Asthma Update
Primary Care Days 2013

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Disclosures

Investigator – CF Clinical Trials

Kalobios Pharmaceuticals
Gilead Sciences, Inc.
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

Available at: http://www.cdc.gov/nchs/products/pubs/pubd/hestats/asthma/asthma.htm
Asthma Remains a Serious Health Risk in the US

Every day in America approximately …

63,000 people miss school or work due to asthma
34,000 people have an asthma attack
5,000 people visit the emergency room due to asthma
1,300 people are admitted to the hospital due to asthma
10 people die from asthma

On average, 3 children in a classroom of 30 are likely to have asthma.
Number and Rate* of Asthma Deaths
United States, 1980-2004

*per million population

Source: National Vital Statistics System, National Center for Health Statistics
Asthma Mortality Rates by Race
United States: 1979-2005

Source: Underlying Cause of Death; CDC National Center for Health Statistics

*Age-adjusted to 2000 U.S. population

ICD-9

ICD-10

Rate per million


Year

Black

Other

White
Definition of Asthma

Asthma is an obstructive pulmonary disease with the following characteristics:

• Airflow obstruction that is reversible (in most patients)

• Airway inflammation

• Increased airway responsiveness

Inflammation in Asthma

Normal

Asthma

Desquamation

BM

Eosinophils
Asthma Diagnosis

- History and pattern of symptoms
- Physical examination
- Measurements of lung function
  - reversibility test
  - diurnal variability
- Evaluation of allergic status
Is It Asthma?

• Symptoms - vary over time and in severity:
  • Breathlessness
  • Cough
  • Wheeze
  • Chest tightness

• Symptoms occur or worsen at night or after exposure to trigger

• Colds “go to the chest” or take >10 days to clear
PFT (Spirometry) Curves

Note: Each FEV\textsubscript{1} curve represents the highest of three repeat measurements.
Flow Volume Loops

Normal

AO

- Flow (L/s)
- Volume (L)

Predicted
Actual

1 sec

TLC RV

Flow (L/s)
Loss of Lung Function in Asthma

Lange P et al, NEJM 1998
## Majority of Asthmatic Patients are Sensitive to Inhaled Allergens

<table>
<thead>
<tr>
<th>Age</th>
<th>6-34</th>
<th>35-54</th>
<th>&gt;55</th>
</tr>
</thead>
<tbody>
<tr>
<td>% with Asthma</td>
<td>8.2</td>
<td>8.6</td>
<td>9.8</td>
</tr>
<tr>
<td>Positive skin test</td>
<td>79%</td>
<td>72%</td>
<td>40%</td>
</tr>
<tr>
<td>% without Asthma</td>
<td>91.8</td>
<td>91.4</td>
<td>90.2</td>
</tr>
<tr>
<td>Positive skin test</td>
<td>44%</td>
<td>40%</td>
<td>23%</td>
</tr>
</tbody>
</table>
Asthma Care
Are we where we should be?
What are the Goals of Asthma Care?

The NIH has established the following goals for asthma management:

• No (or minimal) need for ER visits/hospitalizations
• No missed school or work due to asthma
• No sleep disruption
• Maintenance of normal activity levels
• Normal or near-normal lung function

Are patients in the US achieving asthma control on their current therapy?
Asthma USA Study: A National Survey to Assess Asthma Control in the US

• Objective
  – To evaluate the level of uncontrolled asthma in the general population in the US

Study Design
  – Epidemiological survey administered by mail in May through July 2007 to a representative national sample of 134,401 households
  – Information collected for household members ≥18 years of age with a diagnosis of asthma
  – Usable data returned for 162,269 adults; among these, 10,139 adults with a self-reported physician diagnosis of asthma completed the Asthma Control Test™

Data on file, GlaxoSmithKline (Asthma USA Study – Summer 2007). Asthma Control Test is a trademark of QualityMetric Incorporated.
41% of Patients With Asthma Were “Not Well Controlled”

“Not well controlled asthma” was based on a score of ≤19 on the Asthma Control Test™

Of those uncontrolled:
- 64% were on a controller and 25% were using only a short-acting beta$_2$-agonist
Of the 41% of Patients Who Were “Not Well Controlled”

- Shortness of Breath ≥3 Times/Week: 73%
- Rescue Medication Use ≥2 Times/Week: 75%
- Nighttime Awakenings ≥1 Time/Week: 59%
- Limitation in Daily Activities (Some, Most, or All of the Time): 50%

Data on file, GlaxoSmithKline (Asthma USA Study – Summer 2007).
Of Those Patients Determined to Be Uncontrolled, 85% Considered Their Asthma Somewhat or Completely Controlled

Patient Perception of Control

Well/Completely Controlled: 32%
Somewhat Controlled: 53%
The Majority of Uncontrolled Patients Experienced 1 or More Asthma Exacerbations in the Preceding Year

*Exacerbation defined as requiring either oral corticosteroid, asthma-related emergency department (ED)/urgent care visit, and/or asthma-related hospitalization.

<table>
<thead>
<tr>
<th></th>
<th>Uncontrolled</th>
<th>Controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 Exacerbation*</td>
<td>58%</td>
<td>24%</td>
</tr>
<tr>
<td>Oral Corticosteroid</td>
<td>46%</td>
<td>18%</td>
</tr>
<tr>
<td>Asthma-Related ED Visit</td>
<td>40%</td>
<td>13%</td>
</tr>
<tr>
<td>Asthma-Related Hospitalization</td>
<td>11%</td>
<td>1.4%</td>
</tr>
</tbody>
</table>

*Exacerbation defined as requiring either oral corticosteroid, asthma-related emergency department (ED)/urgent care visit, and/or asthma-related hospitalization.
1 Out of 5 Patients Treated With Albuterol Only Use Their Rescue Inhaler Daily

Data on file, GlaxoSmithKline (Asthma USA Study – Summer 2007).
Asthma Care
Meeting the Mark
Asthma Assessment & Monitoring

The key elements of assessment and monitoring include the concepts of severity, control, and responsiveness to treatment:
Asthma Assessment & Monitoring

**Severity** - intensity of the disease process. Severity is measured most easily and directly in a patient not receiving long-term-control therapy.

Classify severity for initiating therapy

**Control** - degree to which asthma symptoms, functional impairments, and risks of untoward events are minimized and the goals of therapy are met.

Assess control for monitoring and adjusting therapy

**Responsiveness** - the ease with which asthma control is achieved by therapy.
Severity & Control Are Assessed Based On 2 Domains

• **Impairment** – the present
  • Frequency and intensity of symptoms
  • Functional limitations (quality of life)

• **Risk** – the future
  • Likelihood of asthma exacerbations
  • Progressive loss of lung function (reduced lung growth)
  • Risk of adverse effects from medication
Severity: Impairment and Risk Domains

**Severity**
Underlying Intensity of Disease Pretreatment

**Impairment**
- Frequency of symptoms
- Intensity of symptoms
- Measures of lung function
- Functional limitations
- Impairment currently or recently experienced

**Risk**
- Likelihood of future exacerbations or impairment
- History of exacerbations
- Likelihood of progressive lung function decline
Assessing Impairment Domain – The Present

• Assess by taking a careful, directed history and lung function measurement.

• Assess Quality of Life using standardized questionnaires
  • Asthma Control Test (ACT)
  • Childhood Asthma Control Test
  • Asthma Control Questionnaire
  • Asthma Therapy Assessment Questionnaire (ATAQ) control index.

• Some patients, appear to perceive the severity of airflow obstruction poorly.
Assessing Risk Domain – The Future

• Assessment of adverse events in the future, especially of exacerbations and of progressive, irreversible loss of pulmonary function—is more problematic (airway remodeling).

• The test most used for assessing the risk of future adverse events is spirometry.
Severity, Control, and Responsiveness Are Related

Select Appropriate Therapy Step

Step therapy up or down
### Severity Table: How Is it Organized?

<table>
<thead>
<tr>
<th>Component of Severity</th>
<th>Classification of Asthma Severity &gt;12 yrs of age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intermittent Persistent</td>
</tr>
<tr>
<td></td>
<td>Mild               Moderate     Severe</td>
</tr>
</tbody>
</table>

Severity Classification
# Severity Table: Impairment Domain

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<tr>
<td></td>
<td>Intermittent</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
</tr>
<tr>
<td>Nighttime awakening</td>
<td></td>
</tr>
<tr>
<td>SABA use</td>
<td></td>
</tr>
<tr>
<td>Interference with activity</td>
<td></td>
</tr>
<tr>
<td>Lung function</td>
<td></td>
</tr>
</tbody>
</table>

**IMP AIRMENT DOMAIN**

SABA = short-acting β-agonist.
# Severity Table: Risk Domain

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<th>Classification of Asthma Severity &gt;12 yrs of age</th>
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<td>Impairment</td>
<td></td>
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<td>Symptoms</td>
<td></td>
</tr>
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<td>Nighttime awakening</td>
<td></td>
</tr>
<tr>
<td>SABA use</td>
<td></td>
</tr>
<tr>
<td>Interference with activity</td>
<td></td>
</tr>
<tr>
<td>Lung function</td>
<td></td>
</tr>
<tr>
<td>Impairment</td>
<td></td>
</tr>
<tr>
<td>Exacerbations requiring oral steroids</td>
<td></td>
</tr>
</tbody>
</table>

**Risk Domain**

Considers exacerbation severity, frequency, interval since last exacerbation, and potential link between FEV<sub>1</sub> and relative annual risk.
# Severity Table: Initial Treatment Step

## Classification of Asthma Severity >12 yrs of age

<table>
<thead>
<tr>
<th>Component of Severity</th>
<th>Intermittent</th>
<th>Persistent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

### Impairment

- Symptoms
- Nighttime awakening
- SABA use
- Interference with activity
- Lung function

### Risk

- Exacerbations requiring oral steroids

## Recommended Treatment Step

Step of treatment recommended for initial therapy, with follow-up in 2-6 wks
<table>
<thead>
<tr>
<th>Component of Severity</th>
<th>Classification of Asthma Severity (≥12 yrs)</th>
<th>Persistent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intermittent</td>
<td>Mild</td>
</tr>
<tr>
<td>Symptoms</td>
<td>&lt;2 d/wk</td>
<td>&gt;2 d/wk but not daily</td>
</tr>
<tr>
<td>Nighttime awakening</td>
<td>&lt;2 d/mo</td>
<td>3-4x/mo</td>
</tr>
<tr>
<td>SABA use</td>
<td>&lt;2 d/wk</td>
<td>&gt;2 d/wk but not daily &amp; not &gt;1x on any day</td>
</tr>
<tr>
<td>Interference with activity</td>
<td>NONE</td>
<td>Minor limitation</td>
</tr>
<tr>
<td>Lung function</td>
<td>• Normal FEV&lt;sub&gt;1&lt;/sub&gt; between exacerbations</td>
<td>• FEV&lt;sub&gt;1&lt;/sub&gt;: &gt;80% predicted</td>
</tr>
<tr>
<td></td>
<td>• FEV&lt;sub&gt;1&lt;/sub&gt;: &gt;80% predicted</td>
<td>• FEV&lt;sub&gt;1&lt;/sub&gt;/FVC: normal</td>
</tr>
<tr>
<td></td>
<td>• FEV&lt;sub&gt;1&lt;/sub&gt;/FVC: normal</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk</th>
<th>Exacerbations requiring oral steroids</th>
<th>0-1/yr</th>
<th>≥2/yr</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Consider severity and interval since last exacerbation as they may fluctuate over time in any severity category</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommended Treatment Step</th>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3</th>
<th>Step 4 or 5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&amp; consider short OS burst</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Classification of Asthma Severity: Clinical Features Before Treatment – 2002 “Old” Guidelines

<table>
<thead>
<tr>
<th>Step 4</th>
<th>Severe Persistent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days With Symptoms</td>
<td>Continuous</td>
</tr>
<tr>
<td>Nights With Symptoms</td>
<td>Frequent</td>
</tr>
<tr>
<td>PEF or FEV₁</td>
<td>≤ 60%</td>
</tr>
<tr>
<td>PEF Variability</td>
<td>&gt; 30%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 3</th>
<th>Moderate Persistent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days With Symptoms</td>
<td>Daily</td>
</tr>
<tr>
<td>Nights With Symptoms</td>
<td>&gt; 1 night/week</td>
</tr>
<tr>
<td>PEF or FEV₁</td>
<td>&gt; 60% - &lt; 80%</td>
</tr>
<tr>
<td>PEF Variability</td>
<td>&gt; 30%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 2</th>
<th>Mild Persistent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days With Symptoms</td>
<td>&gt; 2/week, &lt;1x/day</td>
</tr>
<tr>
<td>Nights With Symptoms</td>
<td>&gt; 2 nights/month</td>
</tr>
<tr>
<td>PEF or FEV₁</td>
<td>≥ 80%</td>
</tr>
<tr>
<td>PEF Variability</td>
<td>20-30%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Mild Intermittent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days With Symptoms</td>
<td>≤ 2 days/week</td>
</tr>
<tr>
<td>Nights With Symptoms</td>
<td>≤ 2/month</td>
</tr>
<tr>
<td>PEF or FEV₁</td>
<td>≥ 80%</td>
</tr>
<tr>
<td>PEF Variability</td>
<td>&lt; 20%</td>
</tr>
</tbody>
</table>

Footnote: The patient’s step is determined by the most severe feature.
‘Real-life’ Classification of Severity

- Many physicians classify asthma severity based on treatment given rather than treatment needed.
- Patients adjust lifestyle to suit asthma severity: limited expectations rather than optimal quality of life.
- Mild asthma is usually more severe than many physicians and patients realize.
The goal of asthma therapy is to maintain long-term control of asthma with the least amount of medication and hence minimal risk for adverse effects.
Explore the Triggers of Asthma

Symptoms can occur or worsen in the presence of:

**Allergens**
- animal dander
- dust mites
- fungi
- cockroach
- pollen

**Others**
- Exercise
- Viral infection
- GERD
- Smoke and other irritants
- Cold air
- Drugs (NSAIDs, ß-blockers)
- Strong emotional expression
Steps of Therapy: Age ≥12 Years

Intermittent Asthma

Persistent Asthma: Daily Medication
Consult with 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
Alternative:
Cromolyn, LTRA, Nedocromil, or Theophylline

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

Step 5
Preferred:
High-dose ICS + LABA
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)

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

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 oral systemic 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.

Each step: Patient education, environmental control, and management of comorbidities.
Steps 2–4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma (see notes).
Steps of Therapy: Age ≥12 Years

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Step 4

Preferred:
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Alternative:
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(first, check adherence, environmental control, and comorbid conditions)

Each step: Patient education, environmental control, and management of comorbidities.
Steps 2–4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma (see notes).
How can monitoring use of short-acting beta$_2$-agonists help your patients?
How Much Rescue Medication Are Asthma Patients Using?

Most albuterol inhalers have 200 puffs per canister

200 puffs = 100 doses

Patient who uses ≤2 doses/week = 50-week supply*

1 canister should last approximately 1 year.

*Calculation for canister containing 200 inhalations with patient using 2 inhalations per dose. A second canister may be necessary due to priming of the canister.
Short-acting $\beta_2$-agonist Use Was Predictive of Subsequent ED Visits, Hospitalizations, and Oral Corticosteroid Use

Relationship Between Short-Acting Beta$_2$-agonist Use and Subsequent Hospitalizations/ED Visits and Oral Corticosteroid Use in the Following Year

Results of 62,369 adult patients with asthma from a large HMO, 2002 to 2003.

Steps of Therapy: Age ≥12 Years

Interventric Asthma

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

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Alternative:
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Assess control

Step down if possible
(and asthma is well controlled at least 3 months)
Inhaled Corticosteroids: First Line Controller Therapy For Persistent Asthma
The Benefits of Inhaled Corticosteroids

• Improved asthma symptom scores (day & night)
• Reduced need for rescue $\beta$-agonist therapy
• Improved lung function: PEFR, FEV$_1$
• Reduction in bronchial hyperresponsiveness
• Reduction in ER visits / hospitalizations
• Reduction in health-care costs
• Reduction in asthma mortality
Low-dose ICS and the Prevention of Death from Asthma in Canada

Effects of Inhaled Corticosteroids on Inflammation

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

Estimated Comparative Dosages of Inhaled Corticosteroids

• Preparations are not equivalent per puff or per microgram.
• Comparative doses are *estimated*.
  • Few data directly compare preparations.
• Most important determinant of dosing is clinician judgment.
  • Monitor patient’s clinical response to therapy.
  • Adjust dose accordingly.
# Estimated Comparative Daily Dosages of Inhaled Corticosteroids for Adults

<table>
<thead>
<tr>
<th>Drug</th>
<th>Low Dose</th>
<th>Medium Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone</td>
<td>168 - 504 mcg</td>
<td>504 - 840 mcg</td>
<td>&gt; 840 mcg</td>
</tr>
<tr>
<td>Budesonide DPI</td>
<td>200 - 400 mcg</td>
<td>400 - 600 mcg</td>
<td>&gt; 600 mcg</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>500 - 1,000 mcg</td>
<td>1,000 - 2,000 mcg</td>
<td>&gt; 2,000 mcg</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>88 - 264 mcg</td>
<td>264 - 660 mcg</td>
<td>&gt; 660 mcg</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>400 - 1,000 mcg</td>
<td>1,000 - 2,000 mcg</td>
<td>&gt; 2,000 mcg</td>
</tr>
</tbody>
</table>
Safety of Inhaled Corticosteroids

• ICS’s are the most effective long-term therapy available, and are well tolerated and safe at recommended doses.

• The potential but small risk of adverse events from the use of ICS treatment is well balanced by their efficacy.

• The dose-response curve for ICS treatment begins to flatten at low to medium doses.

• Most benefit is achieved with relatively low doses. The risk of adverse effects increases with dose.
The Risks of Inhaled Corticosteroids

• Local effects in the airways and oropharynx
• Hypothalamic-Pituitary-Adrenal axis effects
• Ocular effects
• Effects on bone
  • Growth in children
  • Bone turnover / osteoporosis
  • Failure to achieve maximal bone density
Soothing Patient’s (and Parent’s) Qualms About ICS

• Typical prednisone burst for asthma exacerbation is 40 mg /day for 5 days
• 200 mg = 200,000 mcg (all bioavailable)
• Equivalent to:
  • 200 days Pulmicort Respules, 0.5 mg BID
  • 400 days Pulmicort Respules, .25 mg BID
  • 500 days Azmacort, 200 mcg BID
  • 454 days Flovent, 220 mcg BID
  • 400 days Advair, 250/50 mcg BID
• Only 1-6% of ICS bio-available
Intermittent Asthma

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Steps of Therapy: Age ≥12 Years

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OR
Medium-dose ICS
Alternative: Low-dose ICS + either LTRA, Theophylline, or Zileuton

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

Step 5
Preferred: High-dose ICS + LABA
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, environmental control, and management of comorbidities.
Steps 2–4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma (see notes).

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.
- 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.
Combination Therapy in Persistent Asthma
Long-Acting Beta$_2$-Agonists

- Added to low- or medium-dose ICS improves lung function, decreases symptoms, and reduces exacerbations and use of SABA for quick relief
- Not a substitute for anti-inflammatory therapy
- Not appropriate for monotherapy
- Not for acute symptoms or exacerbations
- The FDA determined that a Black Box warning was warranted on all preparations containing a LABA
FDA Drug Safety Communication: New safety requirements for long-acting inhaled asthma medications called Long-Acting Beta-Agonists (LABAs)

• The use of LABAs is contraindicated without the use of an asthma controller medication (e.g. ICS). Single-ingredient LABAs should only be used in combination with an asthma controller medication; they should not be used alone.

• LABAs should only be used long-term in patients whose asthma cannot be adequately controlled on asthma controller medications.

• LABAs should be used for the shortest duration of time required to achieve control of asthma symptoms and discontinued, if possible, once asthma control is achieved. Patients should then be maintained on an asthma controller medication.

• Pediatric and adolescent patients who require the addition of a LABA to an inhaled corticosteroid should use a combination product containing both an inhaled corticosteroid and a LABA, to ensure compliance with both medications.
FDA Summary: Use of LABAs in Asthma

FDA has determined that the benefits of LABAs in improving asthma symptoms outweigh the potential risks when used appropriately with an asthma controller medication in patients who need the addition of LABAs.
Leukotriene Modifiers

• cys-Leukotriene Receptor Antagonist
  • Montelukast (Singulair®) 10mg per day
  • Zafirlukast (Accolate®) 20 mg twice per day

• 5-Lipoxygenase Inhibitor
  • Zileuton (Zyflo®) 600 mg four times per day
Indications for Leukotriene Modifiers

- 1st line controller therapy in very select groups
- Patients with mild-moderate disease who fail to respond adequately to ICS therapy
- Patients with moderate-severe asthma who are at risk for systemic side effects from high doses of ICS therapy
- Patients with poor adherence to a regimen of ICS
Steps of Therapy: Age ≥12 Years

Intermittent Asthma
Consult with 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
Alternative: Cromolyn, LTRA, Nedocromil, or Theophylline

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

Step 4
Preferred: Medium-dose ICS + LABA
Alternative: Medium-dose ICS + either LTRA, Theophylline, or Zileuton
Consider Omalizumab for patients who have allergies

Step 5
Preferred: High-dose ICS + LABA
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Each step: Patient education, environmental control, and management of comorbidities.
Steps 2–4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma (see notes).
Intermittent Asthma

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

Step 1
Preferred: SABA PRN

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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)

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.
- 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.
Control Is the Goal

Monitoring and Achieving Asthma Control
Asthma Control (Goals of Therapy)

Reducing Impairment

• Prevent chronic & troublesome symptoms

• Prevent frequent use (<2 days / wk) of inhaled SABA for symptoms

• Maintain (near) “normal” pulmonary function

• Maintain normal activity levels (incl. exercise & other physical activity & attendance at work or school)

• Meet patients’ and families’ expectations of and satisfaction with asthma care.
Asthma Control (Goals of Therapy)

Reducing Risk

• Prevent recurrent exacerbations of asthma and minimize the need for ER visits and hospitalizations

• Prevent progressive loss of lung function - *for children, prevent reduced lung growth*

• Provide optimal pharmacotherapy with minimal or no adverse effects
  - Periodic assessments at 1-6 month intervals
  - Patient self-assessment (with clinician)
  - Spirometry testing
## Assessing Asthma Control: Youths ≥12 Years of Age & Adults

### Components of Control

<table>
<thead>
<tr>
<th>Impairment</th>
<th>Classification of Asthma Control (Youths ≥12 years of age and adults)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Well-Controlled</td>
</tr>
<tr>
<td>Symptoms</td>
<td>≤2 days/week</td>
</tr>
<tr>
<td>Nighttime awakening</td>
<td>≤2x/month</td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>None</td>
</tr>
<tr>
<td>Short-acting beta₂-agonist use for symptom control (not prevention of EIB)</td>
<td>≤2 days/week</td>
</tr>
<tr>
<td>FEV₁ or peak flow</td>
<td>&gt;80% predicted/ personal best</td>
</tr>
<tr>
<td>Validated Questionnaires</td>
<td></td>
</tr>
<tr>
<td>ATAQ</td>
<td>0</td>
</tr>
<tr>
<td>ACQ</td>
<td>≤0.75*</td>
</tr>
<tr>
<td>ACT</td>
<td>≥20</td>
</tr>
<tr>
<td>Exacerbations</td>
<td>0–1/year</td>
</tr>
<tr>
<td>Progressive loss of lung function</td>
<td>Evaluation requires long-term followup care</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>
</tr>
</tbody>
</table>
**Actions Once Control Is Assessed**

### Well-Controlled
- Maintain current step
- Regular follow-up every 1-6 mos to maintain control
- Consider STEP DOWN if well-controlled for at least 3 mos

### Not Well-Controlled
- STEP UP 1 step
- Reevaluate in 2-6 wks
- For side effects, consider alternative treatment options

### Very Poorly Controlled
- Consider short course of oral systemic corticosteroids
- STEP UP 1-2 steps
- Re-evaluate in 2 wks
- For side effects, consider alternative treatment options
Ongoing Asthma Management
Monitoring and Control

• Emphasis is placed on routine visits rather than as-needed visits for out-of-control asthma

• Periodic assessments every 1-6 mos recommended to monitor asthma control

• Modifications in therapy are based on assessments of control

• The importance of environmental control and management of comorbidities are stressed

If Good Control Is Not Achieved

Consider possible contribution of:

• Adverse environmental/allergen exposures
• Poor technique
• Poor adherence to therapy
• Comorbidities
Allergy Testing for All Patients With Persistent Asthma: New in EPR-3

• Allergies are significant triggers for asthma in ≥80% of children and 50%-60% of adults

• All patients with persistent asthma are recommended for evaluation of allergens as possible contributing factors
  – Especially perennial allergens
  – Can be done through skin or in vitro testing
Allergy Immunotherapy

A process by which increasing doses of an allergen are injected subcutaneously as a preventative treatment for the symptoms that occur on natural exposure to the allergen.
Specific Immunotherapy in Patients With Asthma and Rhinitis

- **mild rhinitis**
- **moderate rhinitis conjunctivitis**
- **severe rhinitis conjunctivitis**
- **allergen avoidance when possible**
- **pharmacotherapy**
- **consider immunotherapy**

- **intermittent asthma**
- **Mild persistent asthma**
- **Moderate persistent asthma**
- **Severe persistent asthma**
- **allergen avoidance when possible**
- **pharmacotherapy**
- **consider immunotherapy**
Immunotherapy: 4 Levels of Clinical Benefit

• Early Effect
  - effect achieved after initiation of IT

• Persisting Effect
  - effect persisting during IT

• Long-term Effect
  - effect after termination of IT

• Preventative Effect
  - prevention of new sensitivities, development of asthma and exacerbations of disease
Anti-IgE Antibodies in the Treatment of Atopic Asthma
Anti-IgE Therapy

- Omalizumab, a monoclonal anti-IgE antibody, is currently the only approved anti-IgE therapy licensed in the United States.

- Indicated for the prophylaxis of asthma exacerbations and control of symptoms in moderate to severe allergic asthma in patients $\geq$ 12 years of age.

- Given as an add-on therapy to ICS in moderate to severe allergic asthma, it significantly reduces asthma exacerbations and allows doses of ICS to be reduced.
Relationship Between Asthma and Serum IgE Level

Serum IgE (IU/ml)

Odds Ratio for Presence of Asthma

N = 2657

ULN=upper limit of normal.

The Structure of the IgE Molecule

- Light Chain
- Disulphide bond
- FcεR1 Receptor Binding Site
- Fab
- Fc
Anti-IgE: Omalizumab
Appropriate Candidates for Anti-IgE Therapy

Adolescent (≥12 yrs) and adult patients:

- With moderate to severe persistent asthma
- Who demonstrate a positive skin or in vitro reactivity to a perennial aeroallergen
  - Serum IgE between 30-700 IU/mL
  - Symptoms are inadequately controlled with ICS or ICS+LABA
  - Who are not eligible for immunotherapy*
  - Who have adequate coverage or resources for cost of therapy

*poorly controlled asthma is a relative contraindication to immunotherapy
BLACK BOX WARNING FOR OMALIZUMAB:

Anaphylaxis, presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue, has been reported to occur after administration of Xolair. Anaphylaxis has occurred as early as after the first dose of Xolair, but also has occurred beyond 1 year after beginning regularly administered treatment. Because of the risk of anaphylaxis, patients should be closely observed for an appropriate period of time after Xolair administration, and health care providers administering Xolair should be prepared to manage anaphylaxis that can be life-threatening. Patients should also be informed of the signs and symptoms of anaphylaxis and instructed to seek immediate medical care should symptoms occur (see WARNINGS, and PRECAUTIONS, Information for Patients).

When to Refer to an Asthma Specialist

Consider consultation with an asthma specialist if patient:

• is receiving step 3 care but is recommended for step 4 or higher
• has a history of life-threatening asthma exacerbation
• is not meeting therapy goals after 3 to 6 months of treatment
• has signs and symptoms that are atypical, or there are problems in differential diagnosis
• has other conditions that complicate asthma (eg, COPD, VCD, GERD)
• requires additional diagnostic testing
• needs additional education/guidance on complications of therapy, problems with adherence, or allergen avoidance
• is being considered for immunotherapy or omalizumab
An Effective Management Program

- Educate patients to manage their condition
- Identify and avoid triggers that make asthma worse
  - Environmental controls
- Achieve control by selecting appropriate medication
- Effective monitoring - symptoms and lung function
- Treat asthma attacks promptly and effectively
- Monitor and modify asthma care to maintain effective long-term control

GINA Guidelines 1998