td>
<td>• Cromolyn and Nedocromil</td>
</tr>
<tr>
<td>• Systemic Corticosteroids</td>
<td>• Long-Acting β₂-Agonists</td>
</tr>
<tr>
<td></td>
<td>• Methylxanthines</td>
</tr>
<tr>
<td></td>
<td>• Leukotriene modifiers</td>
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<td>• Immunomodulators</td>
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</table>
General Approach to Treatment: Focus on Long-Term Control

• **Inflammation** plays a primary role in the pathogenesis of asthma

• Prevention and suppression of underlying inflammation:
  • reduction of bronchial hyperresponsiveness
  • prevention of **airway remodeling**
  • improvement in long-term control and outcomes
Effects of Inhaled Corticosteroids on Inflammation

Pre- and post-3-month treatment with budesonide (BUD) 600 mcg b.i.d.

Corticosteroids

• Inhaled
  • Beclomethasone dipropionate (QVAR®)
  • Budesonide (Pulmicort®, Pulmicort Respules®)
  • Flunisolide (AeroBid®)
  • Fluticasone (Flovent®, Flovent® HFA)
  • Triamcinolone acetonide (Azmacort®)
  • Mometasone furoate (Asmanex®)
  • Ciclesonide (Alvesco®)

• Systemic
  • Methylprednisolone (Solu-Medrol®, Medrol®)
  • Prednisolone (Prelone®, Orapred®)
  • Prednisone (Deltasone®)
Corticosteroid Indications

• **Inhaled CS**
  • Long-term *prevention* of symptoms in mild, moderate, and severe *persistent* asthma
  • Suppression, control, and reversal of inflammation
  • Reduction of need for systemic CS

• **Systemic CS**
  • Long-term prevention of symptoms in severe persistent asthma
Corticosteroid
Mechanism of Action

• Anti-inflammatory Action:
  • reduction in synthesis and release of pro-inflammatory cytokines
  • reduction in inflammatory cell activation, recruitment, and infiltration
  • reduction in vascular permeability

• Effect on Beta-receptors:
  • increase in number of receptors
  • improve receptor responsiveness to adrenergic stimulation
Comparison of CS Potency

Topical Potency (Skin Blanching)*

Corticosteroid

*values assigned in reference to dexamethasone, which = 1
Bioavailability of INH CS

Illustration adapted from the 1997 NIH NAEPP Report
## Oral Bioavailability of INH CS

<table>
<thead>
<tr>
<th>Corticosteroid</th>
<th>Oral Bioavailability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flunisolide</td>
<td>21%</td>
</tr>
<tr>
<td>Beclomethasone dipropionate</td>
<td>20%</td>
</tr>
<tr>
<td>Budesonide</td>
<td>11%</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>10%</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Mometasone furoate</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Ciclesonide</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

**NOTE:** Approximately 80% of the dose from an MDI without a spacer is swallowed; the rest of the dose is delivered to the lungs and is considered bioavailable.
Growth Suppression with Inhaled Corticosteroids

• Precaution in PI of INH CS about possible growth suppression

• More likely with higher doses

• Is adult height affected? (i.e., does “catch-up growth” occur?)

• Recommend use of lowest effective dose
Growth Suppression with Inhaled Corticosteroids

• 142 budesonide-treated children with asthma followed for average of nine years until adult height attained
• Compared to two control groups
• Significantly less growth noted during first two years of treatment with budesonide
• **No overall differences in mean adult height noted**

Adverse Effects of CS

• Cough, dysphonia
• Oral thrush (candidiasis)

• Systemic effects (more likely to occur with high-dose corticosteroids)
  • adrenal suppression/growth suppression
  • osteoporosis
  • skin thinning/easy bruising
  • weight gain/fluid retention
Tips for CS Users

• Benefits of INH CS generally outweigh potential risks of adverse effects

• To reduce adverse effect potential:
  • Administer INH CS with spacer (if using MDI)!
  • Rinse mouth thoroughly following inhalation!
  • Use lowest effective CS dose
    • Consider adding a long-acting beta-agonist to low-to-med. dose of INH CS before maximizing INH CS dose

• Monitor growth in children
• Consider osteoporosis prophylaxis
Cromolyn Sodium and Nedocromil

- Available Products:
  - Cromolyn Sodium = Intal®
  - Nedocromil = Tilade®

- Often referred to as “mast cell stabilizers”
Cromolyn Sodium and Nedocromil

• **Indications:**
  • Long-term prevention of symptoms
  • Preventive treatment prior to exposure to exercise or known allergen

• **Anti-inflammatory Mechanisms:**
  • stabilize mast cell membranes
  • inhibit activation and release of inflammatory mediators from eosinophils
  • block early and late reaction to allergen
  • inhibit acute response to exercise, cold air, sulfur dioxide
Cromolyn Sodium and Nedocromil

- Overall, extremely well-tolerated

- 15% to 20% of patients complain of unpleasant taste with nedocromil

Overall, safety profile has been cited as the primary advantage of these agents...
Cromolyn Sodium and Nedocromil

- Effective anti-inflammatory agents for mild-persistent asthma
- Have been used as alternatives to INH CS in patients where there is concern for toxicity (e.g., in pediatric patients)
- Can be used for exercise- or known allergen-induced bronchospasm
- *Lack of recent evidence to suggest benefit over INH CS, or INH CS + other Tx; therefore, not preferred treatments (EPR-3)*
Long-Acting Beta$_2$-Agonists

- **Products Approved for Asthma:**
  - Salmeterol (Serevent®)
  - Formoterol (Foradil®)
  - Albuterol Sustained-Release Tablets*

- **Indications for Salmeterol & Formoterol:**
  - Long-term prevention of symptoms (especially nocturnal symptoms) *IN ADDITION TO ANTI-INFLAMMATORY AGENTS*
  - Prevention of exercise-induced bronchospasm

*Inhaled long-acting Beta$_2$-Agonists are preferred over sustained-release tablets due to fewer side effects and longer duration of action.*
## Albuterol vs LABA’s: Pharmacokinetics

<table>
<thead>
<tr>
<th></th>
<th>Albuterol</th>
<th>Salmeterol</th>
<th>Formoterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>5 min</td>
<td>20 min</td>
<td>5 min?</td>
</tr>
<tr>
<td>Duration</td>
<td>4 - 8 hrs</td>
<td>12 hrs</td>
<td>12 hrs</td>
</tr>
</tbody>
</table>

LABA’s should **not** be used to treat acute symptoms!
Salmeterol + Beclomethasone: Early Evidence of Benefit

• Salmeterol 50mcg bid + Beclomethasone 200mcg bid vs Beclomethasone 500mcg bid bid
• Similar asthma exacerbation frequency
• Greater improvement in salmeterol + beclomethasone group:
  • Symptoms of asthma
  • Symptoms requiring additional bronchodilators
  • PEFR in am and pm
  • Nocturnal awakening

Greening et al., Lancet 1994
Change in PEF (am & pm) Over 6 Months

Greening et al., *Lancet* 1994
Salmeterol + Beclomethasone: Defining the role of LABA’s

CONCLUSION

Adding a long-acting $\beta_2$-adrenergic agonist to INH CS treatment may be more effective than increasing the dose of INH CS.

Greening et al., Lancet 1994
Salmeterol + Fluticasone Propionate (FP) vs Increased-Dose FP FP

- **Salmeterol 42 mcg b.i.d.**
  - + **FP 88 mcg b.i.d.**
  - (n = 221)

- **FP 88 mcg b.i.d.**
  - (n = 437)

2-4 week run-in

**Follow-up**

**FP 220 mcg b.i.d.**
- (n = 216)

6-month treatment period

AM Peak Expiratory Flow

*P < 0.001

Percent of Days Without Albuterol

Days Without Albuterol (%)

Weeks of Treatment

*S < 0.001

Change in Percent of Symptom-Free Days

LABA Use in Children

• Salmeterol (Serevent Diskus®)
  – FDA approved for prevention of bronchospasm and EIB in children as young as 4 years of age
  – Dosage: one inhalation every 12 hours

• Formoterol (Foradil® Aerolizer™)
  – FDA approved for prevention of bronchospasm and EIB in children as young as 5 years of age
  – Dose: one 12mcg capsule via inhalation every 12 hours
Current Controversy in Asthma Management: LABA Safety Profile

Salmeterol Multi-center Asthma Research Trial (SMART)

- Compared the safety of salmeterol to placebo in patients with asthma over the course of 28 weeks
- RESULTS: Death-Rate
  - Salmeterol-treated group: 13/13,176 patients
  - Placebo-treated group: 3/13,179 patients
  - Difference not significant
  - Trial discontinued early
- CONCLUSION: Salmeterol may increase the risk of asthma-related death

www.fda.gov/medwatch/safety/2003/serevent.htm
SMART Results: Important Considerations

Differences in Ethnic Groups:

• 71% of the study population were Caucasian
  • *No significant difference in deaths between salmeterol vs. placebo*

• 17% of the study population were African American
  • *Statistically significant greater number of events (including death) in salmeterol treated group vs. placebo*

• *More severe asthma at baseline in African American group*

www.fda.gov/medwatch/safety/2003/serevent.htm
SMART Results: Important Considerations

Differences in Use of Inhaled Corticosteroids:

- 47% overall; 50% Caucasians; 38% African Americans
- No significant difference in deaths among those receiving inhaled corticosteroids
- Statistically significant difference (salmeterol > placebo) in those NOT receiving inhaled corticosteroids

www.fda.gov/medwatch/safety/2003/serevent.htm
Current Controversy in Asthma Management: LABA Safety Profile

The “Black Box” Warning:

- LABA’s “should ONLY be used as additional therapy for patients not adequately controlled on other asthma-controller medications”
- LABA’s are “NOT a substitute for inhaled corticosteroids”
- LABA’s “should NOT be used to treat acute symptoms”
- LABA’s “should NOT be initiated in patients with significantly worsening or acutely deteriorating asthma, which may be a life-threatening condition”
Methylxanthines

• **Available Products:**
  • Theophylline (sustained-release tablets and capsules)

• **Indications:**
  • Long-term control and prevention of symptoms, especially nocturnal symptoms

• **Mechanism:**
  • smooth muscle relaxation/bronchodilation via inhibition of phosphodiesterase
Potential Adverse Effects of Methylxanthines

- Effects associated with **therapeutic** doses:
  - Insomnia
  - GI upset/potentiation of gastroesophageal reflux
  - possible hyperactivity in children

- Effects associated with **toxic** doses (dose-related):
  - tachycardia, tachyarrhythmias
  - nausea and vomiting
  - CNS stimulation
  - headache
  - seizures
  - hypokalemia
Methylxanthines: Place in Therapy

• Due to availability of better agents, theophylline is considered a third/last-line (adjunctive) drug
• Overall, relatively weak bronchodilating properties
• Lacks clinically important anti-inflammatory properties (?)
• Difficult to use:
  • numerous potential drug interactions
  • serum concentration monitoring mandatory
    (narrow therapeutic range: 5-15mcg/mL)
LeukotrieneModifiers

- Available Products:
  - Zafirlukast (Accolate®)
  - Zileuton (Zyflo®, Zyflo CR™)
  - Montelukast (Singulair®)

- Indication:
  - Long-term control and prevention of symptoms in persistent asthma
Leukotriene Pathway

Arachidonic Acid

5-Lipoxygenase

FLAP

Zileuton (Zyflo®, Zyflo CR™)

Zafirlukast (Accolate®)

Montelukast (Singulair®)

LTA₄

LTB₄

LTC₄

LTD₄

LTE₄

Chemotaxis

Immunomodulation

• Bronchoconstriction
• Mucus secretion
• Edema
• Hyperresponsiveness
• Eosinophilia

# General Comparison of Leukotriene Modifiers

<table>
<thead>
<tr>
<th>Consideration</th>
<th>Zafirlukast (Accolate®)</th>
<th>Zileuton (Zyflo®, Zyflo CR™)</th>
<th>Montelukast (Singulair®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>≥ 5 years</td>
<td>≥ 12 years</td>
<td>≥ 1 year</td>
</tr>
<tr>
<td>Usual Dose</td>
<td>20mg bid (adults and children ≥ 12 yrs); 10 mg bid (children 5-11 yrs)</td>
<td>600mg qid (immed. Release); 1200 mg bid (controlled release)</td>
<td>10mg qhs(adults) 5mg chewable qpm (kids 6-14 yrs); 4mg chewable or granules qpm (kids 1-5 yrs)</td>
</tr>
<tr>
<td>Warnings</td>
<td>? Churg-Strauss ? LFTs</td>
<td>Increased LFTs (monitoring req’d)</td>
<td>None</td>
</tr>
<tr>
<td>Metabolism</td>
<td>P450: 3A4, 2C9</td>
<td>P450: 1A2, 3A4, 2C9</td>
<td>P450: 3A4, 2C9</td>
</tr>
<tr>
<td>Dosing Considerations</td>
<td>Empty stomach (food ↓ abs 40%)</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>
Low-Dose Fluticasone vs. Oral Montelukast for First-Line Treatment of Persistent Asthma

Low-Dose Fluticasone vs. Oral Montelukast for First-Line Treatment of Persistent Asthma


*P < 0.001
Salmeterol vs Oral Montelukast in Patients Using ICS

ICS therapy for > 30 days prior to randomization

Run-in

Salmeterol 50 mcg b.i.d. (powder) + ICS

n = 236

Montelukast 10 mg daily + ICS

n = 231

2-Weeks 12 Weeks

AM PEFR

Change From Baseline (L/min)

* $P < 0.05$

Weeks

Salmeterol
Montelukast

Leukotriene Modifiers: Place in Therapy

• Possible initial therapy in mild persistent asthma as an alternative to INH CS or cromolyn
  • Not superior to INH CS alone

• Possible adjunctive therapy in addition to INH CS at any level of asthma severity
  • Not superior to LABA when combined with INH CS

• May be useful in children or adults with poor inhaler technique, or in younger children in whom LABA are not indicated
Immunomodulator Therapy: Omalizumab (Xolair®)

• First humanized antibody for treatment of asthma
• Approved by the FDA in June 2003
• Indicated for adults and adolescents (12 years of age or older) with moderate-to-severe persistent asthma who:
  • have had a positive skin test to a perennial aeroallergen, and
  • have symptoms that are inadequately controlled with inhaled corticosteroids
Omalizumab (Xolair®): Mechanism of Action

- A recombinant DNA-derived humanized monoclonal antibody that selectively binds to human immunoglobulin E (IgE)

- Inhibits binding of IgE to high-affinity IgE receptors on the surface of mast cells and basophils, resulting in a decrease in the release of allergic response mediators

- May also reduce the number of high-affinity IgE receptors present on basophils
Omalizumab (Xolair®): Dosing and Administration

• 150 to 375mg subcutaneously every 2 to 4 weeks

• Dose and frequency determined by the serum total IgE level (IU/mL), measured before the start of treatment, and body weight (kg)
Omalizumab (Xolair®):  
Adverse Effects

- **Malignancy** (0.5% vs. 0.2% control)
  - most patients observed for less than one year
  - impact of long-term administration in higher risk patients unknown

- **Anaphylaxis** (<0.1%; 3 patients in pre-marketing clinical trials)
  - Several post-marketing case reports → **Black Box Warning**
  - w/in 2 hrs of first or subsequent administration
  - observation following injection required

- Other: injection site reaction (5-20%)
Omalizumab (Xolair®): Evidence-Based Medicine

- Pooled analysis of 3 multicenter, RDBCT (phase III)
- Adults/adolescents: n=1071; Children, ages 6-12 (n=334)
- Inclusion:
  - moderate-to-severe allergic asthma of at least one year duration
  - total serum IgE level between 30 and 700 IU/mL (adolescents/adults), or 30 and 1300 IU/mL (children)
  - positive skin prick test to dustmite, cockroach, dog, or cat

Omalizumab (Xolair®): Evidence-Based Medicine

- Intervention:
  - **Randomization**: Omalizumab or placebo injections (subQ) every 2-4 weeks
  - **Steroid-Stable Phase**: Dosages of inhaled beclomethasone dipropionate (INH BDP) kept stable over first 16 weeks
  - **Steroid-Reduction Phase**: INH BDP dosages reduced x 25% every two weeks over an eight week period, with the lowest effective dose maintained over for a further four weeks

Steroid-Stable Phase

Exacerbations (% patients)

- Study 008: P = .009
- Study 009: P < .001
- Study 010: P = .095
- All studies: P < .001

Steroid-Reduction Phase

Exacerbations (% patients)

- Study 008: P = .004
- Study 009: P < .001
- Study 010: P < .001
- All studies: P < .001

Omalizumab vs Placebo

Omalizumab (Xolair®): Evidence-Based Medicine

• Results:
  • Rate of unscheduled, asthma-related outpatient visits lower for omalizumab (rate ratio [95% CI], 0.60 [0.44,0.81]; P < 0.01)
  • Rate of asthma-related ED visits lower for omalizumab (rate ratio [95% CI], 0.47 [0.24,1.01]; P = 0.05)
  • Hospitalizations reduced in omalizumab group (rate ratio [95% CI], 0.08 [0.00,0.25]; P < 0.01)

Comparison of Omalizumab to “Standard of Care”

- Double-blind, parallel group, multi-center study
- 419 patients inadequately controlled despite therapy with high-dose INH CS + LABA
- Randomized to receive omalizumab vs. placebo injections subQ

- RESULTS: Omalizumab significantly reduced the rate of asthma exacerbations and ED visits vs. placebo

Omalizumab (Xolair®): An Emerging Treatment Option?

• Only for patients with known allergy-induced asthma (documented positive skin test) who are poorly controlled on inhaled corticosteroids
• Benefit of reduced steroid dosage relative to total cost of therapy unclear
  • Estimated cost: $5000 - $10,000 per year!
• Risk of anaphylaxis must be considered
• **Role of omalizumab better defined in new NIH asthma guidelines:** After treatment has been “maximized” with high-dose INH CS + LABA
NAEPP Expert Panel Report Guidelines (EPR-3): Where are we today?

1997

2002

2007

### Stepwise Approach for Managing Asthma in Youths > 12 Years and Adults

#### Intermittent Asthma
- Consult with asthma specialist if step 4 or higher care is required
- Consider consultation at step 3

#### 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 systemic oral corticosteroids may be needed.
- Use of beta₂-agonist >2 days a week for symptom control (not prevention of EIB) indicates inadequate control and the need to step up treatment.

#### Step 1
- **Preferred:** SABA prn
- **Alternative:**
  - LTRA, Cromolyn, Theophylline, Or Zileutin

#### Step 2
- **Preferred:** Med-dose ICS OR Low-dose ICS+ either LABA, LTRA, Theophylline Or Zileutin
- **Alternative:**
  - Medium-dose ICS+ either LTRA, Theophylline Or Zileutin

#### Step 3
- **Preferred:** High dose ICS + LABA
- **Alternative:**
  - Consider Omalizumab for patients with allergies

#### Step 4
- **Preferred:** Medium-dose ICS+LABA
- **Alternative:**
  - High dose ICS + LA BA + oral Corticosteroid
  - Consider Omalizumab for patients with allergies

#### Step 5
- **Preferred:** High dose ICS + LABA
- **Alternative:**
  - Consider Omalizumab for patients with allergies

#### Step 6
- **Preferred:**
  - High-dose ICS + LABA + oral Corticosteroid
  - Consider Omalizumab for patients with allergies

#### Assess Control
- Step up if needed (check adherence, environmental control and comorbidities)
- Step down if possible (if asthma well controlled for 3 months)

### Patient Education and Environmental Control at Each Step

**EPR-3**
STEPWISE APPROACH FOR MANAGING ASTHMA IN CHILDREN 5-11 YEARS OF AGE

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

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 systemic oral corticosteroids may be needed.
• Use of beta_2-agonist >2 days a week for symptom control (not prevention of EIB) indicates inadequate control and the need to step up treatment.

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

Step 1
Preferred: SABA prn
Alternative: LTRA
Cromolyn
Theophylline

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

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

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

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

Step 6
Preferred: High-dose ICS + LABA + oral Corticosteroid
Step up if needed (check adherence, environmental control and comorbidities)

Assess Control
Step down if possible (if asthma well controlled for 3 months)

Patient Education and Environmental Control at Each Step

EPR-3
STEPWISE APPROACH FOR MANAGING ASTHMA IN CHILDREN 0 - 4 YEARS OF AGE

Intermittent Asthma

Consult with asthma specialist if step 3 or higher care is required
Consider consultation at step 2

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 systemic oral corticosteroids may be needed.
- Use of beta₂-agonist >2 days a week for symptom control (not prevention of EIB) indicates inadequate control and the need to step up treatment.

Patient Education and Environmental Control at Each Step

**Step 1**
- Preferred: SABA prn
- Alternative: LTRA, Cromolyn

**Step 2**
- Preferred: Low-dose ICS
- Alternative: Medium-dose ICS

**Step 3**
- Preferred: Medium-dose ICS
  - AND
  - either LTRA OR LABA

**Step 4**
- Preferred: Medium-dose ICS
  - AND
  - either LTRA OR LABA

**Step 5**
- Preferred: High dose ICS
  - AND
  - either LTRA OR LABA
  - OR
  - Oral Corticosteroid

**Step 6**
- Preferred: High dose ICS
  - AND
  - either LTRA OR LABA
  - OR
  - Oral Corticosteroid

Assess Control

Step up if needed (check adherence, environmental control)

Step down if possible (if asthma well controlled for 3 months)

EPR-3
# ASSESSED ASTHMA CONTROL AND ADJUSTING THERAPY IN CHILDREN 0 - 4 YEARS OF AGE

<table>
<thead>
<tr>
<th>Components of Control</th>
<th>Classification of Asthma Control</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Well Controlled</td>
</tr>
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<td>≤ 2 days/week</td>
</tr>
<tr>
<td>Exacerbations requiring oral steroids</td>
<td>0-1 per year</td>
</tr>
</tbody>
</table>

**Recommended Action For Treatment**

- Maintain current step
- REGULAR FOLLOW UP EVERY 3 - 6 MONTHS
- Consider step down if well controlled at least 3 months

- Step up 1 step
- Reevaluate in 2 - 6 weeks
- If no clear benefit in 4-6 wks, consider alt. dx or adjust therapy

- Consider oral steroids
- Step up (1-2 steps) and reevaluate in 2 weeks
- If no clear benefit in 4-6 wks, consider alt. dx or adjust therapy

**RISK**

- Medication-related sides effects can vary 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.
### Classification of Asthma Control

#### Components of Control

<table>
<thead>
<tr>
<th>IMPAIRMENT</th>
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</tr>
</tbody>
</table>

#### RISK

| Exacerbations | 0-1/year | >2/year (Consider severity and interval) |
| Lung growth | Evaluation requires long-term follow up care |
| Treatment-related adverse effects | Medication-related sides effects can vary from none to 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. |

#### Recommended Action

<table>
<thead>
<tr>
<th>For Treatment</th>
<th>Maintain current step; consider step down if well controlled x 3mos</th>
<th>Step up 1 step</th>
<th>Consider oral steroids</th>
</tr>
</thead>
<tbody>
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</table>
# ASSESSING ASTHMA CONTROL AND ADJUSTING THERAPY IN YOUTHS > 12 YEARS OF AGE AND ADULTS

## Components of Control

<table>
<thead>
<tr>
<th>Classification of Asthma Control</th>
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<th>Not Well Controlled</th>
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<tr>
<td>Validated questionnaires ATAQ/ACT</td>
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<td><strong>Risk</strong></td>
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## Recommended Action For Treatment

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Self-Assessment Questions and Case Studies in Asthma Management
According to the 2007 NIH asthma guidelines, which of the following medications is the preferred first-line “controller” medication for long-term control of asthma symptoms in a TWO YEAR OLD patient with MILD-PERSISTENT asthma?

a. budesonide (low-dose)
b. formoterol
c. cromolyn
d. theophylline
e. montelukast
Intermittent Asthma

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

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 systemic oral corticosteroids may be needed.
- Use of beta₂-agonist >2 days a week for symptom control (not prevention of EIB) indicates inadequate control and the need to step up treatment.

Patient Education and Environmental Control at Each Step

Step 1
Preferred: SABA prn
Alternative: LTRA Cromoly

Step 2
Preferred: Low-dose ICS
Preferred: Medium-dose ICS
Alternative: LTRA

Step 3
Preferred: Medium-dose ICS
Preferred: Low-dose ICS
AND
either LTRA OR LABA

Step 4
Preferred: Medium-dose ICS
Preferred: High dose ICS
AND
either LTRA OR LABA

Step 5
Preferred: High dose ICS
Preferred: Oral Corticosteroid
AND
either LTRA OR LABA
AND

Step 6
Preferred: High dose ICS
Preferred: Oral Corticosteroid
AND
either LTRA OR LABA
AND

Step up if needed (check adherence, environmental control)
Step down if possible (if asthma well controlled for 3 months)

EPR-3
According to the 2007 NIH asthma guidelines, which of the following medications is the preferred first-line “controller” medication for long-term control of asthma symptoms in a TWO YEAR OLD patient with MILD-PERSISTENT asthma?

a. budesonide (low-dose)
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c. cromolyn
d. theophylline
e. montelukast
For a 21 year old patient who is receiving only a MEDIUM-DOSE inhaled corticosteroid and whose asthma is “not well controlled”, which of following approaches is preferred, according to the 2007 NIH guidelines:

a. Increase the dose of the inhaled corticosteroid
b. Add a long-acting beta agonist
c. Add a mast cell stabilizer
d. Add a leukotriene modifier
e. Add theophylline
STEPWISE APPROACH FOR MANAGING ASTHMA IN YOUTHS > 12 YEARS AND ADULTS

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 systemic oral corticosteroids may be needed.
- Use of beta2-agonist >2 days a week for symptom control (not prevention of EIB) indicates inadequate control and the need to step up treatment.

Patient Education and Environmental Control at Each Step

Step 1
Preferred: SABA prn
Alternative: LTRA, Cromolyn, Theophylline or Zileutin

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

Step 3
Preferred: Medium-dose ICS + LABA
Alternative: High-dose ICS + LABA + oral Corticosteroid
AND
Consider Omalizumab for patients with allergies

Step 4
Preferred: Medium-dose ICS + LABA
Alternative: Medium-dose ICS + either LABA, LTRA, Theophylline or Zileutin
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Step 5
Preferred: High-dose ICS + LABA

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Step 6
Preferred: High-dose ICS + LABA + oral Corticosteroid

Assess Control
Step up if needed (check adherence, environmental control and comorbidities)

Step down if possible (if asthma well controlled for 3 months)
For a 21 year old patient who is receiving only a MEDIUM-DOSE inhaled corticosteroid and whose asthma is “not well controlled”, which of following approaches is preferred, according to the 2007 NIH guidelines:

a. Increase the dose of the inhaled corticosteroid
b. Add a long-acting beta agonist
c. Add a mast cell stabilizer
d. Add a leukotriene modifier
e. Add theophylline
JB is a 33 yof with asthma for which she takes daily fluticasone and has an albuterol inhaler for prn use. She presents to the clinic in no acute distress for a routine follow-up visit to assess her level of asthma control. During her visit she reports having to use her albuterol for symptom relief approximately 3 to 4 times per week during the daytime. She reports no limitations in her activities and no nighttime symptoms due to her asthma. She states that as far as she knows, her PEF’s have been running at or above 80% of her personal best. Based on the information provided by JB about the frequency of her asthma symptoms, how would you classify the level of control of her asthma, according to NIH guidelines?

a. “Well Controlled”

b. “Not Well Controlled”

c. “Very Poorly Controlled”

d. “Out of Control”

e. “Intermittently Controlled”
# Classification of Asthma Control

Classification of Asthma Control in Youth > 12 Years of Age and Adults

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## Impairment

- Medication-related side effects can vary 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.

## Risk

- Evaluation requires long-term follow-up care.

## Recommended Action for Treatment

- Maintenance current step
- Consider step down if well controlled x 3 mos
- Step up 1 step
- Reevaluate in 2 - 6 weeks
- Consider oral steroids
- Step up 1-2 steps and reevaluate in 2 weeks
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e. “Intermittently Controlled”
AB, a SEVEN year old patient who was initially diagnosed with mild persistent asthma and prescribed a low-dose inhaled corticosteroid and an albuterol MDI for prn use, returns to your clinic for follow-up and assessment of asthma control. The patient’s mother indicates that AB needs to use her albuterol approximately three times per week to control her symptoms (cough and shortness of breath) during the day. The patient’s mother also reports that AB is awakened a few (approximately 3) times per month due to a cough. When reviewing AB’s peak flow records, you note that her peak flows have been averaging approximately 75 – 80% of her personal best. According to the 2007 NIH guidelines, which of the following is the most appropriate assessment of AB’s asthma control and recommended action at this time?

a. AB’s asthma is “well controlled”; maintain current therapy and reassess in 3 months
b. AB’s asthma is “well controlled”; consider stepping down therapy at this time
c. AB’s asthma is “not well controlled”; step up therapy and reevaluate in 3 months
d. AB’s asthma is “not well controlled”; step up therapy and reevaluate in 3 weeks
e. AB’s asthma is “very poorly controlled”; step up therapy, add oral methylprednisolone, and reassess in 2 weeks
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d. **AB’s asthma is “not well controlled”; step up therapy and reevaluate in 3 weeks**
e. AB’s asthma is “very poorly controlled”; step up therapy, add oral methylprednisolone, and reassess in 2 weeks
Summary of Key Points

• Baseline assessment of asthma severity can help define initial asthma pharmacotherapy

• Ongoing assessment and management should focus on CONTROL, and therapy should be stepped up or stepped down accordingly
  – INH CS are the preferred first-line agents for “long-term control” regardless of the age of the patient
  – New NIH guidelines provide for the option of titrating to a medium dose of INH CS before adding LABA
  – Role of newer therapies for allergy-related asthma continue to be defined
Thank you for your attention!

Questions?