Defining Phenotypes: Expanding Our Understanding of Asthma Challenges in Treating a Heterogeneous Disease

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National Institute of Allergy and Infectious Diseases
American Academy of Allergy, Asthma & Immunology
American Thoracic Society
European Respiratory Society

Asthma Phenotypes Task Force Goals and Objectives

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NHLBI, NIAID, AAAAI, ATS, ERS Collaboration

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Need for Phenotype Definitions

- Asthma has many distinct phenotypes ("a cluster of characteristics that define a disease and its subsets")
- The lack of common phenotype definitions or controlled vocabulary to describe study populations makes it difficult to interpret & fully use clinical research findings.
Asthma Phenotype Task Force Goal

Collaboration among NHLBI, NIAID, AAAAI, ATS, and ERS to develop definitions of asthma phenotypes that will:

- Enhance interpretation of studies
- Promote appropriate comparisons among studies
- Facilitate genetics research in which phenotype is correlated with genotype
Asthma Phenotype Task Force Process

- Define 9 asthma phenotypes
- Develop “controlled vocabulary checklist” to describe key characteristics regarding a study population’s:
  -- demography
  -- asthma clinical features & comorbidities
  -- asthma physiology
  -- asthma biomarkers
Asthma Phenotypes

• Define 9 phenotypes in 3 general categories:
  - Trigger-induced asthma
    1) Allergic
    2) Non-allergic
    3) Aspirin-exacerbated respiratory disease (AERD)
  4) Infection
  5) Exercise-induced
Asthma Phenotypes

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Allergic Background

- Probably the most common phenotype
- 45-88 % of asthmatic patients in recent studies
- Higher prevalence in children, but 60-75 % prevalence in elderly in two recent studies
- Defined based on sensitization ± clinical correlation
Allergic Proposed Definition

• Sensitization (Required)
  – At least one positive prick puncture or in vitro test for specific IgE
  – Antigens: local pollens, mite, *Alternaria*, *Aspergillus*, *Cladosporium*, cat, dog, roach

• Clinical correlation (Desirable) -- One or more of the following:
  – Perennial with sensitization and exposure
  – Seasonal symptoms
  – Symptoms with exposure to grass, dust, cats, dogs
Allergic Asthma: Demographic and Clinical Characteristics

- Younger patients and onset at earlier age than non-allergic
- More common in males
- Family history of allergies common
- Seasonal variation more common than non-allergic
- Severity data conflicting
- Exercise-symptoms more frequent and severe than non-allergic
Allergic Asthma: Clinical Information Needed to Support Definition

- Sensitization (prick puncture skin tests or in vitro tests for specific IgE)
- Age of onset
- Perennial versus seasonal symptoms
- Allergic rhinoconjunctivitis symptoms
- Allergy triggers (grass, dust, cat, dog)
Asthma Phenotypes

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Non-Allergic Asthma

Background

- Asthma risk increases with increased IgE levels
- Most asthmatics are atopic
- However, non-allergic, “intrinsic” asthma phenotype long recognized

Questions

- How should phenotype be defined?
- Is this phenotype clinically useful?
Non-Allergic Asthma Definition

- Asthma in patients in whom allergic sensitization cannot be demonstrated
- Negative skin prick or RAST testing to a panel of seasonal and perennial allergens: Local pollens (grass, tree, weed), molds (*Alternaria, Aspergillus, Cladosporium*), house dust mite (*Dermatophagoides farinae, D. pteronyssinus*), cockroach, cat, dog
- Minimum panel: Perennial allergens
- Normal or low IgE
Non-Allergic Asthma: 
Demographic and Clinical Characteristics

- Onset: Late, adult
- Gender: Female predominance
- Incidence: 10-33%
- No personal or family history of allergy
- Lack of seasonal or exposure-related triggers
- Symptoms: perennial, sometimes beginning with severe respiratory tract infection
- Severity: More severe than allergic asthma, less responsive to steroids
- Aspirin-sensitive asthma often included
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Aspirin-Exacerbated Respiratory Disease (AERD)

- Aspirin triad
- Sampter’s triad
- Aspirin-sensitive asthma
AERD Background

1. Prevalence by history is variable (3-5%) but may be present in up to 21% of adults and 5% of children in certain populations with asthma when determined by oral provocative challenges.

2. In a study of 300 patients in the United States, 57% of patients with aspirin-sensitive asthma were female. In a European study, females outnumbered males 2.3:1.

3. Usual age of onset of symptoms is 30-34 years of age.

4. No known racial predisposition.

5. No known association with lower socioeconomic status.
AERD Task Force Proposed Definition

DEFINITE CRITERION: Documented asthmatic response to aspirin or other non-steroidal anti-inflammatory drug(s)
AERD Task Force Proposed Definition (cont’d)

PROBABLE CRITERIA, WHEN HISTORY OF ASPIRIN SENSITIVITY IS ABSENT IN A SUBJECT WITH ASTHMA:

- Chronic rhinosinusitis with nasal polyps
- Adult onset (over age 20 years)
- Peripheral blood eosinophilia
AERD Genetics

1. Familial cases reported but relatively rare (5.5%).
2. Association with HLA-DQw2 and DPB1.
3. Genetic polymorphisms found in leukotriene C₄ synthase (LTC₄S), 5-lipoxygenase (5-LO), cyclooxygenase-1 (COX-1), cyclooxygenase-2 (COX-2), prostaglandin E2 receptor genes.
AERD Clinical Features

1. Associated with more severe, refractory asthma, representing a major risk factor for severe asthma in outpatients.

2. ASA may induce severe, life-threatening asthma attacks.

3. Rhinorrhea and nasal congestion are usually the first symptoms of aspirin-sensitive asthma and are commonly poorly responsive to pharmacological treatment.
4. Anosmia is common.

5. Asthma and aspirin sensitivity become apparent 1-5 years after initial onset of upper respiratory symptoms.

6. Symptoms manifest within 1-3 hours of ingestion of aspirin and other COX-1 inhibitors.

7. Refractory period to ASA and other COX-1 inhibitors is 2-5 days after ASA desensitization.
Asthma Phenotypes

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Infection-Induced Asthma: Definition

- An individual in which a *respiratory tract infection* influences his/her asthma in any one of the following ways:
  - Associated with *new onset* of disease (in both children and adults)
  - Associated with *exacerbations* of the disease
    - Only mechanism of exacerbation
    - One of a number of exacerbating factors
    - Infection-induced exacerbations may be severe in nature
  - *Co-morbid condition* (e.g. sinusitis) may influence asthma control
  - Associated with *persistence and/or severity* of the disease
Infection-Induced Asthma: Infectious Agents Responsible

- **New onset**
  - Respiratory syncytial virus (RSV)
  - Rhinovirus
  - Parainfluenza
  - Metapneumovirus

- **Exacerbations**
  - Rhinovirus
  - RSV
  - Influenza/parainfluenza
  - Coronaviruses

- **Persistence/chronicity**
  - Adenovirus
  - Chlamydia
  - Mycoplasma
Infection-Induced Asthma: Histopathology and Biomarkers

- Neutrophil infiltrate acutely; enhanced airway eosinophilia chronically
- ? Defect in asthmatic epithelial cells that permits viral replication as opposed to apoptosis

Asthma Phenotypes

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Background
Exercise-Induced Asthma

- Most patients with asthma will develop EIB if they perform sufficient exercise to reach 80-85% of maximum predicted heart rate.
- EIB has been described in 7-20% of the general population.
- EIB is sometimes (incorrectly) thought of as a unique form of asthma, when it is seen in subjects whose disease is so mild ("mild intermittent"), that they experience bronchoconstriction only when they exercise.
  - However, it can be seen in subjects of all ages and severities, correlating best with degree of bronchial hyperresponsiveness.
Background

Exercise-Induced Asthma

- No apparent gender disparity
- No known racial predisposition
- No known association with socioeconomic status
- No known association with smoking
**Exercise-Induced Bronchospasm: Definition**

- Exercise-induced asthma (EIA) refers to the airway narrowing and resultant decrease in expiratory air flow that occurs following vigorous exercise.

- The term EIA is inaccurate, as exercise induces an asthma attack, not asthma.

- A more precise term, gaining in acceptance, is exercise-induced bronchoconstriction (EIB).
Exercise-Induced Bronchospasm: Definition

- It can be demonstrated in most asthmatics if they exercise to a sufficiently high work load and in a small percentage of non-asthmatic subjects.

- EIB is generally thought to be due to evaporative heat and water loss from the airway and various inflammatory mediators and cells have been invoked in its pathogenesis.
Clinical Characteristics

- EIB occurs after the cessation of exercise, usually within 3-5 minutes, with peak bronchoconstriction occurring at 10-15 minutes. Usually defined as ≥ 10% decrease in FEV1 after exercise.

- EIB may be followed by a “refractory period” of up to 4 hours during which repeated exercise causes less bronchoconstriction.

- Once EIB has occurred, symptoms can be reversed with standard inhaled beta-2-adrenergic therapy.
Asthma Phenotypes

- Clinical presentation of asthma
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Background on Pre-Asthma Wheezing in Infants and Children

Temporal Patterns of Wheezing

• **Episodic (viral) wheeze**
  – Episodic (viral) wheeze occurs at discrete time periods usually with symptoms of a viral cold, and with no wheeze between episodes.

• **Multi-trigger wheeze**
  – Multiple-trigger wheeze is characterized by wheezing present with and apart from acute viral episodes

Pre-Asthma Wheezing in Infants and Children: Definition

A child who wheezes in early life.
Pre-Asthma Wheezing in Infants and Children
Airway Inflammation, Remodeling & Lung Function: Summary

- Increased numbers of inflammatory cells present in recurrent wheezers at 1 yr
- Eosinophilic inflammation, reticular basement member (RBM) thickening & impairment in lung function are not present in first year but are present by 3 years
- Lung function shows differences at age 15mo-3 yrs
Pre-Asthma Wheezing in Infants and Children
Tucson Children’s Respiratory Study Phenotypes
in Early Childhood

Adapted from Martinez F and Godfrey S. Wheezing Disorders in the Preschool Child. 2003
# Pre-Asthma Wheezing in Infants and Children: Tucson Children’s Respiratory Study

<table>
<thead>
<tr>
<th>Wheezing Phenotype</th>
<th>% in each category at age 6 years N = 826</th>
<th>Significant risk factors for each phenotype</th>
<th>% MD dxed asthma age 6 years</th>
<th>% dxed with bronchitis age 6 yrs</th>
<th>% Skin test positive age 6 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never Wheezed</td>
<td>51.5% Reference Group</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>33.8%</td>
</tr>
<tr>
<td>Transient Early Wheezers</td>
<td>19.9% Maternal smoke exposure</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>38.4%</td>
</tr>
<tr>
<td>Late-onset Wheezers</td>
<td>15% Rhinitis apart from URIs Maternal asthma Male sex</td>
<td>22.5%</td>
<td>25%</td>
<td>55.7%</td>
<td></td>
</tr>
<tr>
<td>Persistent Wheezers</td>
<td>13.7% Eczema Rhinitis apart from URIs Maternal asthma Male sex Maternal smoke exposure</td>
<td>46%</td>
<td>22.1%</td>
<td>51.1%</td>
<td></td>
</tr>
</tbody>
</table>
## Pre-Asthma Wheezing in Infants and Children

A Clinical Index to Define Risk of Asthma in Young Children with Recurrent Wheezing

**Castro-Rodriguez JA et al. AJRCCM 162:1403, 2000**

<table>
<thead>
<tr>
<th>Positive Index</th>
<th>= frequent wheezing in the 1st 3 yrs, PLUS 1 Major Criteria OR 2 Minor Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eczema*</td>
<td></td>
</tr>
<tr>
<td>Parental asthma*</td>
<td></td>
</tr>
<tr>
<td>+ Aeroallergen skin test</td>
<td></td>
</tr>
<tr>
<td>+ Food skin test*</td>
<td></td>
</tr>
<tr>
<td>Wheezing without URI</td>
<td></td>
</tr>
<tr>
<td>Eosinophilia (34%)</td>
<td></td>
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</table>

* Doctor-diagnosed

```
“+” Index: 65% chance of asthma by age 6
“-” Index: 95% chance no asthma by age 6
```
Asthma Phenotypes

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Exacerbation Prone Asthma (EPR)

Incidence/US

- 500,000 Hospitalizations
- 2,000,000 ED Visits
- 80% Asthma Costs in 20% of Populations

Exacerbation prone phenotype may define a good part of the 20%

Background
Exacerbation Prone Asthma
Evidence for a Subset

• 122,942 patients – 2 year study
  Exacerbation 1st year-9x more likely to have a second exacerbation, 75% have no second exacerbation
• 4,000 patients - 4 year study
  Exacerbation 1st year – 2x more likely to exacerbate - next 3 years, 42% have no second exacerbation
• Exacerbations occur in 2 groups
  One group truly prone to exacerbation
  Other group exacerbation coincidental, not predisposed

Therefore:
• Exacerbation rate is a Key Factor to Define the Phenotype

Background
Exacerbation Prone Asthma

Relation to Severe Asthma
Factors for Severe Exacerbations

- Low FEV\(_1\)
- African American Ethnicity
- History of Pneumonia
- Early Age of Onset
- NSAID Exacerbated Airway Disease
- Worsening Asthma Symptoms with Menses

Griswald et al, *Chest* 127 1579-86, 2005
Exacerbation Prone Asthma

Definition (EPR 3 based)

- Worsening Asthma Symptoms
- PEF < 69% of Personal Best
- Systemic Corticosteroid Treatment or >2 fold increase of inhaled glucocorticoids

Asthma Phenotypes

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Background

Irreversible Airflow Limitation in Asthma

- The subgroup of asthmatics with Irreversible Airflow Limitation or Persistent Airway Obstruction is thought to represent an important asthma phenotype.

- Limited information is available concerning this subgroup: incidence, associations, biomarkers, pathogenesis, natural history, best treatment approaches.
Irreversible Airflow Limitation in Asthma: Operational Definition

FEV$_1$/FVC ratio below the lower limit of normal for age and FEV$_1$ < 90% predicted in a patient taking corticosteroids, after acute administration of a rapid onset bronchodilator

Operational Defined as:

a) Moderate to high dose inhaled corticosteroid for $\geq$ 4 weeks 
   OR
b) Systemic corticosteroids ($\geq$ 0.5 mg/kg of prednisone or equivalent) for $\geq$ 2 weeks
   AND

After $\geq$ 4 puffs of albuterol (90 micrograms/puff) (or the equivalent) administered before spirometry
Irreversible Airflow Limitation in Asthma: Proposed Definition

Evidence of both airway obstruction (reduced $\text{FEV}_1/\text{FVC}$ ratio) and a reduced $\text{FEV}_1$ in a patient treated with both anti-inflammatory agents (glucocorticosteroids) and bronchodilators (beta-agonists)
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Eosinophilic Asthma: Associations

- Eosinophilic inflammation associated with poor asthma control, increased bronchodilator response, lower lung function and exacerbations in ICS treated pts
- More common in aspirin-sensitive asthma, in association with nasal polyps and in later onset disease
- Lower BMI
- Loosely with FeNO
Definition
Eosinophilic Asthma

Requires sputum analysis
• >2% eosinophils in sputum
  – Likely in the face of ongoing inhaled or oral CS therapy
  – Implications in untreated asthmatics less clear
Asthma Phenotypes

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Background
Neutrophilic Asthma

Clinical characteristics and Rx implications

- More often in severe, older asthmatics
- May be related to lower lung function
- May imply less robust CS response when eosinophilic inflammation absent
  - Possible better response to macrolide antibx
Neutrophilic Asthma

Introduction/Definition
- Much less well described and defined than eosinophilic asthma
- Seems to increase with increasing severity/CS use
- “Definition”/neutrophil % cut-off unclear and may depend on sputum processing method
  - Can be seen in association with eosinophil phenotype
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Summary for Reporting Phenotypes of Study Populations
Summary: Asthma Phenotypes

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Summary: Asthma Phenotype Definitions (cont.)

- Task Force phenotype definitions reveal:
  - Support for emerging conviction that asthma is not a single disease
  - Evidence for distinct phenotypes of asthma
  - Acknowledgement of overlap: a patient can have >1 phenotype
  - Specific questions for future research to refine definitions
Wenzel SE. *Lancet* 2006;368:804-13
Thank you!
Asthma: Challenges in Treating a Heterogeneous Disease

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We look forward to welcoming you to the 2011 World Allergy Congress!

CANCÚN, MÉXICO
4-8 December 2011
www.worldallergy.org/wac2011
Objectives

• Understand phenotypes and co-morbid conditions which adds to the complexity and heterogenicity of asthma
• Understand basic theories of asthma pathogenesis and identify molecular targets for asthma treatment
• Identify standard treatment agents in asthma and understand the rationale for their use
• Discuss NAEPP Guidelines past and present and recognize how they are used to guide asthma treatment
Asthma Is Prevalent: Significant Morbidity and Mortality

32.6 Million People Have Had an Asthma Diagnosis in Their Lifetime

22.2 Million People Are Currently Diagnosed with Asthma

12.2 Million People Suffer From Asthma Attacks Annually

Approximately 4000 Asthma-Related Deaths Occur Annually

Approximately 11 People Die From Asthma Each Day

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Director, Division of Lung Diseases, NHLBI

World Allergy Congress
December 8, 2009
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### NHLBI, NIAID, AAAAI, ATS, ERS Collaboration

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TCRS Phenotypes in Early Childhood

Adapted from Martinez F and Godfrey S. Wheezing Disorders in the Preschool Child. 2003
Co-Morbid Conditions which Complicate the Diagnosis and Treatment of Asthma
1. Food
2. Rhinosinusitis
   a. Allergic
   b. Non-allergic
   c. Infectious
   d. Nasal polyposis
   e. Other
3. Gastroesophageal Reflux Disease (GERD)
4. Vocal Cord Dysfunction (VCD)
5. Obesity
6. Osteopenia and Osteoporosis
7. Psychological Problems
8. Churg-Strauss Disease
9. Sleep Apnea
10. Pregnancy
11. COPD versus Asthma
12. Eczema
13. Smoking Cessation
14. Infection (Vaccination)  
15. Bronchiectasis and Cystic Fibrosis  
16. Exercise-Induced Asthma  
17. Others- Endocrine, Conjunctivitis, Congestive Heart Failure, Pulmonary Embolism, Medications  
18. Primary Ciliary Dyskinesia
You Are Invited to Attend

WAO INTERNATIONAL SCIENTIFIC CONFERENCE

Asthma and Co-morbid Conditions: Expanding the Practice of Allergy for Optimal Patient Care

6–8 DECEMBER 2010
DUBAI, UAE

www.worldallergy.org/2010dubai
Asthma

• Historical Definition:
  – Reversible obstruction of the airways of the lungs
    • Bronchoconstriction
    • Airway inflammation (edema, inflammatory infiltrate)

• Symptoms:
  – Cough
  – Chest congestion (increased mucus)
  – Wheezing
  – Chest tightness/ shortness of breath
Bronchoconstriction

• Caused by inflammatory mediators released from activated leukocytes:
  – Histamine
  – Prostaglandins
  – Leukotrienes

• Rationale:
  – Treatment with beta-2 agonists may help airway obstruction through smooth muscle relaxation.
Airway Inflammation

• Also caused by inflammatory mediators released from activated leukocytes.
  – Histamine
  – Prostaglandins
  – Leukotrienes
  – Tryptase
  – Tissue Growth Factors
  – Chemokines
  – Cytokines

• Rationale:
  – Treatment with local anti-inflammatory agents will decrease inflammatory cell activation and prevent airway edema and inflammatory cell infiltration of airways.
Asthma

• Causes:
  – Infections (viruses or bacteria)
  – Irritants (smoke, perfumes, chemical odors)
  – Exercise/ Cold air
  – Allergies
    • Drugs (aspirin, ibuprofen)
    • Foods (Unusual)
    • Seasonal (pollens of certain size from trees, grasses, weeds, molds)
    • Perennial (indoor allergens from pet danders, dust mites, cockroach,)
Early Phase Reaction (EPR) Occurs Within Minutes of Allergen Exposure in Sensitized Subjects

- **Mast cell**
  - **Neosynthesis**
  - **Degranulation**

  **Allergen**
  - Preformed mediators: Histamine, Proteases
  - Newly generated mediators: Cysteinyl leukotrienes, Prostaglandins, PAF, Bradykinin, Interleukins, TNF-α, GM-CSF

**Symptoms of Asthma**
- Blood vessels, nerves, mucus glands, smooth muscle
- Wheezing, Coughing, Shortness of Breath, Tight Chest
Current Standard Treatments (based on NIH guidelines)

- Short and long-acting inhaled beta-2 agonists
- Inhaled corticosteroids
- Leukotriene modifiers
- Theophylline
- Cromolyn and Nedocromil
Short and long-acting beta-2 agonists

• Short acting: (4-6 hrs.)
  – Albuterol MDI/Neb
  – Pirbuterol MDI
  – Metaproterenol MDI
  – Levalbuterol

• Long acting (12 hrs.)
  – Salmeterol DPI
  – Formoterol DPI
Short and long-acting beta-2 agonists

- Relax airway smooth muscle by stimulating beta-2 adrenergic receptors
- **Strengths:**
  - Inhaled short-acting beta-2 drug of choice for quick relief of acute symptoms *(rescue)* and for prevention of exercise-induced bronchospasm
  - Inhaled long-acting beta-2 good as adjunct **controller** therapy along with inhaled corticosteroids
Short and long-acting beta-2 agonists

• Limitations:
  – Do not treat underlying airway inflammation, therefore, not effective as means of long-term control as monotherapy.
  – Safety concerns when used as monotherapy in persistent asthma

• Side Effects:
  – Tachycardia
  – Skeletal muscle tremor
  – Hypokalemia
  – QT prolongation at high doses
Short and long-acting beta-2 agonists

- Pharmacogenetics:
  - Genetic polymorphism in beta-2 receptor influence clinical response to beta agonists
  - Patients homozygous for Arg/Arg substitution at codon 16 of beta receptor found to do worse on regular use of beta agonist as compared to prn use
  - May affect up to 1:6 asthmatics
Inhaled Corticosteroids (ICS)
# Inhaled Corticosteroids (ICS)

## Adults

<table>
<thead>
<tr>
<th>Drug</th>
<th>Low Daily Dose</th>
<th>Med. Daily Dose</th>
<th>High Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone</td>
<td>80-240 mcg</td>
<td>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</td>
<td>200-600 mcg</td>
<td>600-1200 mcg</td>
<td>&gt;1200 mcg</td>
</tr>
<tr>
<td>200 mcg/inhal.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flunisolide</td>
<td>500-1000 mcg</td>
<td>1000-2000 mcg</td>
<td>&gt;2000 mcg</td>
</tr>
<tr>
<td>250 mcg/puff</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluticasone</td>
<td>88-264 mcg</td>
<td>264-660 mcg</td>
<td>&gt;660 mcg</td>
</tr>
<tr>
<td>44, 110, 220 mcg/puff</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>400-1000 mcg</td>
<td>1000-2000 mcg</td>
<td>&gt;2000 mcg</td>
</tr>
<tr>
<td>100 mcg/puff</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mometasone</td>
<td>200 mcg</td>
<td>400 mcg</td>
<td>&gt;400 mcg</td>
</tr>
<tr>
<td>200 mcg/puff</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Inhaled Corticosteroids (ICS)

• **Strengths:**
  – Anti-inflammatory activity
  – Superior clinical efficacy
  – Safety (compared to systemic steroids)

• **Limitations:**
  – Cost
  – No role in treating acute symptoms (not a rescue medication)
  – BID dosing (except mometasone)
  – Patient adherence
    • “controller medication”
    • Steroid phobia
    • Confusion about dosing, multiple inhalers
Inhaled Corticosteroids (ICS)

• Side Effects:
  – Oral candidiasis
  – Bone mineral density loss with prolonged use at high doses (>1200 mcg fluticasone)
  – Glaucoma
  – Cataracts
  – Transiently decreased growth in children
GC Resistance in Asthma:

• Definitions:
  – For clinical practice:
    • **Type 1:** Relative steroid resistance (steroid dependence) Patient with asthma by ATS criteria on maximal doses of inhaled corticosteroids along with 40 - 60mg prednisone daily in the absence of poorly controlled allergic rhinitis, OSA, GERD and absence of known allergic triggers who is dependent on large doses of steroids for control.
    • **Type 2:** Absolute steroid resistance. Those patients with the above characteristics who have no response to oral steroids.

Leukotriene Modifiers

- **Monteleukast**
  - Receptor antagonist
  - Dose: 10 mg qhs
- **Zafirlukast**
  - Receptor antagonist
  - Dose: 20 mg bid
- **Zileuton**
  - Enzymatic inhibitor (monitor liver enzymes)
  - Dose: 600 mg qid
Leukotriene Modifiers

• Strengths:
  – Available as once daily dosing without an inhaler
  – Specifically targets unique class of inflammatory mediators (phenotype-specific?)
  – Provides alternative add-on therapy for those who cannot tolerate beta-agonists

• Limitations:
  – Modest clinical efficacy
  – Problematic drug interactions
    • Zileuton: theophylline and warfarin
    • Zafirlukast: theophylline and erythromycin
    • Montelukast: phenobarbitol and rifampin
Theophylline

- Methylxanthine with mild to moderate bronchodilator effects
- Possible anti-inflammatory properties at low doses (under investigation)
- Strengths:
  - Once or twice daily oral dosing
  - Cost
Theophylline

• Limitations:
  – Inferior clinical efficacy compared to other products
  – Narrow therapeutic window (blood levels 5-15 mcg/ml)
  – Multiple adverse effects and drug interactions
• Side effects:
  – Tachyarrhythmias, nausea, vomiting, seizures
• Drug interactions:
  – Increased theophylline clearance: phenobarbital, rifampin
  – Decreased clearance: macrolides, ciprofloxacin
Cromolyn and Nedocromil

- Nonsteroidal agents initially used for long-term treatment of asthma in children.
- Anti-inflammatory effects:
  - Decreased histamine release from mast cells
  - Decreased activation of eos, polys, monocytes
- Strengths:
  - Safety profile for use in children
- Limitations:
  - Frequency of dosing
  - Taste
Omalizumab

- FDA-approved for patients 12-64 yrs. with allergic asthma.

- Recombinant humanized monoclonal anti-IgE antibody chimera (5% murine sequences, 95% human)

- Binds IgE at same Fc site as FcεR1, thus binds and attenuates levels of circulating antigen-specific IgE.

- Reduction in serum IgE causes down-regulation of high affinity IgE receptors.
Omalizumab  (cont.)

• In >1000 patients with allergic asthma requiring inhaled corticosteroids but still symptomatic, infusion of omalizumab for 4 weeks allowed more rapid taper of inhaled corticosteroids with fewer exacerbations and improved symptom scores as compared to placebo.

• Adverse Effects:
  – Relatively few - anaphylaxis – especially later onset
  – ? increase in malignancy

• Cost
Main results:

Eight trials were included, contributing a total of 2037 mild to severe allergic asthmatic participants with high levels of IgE.

Treatment with intravenous and subcutaneous Omalizumab significantly reduced free IgE compared with placebo. Omalizumab led to a significant reduction in inhaled steroid consumption compared with placebo: -114 mcg/day (95% CI -150 to -78.13, two trials).

There were significant increases in the number of participants who were able to reduce steroids by over 50%: odds ratio (OR) 2.50, 95% confidence interval (CI) 2.02 to 3.10 (four trials); or completely withdraw their daily steroid intake: OR 2.50, 95%CI 2.00 to 3.13 (four trials).

Participants treated with Omalizumab were less likely to suffer an asthma exacerbation with treatment as an adjunct to steroids (OR 0.49, 95%CI 0.38 to 0.64, four trials), or as a steroid tapering agent (OR 0.47, 95% CI 0.37 to 0.60, four trials).
Omalizumab (Cochrane Database)

• Conclusions:
• Omalizumab was significantly more effective than placebo at increasing the numbers of patients who were able to reduce or withdraw their inhaled steroids, but the mean difference in steroid consumption achieved with Omalizumab was of debatable clinical value.
• The impressive effects observed in control groups bring into question the true effect of Omalizumab.
• Omalizumab was effective in reducing asthma exacerbations as an adjunctive therapy to inhaled steroids. Omalizumab was well tolerated, although the safety profile requires longer term assessment.
• Further assessment in pediatric and severe adult populations is necessary, as is double-dummy comparison with inhaled corticosteroids.
Allergen Immunotherapy

– Allergen immunotherapy has been used for over 100 years to treat hayfever and asthma.

– Particularly with well-standardized allergens, immunotherapy is very effective (>90% of patients) in reducing symptoms and medication requirement for patients with allergic rhinitis and allergic asthma. (No role for hives or food allergy)

– Immunotherapy useful adjunct for patients who have breakthrough symptoms on maximized medications, don’t like taking medications or who cannot tolerate medications.
Update on National Asthma Education and Prevention Program (NAEPP) Guidelines for the Treatment of Asthma
Asthma Assessment and Monitoring: Key Differences From 1997 and 2002 Expert Panel Reports

• Key elements of assessment and monitoring
  – Severity
  – Control
  – Responsiveness to treatment

• Severity emphasized for initiating therapy

• Control emphasized for monitoring and adjusting therapy

• Severity and control defined in terms of 2 domains
  – Impairment
  – Risk

Assessing Asthma Severity: Impairment Domain

Impairment = Frequency and Intensity of Symptoms and Functional Limitations

**Symptoms**
- Nighttime awakenings
- Need for SABAs for quick relief of symptoms
- Work/school days missed
- Ability to engage in normal daily activities or desired activities
- QOL assessments

**Lung Function**
- Spirometry
- Peak flow

SABAs = short-acting β2-agonists; QOL = quality of life.

Assessing Asthma Severity: Risk Domain

- Likelihood of asthma exacerbations, progressive decline in lung function, or risk of adverse effects from medications

- Assessment
  - Frequency and severity of exacerbations
  - Oral corticosteroid use
  - Urgent-care visits
  - Lung function
  - Noninvasive biomarkers may play an increased role in future

Goal of Asthma Therapy: Achieve Control

**Reduce Impairment**
- Prevent chronic and troublesome symptoms
- Require infrequent use of inhaled SABA (≤ 2 days/week)
- Maintain (near) “normal” pulmonary function
- Maintain normal activity levels
- Meet patients’ expectations of, and satisfaction with, asthma care

**Reduce Risk**
- Prevent recurrent exacerbations
- Minimize need for emergency department visits or hospitalizations
- Prevent progressive loss of lung function
- Provide optimal pharmacotherapy, with minimal or no adverse effects
Periodic Assessment of Asthma Control Recommended (1- to 6-month intervals)

- Are goals of therapy being met?
- Are adjustments in treatment necessary?

**Measure**
- Signs and symptoms
- Pulmonary function
- QOL/functional status
- History of exacerbations
- Pharmacotherapy
- Patient-provider communication and patient satisfaction

Classifying Asthma Severity and Assessing Asthma Control

• In patients not on long-term controller medications
  – Severity based upon domains of impairment and risk
  – Level of severity based upon most severe category in which any feature appears

• In patients on long-term controller medications
  – Severity based upon lowest step required to maintain clinical control
  – Control of asthma based upon domains of impairment and risk
    • Level of control based upon most severe impairment or risk category
    • Validated questionnaires may be used in patients aged ≥12 years

Categories of Evidence Used to Support NAEPP Recommendations

<table>
<thead>
<tr>
<th>Evidence Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Randomized, controlled trials (rich body of data)</td>
</tr>
<tr>
<td>B</td>
<td>Randomized, controlled trials (limited body of data)</td>
</tr>
<tr>
<td>C</td>
<td>Nonrandomized trials and observational studies</td>
</tr>
<tr>
<td>D</td>
<td>Panel consensus judgment</td>
</tr>
</tbody>
</table>

# Classifying Asthma Severity and Initiating Treatment in Youths ≥12 Years of Age and Adults

<table>
<thead>
<tr>
<th>Components of Severity</th>
<th>Intermittent</th>
<th>Persistent</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impairment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal FEV₁/FVC:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8-15 yr</td>
<td>85%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-39 yr</td>
<td>80%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-59 yr</td>
<td>75%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60-80 yr</td>
<td>70%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>≤2x/month</td>
<td></td>
<td>3-4x/month</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SABA use for symptom control (not prevention of EIB)</td>
<td>≤2x/month</td>
<td></td>
<td>&gt;2 days/week but not daily</td>
<td>Daily</td>
<td>Throughout the day</td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>None</td>
<td>Minor limitation</td>
<td>Some limitation</td>
<td>Daily</td>
<td>Several times per day</td>
</tr>
<tr>
<td>Lung Function</td>
<td></td>
<td>Normal FEV₁, FEV₁/FVC normal</td>
<td>FEV₁ &gt;80% predicted, FEV₁/FVC normal</td>
<td>FEV₁ &gt;80% but &lt;80% predicted, FEV₁/FVC reduced 5%</td>
<td>FEV₁ &lt;80% predicted, FEV₁/FVC reduced &gt;5%</td>
</tr>
</tbody>
</table>

**Exacerbations requiring oral systemic corticosteroids**

- **Risk:**
  - 6-1/year
  - ≥2/year
  - Consider severity and interval since last exacerbation
  - Frequency and severity may fluctuate over time for patients in any severity category
  - Relative annual risk of exacerbations may be related to FEV₁

**Recommended Step for Initiating Treatment**

- **Step 1**: In 2 to 6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly
- **Step 2**: Step 3 and consider short course of oral systemic corticosteroids
- **Step 3 or 4 or 5**

---

### Stepwise Approach for Managing Asthma in Patients Aged ≥12 Years

<table>
<thead>
<tr>
<th>Intermittent Asthma</th>
<th>Persistent Asthma: Daily Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong> Preferred: SABA PRN</td>
<td>Consult with asthma specialist if Step 4 care or higher is required. Consider consultation at Step 3.</td>
</tr>
</tbody>
</table>

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

**Step 3**  
Preferred: Low-dose ICS + LABA (A) OR Medium-dose ICS (A)  
Alternative: Medium-dose ICS + either LTRA (B), Theophylline (B), or Zileuton (D)

**Step 4**  
Preferred: High-dose ICS + LABA (B) AND Consider Omalizumab for Patients Who Have Allergies (B)  
Alternative: High-dose ICS + LABA (B) AND Consider Omalizumab for Patients Who Have Allergies (B)

**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

**Step Up If Needed** (first, check adherence, environmental control, and comorbid conditions)

**Step Down If Possible** (and asthma is well controlled at least 3 months)

**Assess Control**

**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 SABA ≥2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.

ICS = inhaled corticosteroids; LABA = long-acting β₂-agonist; LTRA = leukotriene receptor antagonist.

Estimated Comparative Daily Dosages for ICS in Patients Aged ≥12 Years

<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>Beclomethasone HFA 40 or 80 µg/puff</td>
<td>80-240 µg</td>
<td>&gt;240-480 µg</td>
<td>&gt;480 µg</td>
</tr>
<tr>
<td>Budesonide DPI 90, 180, or 200 µg/inhalation</td>
<td>180-600 µg</td>
<td>&gt;600-1200 µg</td>
<td>&gt;1200 µg</td>
</tr>
<tr>
<td>Flunisolide 250 µg/puff</td>
<td>500-1000 µg</td>
<td>&gt;1000-2000 µg</td>
<td>&gt;2000 µg</td>
</tr>
<tr>
<td>Flunisolide HFA 80 µg/puff</td>
<td>320 µg</td>
<td>&gt;320-640 µg</td>
<td>&gt;640 µg</td>
</tr>
<tr>
<td>Fluticasone HFA MDI 44, 110, or 220 µg/puff</td>
<td>88-264 µg</td>
<td>&gt;264-440 µg</td>
<td>&gt;440 µg</td>
</tr>
<tr>
<td>Fluticasone DPI 50, 100, or 250 µg/inhalation</td>
<td>100-300 µg</td>
<td>&gt;300-500 µg</td>
<td>&gt;500 µg</td>
</tr>
<tr>
<td>Mometasone DPI 200 µg/inhalation</td>
<td>200 µg</td>
<td>400 µg</td>
<td>&gt;400 µg</td>
</tr>
<tr>
<td>Triamcinolone acetonide 75 µg/puff</td>
<td>300-750 µg</td>
<td>&gt;750-1500 µg</td>
<td>&gt;1500 µg</td>
</tr>
</tbody>
</table>

Note that some of the doses, particularly in the high-dose range, may be outside the recommended labeling for that product.

Assessing Asthma Control and Adjusting Therapy in Youths ≥12 Years of Age and Adults

<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>Symptoms</td>
<td>≤2 days/week</td>
<td>&gt;2 days/week</td>
<td>Throughout the day</td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>≤2x/month</td>
<td>1-3x/week</td>
<td>≥4x/week</td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>None</td>
<td>Some limitation</td>
<td>Extremely limited</td>
</tr>
<tr>
<td>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>FEV₁ or peak flow</td>
<td>≥80% predicted/personal best</td>
<td>60%-86% predicted/personal best</td>
<td>&lt;60% predicted/personal best</td>
</tr>
<tr>
<td>Validated questionnaires</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATAG</td>
<td>0</td>
<td>1-2</td>
<td>3-4</td>
</tr>
<tr>
<td>ACQ</td>
<td>≤0.75</td>
<td>≥1.6</td>
<td>N/A</td>
</tr>
<tr>
<td>ACT</td>
<td>≥20</td>
<td>18-19</td>
<td>≥15</td>
</tr>
</tbody>
</table>

| Exacerbations requiring oral systemic corticosteroids | 0-1/year | ≥2/year | Consider severity and interval since last exacerbation |

**Impairment**

**Risk**

Recommended Action for Treatment

- Maintain current step
- Regular follow-ups every 1-3 months to maintain control
- Consider step down if well controlled for at least 3 months

- Step up 1 step and
- Reevaluate in 2 to 6 weeks
- For side effects, consider alternative treatment options

- Consider short course of oral systemic corticosteroids
- Step up 1-2 steps, and
- Reevaluate in 2 weeks
- For side effects, consider alternative treatment options

Classifying Asthma Severity and Initiating Treatment in Children 0 to 4 Years of Age

<table>
<thead>
<tr>
<th>Components of Severity</th>
<th>Intermittent</th>
<th>Persistent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild</td>
<td>Moderate</td>
</tr>
<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>0</td>
<td>1-2×/month</td>
</tr>
<tr>
<td>SABA use for symptom control (not prevention of EE)</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>Risk</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exacerbations requiring oral systemic corticosteroids</td>
<td>0-1/year</td>
<td>≥2 exacerbations in 6 months requiring oral systemic corticosteroids, or ≥4 wheezing episodes/1 year lasting &gt;1 day AND risk factors for persistent asthma</td>
</tr>
</tbody>
</table>

**Recommended Step for Initiating Treatment**

- **Step 1**
  - In 2 to 6 weeks, depending on severity, evaluate level of asthma control that is achieved. If no clear benefit is observed in 4 to 6 weeks, consider adjusting therapy or alternative diagnoses.

- **Step 2**
  - Consider short course of oral systemic corticosteroids

Stepwise Approach for Managing Asthma in Children Aged 0 to 4 Years

<table>
<thead>
<tr>
<th>Intermittent Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong>&lt;br&gt;Preferred: SABA PRN</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Persistent Asthma: Daily Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consult with asthma specialist if Step 3 care or higher is required. Consider consultation at Step 2.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 2</th>
<th>Step 3</th>
<th>Step 4</th>
<th>Step 5</th>
<th>Step 6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preferred:</strong> Medium-dose ICS (A) or Montelukast (A)</td>
<td><strong>Preferred:</strong> Medium-dose ICS + either LABA (D) or Montelukast (D)</td>
<td><strong>Preferred:</strong> High-dose ICS + either LABA (D) or Montelukast (D)</td>
<td><strong>Preferred:</strong> High-dose ICS + either LABA or Montelukast and Oral Systemic Corticosteroids (D)</td>
<td></td>
</tr>
<tr>
<td>Alternative: Cromolyn (B) or Montelukast (A)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Step 4**<br>Preferred: Medium-dose ICS + either LABA or Montelukast and Oral Systemic Corticosteroids (D)

**Step 5**<br>Preferred: High-dose ICS + either LABA or Montelukast and Oral Systemic Corticosteroids (D)

**Step 6**<br>Preferred: High-dose ICS + either LABA or Montelukast and Oral Systemic Corticosteroids (D)

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

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

### Estimated Comparative Daily Dosages for ICS in Children Aged 0 to 4 Years

*Only products with indications in the 0-4 range. Note that some of the doses, particularly in the high-dose range, may be outside the recommended labeling for that product.


<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>Beclomethasone HFA</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>40 or 80 µg/puff</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Budesonide DPI</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>90, 180, or 200 µg/inhalation</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><em>Budesonide inhalation suspension for nebulization (child dose)</em></td>
<td>0.25-0.5 mg</td>
<td>&gt;0.5-1.0 mg</td>
<td>&gt;1.0 mg</td>
</tr>
<tr>
<td>Flunisolide 250 µg/puff</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Flunisolide HFA</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>80 µg/puff</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><em>Fluticasone HFA MDI: 44, 110, or 220 µg/puff</em></td>
<td>176 µg</td>
<td>&gt;176-352 µg</td>
<td>&gt;352 µg</td>
</tr>
<tr>
<td>Fluticasone DPI</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>50, 100, or 250 µg/inhalation</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Mometasone DPI</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>200 µg/inhalation</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Triamcinolone acetonide 75 µg/puff</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>
Assessing Asthma Control and Adjusting Therapy in Children 0 to 4 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</td>
<td>&gt;2 days/week</td>
<td>Throughout the day</td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>≥1 x/month</td>
<td>&gt;1 x/month</td>
<td>≥1 x/week</td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>None</td>
<td>Some limitation</td>
<td>Extremely limited</td>
</tr>
<tr>
<td>SABA use for symptom control (not prevention of BIB)</td>
<td>≤2 days/week</td>
<td>&gt;2 days/week</td>
<td>Several times per day</td>
</tr>
<tr>
<td>Risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exacerbations requiring oral systemic corticosteroids</td>
<td>0-1/year</td>
<td>2-3/year</td>
<td>&gt;3/year</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>

**Recommended Action for Treatment**

**Well Controlled**
- Maintain current treatment
- Regular follow-up every 1 to 6 months
- Consider step-down if well controlled for at least 3 months

**Not Well Controlled**
- Step up (1 step) and reevaluate in 2 to 6 weeks
- If no clear benefit in 4 to 6 weeks consider alternative diagnoses or adjusting therapy
- For side effects, consider alternative treatment options

**Very Poorly Controlled**
- Consider short course of oral systemic corticosteroids
- Step up (1-2 steps) and reevaluate in 2 weeks
- If no clear benefit in 4 to 6 weeks, consider alternative diagnoses or adjusting therapy
- For side effects, consider alternative treatment options

## Classifying Asthma Severity and Initiating Treatment in Children 5 to 11 Years of Age

<table>
<thead>
<tr>
<th>Components of Severity</th>
<th>Intermittent</th>
<th>Persistent</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Impairment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>≤2 days/week</td>
<td>&gt;2 days/week but not daily</td>
<td>Daily</td>
<td>Throughout the day</td>
<td></td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>≤2x/month</td>
<td>3-4x/month</td>
<td>&gt;1x/week but not nightly</td>
<td>Often 7x/week</td>
<td></td>
</tr>
<tr>
<td>SABA use for symptom control (not prevention of EE)</td>
<td>≤2 days/week</td>
<td>&gt;2 days/week but not daily</td>
<td>Daily</td>
<td>Several times per day</td>
<td></td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>None</td>
<td>Minor limitation</td>
<td>Some limitation</td>
<td>Extremely limited</td>
<td></td>
</tr>
<tr>
<td>Lung Function</td>
<td>Normal FEV₁ between exacerbations</td>
<td>FEV₁ &gt;80% predicted</td>
<td>FEV₁,FVC &gt;80%</td>
<td>FEV₁ = 60%-80% predicted</td>
<td>FEV₁,FVC = 75%-80%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk</th>
<th>Exacerbations requiring oral systemic corticosteroids</th>
<th>0-1 year</th>
<th>≥2 year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Consider severity and interval since last exacerbation</td>
<td>Frequency and severity may fluctuate over time for patients in any severity category</td>
<td>Relative annual risk of exacerbations may be related to FEV₁</td>
</tr>
</tbody>
</table>

### Recommended Step for Initiating Treatment

- **Step 1**: In 2 to 6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.

## Stepwise Approach for Managing Asthma in Children Aged 5 to 11 Years

<table>
<thead>
<tr>
<th>Intermittent Asthma</th>
<th>Persistent Asthma: Daily Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong> Preferred: SABA PRN</td>
<td>Consult with asthma specialist if Step 4 care or higher is required. Consider consultation at Step 3.</td>
</tr>
</tbody>
</table>

### Each Step: Patient education, environmental control, and management of comorbidities
Steps 2-4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma

### 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

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

### Step 3
- **Preferred:** EITHER Low-dose ICS + either LABA (B), LTRA (B), or Theophylline (B) OR Medium-dose ICS (B)
- **Alternative:** Medium-dose ICS + either 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 or Theophylline and Oral Systemic Corticosteroid (D)

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

Estimated Comparative Daily Dosages for ICS in Children Aged 5 to 11 Years

<table>
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<tr>
<td>Beclomethasone HFA 40 or 80 µg/puff</td>
<td>80-160 µg</td>
<td>&gt;160-320 µg</td>
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<td>Budesonide DPI 90, 180, or 200 µg/inhalation</td>
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<td>&gt;400-800 µg</td>
<td>&gt;800 µg</td>
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<tr>
<td>Budesonide inhalation suspension for nebulization (child dose)</td>
<td>0.5 mg</td>
<td>1.0 mg</td>
<td>2.0 mg</td>
</tr>
<tr>
<td>Flunisolide 250 µg/puff</td>
<td>500-750 µg</td>
<td>1000-1250 µg</td>
<td>&gt;1250 µg</td>
</tr>
<tr>
<td>Flunisolide HFA 80 µg/puff</td>
<td>160 µg</td>
<td>320 µg</td>
<td>≥640 µg</td>
</tr>
<tr>
<td>Fluticasone HFA MDI 44, 110, or 220 µg/puff</td>
<td>88-176 µg</td>
<td>&gt;176-352 µg</td>
<td>&gt;352 µg</td>
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<tr>
<td>Fluticasone DPI 50, 100, or 250 µg/inhalation</td>
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<td>&gt;200-400 µg</td>
<td>&gt;400 µg</td>
</tr>
<tr>
<td>Mometasone DPI 200 µg/inhalation</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Triamcinolone acetonide 75 µg/puff</td>
<td>300-600 µg</td>
<td>&gt;600-900 µg</td>
<td>&gt;900 µg</td>
</tr>
</tbody>
</table>

NA = not approved and no data available for children less than 12 years of age.

Note that some of the doses, particularly in the high-dose range, may be outside the recommended labeling for that product.

## Assessing Asthma Control and Adjusting Therapy in Children 5 to 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><strong>Impairment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>2 days/week but not more than once on each day</td>
<td>2 days/week or multiple times on ≤2 days/week</td>
<td>Throughout the day</td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>≤1×/month</td>
<td>≥2×/month</td>
<td>≥2×/week</td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>None</td>
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<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</td>
<td>60%-80% predicted/personal best</td>
<td>&lt;60% predicted/personal best</td>
</tr>
<tr>
<td>• FEV₁/FVC</td>
<td>&gt;80%</td>
<td>75%-80%</td>
<td>&lt;75%</td>
</tr>
<tr>
<td><strong>Exacerbations requiring oral systemic corticosteroids</strong></td>
<td>0-1/year</td>
<td>≥2/year</td>
<td>Consider severity and interval since last exacerbation</td>
</tr>
<tr>
<td><strong>Risk</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduction in lung growth</td>
<td>Evaluation requires long-term follow-up</td>
<td>Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk</td>
<td></td>
</tr>
<tr>
<td>Treatment-related adverse effects</td>
<td>Maintain current step, step up at least 1 step and reevaluate in 2 to 6 weeks, for side effects, consider alternative treatment options</td>
<td>Step up at least 1 step and reevaluate in 2 to 6 weeks, for side effects, consider alternative treatment options</td>
<td>Consider short course of oral systemic corticosteroids, step up 1 or 2 steps, and reevaluate in 2 weeks, for side effects, consider alternative treatment options</td>
</tr>
</tbody>
</table>

**Recommended Action for Treatment**

Summary

• Defining asthma phenotypes will permit targeted therapy.

• Control of co-morbid conditions is necessary to properly treat asthma.

• Asthma is a complex disease that represents an interplay of both airway obstruction and airway inflammation.

• To control persistent asthma, one must treat airway inflammation.

• NIH guidelines provide a framework to guide asthma treatment, however treatment should be personalized to the individual.

• The goals of asthma treatment are minimal symptoms, minimal rescue medication, and no restriction on activity.
Conclusions

• Severity, control, and responsiveness to treatment are key elements of asthma assessment and monitoring

• The goal of asthma therapy is to achieve control based on NAEPP guidelines

• Clinical assessment and patient self-assessment are primary methods for monitoring asthma control

• ICS is preferred monotherapy to help achieve asthma control in patients with persistent asthma

• LABAs are preferred adjunctive agents in patients aged ≥12 years who cannot be controlled with ICS monotherapy
Asthma Phenotypes

Trigger-induced asthma
1) Allergic
2) Non-allergic
3) Aspirin-exacerbated respiratory disease (AERD)
4) Infection
5) Exercise-induced
- Clinical presentation of asthma
  6) Pre-asthma wheezing in infants
     - Episodic (viral) wheeze
     - Multi-trigger wheezing
  7) Exacerbation-prone asthma
  8) Asthma associated with apparent irreversible airflow limitation
- Inflammatory markers of asthma
  9) Eosinophilic and neutrophilic asthma