Recent Developments in Asthma Research, Diagnosis, and Treatment

Thomas L. Mertz, DO, PharmD

Asthma is a clinical syndrome that typically consists of increased airway hyperresponsiveness and recurrent episodes of airway obstruction and inflammation with subsequent remodeling. As one of the most common conditions seen in the primary care setting, asthma is of great interest to the US Centers for Disease Control and Prevention (CDC).

The CDC recently revealed that the prevalence of asthma between 2001 and 2009 increased in the US population from 7.3% (20.3 million individuals) to 8.2% (24.6 million individuals), representing a 12.3% increase. In addition, the CDC reported that individuals with low economic means are most commonly affected by asthma. The CDC further found that only 34.2% of persons with asthma reported that they had been given a written action plan by their health-care providers, and 68.1% of persons with asthma said they had been educated on the proper steps to take during an asthma attack.

Fractional Excretion of Nitric Oxide

There have been advances in the diagnostic evaluation of patients suspected of having asthma. Measurement of fractional excretion of nitric oxide (FeNO) is a new and efficient office-based modality that can help clarify if a diagnosis of asthma is in question or if a patient is likely to respond to treatment with inhaled corticosteroids (ICSs). Nitric oxide is a gas that is released into the airway during an inflammatory response. It is an indirect marker of eosinophilic airway inflammation. Patients with asthma or active inflammation have higher levels of FeNO than do patients without asthma.

The normal range of FeNO is 0 to 20 parts per billion. Levels of FeNO higher than 35 parts per billion would be consistent with active eosinophilic inflammation, though atopic individuals generally tend to have higher FeNO levels.

Mannitol Bronchial Challenge Test

Historically, the gold standard for ruling out an asthma diagnosis has been the methacholine challenge. This test is expensive and difficult to perform and has many other potential pitfalls. A positive result in the methacholine challenge is defined as the dose of methacholine that causes a decrease in forced expiratory volume in 1 second (FEV₁) of at least 20%—or a provocative concentration causing a 20% decrease (PC20).

Recently, an alternative to the methacholine challenge has been approved by the US Food and Drug Administration (FDA). Aridol (mannitol inhalation powder; Pharmaxis Ltd, Frenchs Forest, Australia) is now available as a bronchial challenge test kit for the assessment of bronchial hyperresponsiveness. This indirect test offers the advantages of office administration, ease of use, and lower cost than the methacholine challenge. Aridol is helpful for determining those patients who are most likely to respond to anti-inflammatory treatment, as well as for eliciting the patient’s specific asthma phenotype.

Update on Treatment of Adults

Previously, use of inhaled anticholinergic agents had been reserved for treatment of patients with acute asthma exacerbations, and the only approved long-acting anticholinergic agent has been used primarily for the treatment of patients with chronic obstructive pulmonary disease (COPD). In an article published in The New England Journal of Medicine, Peters et al. reported results of the addition of the long-acting anticholinergic bronchodilator tiotropium bromide to an inhaled glucocorticoid in patients with inadequately controlled asthma. In the 3-way, double-blind, triple-dummy crossover trial, which included 210 patients with asthma, tiotropium bromide was shown to be of equal efficacy to the long-acting β-agonist (LABA) salmeterol as a step-up therapy. Thus, tiotropium bromide represents an important alternative treatment for adults with poorly controlled, chronic asthma.

Black Box Warning for Long-Acting β-Agonists

The use of a LABA, combined with an ICS, is a mainstay of treatment for patients with moderate to severe asthma. Long-acting β-agonists should be used only in combination with ICSs, as indicated by the FDA “black box” warning pointing out that using LABAs alone carries the increased risks of worsening asthma and asthma-related deaths.

This information was first reported in the Salmeterol Multicenter Asthma...
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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 adherence with both medications.

The FDA also requires that manufacturers of LABAs complete postmarketing safety trials of these medications.

Pharmacokinetics of LABAs
Salmeterol, formoterol, and aformoterol are the 3 formulations of LABAs currently approved for use in the United States. These agents are not indicated for single use in the treatment of asthma and should always be combined with an ICS. Currently there is a black box warning issued by the FDA regarding this practice.

All these agents carry similar warnings and have similar efficacy in the treatment of patients with asthma or COPD, though there are important pharmacokinetic differences between them. The use of any of these LABAs results in improvement in FEV₁ for as long as 12 hours, compared to 3 to 4 hours with the use of albuterol. This extension of the duration of action is accomplished as a result of the large lipophilic side chains on the LABA molecules. Although the LABAs have a longer duration of action, they do have a slower onset compared to the rescue inhaler albuterol.

The main pharmacokinetic differences among the LABAs include a quicker onset of action for formoterol (3 minutes) compared to salmeterol (30-48 minutes). This rapid action has led to the use of the budesonide/formoterol combination as a rescue inhaler in Europe, though it does not have that indication in the United States. A review in the European Respiratory Journal by Barnes suggested that a combination ICS/LABA inhaler can be used as maintenance or rescue therapy. The corticosteroid component of this combination appears to play an important role in rescue therapy.

Hozawa et al recently performed a comparison of budesonide/formoterol with fluticasone/salmeterol for treatment effects on small airway impairment and airway inflammation in patients with asthma. They found a statistically significant improvement in small airway impairment (ie, forced respiratory flow at 25% point to the 75% point of forced vital capacity) and airway inflammation (ie, FeNO) in the budesonide/formoterol group compared to the fluticasone/salmeterol group. The P-Value was <0.001 in both groups. This finding ultimately could lead to the use of budesonide/formoterol to improve asthma control in patients.

Update on Treatment of Children with Asthma
Asthma is prevalent in 9.6% of children in the United States, making it a common condition encountered in the pediatric clinical setting. Inhaled corticosteroids are effective maintenance medications for the treatment of patients with asthma. Many children have frequent exacerbations of asthma despite achieving good control between attacks.

The ICS beclomethasone dipropionate was investigated as a rescue treatment for children with mild persistent asthma. In the TREXA study, treatment of patients with acute asthma exacerbation using the combination of albuterol and beclomethasone dipropionate was found to be more effective than treatment with albuterol alone. Thus, beclomethasone dipropionate represents an alternative treatment for patients with asthma exacerbations, likely helping this population achieve compliance with long-term regimens that are often problematic. Intermittent use of an ICS would also lower the risk for development of growth impairment.

Research Trial (SMART), a large, randomized, double-blind clinical trial performed in 2006. In that study, 26,355 patients with asthma were randomly assigned to receive either salmeterol or placebo for 28 weeks. The salmeterol group was associated with small but statistically significant increased risks of respiratory-related deaths, asthma-related deaths, and combined asthma-related deaths or life-threatening experiences, compared to the placebo group.

The FDA black box warnings for LABAs in asthma treatment are as follows:

- Use of a LABA alone without use of a long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated in the treatment of asthma.
- LABAs should not be used in patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.
- LABAs should only be used as additional therapy for patients with asthma who are currently taking but are not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid.
- Once asthma control is achieved and maintained, patients should be assessed at regular intervals and step-down therapy should begin (eg, discontinue LABA), if possible without loss of asthma control, and the patient should continue to be treated with a long-term asthma control medication, such as an inhaled corticosteroid.
- 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 adherence with both medications.

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Effective Add-On Treatments to Inhaled Corticosteroids
In children whose asthma remains uncontrolled despite receiving ICSs, evidence is lacking regarding the appropriate choice of step-up therapy. Recently, Lemanske et al\(^{12}\) studied step-up therapy for children with uncontrolled asthma in the Best Add-on Therapy Giving Effective Responses (BADGER) study. Although the children in that study each had individual responses to the various treatments, LABAs were found to be the most effective add-on medication to an ICS.

Thus, in most cases, a LABA should be the first medication added to the treatment of a patient taking an ICS. However, treatment should be individualized and closely monitored for patients.\(^ {12}\)

Treatment with ICSs in Early Wheezers
Asthma is a chronic disease state with chronic inflammation. It was previously unknown if treatment with ICSs early in life could modify the natural course of asthma in high-risk preschool children. The Prevention of Early Asthma in Kids (PEAK) study\(^ {13}\) addressed this question. In the study, preschool children who were considered at high risk for asthma were treated for 2 years with ICSs. This treatment did not affect the propensity for development of asthma symptoms or alterations in lung function at 1 year after discontinuation of the ICS, compared to masked placebo.\(^ {13}\)

Use of Omalizumab in Inner-City Children
Children residing in the inner city have persistent exposure to many triggering aeroallergens, and they often experience difficulty in their asthma treatments despite environmental avoidance measures.

In a study of the effectiveness of omalizumab (antibody to immunoglobulin E) by Busse et al\(^ {14}\) inner-city children with persistent asthma were randomly assigned to receive either omalizumab or placebo. When added to a regimen of guideline-based therapy, omalizumab improved asthma control, decreased exacerbations, and reduced the need for other medications to control asthma.

Final Notes
Asthma is a chronic disease state with many different phenotypes. This is a condition commonly managed by primary care physicians. Medicine is ever changing, and new treatment strategies and ancillary diagnostic testing are now available. Therefore, keeping abreast of the new innovations and treatments can help to reduce morbidity and mortality in patients with asthma.

Resources for Asthma Information
The following online resources provide useful diagnostic and treatment information for patients with asthma.

- **American Academy of Allergy, Asthma & Immunology**

- **American Academy of Pediatrics**

- **American Lung Association**
  [http://www.lungusa.org](http://www.lungusa.org)

- **Asthma and Allergy Foundation of America**

- **Asthma Information and Treatment Guidelines**
  [http://www.asma.com](http://www.asma.com)

- **Asthma Information: Causes, Symptoms, and Treatment—American College of Allergy, Asthma & Immunology**
  [http://www.acaai.org/allergist/asthma/Pages/default.aspx](http://www.acaai.org/allergist/asthma/Pages/default.aspx)

References


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**Thomas L. Mertz, DO, PharmD, is a licensed pharmacist, board certified in Internal Medicine and Pediatrics, and is currently a second-year fellow in Allergy, Asthma and Immunology at the Pennsylvania State University Milton S. Hershey Medical Center. He can be reached at tmertz@hmc.psu.edu.**